

**Evidence Reports of Kampo Treatment 2013:
402 Randomized Controlled Trials
(EKAT 2013)**

漢方治療エビデンスレポート 2013 - 402 の RCT -

31 December 2013

**Task Force for Evidence Reports / Clinical Practice Guidelines
(ER/CPG-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)**

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Notes on the current version

Since 2007, the Task Force for Evidence Reports/Clinical Practice Guidelines (ER/CPG-TF) of the Japan Society for Oriental Medicine EBM Committee has been exhaustively collecting randomized controlled trials (RCTs) of Kampo medicines in Japan, and then prepared and published structured abstracts (SAs) on the Japan Society for Oriental Medicine (JSOM) website as Kampo Chiryō Ebidensu Repoto (Evidence Reports of Kampo Treatment: EKAT). As indicated in the History of version upgrades on the previous page, the complete version of EKAT 2010 at that time was released on 1 June 2010 which was a listing of 345 RCTs and 1 meta-analysis dating from 1986 to early 2009. The year 1986 is a year in which the current quality standard for Kampo medicines for prescription came into effect.

JSOM has since continued to produce EKATs, but budget considerations delayed complete revision of the website, limiting publication on the website to EKAT Appendix 2011 in October 2011 and EKAT Appendix 2012 in December 2012, which included only the additions and revisions since EKAT 2010. In 2013 after a three-year hiatus, JSOM published a completely revised EKAT, “漢方治療エビデンスレポート 2013 – 402 の RCT – (Kampo Chiryō Ebidensu Repoto 2013 – 402 no RCT –)” (Evidence Reports of Kampo Treatment: 402 Randomized Controlled Trials: EKAT 2013).

EKAT 2013 compiles the SAs published in EKAT 2010, an additional 14 new SAs included in EKAT Appendix 2011, a further 20 new SAs included in EKAT Appendix 2012 as well as 25 new SAs prepared in 2013.

Because the Japan Kampo Medicine Manufacturers Association (JKMA) database now allows additional keyword searches such as “来院順 (rainjun, order of presentation),” which corresponds to quasi-randomization, an EKAT Appendix 2012 search finds RCT papers from 2011 (first half) or earlier. Accordingly, the 25 new SAs prepared for the current version are not necessarily SAs of new papers since 2011 (first half): 10 of them are papers from 2011 (first half) or earlier.

Since it has been confirmed that a SA included in EKAT 2010 (Ito K, Yamamoto H, Saibara T, et al. The usefulness of Kanebo Hachimijiogan in patients with hypertension or cerebrovascular disease [excluding acute phase symptoms] and their concomitant symptoms: a multicenter, double-blind, crossover study*. *Shindan to Chiryō [Diagnosis and Treatment]* 1988; 76: 1096–114 [in Japanese]) was based on a study that used products manufactured in 1985 and failed to meet current Kampo product quality standards, this study was removed prior to publication of EKAT Appendix 2012.

EKAT 2013 therefore compiles SAs of 402 RCTs and one meta-analysis.

In the current version, in addition to the already compiled SAs, the committee’s work has included adding references, correcting errors, and formatting the style uniform. In the previous versions of EKAT, if one SA has been based on multiple references, the bibliographic information appears at the top of the SA, however, some SAs showed that information at the top and in the Abstractor’s comments. This version has brought uniformity to that information by showing all the bibliographic information for references used for the SA at the top of the SA, in order of publication, with the principle reference appearing in bold type.

History of version upgrades

- 31 Dec. 2013: Kampo Chiryō Ebidensu Repoto 2013 – 402 no RCT (Evidence Reports of Kampo Treatment: 402 Randomized Controlled Trials)
- 31 Dec. 2012: Kampo Chiryō Ebidensu Repoto Appendix 2012 (Evidence Reports of Kampo Treatment Appendix 2012)
- 1 Oct. 2011: Kampo Chiryō Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)
- 1 Jun. 2010: Kampo Chiryō Ebidensu Repoto 2010 – 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)
- 1 Jun. 2009: Kampo Chiryō Ebidensu Repoto 2009 – 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)
- 1 Apr. 2008: Kampo Chiryō Ebidensu Repoto Dai 2-han – RC T wo Shu ni Shite- Chukan Hokoku 2007 ver 1.1 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007 ver.1.1)
- 15 Jun. 2007: Kampo Chiryō Ebidensu Repoto Dai 2-han –RC T wo Shu ni Shite- Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007)
- 20 Jul. 2005: Kampo Chiryō niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (*Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2005: 56, EBM supplementary issue)
- 20 Sept. 2002: Kampo Chiryō niokeru EBM – 2002 nen Chukan Hokoku (EBM in Kampo 2002, Interim Report) (*Nihon Toyo Igaku Zasshi [Japanese Journal of Oriental Medicine]* 2002: 53 [5], supplementary issue)

Version/date	Title	Year of publication of target references	No. of references	No. of structured abstracts (SAs)	No. of excluded references
2013.12.31	Evidence Reports of Kampo Treatment, 2013 - 402 Randomized Controlled Trials	1986-2012 (First half)	494 ²⁾	403 ^{1), 2)}	159
2012.12.31	Evidence Reports of Kampo Treatment, Appendix 2012 (EKAT appendix 2012)	From EKAT 2011 2011 (First half)	457	379 ^{1), 3)}	150 ³⁾
2011.10.1	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT appendix 2011)	From EKAT 2010 2010 (First half)	432	360 ^{1), 4)}	-
2010.6.1	Evidence Reports of Kampo Treatment, 2010 - 345 Randomized Controlled Trials (EKAT 2010)	1986-2009 (First half)	416	346 ¹⁾	132
2009.6.1	Evidence Reports of Kampo Treatment, 2009 - 320 Randomized Controlled Trials (EKAT 2009)	1986-2008 (First half)	385	321 ¹⁾	111
2008.4.1	Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs - Interim Report 2007 ver1.1	1999-2005	116	98	32
2007.6.15	Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs - Interim Report 2007	1999-2005	104	102	42

¹⁾ Including 1 meta-analysis

²⁾ Because literature search methods were improved in EKAT 2013, the additions subsequent to EKAT Appendix 2012 may not necessarily be references subsequent to the first half of 2011.

³⁾ Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012.

⁴⁾ Total of all references added in EKAT 2010 and EKAT Appendix 2011.

Executive summary

The Special Committee for Evidence Based Medicine (EBM), established in June 2001 by the Japan Society for Oriental Medicine (JSOM), issued the “EBM in Kampo 2002, Interim Report” (*Nihon Toyo Igaku Zasshi* [Japanese Journal of Oriental Medicine] 2002: 53 (5), supplementary issue) in 2002, followed by “Evidence Reports of Kampo Treatment” (*Nihon Toyo Igaku Zasshi* [Kampo Medicine] 2005: 56, EBM supplementary issue) in 2005. These publications were intended to present the evidence from “good” studies, including randomized controlled trials (RCTs), of Kampo products published between 1986 and 2002. However, those studies had several methodological limitations, such as lack of clear inclusion/exclusion criteria. Thus, questions were raised by readers such as why particular existing articles had or had not been included.

Accordingly, the improvements listed below were included in the JSOM Task Force for Evidence Report (ER-TF), the second phase of the EBM Special Committee, starting in 2005. These improvements were continued in the Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF), the third phase of the EBM Special Committee (changed to EBM Committee in June 2012), starting in 2009, and the fourth phase of the EBM Committee starting in 2013.

- (1) RCT articles with high levels of evidence were exhaustively included for review.
- (2) The methods for literature search and review processes were specified to enhance accuracy and transparency.
- (3) The reports were presented in the form of structured abstracts consisting of 8 items in accordance with world standards, i.e., “objectives,” “design,” “setting,” “participants,” “intervention,” “main outcome measures,” “main results,” and “conclusions,” and four additional items, i.e., “from Kampo medicine perspective,” “safety assessment in the article,” “abstractor’s comments,” and “abstractor’s name and date.”
- (4) Excluded references were listed along with the reasons for their exclusion.
- (5) Partly because of establishment of the Task Force for Clinical Practice Guidelines in 2005, “recommendations” included in the first report compilations were excluded.
- (6) A system to enable feedback from readers through the internet and other media on the current reports was established.
- (7) To enhance transparency and accountability, conflicts of interests (COI) among persons concerned were disclosed.
- (8) A search function was added to the website (<http://www.jsom.or.jp/medical/ebm/index.html>). Links to the web pages on which references are published were provided.

The inclusion criteria were RCT articles using Kampo formulations (extract and pills) approved for manufacture and sale in Japan that were published between 1986, when the quality of Kampo formulations reached present levels, and the first half of 2012. Studies of in-house formulations such as decoctions were excluded, as in the report compilations in the first phase. The phase 2 report included only RCTs of Kampo products (extract granules, tablets, and capsules, or pills, approved for sale as Kampo formulations for prescription in Japan). It excluded studies of in-house formulations such as decoctions, since no quality control criteria have been established.

The data sources of searches were (1) the Cochrane Library (CENTRAL), (2) *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicana* [JCRM], Ichushi) web, and (3) the database offered by the Japan Kampo Medicines Manufacturers Association (JKMA).

Structured abstracts were arranged in the order used in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10).

Finally, out of 494 references, 402 RCTs and 1 meta-analysis were prepared as structured abstracts. The 159 references not satisfying the inclusion criteria were listed as excluded references along with their bibliographic items and the reason for exclusion.

We would appreciate your comments on compilation method, the contents of the structured abstracts, information on references not included in the report compilations, if any, and other matters. Please send your comments to ebm-er@jsom.or.jp.

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1. Lists of Structured Abstracts

(Lists of structured abstracts and included references: 403 abstracts, 494 references)

Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).

Abbreviations: C: The Cochrane Library (CENTRAL), I: *Igaku Chuo Zasshi (Japania Centra Revuo Medicana, Ichushi)*, N: Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

<<Structured Abstracts Describing RCTs and the References Reporting Them>>

1. Infections (including Viral Hepatitis) (20 abstracts, 26 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
A08.0	To evaluate the efficacy of saireito (柴苓湯) for rotavirus infection.	saireito (柴苓湯)	Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. <i>Nihon Shonika Rinsho (Japanese Journal of Pediatrics)</i> . 1992; 45: 1889-91 (in Japanese).	quasi-RCT	N	94
			Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection*. <i>Dai 9-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku Nihon Shoni Toyo Igakkaishi (Proceedings of the 9th meeting of the Japan Pediatric Society for Oriental Medicine)</i> 1993; 9: 20-3 (in Japanese).			
A09	Efficacy of keihito for diarrhea in children.	keihito (啓脾湯)	Miyazaki R, Tomita H. A study of the efficacy of keihito for diarrhea in children*. <i>Kampo no Rinsho (Journal of Kampo Medicine)</i> 1996; 43: 217-23 (in Japanese).	quasi-RCT	N	95
A09.0	To evaluate the effectiveness of Kampo therapy for infectious diarrhea.	goreisan (五苓散), goreisan (五苓散)+ shakuyakuzanzoto (芍薬甘草湯)	Miura Y, Yamagishi Y, Mikamo H, et al. Investigation into the effects of Kampo therapy for infectious diarrhea.* <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2011; 28: 102-4 (in Japanese).	RCT-envelope	I	96
A16.2	Improvement effects on appetite and host defense in patients undergoing chemotherapy for pulmonary tuberculosis.	Hochuekkito (補中益気湯), hochuekkito (補中益気湯) + shosaikoto (小柴胡湯)	Watanabe A, Hasegawa S. Effect of combined Kampo medicines as adjuvant therapy for pulmonary tuberculosis*. <i>Nippon Iji Shinpo (Japan Medical Journal)</i> 1992; (3553): 76-7 (in Japanese).	RCT	N	97
		hochuekkito (補中益気湯)	Watanabe A, Takahashi N, Uchida Y, et al. Efficacy of hochuekkito as adjuvant therapy for pulmonary tuberculosis*. <i>JAMA (Japanese version)</i> 1992; 13 (6) suppl: 20-1 (in Japanese).			
A16.2	To determine the efficacy of hochuekkito (補中益気湯) for reducing hepatic dysfunction and improving digestion and malabsorption in tuberculosis patients undergoing chemotherapy	hochuekkito (補中益気湯)	Shijubo N, Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis – the reducing effect on hepatic dysfunction occurring as an adverse drug reaction*. <i>Kampo Igaku (Kampo Medicine)</i> 1993; 17: 241-3 (in Japanese).	RCT	N	98
			Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis*. <i>Nikkei Medical</i> 1994; 23 (12): 24-5 (in Japanese).			
A49.0	To evaluate whether hochuekkito has efficacy in preventing colonization and infection with methicillin-resistant <i>Staphylococcus aureus</i> (MRSA).	hochuekkito (補中益気湯)	Seki T, Matsumoto T, Deguchi H, et al. Evaluation of the efficacy of hochuekkito in preventing MRSA colonization and infection*. <i>Kampo Igaku (Kampo Medicine)</i> 1999; 23: 196-7 (in Japanese).	RCT-envelope	I	99

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
A49.0	To evaluate whether hochuekkito can improve immune and nutritional status in immuno-compromised hosts.	hochuekkito (補中益氣湯)	Suzuki J, Arata S, Sugiyama M. Improvement of immunity and nutrition by hochuekkito in immuno-compromised hosts – for the control of MRSA –. <i>Progress in Medicine</i> 2002; 22: 1362-3 (in Japanese).	RCT	I	100
A49.8	To evaluate the efficacy and safety of triple therapy with proton pump inhibitor, antibiotic, and goshuyuto for <i>Helicobacter pylori</i> (<i>H. pylori</i>) infection.	goshuyuto (呉茱萸湯)	Higuchi K, Arakawa T, Ando K, et al. Eradication of <i>Helicobacter pylori</i> with a Chinese Herbal medicine without emergence of resistant colonies. <i>American Journal of Gastroenterology</i> 1999; 94: 1419-20.	RCT	C	101
B02.2	To evaluate whether hochuekkito has a preventive effect on postherpetic neuralgia (PHN).	hochuekkito (補中益氣湯)	Taniguchi S, Terai T, Kono T, et al. The effect of hochuekkito on postherpetic neuralgia*. <i>Hifu no Rinsho (Clinical Practice of Dermatology)</i> 1999; 41: 601-3 (in Japanese).	RCT	I	102
			Taniguchi S, Kono T, Terai T. Preventive effect of hochuekkito on postherpetic neuralgia*. <i>Progress in Medicine</i> 2002; 22: 863-5 (in Japanese).		N	
B18.1	Therapeutic effect of shosaikoto combined with interferon (IFN) -beta therapy on chronic active hepatitis B.	shosaikoto (小柴胡湯)	Sata M, Amagase H, Koga S, et al. Therapeutic effect of IFN-β (Feron) plus shosaikoto combination therapy on chronic active hepatitis B*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1994; 71: 814-20 (in Japanese).	RCT-envelope	I	103
B18.1	Efficacy of shosaikoto on chronic hepatitis B.	shosaikoto (小柴胡湯)	Sato S, Ishikawa K, Chiba T. Efficacy of sho-saiko-to on chronic type B hepatitis. <i>Shokakika (Gastroenterology)</i> 1991; 15: 39-49 (in Japanese).	RCT-envelope	N	104
B18.1	Efficacy and safety in children with HBe antigen-positive chronic hepatitis B	shosaikoto (小柴胡湯)	Shiraki K, Tanimoto K, Togashi T, et al. A study of the efficacy of shosaikoto in children with HBe antigen-positive chronic hepatitis B*. <i>Shonika Rinsho (Japanese Journal of Pediatrics)</i> 1991; 44: 2146-51 (in Japanese).	RCT	N	105
			Shiraki K, Tanimoto K. Clinical Evaluation of the efficacy of TSUMURA Shosaikoto in children with chronic hepatitis B*. <i>Dai 7-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 7th meeting of the Japan Pediatric Society for Oriental Medicine)</i> 1991; 7: 18-22 (in Japanese).		N	
B18.2	Determination of efficacy and safety of shosaikoto for type C chronic liver diseases.	shosaikoto (小柴胡湯)	Hatakeyama S, Ueki J, Ishizuka M, et al. Comparative study of ursodeoxycholic acid and shosaikoto as treatment for chronic liver diseases type C. <i>Yakuri to Chiryu (Japanese Pharmacology & Therapeutics)</i> 1994; 22: 3295-305 (in Japanese).	RCT-envelope	I	106
B18.2	Efficacy of shosaikoto combined with interferon for reducing adverse effects in patients with chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M. Interferon plus shosaikoto combination therapy for chronic hepatitis C (the first report) - effectiveness in reducing adverse effects of interferon*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> . 1993; 70: 2994-3002 (in Japanese).	RCT-envelope	I	107
B18.2	Efficacy and safety of shosaikoto in chronic hepatitis C after interferon therapy.	shosaikoto (小柴胡湯)	Sone M, Nakajima O. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1995; 72: 3193-7 (in Japanese).	RCT	I	108
			Nakajima O, Sone M. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy - the second report*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1998; 75: 1883-8 (in Japanese).		I	
B18.2	To confirm the efficacy of shosaikoto for interferon-resistant chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M, Kurokawa K, et al. The Complementary treatment for chronic hepatitis C. <i>Kagaku Ryoho Kenkyusyo Kiyo (Bulletin of the Institute of Chemotherapy)</i> 2003; 34: 40-51 (in Japanese with English abstract).	RCT-envelope	I	109

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
B18.2	To confirm the efficacy of shosaikoto for chronic hepatitis C.	shosaikoto (小柴胡湯)	Nakajima O, Sone M, Onishi H, et al. Preventive effect of shosaikoto on the progression of chronic hepatitis C to cirrhosis*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1999; 76: 1008-16 (in Japanese).	RCT	I	110
B18.2	Efficacy of interferon plus shosaikoto combination therapy for chronic hepatitis C	shosaikoto (小柴胡湯)	Tanaka N, Matsuzaki Y, Osuga T, et al. A comparative study of IFN monotherapy versus IFN plus TJ-9 Shosaikoto combination therapy in patients with chronic hepatitis C (interim report)*. <i>Progress in Medicine</i> 1993; 13: 2868-72 (in Japanese).	RCT-envelope	N	111
B18.2	Efficacy for reducing adverse effects of interferon therapy in patients with chronic hepatitis C	maoto (麻黄湯) + keishito (桂枝湯) + kojimatsu (紅參末)	Isai H. Efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C*. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1996; 84: 1505-9 (in Japanese).	RCT	N	112
B24.0	Efficacy and safety in the treatment of HIV infection	shosaikoto (小柴胡湯)	Fukue H, Hagiwara T, Yoshida S, et al. Efficacy of high-dose shosaikoto for HIV infection*. <i>HIV Kansensha Hassho Yobo, Chiryō ni kansuru Kenkyūhan Heisei 7 Nendo Kenkyū Hokokusho (Research Report by the Study Group on Prevention and Treatment of HIV Infection)</i> 1996: 203-10 (in Japanese).	DB-RCT	N	113

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs) (31 abstracts, 37 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C16.9	Improvement effect on host-immunity in patients undergoing postoperative adjuvant chemotherapy (UFT 300 mg/day) for gastric cancer.	juzentaihoto (十全大補湯)	Konno H, Maruo Y, Baba S, et al. Improvement of host-immunity by Juzen-taiho-to in the postoperative adjuvant chemotherapy for patients with gastric cancer. <i>Biotherapy</i> 1997; 11: 193-9 (in Japanese with English abstract).	RCT-envelope	N	114
C16.9	Efficacy for reducing adverse effects and improving performance status in patients undergoing postoperative adjuvant chemotherapy (floropyrimidine anticancer drug) for gastric cancer.	ninjin'yoeito (人參養榮湯)	Sugimachi K. A study of the usefulness of ninjin'yoeito in the postoperative adjuvant chemotherapy for gastric cancer*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1995; 72: 454-8 (in Japanese).	RCT-envelope	I	115
C16.9	Efficacy of juzentaihoto combined with oral 5-FU as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.	juzentaihoto (十全大補湯)	Yamada T. Randomized controlled trial of the efficacy of Juzentaihoto (TJ-48) combined with oral 5-FU for gastric cancer*. <i>Progress in Medicine</i> . 2004; 24: 2746-7 (in Japanese)	RCT	N	116
C18.9	To elucidate the mechanism by which juzentaihoto reduces the adverse reaction to treatment with 5-fluorouracil (5-FU) (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.	juzentaihoto (十全大補湯)	Toda T, Matsuzaki K, Kawano T, et al. Preoperative and postoperative combination therapy with slow-release tegafur capsules and juten-taiho-to in patients with colorectal cancer - Tissue concentrations and thymidine phosphorylase activity -. <i>Gan no Rinsho (Japanese Journal of Cancer Clinics)</i> 1998; 44: 317-23 (in Japanese with English abstract).	RCT-envelope	N	117
C18.9	Immunostimulation and suppression of liver metastasis in postoperative patients with colorectal cancer	shosaikoto (小柴胡湯)	Sasaki K, Takashima K, Kitagawa K, et al. Immunostimulation and suppression of liver metastasis by Kampo medicines in postoperative patients with colorectal cancer*. <i>Progress in Medicine</i> 1992; 12: 1652-5 (in Japanese).	RCT	N	118
C18.9	Immunostimulation and improvement of nutritional status in postoperative patients with colorectal cancer	ninjin'yoeito (人參養榮湯)	Araki Y, Tanaka T, Ogata Y, et al. Immunological evaluation of the efficacy of Kampo prescription for postoperative patients with colorectal cancer*. <i>Shinyaku to Rinsho (Journal of New Remedies and Clinic)</i> 1992; 41: 1670-6 (in Japanese).	RCT-envelope	N	119

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C18.9	To evaluate the clinical efficacy of jumentaihoto for the prevention of postoperative recurrence of colorectal cancer.	jumentaihoto (十全大補湯)	Sasaki K, Ezoe E, Araya J, et al. Effects of Kampo medicine on the immune Functions in gastroenteric cancer patients. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 2006; 15: 9-14 (in Japanese).	RCT	N	120
			Sasaki K, Takasaka H, Furuhashi T, et al. Effect of Kampo medicine on cancer chemotherapy. <i>Geka Chiryō (Surgical Therapy)</i> 2007; 97: 504-10 (in Japanese).		N	
C18.9	To evaluate the efficacy of 1-week preoperative treatment with hochuekkito for improving pre- and postoperative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma.	hochuekkito (補中益氣湯)	Nishimura G. Evaluation of clinical efficacy of hochuekkito in improving nutritional/immune status in patients with surgery for large intestine carcinoma*. <i>Progress in Medicine</i> 2009; 29: 84-5.	RCT-envelope	N	121
C18.9	To evaluate the reduction in the number of days to postoperative flatulence and the anti-inflammatory efficacy of daikenchuto in patients who underwent laparotomy for large intestine carcinoma.	daikenchuto (大建中湯)	Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto —A study in a fasted rat model and a randomized controlled trial in postoperative patients with colorectal cancer—. <i>Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai (5th Annual Meeting of the Japanese Gastroenterological Association)</i> (Workshop 5) 2009:9-10.	RCT	N	122
C20.0	To evaluate the effects of daikenchuto on intestinal obstruction following colorectal cancer surgery.	daikenchuto (大建中湯)	Takagi K, Nagata H, Horie T, et al. Effect of the preventive herbal therapy using dai-kenchu-to on intestinal obstruction following curative resection for colorectal cancer: prospective, randomized study. <i>Kampo Kenkyū (Kampo Research)</i> 2007; (429): 270-1 (in Japanese).	RCT	I	123
C22.0	To evaluate the effect of jumentaihoto for reducing adverse effects of Spongol + Lipiodol + phosphatidyl choline + cisplatin treatment in transarterial embolization (TAE) for hepatocellular carcinoma.	jumentaihoto (十全大補湯)	Nagatomo H, Shigehira M. Efficacy of TSUMURA Jumentaihoto for reducing the adverse effects of the anticancer drug cisplatin*. <i>Kampo Igaku (Kampo Medicine)</i> 1992; 16: 116-9 (in Japanese).	RCT	N	124
C22.0	Preventive effect on the progression of cirrhosis to liver cancer	shosaikoto (小柴胡湯)	Ayukawa K, Sato T, Nagase S, et al. Preventive effect of shosaikoto on liver carcinogenesis*. <i>Rinsho to Kenkyū (Japanese Journal of Clinical and Experimental Medicine)</i> 1994; 71: 1874-6 (in Japanese).	quasi-RCT	I	125
C22.0	To evaluate the anti-inflammatory efficacy of daikenchuto in postoperative patients with liver carcinoma.	daikenchuto (大建中湯)	Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto —A study in a fasted rat model and a randomized controlled trial in postoperative patients with colorectal cancer—. <i>Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai (5th Annual Meeting of the Japanese Gastroenterological Association)</i> (Workshop 5) 2009:9-10.	RCT	N	126
C34.9	Preventive effect on myelosuppression in patients undergoing chemotherapy for primary lung cancer.	jumentaihoto (十全大補湯)	Yamagata T, Ajimura K, Yukawa S. Effect of jumentaihoto on myelosuppression during lung cancer chemotherapy*. <i>Therapeutic Research</i> 1998; 19: 705-8 (in Japanese).	RCT-envelope	N	127
C34.9	Preventive effect of hochuekkito on general malaise in patients undergoing chemotherapy for advanced primary lung cancer.	hochuekkito (補中益氣湯)	Inui H, Yamagata T, Minakata Y, et al. Prevention of side effects during lung cancer chemotherapy by Hochuekki-to. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 1993; 2: 56-60 (in Japanese).	RCT-cross over	N	128
C34.9	To evaluate the efficacy of hochuekkito combined with clarithromycin (CAM) for improvement in the prognosis of lung cancer.	hochuekkito (補中益氣湯)	Kato S, Kishiro I, Machida S, et al. Combined effects of hochu-ekki-to (bu-zhong-yi-qi-tang) and clarithromycin on Lung Carcinoma. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)</i> 1999; 13: 83-8 (in Japanese with English abstract).	RCT	N	129

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C34.9	To evaluate the efficacy of hochuekkito for the prevention and relief of general malaise related to chemotherapy for primary lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma).	hochuekkito (補中益氣湯)	Mori K, Saito Y, Tominaga K. Utility of hochu-ekki-to in general malaise accompanying lung cancer chemotherapy. <i>Biotherapy</i> 1992; 6: 624-7 (in Japanese with English abstract).	RCT	I	130
C50.9	To evaluate the efficacy of hochuekkito or ninjin'yoeito for reducing adverse drug reactions and improving quality of life (QOL) in breast cancer patients undergoing postoperative (after curative resection or initial treatment) Sunfral S (800 mg/day).	ninjin'yoeito (人參養榮湯) or hochuekkito (補中益氣湯)	Nagao K, Nishimura R, Matsuda M, et al. Clinical evaluation of the combined effect of tegafur and hozai (traditional Chinese medicine)*. <i>Toho Igaku (Eastern Medicine)</i> 1998; 14: 63-71 (in Japanese with English abstract).	RCT-envelope	N	131
C50.9	Efficacy of supportive therapy for advanced breast cancer patients.	juzentaihoto (十全大補湯)	Adachi I. Supporting therapy with shi quan da bu tang in advanced breast cancer patients. <i>Biomedical Research</i> 1990; 11 suppl: 25-31.	RCT-envelope	N	132
			Adachi I, Watanabe T, Chen JY, et al. Supportive therapy of oriental medicine for patients with advanced breast cancer. <i>Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)</i> 1989; 16: 1538-43 (in Japanese with English abstract).		C&I	
			Adachi I. Juzen-taiho-to as a supporting therapy in advanced breast cancer. <i>Biotherapy</i> 1989; 3: 782-8 (in Japanese with English abstract).		I	
C57.9	Efficacy for relieving subjective symptoms and improving activities of daily living in patients following gynecologic cancer surgery.	ninjin'yoeito (人參養榮湯)	Mizuno M, Yoshikawa H, Taketani Y, et al. Clinical effects of ninjin'yoeito on performance status (PS) and recovery of physical strength in patients following gynecologic cancer treatment – comparison with no-treatment controls*. <i>Sanka to Fujinka (Obstetrics and Gynecology)</i> 1993; 60: 1533-45 (in Japanese).	RCT	I	133
C57.9	To evaluate the efficacy of combination of ninjin'yoeito and juzentaihoto for reducing adverse effects of cyclophosphamide, adriamycin, cisplatin (CAP) chemotherapy including myelosuppression, renal impairment, and gastrointestinal symptoms.	ninjin'yoeito (人參養榮湯) + juzentaihoto (十全大補湯)	Hasegawa K, Fukunishi H, Kiyoshige K, et al. Clinical usefulness of Kampo medicines (ninjin-yoei-to, juzen-taiho-to) for side effects in gynecologic cancer chemotherapy – Effects on reducing side effects by CDDP in CAP therapy-. <i>Wakan Iyaku-gaku Zasshi (Journal of Traditional Medicines)</i> 1994; 11: 181-7 (in Japanese with English abstract).	RCT	N	134
C57.9	Efficacy of ninjin'yoeito on subjective and objective symptoms and bone-marrow function during postoperative chemotherapy or radiotherapy in female patients with genital cancer.	ninjin'yoeito (人參養榮湯)	Yamamoto T, Fujita H, Okada H, et al. Clinical evaluation of the effects of ninjin'yoeito on subjective and objective symptoms and bone-marrow function during chemotherapy or radiotherapy in female patients with genital cancer*. <i>Oncology & Chemotherapy</i> 1994; 10: 126-34 (in Japanese).	RCT-envelope	N	135
C57.9	To evaluate the efficacy of ninjin'yoeito for reducing myelosuppression due to chemotherapy for gynecologic cancer.	ninjin'yoeito (人參養榮湯)	Oda T. My prescription – clinical application of ninjin'yoeito in gynecologic cancer – a preventive effect on bone marrow suppression*. <i>WE</i> 2004; 9: 5-6.	quasi-RCT	I	136
			Oda T, Ohnuki T, Kihara K, et al. A clinical study of a traditional Chinese herbal medicine, ninjin-yoei-to in bone marrow suppression due to chemotherapy in gynecologic cancer. <i>Yamagata Kenritsu Byoin Igaku Zasshi (The Yamagata Journal of Medicine)</i> 2004; 38: 6-9 (in Japanese).		I	

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C67.9	To evaluate the effect of postoperative adjuvant chemotherapy for bladder cancer on survival (the efficacy of the combination with juzentaihoto was assessed in patients stratified into 3 groups).	juzentaihoto (十全大補湯)	Fukui I, Gotoh S, Kihara K, et al. Adjuvant chemotherapy for invasive bladder cancer: multicenter study. <i>Nippon Hinyokika Gakkai Zasshi (Japanese Journal of Urology)</i> 1992; 83: 1633-9 (in Japanese with English abstract).	RCT	N	137
C68.9	Efficacy and safety of saireito for relieving the adverse urological effects of anticancer drugs.	saireito (柴苓湯)	Ohkawa T, Ebisuno S, Watanabe T, et al. Clinical evaluations of saireito, a herbal drug, for the side-effects of cancer chemotherapy in urological field. <i>Biotherapy</i> 1990; 4: 1445-60 (in Japanese with English abstract).	RCT-envelope	I	138
C80.0	To evaluate the efficacy of juzentaihoto for reducing adverse effects and improving quality of life (QOL) in postoperative patients undergoing chemotherapy (tegafur-uracil [UFT] 4 capsules/day) for gastric, colorectal, or breast cancer (curative resection/non-curative resection).	juzentaihoto (十全大補湯)	Kosaka A, Hojyo M, Osaku M, et al. The value of TSUMURA Juzentaihoto (TJ-48) in reducing adverse effects of anticancer drugs from the perspective of QOL improvement*. <i>Progress in Medicine</i> 1993; 13: 1072-9 (in Japanese). Kosaka A, Kamiya T, Sumiyama M, et al. Usefulness of TSUMURA Juzentaihoto (TJ-48) for reducing adverse effects of anticancer drugs and improving QOL*. <i>Progress in Medicine</i> 1994; 14: 2259-64 (in Japanese).	RCT-envelope	N N	139
C80.0	Efficacy and safety for reducing adverse reactions during cancer radiotherapy.	juzentaihoto (十全大補湯)	Tanaka Y, Hashimoto S. Effects of TSUMURA Juzentaihoto on various complaints occurring as adverse reactions during radiotherapy*. <i>JAMA (Japanese version)</i> 1988; (6) suppl: 70-1 (in Japanese). Hashimoto S, Tanaka Y. Adverse reactions to cancer radiotherapy*. <i>Sanfujinka no Sekai (World of Obstetrics and Gynecology)</i> 1990; 42 suppl: 176-84 (in Japanese).	RCT-envelope	N N	140
C80.0	Effect on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer.	juzentaihoto (十全大補湯)	Yamada T. Clinical study of Juzen-taiho-to administration for postoperative esophageal carcinoma, gastric carcinoma, and colorectal carcinoma – Influence of surgical intervention and postoperative chemotherapy on cell mediated immunity-. <i>Wakan Iyaku Gakkaiishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1992; 9: 157-64 (in Japanese with English abstract).	RCT-envelope	N	141
C80.0	Clinical effects in patients undergoing chemotherapy (tegafur).	hochuekkito (補中益氣湯), ninjin'yoeito (人參養榮湯)	Ohara T, Onda M, Futagawa S, et al. Clinical evaluation of the combined effect of bu-zhong-yi-qi-tang (Japanese name, hochu-ekki-to) or ren-shen-yang-rong-tang (Japanese name, ninjin-yoei-to) and the anticancer drug tegafur. <i>Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)</i> 1993; 21: 4423-34 (in Japanese).	RCT-envelope	C&I	142
C80.0	To evaluate whether preoperative administration of hochuekkito relieves surgical stress in patients with gastric or colorectal cancer.	hochuekkito (補中益氣湯)	Saito S, Iwagaki H, Kobayashi N, et al. Effects of a Japanese herbal medicine (TJ-41) on surgical stress of patients with gastric and colorectal cancer*. <i>Nihon Rinsho Geka Gakkai Zasshi (Journal of Japan Surgical Association)</i> 2006; 67: 568-74 (in Japanese).	RCT	I	143
D25.9	To evaluate the anti-tumor effect of keishibukuryogan in patients with hysteromyoma/uterine adenomyosis.	keishibukuryogan (桂枝茯苓丸)	Yamamoto K, Hirano F, Ikoma N, et al. Efficacy of keishibukuryogan for hysteromyoma/uterine adenomyosis. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2003; 20: 135-7 (in Japanese).	RCT	I	144

3. Blood Diseases including Anaemia (15 abstracts, 18 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
D50.0	To evaluate the efficacy and safety of tokishakuyakusan for hypochromic anemia in patients with uterine myoma.	tokishakuyakusan (当帰芍薬散)	Akase T, Akase T, Onodera S, et al. A comparative study of the usefulness of toki-shakuyaku-san and an oral iron preparation in the treatment of hypochromic anemia in cases of uterine myoma. <i>Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan)</i> 2003; 123: 817-24.	RCT	C&I	145

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
D50.8	Efficacy of ninjin'yoeito for iron deficiency anemia due to menorrhagia.	ninjin'yoeito (人參養榮湯)	Yanagihori A, Miyagi M, Hori M, et al. Efficacy of ninjin'yoeito for iron deficiency anemia*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1995; 72: 2605-8 (in Japanese).	RCT-envelope	I	146
D50.8	Combined effect of erythropoietin and ninjin'yoeito on anemia after autologous blood donation.	ninjin'yoeito (人參養榮湯)	Aoe H, Takada K, Kawahara N, et al. Effectiveness of erythropoietin and ninjin'yoeito in preoperative autologous blood donation*. <i>Jikoketsu Yuketsu (Journal of Japanese Society of Autologous Blood Transfusion)</i> 1997; 10: 145-51 (in Japanese).	RCT	N	147
D50.8	To evaluate the efficacy of juzentaihoto and ninjin'yoeito combined with an erythropoietin (EPO) preparation in preoperative autologous blood donation in cancer patients.	juzentaihoto (十全大補湯), ninjin'yoeito (人參養榮湯)	Aoe H, Sumida Y, Kawahara N, et al. Efficacy of an erythropoietin preparation and Kampo medicines in preoperative autologous blood donation in cancer patients*. <i>Jikoketsu Yuketsu (Journal of Japanese Society of Autologous Blood Transfusion)</i> 1999; 12: 100-4 (in Japanese).	RCT	N	148
D50.8	To evaluate the efficacy of using juzentaihoto to augment preoperative autologous blood donation in cancer patients.	juzentaihoto (十全大補湯)	Aoe H, Matsuo T, Ebisutani M, et al. Effects of juzentaihoto (ten strong tonic herbs decoction) on presurgical autologous blood pooling in cancer patients*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2000; 17: 67-71 (in Japanese).	RCT	I	149
			Aoe H, Ota M, Kawahara N, et al. Effects of juzentaihoto in preoperative autologous blood pooling*. <i>Rinsho Kensa (Journal of Medical Technology)</i> 2003; 47: 395-9 (in Japanese).		N	
			Aoe H. Effect of Juzen-taiho-to on haematological recovery from predeposit autologous blood donation*. <i>Pharma Medica</i> 2007; 25: 11-4 (in Japanese).		I	
D64.8	To evaluate the efficacy and safety of ninjin'yoeito for ribavirin-induced anemia.	ninjin'yoeito (人參養榮湯)	Motoo Y, Mouri H, Ohtsubo K, et al. Herbal medicine ninjinyoeito ameliorates ribavirin-induced anemia in chronic hepatitis C: A randomized controlled trial. <i>World Journal of Gastroenterology</i> 2005; 11: 4013-7.	RCT	C	150
D64.8	To evaluate the efficacy and safety of juzentaihoto (十全大補湯) for erythropoietin-resistant anemia in patients on hemodialysis.	juzentaihoto (十全大補湯)	Nakamoto H, Mimura T, Honda N. Orally administrated Juzen-taiho-to/TJ-48 ameliorates erythropoietin (rHuEPO)-resistant anemia in patients on hemodialysis. <i>Hemodialysis International</i> 2008; 12: S9-14.	RCT	C	151
D69.6	Efficacy of goreisan for thrombocytopenia after cholecystectomy.	goreisan (五苓散), shosaikoto (小柴胡湯)	Seki M. Efficacy of goreisan for preventing thrombocytopenia and activating vascular endothelial cells after cholecystectomy*. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1990; 7: 510-1 (in Japanese).	RCT	N	152
D69.6	Effects of preoperative administration of shosaikoto on thrombocytopenia in gynecologic cancer patients receiving anti-cancer drugs.	shosaikoto (小柴胡湯)	Mori T, Tauchi K, Yokoyama S, et al. Effects of sho-saiko-to (xiao-chai-hu-tang) on thrombocytopenia bei therapy with anti-cancer drugs. <i>Sanfujinka Chiryu (Obstetrical and Gynecological Therapy)</i> 1992; 65: 102-5 (in Japanese).	RCT	N	153
D70	Improvement in thrombocytopenia and leukopenia by kamikihito administration in patients receiving anti-cancer drugs.	kamikihito (加味帰脾湯)	Inoue S, Kuwahara H, Kato Y, et al. Thrombopoietic and leukopoietic effects of a traditional Chinese herbal medicine, formula reverti lienalis compositae (Japanese name: <i>Kami-kihi-to TJ-137</i>) in cancer patients. <i>Biotherapy</i> 1998; 12: 1071-6 (in Japanese with English abstract).	RCT-cross over	N	154
D70	Effects of juzentaihoto on leukopenia in patients receiving cancer chemotherapy.	juzentaihoto (十全大補湯)	Suzuki S, Abe R, Nomizu T, et al. Effect of Juzentaihoto (TJ-48) on leukopenia in patients receiving cancer chemotherapy*. <i>Progress in Medicine</i> 1995; 15: 1968-71 (in Japanese).	RCT-envelope	I	155
D70	Improvement in subjective symptoms and leukopenia by ninjin'yoeito administration in patients undergoing radiotherapy for thoracoabdominal tumors.	ninjin'yoeito (人參養榮湯)	Okawa T, Hashimoto S, Sakamoto S, et al. Ninjin-yoei-to in the treatment of leukopenia and symptoms associated with radiotherapy of malignant tumors. <i>Gan no Rinsho (Japanese Journal of Cancer Clinics)</i> 1995; 41: 41-51 (in Japanese with English abstract).	RCT	I	156

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
D72.8	Preventive effect of preoperative administration of shosaikoto on postoperative lymphopenia in female patients.	shosaikoto (小柴胡湯)	Hatano T. Mitigation of postoperative lymphopenia and protection of T cells by preoperative administration of xial-chai-hu-tang. <i>Saitama Ika Daigaku Zasshi (Journal of Saitama Medical School)</i> 1990; 17: 357-63 (in Japanese with English abstract).	RCT	N	157
D75.8	Effect of combined juzentaihoto during chemotherapy in patients with gynecologic cancers.	juzentaihoto (十全大補湯)	Fujiwara M, Koumoto Y. Effect of juzentaihoto on myelosuppression due to chemotherapy for gynecologic malignant tumor*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 1998; 15: 86-9 (in Japanese).	RCT-cross over	N	158
D86.0	Effects of keishikajutsubuto on the levels of angiotensin-converting enzyme and lysozyme in sarcoidosis patients.	keishikajutsubuto (桂枝加朮附湯)	Inagaki M, Nakazawa T, Michimata H, et al. Treatment experience with TSUMURA Keishikajutsubuto for pulmonary sarcoidosis*. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1990; 7: 316-7 (in Japanese).	RCT	N	159
			Inagaki M. Effectiveness of Kampo medicine in relieving complaints associated with chronic intractable diseases*. <i>Kampo Shinryo</i> 1993; 12: 1-3 (in Japanese).		N	

4. Metabolism and Endocrine Diseases (11 abstracts, 15 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
E11.9	Efficacy and safety of seishinrenshiin on improvement in glucose tolerance.	seishinrenshiin (清心蓮子飲)	Azuma M, Motomiya M, Toyota T. Effects of Seishin-renshi-in (TJ-111) on blood sugar levels of patients with non-insulin-dependent diabetes mellitus. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1994; 45: 339-44 (in Japanese with English abstract).	RCT-envelope	N	160
E22.9	To evaluate the efficacy of unkeito for reducing high luteinizing hormone (LH) levels and improving ovulation disorder.	unkeito (溫經湯)	Ushiroyama T, Ikeda A, Sakai M, et al. Effects of unkei-to, an herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion. <i>The Journal of Reproductive Medicine</i> 2001; 46: 451-6.	RCT-envelope	C	161
E28.2	To evaluate the efficacy of switching to unkeito from treatment based on the traditional diagnostic criterion "eight-principle pattern identification" in women with polycystic ovary syndrome (PCOS).	unkeito (溫經湯), tokisyakuyakusan (當歸芍藥散), keishibukuryogan (桂枝茯苓丸)	Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. <i>The American Journal of Chinese Medicine</i> 2006; 34: 177-87.	RCT-envelope	C	162
E28.3	To evaluate the efficacy of unkeito for luteal phase deficiency.	unkeito (溫經湯)	Ushiroyama T, Ikeda A, Higashio S, et al. Unkei-to for correcting luteal phase defects. <i>The Journal of Reproductive Medicine</i> 2003; 48: 729-34.	RCT-envelope	C	163
E66.9	To evaluate the anti-obesity effect of bofutsushosan extract granules in obese patients and the course of high-sensitivity C-reactive protein (HS-CRP) as an arteriosclerosis-promoting factor.	bofutsushosan (防風通聖散)	Namiki T. Basic and clinical investigation of the effect of Kampo medicines on arteriosclerosis*. <i>Uehara Kinen Seimei Kagaku Zaidan Kenkyu Hokokushu (Research Reports of Uehara Memorial Foundation)</i> 2007; 21: 60-3 (in Japanese).	RCT-envelope	I	164
E78.5	Efficacy and safety of daisaikoto combined with probucol in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Takashima T, Ohmori K, Higuchi N, et al. Combination therapy with probucol and daisaikoto (a Kampo medicine) - Effects of daisaikoto on HDL metabolism -. <i>Domyaku Koka (The Journal of Japan Atherosclerosis Society)</i> 1993; 21: 47-52 (in Japanese with English abstract).	RCT-envelope	N	165
			Yamamoto K. A study of the hepatic triglyceride (TG)-lowering effects and antioxidant capacity of various Kampo preparations*. <i>Proceedings of the 4th Kampo Treatment Seminar at Kyoto University</i> 1995: 48-56 (in Japanese).			
E78.5	Efficacy and safety of daisaikoto in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Sasaki J, Matsunaga A, Handa K, et al. Effect of daisaikoto on hyperlipidemia - comparison with clinofibrate -*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1991; 68: 3861-71 (in Japanese).	RCT	I	166

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
E78.5	Efficacy and safety of daisaikoto combined with bezafibrate in patients with hyperlipidemia.	daisaikoto (大柴胡湯)	Muramatsu N, Okayasu M. Clinical study on hyperlipidemia at bezafibrate and da-chai-hu-tang (dai-saiko-to) for the combination therapy. <i>Shigaku (Odontology)</i> 1993; 81: 94-9 (in Japanese with English abstract).	RCT	N	167
E78.5	Effects of daisaikoto on serum lipid level and cerebral circulation.	daisaikoto (大柴胡湯)	Yamano S, Sawai F, Hashimoto T, et al. Comparative effects between dai-saiko-to and elastase on lipid metabolism and cerebral circulation in patients with hyperlipidemia. <i>Kampo to Saishin-chiryō (Kampo & The Newest Therapy)</i> 1995; 4: 309-13 (in Japanese).	RCT-envelope	N	168
E87.8	Efficacy and safety of goreisan in the treatment of hyponatremia after surgery for cholelithiasis or gallbladder polyps.	goreisan (五苓散), shosaikoto (小柴胡湯)	Takagi S. Mitigation of hyponatremia after operation for cholelithiasis or gallbladder polyp by preoperative administration of wu-ling-san. <i>Journal of Saitama Medical School</i> 1990; 17: 145-50 (in Japanese with English abstract).	RCT	N	169
			Seki M, Fujioka M, Hatano T, et al. Analysis of regulatory effects of gorei-san on circulatory, metabolic and diuretic function - especially in relation to endothelial activation and increase of urinary 6-keto-prostaglandin F _{1α} level-. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1992; 42: 313-22 (in Japanese with English abstract).		N	
E88.9	To evaluate whether bofutsushosan (防風通聖散) reduces obesity.	bofutsushosan (防風通聖散)	Uebaba K, Xu F. Association between the SNP in sympathetic b3-adrenergic receptor gene and the efficacy of bofutsushosan*. <i>Nihon Toyo Igaku Zasshi (Kampo medicine)</i> 2003; 54: S225.	DB-RCT	N	170
			Kamohara S, Kawakami T, Uebaba K, et al. A study on the development of individualized medicine for the prevention, diagnosis, and treatment of metabolic syndrome using an integrative approach*. <i>Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (Research Papers of the Suzuken Memorial Foundation)</i> 2009; 26: 399-403.		N	
			Xu FH, Uebaba K, Ogawa H, et al. Personalized effects of a Kampo herbal formulation on metabolism — A randomized, double-blind, placebo controlled study of bohutusei-san — <i>Toho Igaku (Eastern Medicine)</i> 2012; 28: 37-59 (in Japanese).		I	

5. Psychiatric/Behavioral Disorders (13 abstracts, 15 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
F01.9	Efficacy of chotosan in the treatment of vascular dementia.	chotosan (釣藤散)	Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of choto-san and placebo in the treatment of vascular dementia. <i>Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)</i> 1994; 11: 246-55.	RCT-envelope	I	171
			Shimada Y, Terasawa K, Yamamoto T, et al. Efficacy of choto-san on vascular dementia: A well, placebo-controlled study. <i>Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)</i> 1994; 11: 370-1 (in Japanese).		I	
F01.9	Efficacy of chotosan in the treatment of vascular dementia.	chotosan (釣藤散)	Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. <i>Phytomedicine</i> 1997; 4: 15-22.	DB-RCT	N	172
			Terasawa K. Chotosan in the treatment of vascular dementia. <i>Pharma Medica</i> 2007; 25: 57-9 (in Japanese).		I	
F03	To evaluate the efficacy of hachimijiogan for dementia.	hachimijiogan (八味地黄丸)	Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine “ba wei di huang wan” in the treatment of dementia. <i>Journal of the American Geriatrics Society</i> 2004; 52: 1518-21.	DB-RCT	C	173
F03	To evaluate the efficacy of chotosan for improvement of cognitive function and activities of daily living in dementia patients.	chotosan (釣藤散), goshajinkigan (牛車腎気丸)	Suzuki T, Futami S, Igari Y, et al. A Chinese herbal medicine, choto-san, improves cognitive function and activities of daily living of patients with dementia: A double-blind, randomized, placebo-controlled study. <i>Journal of the American Geriatrics Society</i> 2005; 53: 2238-40.	DB-RCT	C	174

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
F03	To evaluate the efficacy and safety of yokukansan for treating behavioral disorders and improving activities of daily living in dementia patients.	yokukansan (抑肝散)	Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine yi-gan san for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. <i>Journal of Clinical Psychiatry</i> 2005; 66: 248-52.	RCT	C	175
F03	To evaluate the efficacy and safety of yokukansan in the treatment of behavioural and psychological symptoms of dementia.	yokukansan (抑肝散)	Mizukami K, Asada T, Kinoshita T, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. <i>The International Journal of Neuropsychopharmacology</i> 2009; 12: 191-9.	RCT-cross over	C	176
F05.9	To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.	yokukansan (抑肝散)	Takase S. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. <i>Kampo Igaku (Science of Kampo Medicine)</i> 2010; 34: 132-4 (in Japanese).	RCT-envelope	N	177
F20.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.	yokukansan (抑肝散)	Miyaoka T, Furuya M, Yasuda H, et al. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: an open-label study. <i>Clinical Neuropharmacology</i> 2009; 32: 6-9.	RCT	N	178
F41.9	To evaluate the efficacy of saibokuto as a potentiator of the anxiolytic and antidepressant effects of diazepam.	saibokuto (柴朴湯)	Ishida H, Otake T, Kurihara H, et al. Clinical study on augmentative effect of Saiboku-to for anxiolytic and antidepressive action of diazepam. <i>Pain Clinic</i> , 1999; 20: 395-9 (in Japanese).	RCT	N	179
F45.3	Efficacy for relieving discomfort in the throat.	saibokuto (柴朴湯)	Yamagiwa M, Sakakura Y, Harada T, et al. Therapeutic response to various drugs in patients with continuous or periodic discomfort in the throat. <i>Jibiinkoka Rinsho (Practica otologica)</i> 1990; 83: 1687-92 (in Japanese with English abstract).	RCT	N	180
F45.3	To evaluate the efficacy of lansoprazole in patients with pharyngolaryngeal paresthesia and acid reflux symptoms (compared with rikkunshito as a control).	rikkunshito (六君子湯)	Yamagiwa M, Fujita K. Effect of treatment using lansoprazole on patients with an abnormal sensation in the throat and concomitant heart burn. <i>Jibi to Rinsho (Otologia Fukuoka)</i> 2007; 53: 109-15 (in Japanese with English abstract).	quasi-RCT	I	181
F45.9	Symptom-relieving effects in elderly patients with underlying chronic disease.	hachimijiojan (八味地黄丸) + kojimatsu (紅參末)	Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of combination treatment of hatimi-zio-gan and Red Ginseng powder on unidentified clinical complaints - estimation of double blind comparative study in many hospitals -. <i>Therapeutic Research</i> 1989; 10: 4951-65 (in Japanese).	DB-RCT-envelope	I	182
F52.2	Efficacy and safety of oral prostaglandin E1 in the treatment of erectile dysfunction.	goshajinkigan (牛車腎気丸)	Sato Y, Horita H, Adachi N, et al. Effect of oral administration of prostaglandin E1 on erectile dysfunction. <i>British Journal of Urology</i> 1997; 80: 772-5.	quasi-RCT	N	183

6. Nervous System Diseases (including Alzheimer's Disease) (15 abstracts, 17 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
G10	Efficacy and safety of yokukansan in patients with Huntington's disease.	yokukansan (抑肝散), saikokaryukostuboreito (柴胡加竜骨牡蛎湯)	Satoh T, Takahashi T, Iwasaki K, et al. Traditional Chinese Medicine on four patients with Huntington's disease. <i>Movement Disorders</i> 2009; 24: 453-5.	RCT-cross over	N	184

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
G30.1	Efficacy and safety of yokukansan in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease.	yokukansan (抑肝散)	Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease. <i>Progress in Neuro-Psychopharmacology & Biological Psychiatry</i> 2009; 33: 308-11.	RCT	N	185
			Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer's disease – Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. <i>No 21 (Brain 21)</i> 2009; 12: 446-51 (in Japanese).		I	
G30.1	To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).	yokukansan (抑肝散)	Okahara K, Ishida Y, Hayashi Y, et al. Effects of yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. <i>Progress in Neuro Psychopharmacology & Biological Psychiatry</i> 2010; 34: 532-6.	RCT	C	186
G30.1	To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD)	yokukansan (抑肝散)	Furuhashi Y. Comparative efficacy of risperidone versus yokukansan (抑肝散) on behavioral and psychological symptoms of dementia in patients with Alzheimer's disease*. <i>Kampo Igaku (Science of Kampo Medicine)</i> 2010; 34: 120-1 (in Japanese).	RCT	N	187
G30.9	To evaluate the efficacy and safety of kihito for Alzheimer-type dementia.	kihito (婦脾湯), goshajinkigan (牛車腎氣丸)	Higashi K, Rakugi H, Yu H, et al. Effect of kihito extract granules on cognitive function in patients with Alzheimer's-type dementia. <i>Geriatrics & Gerontology International</i> 2007; 7: 245-51.	RCT	I	188
G43.9	To evaluate the efficacy and safety of goshuyuto for treatment of migraine.	goshuyuto (呉茱萸湯)	Maruyama T. Goshuyuto versus lomerizine hydrochloride in the prophylactic treatment of migraine headaches: an open crossover trial. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 2006; 16: 30-9 (in Japanese with English abstract).	RCT-cross over	I	189
G47.0	To evaluate the efficacy and safety of DS-4773 for sedation versus sansoninto used as control.	sansoninto (酸棗仁湯)	Matsushita M, Saito M, Katayama S, et al. Clinical evaluation of DS-4773 on sedative effect: a cross-over trial. <i>Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)</i> 1994; 22: 2371-82 (in Japanese).	RCT-cross over	I	190
G47.1	Effect of kakkonto on sleepiness after sleep deprivation.	kakkonto (葛根湯)	Zhuang H.Y., Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation of normal young adults. <i>Shinkei Seishin Yakuri (Japanese journal of neuropsychopharmacology)</i> 1992; 14: 319-25 (in Japanese with English abstract).	DB--RCT-cross over	I	191
			Hagino H, Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation with quantitative EEG method. <i>Noha to Kindenzu (Japanese Journal of Electroencephalography and Electromyography)</i> 1995; 23: 361-7 (in Japanese with English abstract).		N	
G47.9	Effectiveness of orengedokuto on sleep disorder in patients in the acute phase of psychotic disorders.	orengedokuto (黃連解毒湯)	Yamada K, Kanba S, Ohnishi K, et al. Clinical effectiveness of oren-gedoku-to for sleep disorder associated with acute schizophrenia and other psychotic disorders. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1997; 47: 827-31 (in Japanese with English abstract).	RCT-envelope	N	192
G47.9	To evaluate the efficacy of yokukansankachimpihange for sleep disorders.	yokukansanka chimpihange (抑肝散加陳皮半夏), anchusan (安中散)	Aizawa R, Kanbayashi T, Saito Y, et al. Effects of yoku-kan-san ka chimpi-hange on the sleep of normal healthy adult subjects. <i>Psychiatry and Clinical Neurosciences</i> 2002; 56: 303-4.	RCT-cross over	C&I	193
G51.3	Efficacy of shakuyakukanzoto for relieving facial spasm.	shakuyakukanzoto (芍藥甘草湯)	Kimura H, Otake T, Ishikura H. Efficacy of shakuyakukanzoto for relieving facial spasm*. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1991; 79: 2505-8 (in Japanese).	RCT	N	194
G54.4	To evaluate the efficacy of goshajinkigan for treatment of lumbar (low back) and leg pain.	goshajinkigan (牛車腎氣丸)	Sekine R, Watanabe H, Mimura M, et al. The effects of Goshajinkigan on the low back pain and lower limb pain caused by the lumbar spine: A comparison of Goshajinkigan with Benfotiamine. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 2003; 13: 84-7 (in Japanese)	RCT-cross over	I	195

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
G62.9	To evaluate the potential use of sokeikakketsuto and shakuyakukanzoto by current perception threshold measurement in preventing peripheral nerve disorder in patients receiving taxol.	sokeikakketsuto (疎経活血湯)	Miyabe Y, Taniguchi C, Kawashima M, et al. Effect of Kampo medicines (sokeikakketsuto, shakuyakukanzoto) for taxol-caused peripheral nerve disorder – evaluation by current perception threshold measured by Neurometer®. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2006; 23: 65-8 (in Japanese).	RCT-cross over	N	196
G62.9	To clarify the efficacy and adverse effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by oxaliplatin therapy for advanced or recurrent colorectal cancer.	goshajinkigan (牛車腎気丸)	Nishioka M, Shimada M, Kurita N, et al. The Kampo medicine, goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. <i>International Clinical Journal of Oncology</i> 2011; 16: 322-7.	RCT	N	197
G62.9	To evaluate the efficacy of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by chemotherapy (paclitaxel and carboplatin) for uterine and ovarian cancer.	goshajinkigan (牛車腎気丸)	Kaku H, Kumagai S, Onoue H, et al. Objective evaluation of the alleviating effects of goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study. <i>Experimental and Therapeutic Medicine</i> 2012; 3: 60-5.	RCT	N	198

7. Eye Diseases (4 abstracts, 5 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
H00.0	To evaluate the efficacy of hainosankyuto for internal hordeolum in the acute phase.	hainosankyuto (排膿散及湯)	Takama N, Fujiwara T. The Efficacy of hainou-san-kyu-to for internal hordeolum. <i>Ganka Rinsho Iho (Japanese Review of Clinical Ophthalmology)</i> 2006; 100: 9-11 (in Japanese).	RCT	I	199
H18.9	To evaluate the efficacy of goshajinkigan for corneal sensitivity, superficial keratitis, and tear secretion in patients with insulin-dependent (type 1) diabetes mellitus.	goshajinkigan (牛車腎気丸)	Nagaki Y, Hayasaka S, Hayasaka Y, et al. Effects of goshajinkigan on corneal sensitivity, superficial punctate keratopathy and tear secretion in patients with insulin-dependent diabetes mellitus. <i>American Journal of Chinese Medicine</i> 2003; 31: 103-9.	DB-RCT	C	200
			Nagaki Y. Effects of goshajinkigan on diabetic keratopathy*. <i>Kampo Igaku (Kampo Medicine)</i> 2004; 28: 63-5 (in Japanese).		N	
H25.9	To evaluate the efficacy of Kampo medicines for aqueous flare elevation after small-incision cataract surgery.	orengedokuto (黄連解毒湯), kakkonto (葛根湯), saireito (柴苓湯)	Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. <i>Journal of Ocular Pharmacology and Therapeutics</i> 2001; 17: 59-65.	RCT	C	201
H25.9	To evaluate the efficacy of Kampo medicines for aqueous flare elevation after complicated cataract surgery.	kakkonto (葛根湯), saireito (柴苓湯)	Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of kakkon-to and sairei-to on aqueous flare elevation after complicated cataract surgery. <i>American Journal of Chinese Medicine</i> 2002; 30: 347-53.	RCT	C	202

8. Ear Diseases (7 abstracts, 7 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
H65.0	To evaluate the efficacy of shoseiryuto combined with eppikajutsuto for otitis media with effusion (OME) in adults.	shoseiryuto (小青竜湯) + eppikajutsuto (越婢加朮湯)	Inoue H. Rapid effect of combination therapy with shoseiryuto and eppikajutsuto for acute otitis media with effusion in adults. <i>Jibi to Rinsho (Otologia Fukuoka)</i> 2001; 47: 361-6 (in Japanese).	quasi-RCT	I	203
H65.9	Efficacy of saireito for otitis media with effusion.	saireito (柴苓湯)	Machii K, Ikezono T, Utsato S, et al. Comparative study of the efficacy of saireito monotherapy versus antiallergic agent plus carbocysteine combination therapy for otitis media with effusion*. <i>Kampo Igaku (Kampo Medicine)</i> 1992; 16: 200-3 (in Japanese).	RCT	N	204
H65.9	Efficacy of saireito for otitis media with effusion.	saireito (柴苓湯)	Sato H, Nakamura H, Honjo I, et al. Clinical evaluation of Tsumura-Saireito in children with otitis media with effusion - A comparative randomized controlled study of cepharanthine -. <i>Jibiinkoka Rinsho (Practica otologica)</i> 1988; 81: 1383-7 (in Japanese with English abstract).	RCT	N	205

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
H90.5	To compare the effectiveness of saireito (柴苓湯) and isosorbide for low-frequency sensorineural hearing loss.	saireito (柴苓湯)	Kaneko T. Comparison of saireito and isosorbide in efficacy against low-frequency sensorineural hearing loss. <i>Kampo to Saishin Chiryō</i> (Kampo and the Newest Therapy) 2010; 19: 233–9 (in Japanese with English abstract).	quasi-RCT	I	206
H93.1	Efficacy of saireito for tinnitus.	saireito (柴苓湯)	Tanaka H. Efficacy of a Kampo preparation combined with tranquilizers in patients with tinnitus. <i>Jibiinkoka Rinsho (Practica otologica)</i> 1996; suppl 89: 8 (in Japanese).	RCT-cross over	N	207
H93.1	To evaluate the efficacy of chotosan for tinnitus.	chotosan (釣藤散)	Suzuki T. <i>Clinical efficacy of chotosan for tinnitus. Pathology and treatment of tinnitus and dizziness.</i> The 28th Chiba Symposium of Japanese Traditional Medicine Tokyo: Kudansha; 2001:8-20 (in Japanese).	RCT-cross over	I	208
H93.1	To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸), chotosan (釣藤散) for tinnitus.	goshajinkigan (牛車腎気丸), chotosan (釣藤散)	Onishi S. Kampo treatment for tinnitus and hearing impairment*. <i>JOHNS</i> 1990; 6: 535-9 (in Japanese).	quasi-RCT	N	209

9. Cardiovascular Diseases (15 abstracts, 18 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
I10	To evaluate the efficacy of chotosan and orengedokuto for hypertension using ambulatory blood pressure monitoring.	chotosan (釣藤散), orengedokuto (黄連解毒湯)	Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitor. <i>Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)</i> 1994; 11: 282-3 (in Japanese).	RCT	N	210
			Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring*. <i>Kampo Shinryo</i> 1996; 15: 34-5 (in Japanese).		N	
I10	Efficacy and safety of daisaikoto and chotosan in patients with essential hypertension.	daisaikoto (大柴胡湯), chotosan (釣藤散)	Sasaki J, Matsunaga A, Kusuda M, et al. Efficacy of daisaikoto and chotosan in patients with essential hypertension*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1993; 70: 1965-75 (in Japanese).	RCT-envelope	I	211
I10	Effects of daisaikoto and saikokaryukotsuboreito on serum lipid levels in patients with mild to moderate hypertension.	daisaikoto (大柴胡湯), saikokaryukotsuboreito (柴胡加竜骨牡蠣湯)	Saku K, Hirata K, Zhang B, et al. Effects of Chinese herbal drugs on serum lipids, lipoproteins and apolipoproteins in mild to moderate essential hypertensive patients. <i>Journal of Human Hypertension</i> 1992; 6: 393-5.	RCT	C	212
I10	To evaluate the efficacy and safety of orengedokuto in patients with hypertension symptoms.	orengedokuto (黄連解毒湯)	Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orengedokuto (TJ-15) for the treatment of accessory symptoms of hypertension*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Study)</i> 2003; 80: 354-72 (in Japanese)	DB-RCT	I	213
			Arakawa K, Saruta T, Abe K, et al. Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: a double-blind, placebo-controlled study. <i>Phytomedicine</i> 2006; 13: 1-10.		C	
I51.9	Efficacy and safety of orengedokuto plus red ginseng combination therapy for relieving symptoms associated with hypertension.	orengedokuto (黄連解毒湯) orengedokuto (黄連解毒湯)+ kojimatsu (紅參末)	Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of the effect of ohrengedoku-toh and ohrengedoku-toh - Red Ginseng mixture on chronic cardiovascular disorders in middle and aged patients. <i>The Ginseng Review</i> 1991; 12: 89-93 (in Japanese with English abstract).	DB-RCT	N	214
I62.0	To evaluate the effectiveness and safety of goreisan (五苓散) after chronic subdural hematoma surgery in elderly people.	goreisan (五苓散)	Yoshikawa T, Munakata S, Okuma H. Effectiveness of goreisan for recurrence prevention in elderly cases of chronic subdural hematoma surgery— Interim report on a comparative trial.* <i>Noshinkei Geka to Kampo (Neurosurgery and Kampo)</i> 2010; 16 (in Japanese).	RCT	N	215

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
I63.9	Efficacy and safety of orengedokuto in the treatment of cerebral infarction.	orengedokuto (黄連解毒湯)	Ito E, Takahashi A, Kuzuya F. Clinical effectiveness of TSUMURA Orengedokuto in the treatment of cerebral infarction*. <i>Geriatric Medicine</i> 1991; 29: 303-13 (in Japanese).	RCT-envelope	I	216
I67.9	Efficacy and safety of orengedokuto for relieving psychiatric symptoms in patients with late effects of cerebrovascular disease.	orengedokuto (黄連解毒湯)	Otomo E, Togi H, Kogure K, et al. Clinical usefulness of TSUMURA Orengedokuto for the treatment of cerebrovascular disease: a well-controlled study comparing TSUMURA Orengedokuto versus Ca hopantenate, using sealed envelopes for allocation*. <i>Geriatric Medicine</i> 1991; 29: 121-51 (in Japanese).	RCT-envelope	I	217
I69.4	To evaluate the efficacy and safety of tokishakuyakusan for treatment of hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder.	tokishakuyakusan (当帰芍薬散)	Shimada Y. Efficacy of tokishakuyakusan for hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder*. <i>Kosei Rodo Kagaku Kenkyuui Hojokin Chouju Kagaku Kenkyu Jigyo: Koreisha no Nokekkan Shogai no Shinten Yobo wo Mokuteki to Shita Kampoyaku niyoru Tailor-made Iryo no Kaihatsu, Heisei 18 Nendo Buntan Kenkyu Hokokusho (Ministry of Health, Labour and Welfare, Science Research Grant, Comprehensive Studies on Science of Aging, Development of Personalized Medicine using Kampo Medicines to Prevent Progression of Cerebrovascular Disorders in the Elderly, Working-group Research Report Fiscal Year 2006)</i> 2007: 22-30 (in Japanese)	RCT	N	218
I69.4	To evaluate the effectiveness of tokishakuyakusan in reducing impairment and increasing independence in post-stroke patients.	tokishakuyakusan (当帰芍薬散)	Goto H, Satoh N, Hayashi Y, et al. A Chinese herbal medicine, tokishakuyakusan, reduces the worsening of impairments and independence after stroke: A 1-year randomized, controlled trial. <i>Evidence-based complementary and Alternative Medicine</i> 2009: 1-6. (2011: 1-6. doi: 10.1093/ecam/nep026)	RCT	N	219
I73.0	To evaluate the effectiveness of orengedokuto in improving peripheral circulation in Raynaud's phenomenon.	tokishakuyakusan (当帰芍薬散), orengedokuto (黄連解毒湯)	Akiyama Y, Ohno S, Asaoka T, et al. The combination therapy with sarpogrelate hydrochloride and Kampo medicine (oren-gedoku-to or toki-shakuyaku-san) for Raynaud's phenomenon. <i>Japanese Journal of Oriental Medicine</i> 2001; 51: 1101-8 (in Japanese with English abstract).	quasi-RCT	N	220
I80.3	To evaluate the effect of keishibukuryogan on swelling in patients with deep vein thrombosis (DVT) of the lower limb.	keishibukuryogan (桂枝茯苓丸)	Uchida N. A Randomized controlled trial of the Chinese herbal medicine kei-shi-bukuryo-gan (gui-zhi-fu-ling-wan) in the treatment of deep vein thrombosis. <i>Jomyakugaku (The Japanese Journal of Phlebology)</i> 2009; 20:1-6 (in Japanese with English abstract).	RCT	I	221
I84.9	To evaluate the clinical efficacy of otsujito combined with aluminum potassium sulfate/tannic acid (ALTA) sclerotherapy, the latest treatment for hemorrhoids.	otsujito (乙字湯)	Kato N, Kato K, Hosoi Y. Effects of Otsuji-to in patients with hemorrhoid using ALTA and LE combined therapy*. <i>Igaku to Yakugaku (Journal of Medicine and Pharmaceutical Science)</i> 2008; 60:747-53 (in Japanese).	RCT	I	222
I89.0	To evaluate the efficacy and safety of goshajinkigan in the treatment of lymphedema.	goshajinkigan (牛車腎気丸)	Abe Y. The efficacy of goshajinkigan against lymphedema*. <i>Kampo Igaku (Kampo Medicine)</i> 2002; 25: 284-7 (in Japanese).	RCT	I	223
			Abe Y, Kosugi I, Kasashima F, et al. Lymphedema and Kampo*. <i>Progress in Medicine</i> 2003; 23: 1538-9 (in Japanese).		N	
I95.1	To evaluate the safety and efficacy of goreisan in the treatment of orthostatic hypotension in patients with diabetes mellitus.	goreisan (五苓散)	Nakamura H, Nakamura T, Nakagawa S et al. Efficacy of goreisan in treatment of orthostatic hypotension in patients with diabetes mellitus*. <i>Diabetes Frontier</i> 2000; 11: 561-3 (in Japanese).	RCT-cross over	I	224

10. Respiratory Diseases (including Influenza and Rhinitis) (52 abstracts, 68 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
J00	To compare the efficacy of Kampo treatment and fenopufen as antipyretics in patients with common cold syndrome associated with fever.	kakkonto (葛根湯), maoto (麻黃湯), keimakakuhanto (桂麻各半湯), chikujountanto (竹ジョ温胆湯), shoseiryuto (小青竜湯), keishikashakuyakuto (桂枝加芍薬湯), kososan (香蘇散)	Homma Y. Kampo treatment of patients with common cold syndrome associated with fever. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1995; 46: 285-91 (in Japanese with English abstract).	RCT-envelope	N	225
J00	Effect on the duration and resolution of symptoms and treatment efficacy in patients with common cold syndrome.	maobushisaishinto (麻黄附子細辛湯)	Homma Y, Takaoka K, Yozawa H, et al. Effectiveness of mao-bushi-saishin-to in treating common cold syndrome - controlled comparative study using the sealed envelope method -. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1996; 47: 245-52 (in Japanese with English abstract). Homma Y. Treatment of common cold by a Kampo medicine - maobushisaishin-tou-. <i>Pharma Medica</i> 2007; 25: 19-21 (in Japanese).	RCT-envelope	I	226
J00	To evaluate the efficacy and safety of shosaikoto in patients with common cold.	shosaikoto (小柴胡湯)	Kaji M, Kashiwagi S, Yamakido M, et al. A double-blind, placebo-controlled study of TSUMURA Shosaikoto (TJ-9) for common cold*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Study)</i> 2001; 78: 2252-68 (in Japanese).	DB-RCT	I	227
J00	To evaluate the efficacy and safety of bakumondoto for postinfectious cough.	bakumondoto (麦門冬湯)	Fujimori K, Suzuki E, Simojo F. Comparison between bakumondoto (mai men dong tang) and dextromethorphan hydrobromide in terms of effect on postinfectious cough: a pilot study. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 2000; 51: 725-32	RCT	I	228
J00	To compare the cough-improvement effect of maobushisaishinto and western drugs in patients with the common cold.	maobushisaishinto (麻黄附子細辛湯)	Nishizawa Y, Nagano F, Yamada M, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and western drugs for cold in common patients with allergic cold syndrome. <i>Kampo to Meneki Arerugi (Kampo and Immuno-Allergy)</i> 2005; 18: 56-67 (in Japanese with English abstract).	RCT	N	229
J00	To compare the effects of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.	Kampo medicine (maoto [麻黃湯], keimakakuhanto [桂麻各半湯], etc.)	Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. <i>Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine)</i> 1993; 10: 19-23 (in Japanese).	quasi-RCT	N	230
J00	To compare the effects of two different treatments, Western medicine and byakkokaninjinto (白虎加人參湯), on summertime cold.	byakkokaninjinto (白虎加人參湯)	Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. <i>Nihon Shoni Toyo Igakkaishi (Journal of the Japan Pediatric Society for Oriental Medicine)</i> 2003; 19: 46-52 (in Japanese).	quasi-RCT	N	231
J10.1	To evaluate the effect of maoto in combination with oseltamivir on the duration of fever.	maoto (麻黃湯)	Kubo T. Effect of maoto for treatment of influenza in children (from The 56th General Meeting of The Japan Society for Oriental Medicine, presentation C-41)*. <i>Medicament News</i> 2005 Sep 5; 1846: 15. Kubo T, Nishimura H. Antipyretic effect of mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. <i>Phytomedicine</i> 2007; 14: 96-101.	RCT	C N	232

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
J10.1	To evaluate the efficacy of combined oseltamivir phosphate and maoto for the treatment of pediatric influenza.	maoto (麻黄湯)	Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza – 3 rd report-. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 2006; 19: 17-25 (in Japanese with English abstract).	quasi-RCT	N	234
J10.1	To evaluate the efficacy and safety of maobushisaishinto as an adjuvant for influenza vaccination in the elderly.	maobushisaishinto (麻黄附子細辛湯)	Iwasaki K, Taguchi M, Cyong JC, et al. Effects of mao-bushi-saishin-to on influenza vaccination in elderly subjects; a randomized control study. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)</i> 2004; 17: 97-103 (in Japanese with English abstract)	RCT-envelope	N	235
			Iwasaki K. Influenza and Kampo in the elderly*. <i>TSUMURA Mail Magazine</i> 2008; Suppl: 22-3 (in Japanese)		N	
J10.1	To evaluate the efficacy of coadministration of maoto (麻黄湯) and Shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.	maoto (麻黄湯) and shosaikoto (小柴胡湯)	Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. <i>Nihon Hokan Daitai Iryo Gakkaishi (Japanese Journal of Complementary and Alternative Medicine)</i> . 2010; 7: 59–62 (in English with Japanese summary).	RCT	N	236
J10.1	To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.	maoto (麻黄湯)	Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. <i>Kampo to Meneki Arerugi (Kampo and Immuno-allergy)</i> . 2010; 23: 17–26 (in Japanese with English abstract).	RCT	N	237
			Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. <i>Health</i> 2011; 3: 300-3.		N	
J10.1	To compare the effectiveness of oseltamivir, zanamivir, and maoto (麻黄湯) in adult influenza patients.	maoto (麻黄湯)	Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. <i>Journal of Infection and Chemotherapy</i> 2012; 18: 534-43.	RCT	N	238
J10.1	To compare the effects of two different treatments (a Kampo medicine treatment and a Western medicine treatment) on influenza.	Kampo medicine (maoto [麻黄湯], keimakakuhanto [桂麻各半湯], etc.)	Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. <i>Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine)</i> 1993; 10: 19–23 (in Japanese).	quasi-RCT	N	239
J10.1	To compare the effects on influenza of treatment with byakkokaninjinto (白虎加人參湯), maoto (麻黄湯), antibiotics, and amantadine.	byakkokaninjinto (白虎加人參湯), maoto (麻黄湯)	Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. <i>Nihon Shoni Toyo Igakkaishi (Journal of the Japan Pediatric Society for Oriental Medicine)</i> 2003; 19: 46–52 (in Japanese).	quasi-RCT	N	240
J10.1	To evaluate the effectiveness of two brands of maoto (麻黄湯) and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients.	maoto (麻黄湯)	Kawamura K. No difference between two brands of maoto and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients*. <i>Nihon Shonika Rinsho (Japanese Journal of Pediatrics)</i> 2009; 62: 1855-61 (in Japanese).	quasi-RCT	N	241
J10.1	To compare the effect the combination of oseltamivir phosphate and Western medications with that of oseltamivir phosphate and maoto (麻黄湯) for pediatric influenza.	maoto (麻黄湯)	Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza. <i>Kampo to Meneki-Allergy (Kampo and Immunoallergy)</i> 2005; 18: 47-55 (in Japanese with English abstract).	quasi-RCT	N	242

J20.0	To compare the efficacy of bakumondoto and tipepidine hibenzate as antitussive agents in patients with mycoplasma bronchitis.	bakumondoto (麦門冬湯)	Watanabe N, Miyazawa T. Comparative study of the effect of bakumondoto and tipepidine hebinzate on cough in patients with mycoplasma bronchitis. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)</i> 2007; 21: 31-6 (in Japanese). Watanabe N, Nakagawa T, Miyazawa T. Examination of effective antitussive against cough caused by mycoplasma bronchitis. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)</i> 2008; 22: 63-8 (in Japanese with English abstract).	RCT-envelope	N I	243
J30.1	Preventive effect and safety of preseasonal administration of shoseiryuto in patients with cedar pollen allergy (hay fever).	shoseiryuto (小青竜湯)	Ohya Y. Kampo treatment for allergic diseases: from the perspective of a general hospital. <i>Progress in Medicine</i> 1988; 8: 604-12 (in Japanese). Ohya Y. Efficacy of preseasonal administration of shoseiryuto for cedar pollen allergy. <i>Kampo Shinryo</i> 1991; 10: 42-8 (in Japanese).	RCT	N N	244
J30.1	Effects of shoseiryuto and ryokankyomishingeninto on springtime nasal allergy.	shoseiryuto (小青竜湯), ryokankyomishingeninto (苓甘姜味辛夏仁湯)	Mori H. Comparative study of Kampo preparations sho-seiryu-to and ryokankyomishingenin-to for nasal allergy. <i>Therapeutic Research</i> 1996; 17: 3691-6 (in Japanese with English abstract).	quasi-RCT	N	245
J30.1	Effects of shoseiryuto and eppikajutsuto on springtime nasal allergy.	shoseiryuto (小青竜湯), eppikajutsuto (越婢加朮湯)	Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations sho-seiryu-to and eppika-jutsu-to for nasal allergy and allergic conjunctivitis. <i>Therapeutic Research</i> 1997; 18: 3093-9 (in Japanese with English abstract).	quasi-RCT	N	246
J30.1	Effects of shoseiryuto and daiseiryuto on springtime nasal allergy.	shoseiryuto (小青竜湯), daiseiryuto (大青竜湯) [keishitogomakyokansekito (桂枝湯合麻杏甘石湯)]	Mori H. Comparative study of Kampo preparations sho-seiryu-to and dai-seiryu-to for nasal allergy and allergic conjunctivitis. <i>Therapeutic Research</i> 1998; 19: 3299-307 (in Japanese with English abstract).	quasi-RCT	N	247
J30.1	To compare the efficacy of shoseiryuto and keimakakuhanto in treating springtime nasal allergy and allergic conjunctivitis.	shoseiryuto (小青竜湯) and keimakakuhanto (桂麻各半湯) [keisito+maoto (桂枝湯+麻黃湯)]	Mori H, Kurata H, Shimazaki Y, et al. Comparative study of Kampo preparations sho-sei-ryu-to and kei-ma-kakuhan-to for nasal allergy and allergic conjunctivitis in spring. <i>Therapeutic Research</i> 1999; 20: 2941-7 (in Japanese with English abstract).	quasi-RCT	N	248
J30.1	To compare the effects of shoseiryuto and maobushisaishinto in treating springtime nasal allergy and allergic conjunctivitis.	shoseiryuto (小青竜湯), maobushisaishinto (麻黃附子細辛湯)	Yoshimoto T, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and maoh-bushi-saisin-to for nasal allergy and allergic conjunctivitis in spring. <i>Therapeutic Research</i> 2002; 23: 2253-9 (in Japanese with English abstract).	quasi-RCT	I	249
J30.1	To compare the effects of shoseiryuto and gokoto in subjects with nasal allergy and allergic conjunctivitis in spring.	shoseiryuto (小青竜湯), gokoto (五虎湯)	Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and go-ko-to for nasal allergy and allergic conjunctivitis in spring. <i>Therapeutic Research</i> 2001; 22: 2385-91 (in Japanese with English abstract).	quasi-RCT	I	250
J30.3	Efficacy and safety of shoseiryuto in the treatment of perennial nasal allergy.	shoseiryuto (小青竜湯)	Baba S, Takasaka T, Inamura N, et al. Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. <i>Jibiinkoka Rinsho (Practica otologica)</i> 1995; 88: 389-405 (in Japanese with English abstract).	DB-RCT	C&I	251
J303	To evaluate the efficacy and safety of maobushisaishinto extract granules prepared based on Shanghanlun (傷寒論, Treatise on Cold Damage Diseases) and conventionally-prepared maobushisaishinto extract powder in the treatment of perennial nasal allergy.	maobushisaishinto (麻黃附子細辛湯)	Nakai Y, Ohashi Y, Esaki Y, et al. Clinical evaluation of maobushisaishinto for nasal allergy. <i>Jibi-inkouka Tenbou (Oto-Rhino-Laryngology, Tokyo)</i> 1990; 33: 655-73 (in Japanese).	quasi-RCT	N	252

J32.9	Effectiveness of shin'iseihaito and shigyakusan for chronic rhinitis and sinusitis.	shin'iseihaito (辛夷清肺湯), shigyakusan (四逆散)	Sakurada T, Ikeda K, Takasaka T, et al. Clinical effectiveness of Kampo medicine for chronic rhinitis and sinusitis. <i>Jibiinkoka Rinsho (Practica otologica)</i> 1992; 85: 1341-6 (in Japanese with English abstract).	RCT-envelope	N	253
J39.2	Efficacy of saibokuto for relieving complaints after thyroid or parathyroid surgery.	saibokuto (柴朴湯)	Suzuki S, Furukawa H, Ami H, et al. Experience with TSUMURA Saibokuto (TJ-96) in patients who underwent thyroid or parathyroid surgery*. <i>Progress in Medicine</i> 1994; 14: 2254-8 (in Japanese).	RCT-envelope	I	254
J39.2	Healing effect of saibokuto on mucositis induced by head-and-neck and mediastinal irradiation.	saibokuto (柴朴湯)	Saito Y, Mitsuhashi N, Takahashi I, et al. Effect of TSUMURA Saiboku-to as an agent for healing damage in treatment of radiomucositis due to irradiation of the head and neck area and mediastinum. <i>Biotherapy</i> 1992; 6: 1899-906 (in Japanese with English abstract).	RCT	N	255
J40	To evaluate the efficacy and safety of shoseiryuto in the treatment of bronchitis.	shoseiryuto (小青竜湯)	Miyamoto T, Inoue H, Kitamura S, et al. Effect of TSUMURA Sho-seiryu-to (TJ-19) on bronchitis in a double-blind placebo-controlled study. <i>Rinsho Iyaku (Journal of Clinical Therapeutics & Medicine)</i> 2001; 17: 1189-214 (in Japanese with English abstract).	DB-RCT	I	256
			Miyamoto T. Clinical effectiveness of shosei-ryuto in bronchitis. <i>Pharma Medica</i> 2007; 25: 23-5 (in Japanese).		I	
J44.9	Effectiveness of bakumondoto as an expectorant.	bakumondoto (麦門冬湯)	Sasaki H, Satou K, Sasaki M, et al. Usefulness of bakumondo-to in senile chronic respiratory disease patients having difficulty in expectoration: comparison with bromhexine hydrochloride preparations. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 1993; 7: 139-45 (in Japanese with English abstract).	RCT-envelope	N	257
J44.9	To determine the efficacy of smoking cessation combined with administration of seihaito for chronic obstructive pulmonary disease (COPD).	seihaito (清肺湯)	Kato S, Matsuda T, Nakajima T, et al. Clinical significance of the combination therapy of smoking cessation and seihaito for chronic obstructive pulmonary disease. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 2005; 14: 260-5 (in Japanese).	RCT-envelope	I	258
			Kato S, Oda K, Hasumi H, et al. The combined effect of smoking cessation and seihai-to on airway clearance on COPD patients. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)</i> 2006; 19: 26-35 (in Japanese with English abstract).		N	

J44.9	To investigate the effect of hochuekkito on systemic inflammation in subjects with chronic obstructive pulmonary disease (COPD).	hochuekkito (補中益氣湯)	Shinozuka N, Tatsumi K, Nakamura A, et al. Evaluation of systemic inflammation and utility of hochuekkito administration in subjects with COPD*. <i>Kosei Rodosho Kagaku Kenkyu Kenkyuhoi Hojokin Nanchisei Shikkan Kokufuku Kenkyu Jigyo Kokyufuzen ni Kansuru Chosa Kenkyu Heisei 18 Nendo Buntan Kenkyu Hokokusho (Ministry of Health, Labour and Welfare, Science Research Grant: The Intractable Disease Treatment Research Project, Research on Respiratory Failure, Working-group Research Report Fiscal Year 2006)</i> 2007;94-9 (in Japanese).	RCT-envelope	N	259	
			Shinozuka N, Tatsumi K, Nakamura A, et al. A traditional herbal medicine hochuekkito improves systemic inflammation in patients with COPD. <i>American Journal of Respiratory and Critical Care Medicine</i> 2007; 175: A638.				C
			Shinozuka N, Tatsumi K, Nakamura A, et al. The traditional herbal medicine Hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. <i>Journal of the American Geriatrics Society</i> 2007; 55: 313-4.				C
			Fukuchi Y, Tatsumi K. Utility evaluation of Kampo in the treatment of chronic obstructive pulmonary disease*. <i>Kosei Rodosho Kagaku Kenkyuhoi Hojokin Chouju Kagaku Sogo Kenkyu Jigyo: Mansei Heisokusei Shikkan ni Taisuru Kampochiryu no Yuyosei Hyoka ni Kansuru Kenkyu, Heisei 18 Nendo Sokatsu Kenkyusyo Hokokusho (Ministry of Health, Labour and Welfare, Science Research Grant: Comprehensive Studies on Science of Aging, Study on Evaluation of Usefulness of Kampo Treatment for Chronic Obstructive Pulmonary Disease, Summary Report Fiscal Year 2006)</i> , 2007:1-31 (in Japanese).				N
			Tatsumi K, Shinozuka N, Nakayama K, et al. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. <i>The American Geriatrics Society</i> 2009; 57: 169-70.				N
J44.9	To evaluate the effect of bakumondoto (麦門冬湯) on cough in patients with chronic obstructive pulmonary disease (COPD).	bakumondoto (麦門冬湯)	Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. <i>Phytomedicine</i> 2011; 18: 625-9.	RCT-cross over	N	260	
			Hattori N, Mukaida K, Haruta Y, et al. A pilot study of the effects of Bakumondoto (TJ-29) on cough in chronic obstructive pulmonary disease (COPD)*. <i>Kampo to Meneki – Alerugi (Kampo and Immuno-Allergy)</i> 2011; 24: 38-45 (in Japanese with English abstract).				N
J45.0	Development of saibokuto inhalation therapy, and to evaluate its efficacy in preventing attacks of aspirin-induced asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, saiboku-to (cai-pu-tang) on brochospasms in aspirin-induced bronchial asthmatic patients. A randomized, double-blind test. <i>Jibi-inkoka Tenbo (Oto-Rhino-Laryngology Tokyo)</i> 2001; 44: 5-13 (in Japanese with English abstract).	DB-RCT	I	261	
J45.0	To evaluate the efficacy of short-term inhaled saibokuto in suppressing airway constriction, and long-term inhaled saibokuto in alleviating psychological suffering.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 2001; 11: 14-21 (in Japanese with English abstract).	RCT-cross over	I	262	
J45.0	To investigate the clinical effect of saibokuto for the treatment of atopic asthma.	saibokuto (柴朴湯)	Urata Y, Yoshida S, Irie Y, et al. Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial. <i>Respiratory Medicine</i> 2002; 96: 469-74.	RCT-cross over	C	263	
J45.0	To evaluate the efficacy and safety of inhaled shinpito for the control of aspirin-induced asthma.	shinpito (神秘湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-intolerant bronchial asthmatic patients – a randomized, group-paralleled comparative trial –. <i>Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)</i> 2003; 46: 3-14 (in Japanese with English abstract).	RCT	C&I	264	

J45.0	To evaluate the efficacy and safety of inhaled shinpito therapy for improving asthma symptoms in patients with aspirin-induced asthma.	shinpito (神秘湯)	Nishizawa Y, Nishizawa Y, Goto GH, et al. A randomized, group-parallel comparative trial of the suppressive effect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium cromoglycate inhalation in improving subjective and objective symptoms in bronchial asthmatics. <i>Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)</i> 2004; 47: 20-7 (in Japanese with English abstract).	RCT	C&I	265
J45.0	To investigate the effect of saibokuto inhalation therapy in improving quality of life (QOL) in patients with aspirin-intolerant asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Goto HG. Chronic pain in intractable and chronic medical conditions. <i>Mansei Totsu (The Journal of the Japanese Society for the Study of Chronic Pain)</i> 2002; 21: 67-77 (in Japanese with English abstract).	RCT	I	266
J45.9	Efficacy and safety of saibokuto in patients with steroid-dependent bronchial asthma.	saibokuto (柴朴湯)	Egashira Y, Nagano H, et al. Results of a comparative clinical study of the effect of "TSUMURA Saiboku-to" (TJ-96) against steroid dependent bronchial asthma in 2 groups, a Saiboku-to administration group and a non-administration group, divided by the envelope method. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 1990; 4: 128-44 (in Japanese with English abstract).	RCT-envelope	N	267
			Egashira Y, Nagano H. A multicenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthma. A comparison of groups allocated by the envelope method. <i>Annals of the New York Academy of Science</i> 1993; 685: 580-3.		C	
J45.9	Efficacy and safety of saibokuto in the treatment of bronchial asthma in children.	saibokuto (柴朴湯)	Ito S, Mikawa H. Effect of "TSUMURA Saiboku-to" (TJ-96) on bronchial asthma in children. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 1990; 4: 115-25 (in Japanese with English abstract).	RCT-envelope	I	268
			Ito S, Mikawa H. Clinical evaluation of saibokuto in the treatment of children with bronchial asthma. <i>Kiso to Rinsho (The Clinical Report)</i> 1992; 26: 3993-8 (in Japanese).		N	
J45.9	Efficacy of shinpito for inhibiting exercise-induced asthma and relieving clinical symptoms in patients with moderate or worse bronchial asthma.	shinpito (神秘湯)	Tubaki T, Ebisawa M, Akimoto K, et al. Effects of shinpito (shenbi-tang) on bronchial asthma. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 1994; 8: 65-71 (in Japanese with English abstract).	RCT	N	269
J45.9	To assess the efficacy and safety of inhaled saibokuto while reducing the amount of inhaled beclomethasone during the course of treatment for bronchial asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Nagano F, et al. Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropionate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation. <i>Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)</i> 2002; 45: 8-15 (in Japanese with English abstract).	RCT	C&I	270
J45.9	To compare the efficacy of the anxiolytic-like agent saibokuto with that of shoseiryuto in patients with bronchial asthma.	saibokuto (柴朴湯), shoseiryuto (小青竜湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-qing-long tang (Japanese name: shoseiryuto) in asthmatics with anxiety and depression due to asthmatic attacks. <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2003; 18: 11-7 (in Japanese with English abstract).	RCT	I	271
J45.9	To assess the efficacy of the anxiolytic-like agent, saibokuto, in treating bronchial asthma.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clonazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial. <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2002; 17: 20-7 (in Japanese with English abstract).	RCT	I	272

J45.9	To evaluate the efficacy and safety of saibokuto in patients with asthma exacerbations based on anticipatory anxiety.	saibokuto (柴朴湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of chai-po-tang (Japanese name: saiboku-to), a Chinese traditional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: a multicenter, randomized, double-blinded, placebo-controlled study. <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental and Psychosomatic Medicine)</i> 2004; 19:37-41 (in Japanese with English abstract).	RCT	I	273
J69.0	To investigate whether hangekobokuto (banxia houpu tang) improves cough reflex in elderly patients likely to have aspiration pneumonia.	hangekobokuto (半夏厚朴湯)	Iwasaki K, Cyong JC, Kitada S, et al. A traditional Chinese herbal medicine, banxia houpu tang, improves cough reflex of patients with aspiration pneumonia. <i>Journal of the American Geriatrics Society</i> 2002; 50: 1751-2.	RCT	C	274
J69.0	To evaluate whether hangekobokuto prevents aspiration pneumonia and pneumonia-related mortality in elderly people with dementia.	hangekobokuto (半夏厚朴湯)	Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in older adults with dementia. <i>Journal of the American Geriatrics Society</i> 2007; 55: 2035-40.	RCT	C	275
			Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in brain-damaged elderly. <i>International Journal of Stroke</i> 2010; 5 suppl 2: 38-9.		C	
J98.8	To evaluate the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampo combination therapy for bacterial respiratory infections.	juzentaihoto (十全大補湯), kakkonto (葛根湯), keishito (桂枝湯), kososan (香蘇散), shosaikoto (小柴胡湯), hochuekkito (補中益氣湯)	Mikamo H, Tamaya T. Usefulness of Kampo medicine for the treatment of infections from the perspective of medical economics*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2007; 24: 105-8 (in Japanese).	RCT	I	276

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (70 abstracts, 92 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K11.7	Efficacy of ninjin'yoeito for improvement of xerostomia induced by oxybutynin hydrochloride.	ninjin'yoeito (人參養榮湯)	Miyazaki Y, Yamada A, Saitou M. Effect of ninjin-yoei-tou on xerostomia induced by oxybutynin hydrochloride. <i>Shinyaku to Rinsho (Journal of New Remedies and Clinics)</i> 1994; 43: 2613-7 (in Japanese).	RCT	N	277
K11.7	To compare the efficacy of bakumondoto versus cevimeline hydrochloride hydrate (Evoxac) or nizatidine (Acinon) for treating dry mouth.	bakumondoto (麥門冬湯)	Umemoto M, Nin T, Miuchi S, et al. Treatment of human dry mouth using various medicines. <i>Jibiinkoka Rinsho (Practica otologica)</i> 2007; 100: 145-52 (in Japanese with English abstract).	RCT	I	278
K11.7	To evaluate the effects of bakumondoto (麥門冬湯) on neuropeptide levels in human plasma and saliva	bakumondoto (麥門冬湯)	Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. <i>Journal of Traditional Medicines</i> 2009; 26: 122-30.	RCT-cross over	I	279
K12.1	Efficacy and safety of orento for treating stomatitis.	orento (黃連湯)	Oka S. The effects of Oren-to on stomatitis. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1995; 46: 439-45 (in Japanese with English abstract).	RCT	N	280
K14.6	To evaluate the efficacy of saibokuto compared with tranquilizer plus vitamin B complex combination therapy for patients with glossodynia.	saibokuto (柴朴湯)	Bessho K, Okubo Y, Hori S, et al. Effectiveness of Kampo medicine (Sai-Boku-To) in treatment of patients with glossodynia. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology</i> 1998; 86: 682-6.	RCT	C	281
			Yamada T, Bessho K, Murakami K, et al. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. <i>Shika Yakubutsu Ryoho (Oral Therapeutics and Pharmacology)</i> 1998; 17: 18-22 (in Japanese with English abstract).		N	
			Yamada T, Bessho K. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 1999; 8: 261-5 (in Japanese).		I	

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K21.0	To evaluate the preventive effect of rikkunshito on postoperative reflux esophagitis.	rikkunshito (六君子湯)	Mizuno S, Yamagiwa K, Iwata M, et al. Effect of early treatment with TSUMURA Rikkunshito on gastrointestinal symptoms after resection of gastric cancer – focusing on reflux esophagitis [*] . <i>Progress in Medicine</i> 2001; 21: 1366-7 (in Japanese).	RCT	I	282
K21.0	To evaluate the efficacy of rikkunshito combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).	rikkunshito (六君子湯)	Koide A. Effect and role of TJ-43: rikkun-shi-to from the aspects of endoscopic findings and QOL improvement in GERD patients. <i>Medical Tribune Online (Digestive Disease Week: DDW)</i> 2005: 6-7 (in Japanese).	RCT	N	283
K21.0	To evaluate the efficacy of hangekobokuto-combined treatment in patients with respiratory symptoms associated with refractory gastroesophageal reflux disease (GERD).	hangekobokuto (半夏厚朴湯)	Kato S, Nakajima T, Matsuda T, et al. The effectiveness of the traditional Kampo medicine, “banxia houpu tang (hangekobokuto)” to respiratory disturbance by esophageal reflux disease. <i>Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)</i> 2005; 14: 333-8 (in Japanese).	RCT-envelope	I	284
K21.9	To evaluate the efficacy of TSUMURA Rikkunshito Extract Granules for treatment of non-erosive reflux disease (NERD) unresponsive to proton pump inhibitors (PPIs).	rikkunshito (六君子湯)	Koide A. Establishment of new treatment strategy for non-erosive reflux disease (endoscopy-negative gastroesophageal reflux disease) – potential of rikkunshito [*] . <i>MedicalQ</i> 2006; 187 (in Japanese).	RCT	N	285
K21.9	To evaluate the effectiveness of rikkunshito (六君子湯) for patients with proton pump inhibitor (PPI)-resistant gastroesophageal reflux disease (GERD, and especially non-erosive reflux disease [NERD]).	rikkunshito (六君子湯)	Tominaga K, Fujiwara Y, Shimoyama Y, et al. Rikkunshito improves PPI-refractory NERD: a prospective randomized multi-center trial in Japan. <i>Gastroenterology</i> 2010; 138: S655-6.	RCT	N	286
			Tominaga K, Fujiwara Y, Arakawa T, et al. GERD — Rikkunshito [*] . <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 2011; 99: 771–6 (in Japanese).		N	
			Tominaga K, Iwakiri R, Fujimoto K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. <i>Journal of Gastroenterology</i> 2012; 47: 284-92.		N	
K21.9	To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.	rikkunshito (六君子湯)	Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. <i>Nikkei Medical (Supplement)</i> 2010; 8: 27 (in Japanese).	DB-RCT-cross over	N	287
			Morita T, Furuta K, Adachi K, et al. Effects of Rikkunshito (TJ-43) on esophageal motor function and gastroesophageal reflux. <i>Journal of Neurogastroenterology and Motility</i> 2012; 18: 181-6.		N	
K21.9	To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.	rikkunshito (六君子湯)	Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. <i>Nikkei Medical (Supplement)</i> 2010; 8: 27 (in Japanese).	DB-RCT-cross over	N	288
K25.9	To compare the efficacy of saikokeishito, H2 receptor antagonist, or their combination for preventing recurrence of gastric ulcer.	saikokeishito (柴胡桂枝湯)	Nakahara A, Kashimura H, Fukutomi H. Gastric ulcer - saikokeishito or shigyakusan monotherapy [*] . <i>Nikkei Medical (separate-volume supplement)</i> 1988; 17: 20-1 (in Japanese).	RCT-envelope	N	289
			Fukutomi H, Nakahara A. Traditional oriental therapy of the gastric ulcer. <i>Shokakika (Gastroenterology)</i> 1990; 12: 159-65 (in Japanese).		N	
K27.9	To evaluate the usefulness of H2-blocker (cimetidine) combined with Kampo medicine (shigyakusan, saikokeishito) as a maintenance therapy for peptic ulcer.	shigyakusan (四逆散), saikokeishito (柴胡桂枝湯)	Watanabe H. A study of peptic ulcer maintenance therapy combined with Kampo medicines [*] . <i>Kampo Igaku (Kampo Medicine)</i> 1995; 19: 18-21 (in Japanese).	RCT	N	290

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K29.7	Efficacy and safety of rikkunshito and hangeshashinto for treating acute gastritis and acute exacerbation of chronic gastritis.	rikkunshito (六君子湯), hangeshashinto (半夏瀉心湯)	Ohta Y, Nishioka M, Yamamoto Y, et al. Multicenter clinical evaluation of Kampo preparations for medical use in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - comparison with gefarnate as a control *. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1990; 78: 2935-46 (in Japanese).	RCT-envelope	N	291
K29.7	Efficacy and safety of rikkunshito for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis).	rikkunshito (六君子湯)	Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - multicenter comparative study using sodium azulene sulfonate as a control *. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1991; 79: 789-810 (in Japanese).	RCT-envelope	N	292
K29.7	To evaluate the efficacy and safety of TSUMURA Rikkunshito for treating gastritis in a comparison with cetraxate as a control.	rikkunshito (六君子湯)	Takemoto T, Matsuda K, Tada M, et al. Clinical evaluation of the efficacy of TJ-43 Tsumura Rikkunshi-To on gastritis with abdominal symptom - multicenter group study in comparison with cetraxate -. <i>Shokakika (Gastroenterology)</i> 1990; 12: 223-34 (in Japanese with English abstract).	RCT-envelope	N	293
K30	Efficacy and safety of rikkunshito for treating epigastric indefinite complaints complicated by depression.	Rikkunshito (六君子湯)	Kawamura S, Okita K, Tada M, et al. Clinical comparison of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress - mainly the antidepressive effect and the improvement of gastric emptying *. <i>Progress in Medicine</i> 1992; 12: 1156-62 (in Japanese).	RCT-envelope	N	294
K30	Efficacy of rikkunshito for treating indefinite complaints of epigastric distress.	rikkunshito (六君子湯)	Komatsuzaki O. Clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress - comparison with a control agent, and assessment mainly based on the endoscopic findings and the histology of gastric mucosal biopsy specimens before and after the treatment *. <i>Kampo Igaku (Kampo Medicine)</i> 1993; 17: 120-31 (in Japanese).	RCT-envelope	N	295
K30	Efficacy of saireito for post-infectious dyspepsia in infants.	saireito (柴苓湯)	Ito J, Ito Y, Asai M, et al. Efficacy of Saireito (TSUMURA) for post-infectious dyspepsia in infants: comparison with intestinal regulators *. <i>Shonika Shinryo (Journal of Pediatric Practice)</i> 1992; 55: 2089-92 (in Japanese).	RCT	I	296
K30	Efficacy of rikkunshito in dyspeptic patients.	rikkunshito (六君子湯)	Tatsuta M, Iishi H. Effect of treatment with Liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. <i>Alimentary Pharmacology and Therapeutics</i> 1993; 7: 459-62.	RCT	C	297
K30	Efficacy and safety of rikkunshito for treating complaints of gastrointestinal disorders including chronic gastritis.	rikkunshito (六君子湯)	Miyoshi A, Yachi A, Masamune O, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis - a multicenter comparative study using cisapride as a control *. <i>Progress in Medicine</i> 1991; 11: 1605-31 (in Japanese).	RCT-envelope	N	298
K30	To evaluate the efficacy of rikkunshito as an agent to improve symptoms before endoscopy in patients with upper abdominal symptoms and need for endoscopy of the upper gastrointestinal tract.	rikkunshito (六君子湯)	Koide A. Adoption of rikkunshito before endoscopy in patients with upper abdominal symptoms*. <i>Nikkei Medical</i> 2002; 31: 22-3 (in Japanese).	RCT-envelope	N	299
			Koide A. The improvement of QOL by rikkunshito in patients with need for endoscopy*. <i>Medical Tribune</i> 2004; 45 (in Japanese)		N	
			Yamaguchi T, Koide A. Usefulness of Rikkun-shi-to (TJ-43), a Chinese herbal medicine, for the treatment of gastro-esophageal reflux disease (GERD). <i>Medical Science Digest</i> 2007; 33: 748-52 (in Japanese).		N	

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K30	To evaluate the efficacy and safety of TJ-43 TSUMURA Rikkunshi-to in patients with dyspepsia caused by dysfunction of the upper gastrointestinal tract.	rikkunshito (六君子湯)	Harasawa S, Miyoshi A, Miwa T, et al. Double-blind multicenter post-marketing clinical trial of TJ-43 TSUMURA Rikkunshi-to for the treatment of dysmotility-like dyspepsia. <i>Igaku no Ayumi (Journal of Clinical and Experimental Medicine)</i> 1998; 187: 207-29 (in Japanese).	DB-RCT	I	300
			Harasawa S. The role of rikkunshito against NUD (non-ulcer dyspepsia) – especially its efficacy in dysmotility-like NUD*. <i>Progress in Medicine</i> 1999; 19: 843-8 (in Japanese).			
			Harasawa S. Evidence from an RCT of rikkunshito (六君子湯) for epigastric complaints*. <i>Kampo Igaku (Science of Kampo Medicine)</i> 2011; 35: 113-7 (in Japanese).			
K30	To clarify the effect of rikkunshito (六君子湯) on increasing ghrelin secretion and improving symptoms and its mechanism of action in patients with functional dyspepsia (FD).	rikkunshito (六君子湯)	Arai M. Rikkunshito significantly enhances the secretion of ghrelin in patients with functional dyspepsia*. <i>Kampo Igaku (Kampo Medicine)</i> 2009; 33: 405-6.	RCT	N	301
			Matsumura T, Arai M, Suzuki T, et al. The traditional Japanese medicine rikkunshito improves upper gastrointestinal symptoms in patients with functional dyspepsia. <i>Gastroenterology</i> 2010; 138: S471.		C	
			Arai M, Matsumura T, Yoshikawa M, et al. Analysis of the Rikkunshito efficacy on patients with functional dyspepsia*. <i>Nihon Yakurigaku Zasshi (Folia Pharmacologica Japonica)</i> 2011; 137: 18–21. (in Japanese).		N	
			Arai M, Matsumura T, Tsuchiya N, et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. <i>Hepato-Gastroenterology</i> 2012; 59: 62-6.		N	
K30.0	To evaluate the efficacy of TSUMURA Rikkunshito Extract Granules for stimulating gastrointestinal emptying in patients after pylorus-preserving gastrectomy (PPG).	rikkunshito (六君子湯)	Nishida T. Effect of rikkunshito on gastrointestinal function in patients after gastrectomy*. <i>Progress in Medicine</i> 2006; 26: 3224-5 (in Japanese).	RCT-cross over	N	302
			Takahashi T, Endo S, Nakajima K, et al. Effect of rikkunshito, a Chinese herbal medicine, on stasis in patients after pylorus-preserving gastrectomy. <i>World Journal of Surgery</i> 2009; 33: 296-302.		C	
K30.0	To evaluate the effects of rikkunshito (六君子湯) on gastric contraction and expansion.	rikkunshito (六君子湯)	Shiratori M, Shoji T, Kanazawa M, et al. Effect of rikkunshito on gastric sensorimotor function under distention. <i>Neurogastroenterology & Motility</i> 2011; 23: 323-9, e155-6.	RCT-cross over	N	303
K30.0	To evaluate the effectiveness of rikkunshito (六君子湯) for gastrointestinal symptoms after endoscopic submucosal dissection (ESD) for early gastric cancer.	rikkunshito (六君子湯)	Uehara R. An evaluation of gastrointestinal symptoms and gastric mobility after endoscopic submucosal dissection (ESD) and an investigation of the usefulness of Rikkunshito (TJ-43)*. <i>Dai 8 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai Workshop 4 PROCEEDING Jobu Shokaki Shojo to Kampo (Workshop 4 Proceedings of the 8th Annual Meeting of the Japanese Gastroenterological Association: Upper Gastrointestinal Symptoms and Kampo)</i> 2012: 16-7 (in Japanese).	RCT	N	304
K31.9	To evaluate the effects of daikenchuto (大建中湯) and orengekuto (黄連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.	daikenchuto (大建中湯) and orengekuto (黄連解毒湯)	Takayama S, Seki T, Watanabe M, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. <i>The Tohoku Journal of Experimental Medicine</i> 2009; 219: 319-30.	RCT-cross over	C&I	305
K31.9	Comparative evaluation of the regulatory effects of thermal stimulation to the abdomen and Daikenchuto (大建中湯) on superior mesenteric artery (SMA) blood flow in healthy people.	rikkunshito (六君子湯)	Takayama S, Seki M, Watanabe M, et al. The effect of warming of the abdomen and of herbal medicine on superior mesenteric artery blood flow - a pilot study. <i>Forschende Komplementärmedizin</i> 2010; 17: 195-201.	RCT	N	306

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K52.9	To evaluate the safety and efficacy of hangeshashinto for CPT-11-induced diarrhea during combination chemotherapy with cisplatin (CDDP) plus irinotecan hydrochloride (CPT-11) for advanced non-small-cell lung cancer (NSCLC).	hangeshashinto (半夏瀉心湯)	Mori K, Machida S, Yoshida T, et al. Usefulness of Kampo medicine (hangeshashin-to) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. <i>Proceedings of the American Society of Clinical Oncology</i> 1999; 18: 518a, Abstract 1996	RCT-envelope	C	307
			Mori K, Hirose T, Machida S, et al. Kampo medicines for the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. <i>Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)</i> 1998; 25: 1159-63 (in Japanese with English abstract).			
			Mori K. Hangeshashin-to (Kampo medicined) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. <i>Progress in Medicine</i> 1999; 19: 886-90 (in Japanese with English abstract).			
			Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. <i>Cancer Chemotherapy and Pharmacology</i> 2003; 51: 403-6.			
K52.9	To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.	hangeshashinto (半夏瀉心湯)	Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. <i>Gan to Kagaku Ryoho (Japanese Journal of Cancer Chemotherapy)</i> 2009; 36: 1485-8 (in Japanese with English abstract).	RCT-envelope	C&I	308
K52.9	To compare the preventive effects of hangeshashinto (半夏瀉心湯) for delayed diarrhea following administration of CPT-11 for colorectal cancer.	hangeshashinto (半夏瀉心湯)	Miyauchi H. A comparative study of the preventive effects of hangeshashinto and oral alkalizer for delayed diarrhea in chemotherapy for colorectal cancer (FOLFILI)*. <i>Progress in Medicine</i> 2012; 32: 628-9 (in Japanese).	RCT	N	309
K56.0	Effects of daikenchuto on intestinal paralysis after surgery for colorectal cancer	daikenchuto (大建中湯)	Nagashima Y, Tanaka N, Furukawa K, et al. Effects of daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer*. <i>Progress in Medicine</i> 1998; 18: 903-5 (in Japanese).	RCT	N	310
K56.0	To evaluate the efficacy and safety of daikenchuto for improving intestinal peristalsis in patients with intestinal paralysis after surgery for abdominal aortic aneurysm (AAA).	daikenchuto (大建中湯)	Takagaki Y, Kawasaki S, Komai H, et al. The effect of Chinese herb medicine (dai-kenchu-to) on paralytic ileus after repair of abdominal aortic aneurysm. <i>Nihon Rinsho Geka Gakkai Zasshi (Journal of Japan Surgical Association)</i> 2000; 61: 325-8 (in Japanese with English abstract).	RCT	N	311
K56.5	Efficacy of daikenchuto in patients with adhesive ileus.	daikenchuto (大建中湯)	Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial*. <i>Progress in Medicine</i> 1995; 15: 1954-8 (in Japanese).	RCT-envelope	I	312
K58.9	Efficacy of saikokeishito and keishikashakuyakuto for irritable bowel syndrome (IBS).	saikokeishito (柴胡桂枝湯), keishikashakuyakuto (桂枝加芍藥湯)	Ishii F, Iizuka B, Nagasako K, et al. Evaluations of the therapeutic efficacy of Saikokeishito (TJ-10) versus Keishikashakuyakuto (TJ-60) for irritable bowel syndrome and Saireito (TJ-114) for ulcerative colitis*. <i>Progress in Medicine</i> 1993; 13: 2893-900 (in Japanese).	RCT	N	313
K58.9	Efficacy and safety of keishikashakuyakuto for irritable bowel syndrome.	keishikashakuyakuto (桂枝加芍藥湯)	Sasaki D, Uehara A, Hiwatashi N, et al. Clinical efficacy of keishikashakuyakuto for irritable bowel syndrome - a multicenter, randomized, parallel-group clinical trial -*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1998; 75: 1136-52 (in Japanese).	DB-RCT	I	314
K59.0	Efficacy of junchoto and mashingan for atonic constipation in the elderly.	junchoto (潤腸湯), mashingan (麻子仁丸)	Ishioka T. Comparison of the efficacy of junchoto and mashingan for atonic constipation in the elderly stratified by physical strength*. <i>Kampo no Rinsho (Journal of Kampo Medicine)</i> 1996; 43: 1431-7 (in Japanese).	RCT-cross over	N	315

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K59.0	A preceding double-blinded controlled trial of daiokanzoto, compared with placebo, in the treatment of constipation found it was effective against constipation, but not useful (no details available). The objective of this study was to reexamine the effects of daiokanzoto on constipation using a newly-defined assessment standard and the same results mentioned above.	daiokanzoto (大黃甘草湯)	Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-To Extract Granules for ethical use (TJ-84) on constipation using double blind test. <i>Shokakika (Gastroenterology)</i> 1994; 18: 299-312 (in Japanese with English abstract).	DB-RCT	I	316
			Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-to Extract Granules for ethical use (TJ-84) against the constipation based on the new standard. <i>Shokakika (Gastroenterology)</i> 1996; 22: 314-28 (in Japanese with English abstract).		I	
			Harasawa S, Miyoshi A. Reevaluation of Kampo medicine in patients with constipation - efficacy of Daio-kanzo-to -. <i>Shokakigan (Japanese Journal of Cancer of the Digestive Organs)</i> 1996; 6: 271-7 (in Japanese with English abstract).		I	
K59.0	To evaluate the efficacy and safety of kumibinroto for chronic constipation in elderly dialysis patients.	kumibinroto (九味檳榔湯)	Nishizawa Y, Nishizawa Y, Goto HG, et al. Prospective multicenter randomized group-parallelled study: effect of Chinese traditional herb medicine, jiu-wei-bing-lang-tang (Japanese name: kumi-binro-to) on constipation in elderly patients with renal dialysis. <i>Kampo Kenkyu (Kampo Research)</i> 2004; 388: 132-8 (in Japanese).	RCT	I	317
K59.0	To evaluate the effects of daikenchuto (大建中湯) in combination for chronic constipation patients taking sennoside.	daikenchuto (大建中湯)	Horiuchi A, Nakayama Y, Tanaka N. Effect of traditional Japanese medicine, Daikenchuto (TJ-100) in patients with chronic constipation. <i>Gastroenterology Research</i> 2010; 3: 151-5.	RCT	N	318
K59.8	To verify inhibition of inflammatory cytokine production and post-operative enhanced reactivation of intestinal function by daikenchuto (大建中湯) in colorectal cancer patients.	daikenchuto (大建中湯)	Ota M. A Randomized controlled trial of perioperative daikenchuto for colorectal cancer surgery*. <i>Progress in Medicine</i> 2012; 32: 618-9 (in Japanese).	RCT	N	319
K59.8	To verify the anti-inflammatory effects of daikenchuto (大建中湯) on intestinal distress in the aftermath of gastrointestinal surgery.	daikenchuto (大建中湯)	Ikemoto T. The role of Kampo in gastrointestinal surgery and the effectiveness of daikenchuto (大建中湯) for intestinal stress - From bacterial translocation to microbiome*. <i>Progress in Medicine</i> 2011; 31: 466-7 (in Japanese).	RCT	N	320
K59.8	To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after gastric cancer and total gastrectomy.	daikenchuto (大建中湯)	Omori K. Prospective randomized controlled study of daikenchuto for postoperative dysmotility after total gastrectomy*. <i>Progress in Medicine</i> 2012; 32: 614-5 (in Japanese).	RCT	N	321
K59.8	To evaluate the efficacy and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after laparoscopic surgery.	daikenchuto (大建中湯)	Yaegashi M. Usefulness of daikenchuto in the laparoscopic colorectal cancer perioperative period*. <i>Progress in Medicine</i> 2012; 32: 616-7 (in Japanese).	RCT	N	322
K70.9	Efficacy of Kampo medicines for alcoholic liver disease.	shosaikoto (小柴胡湯), shosaikoto (小柴胡湯) + inchingoreisan (茵陳五苓散)	Takahashi H, Maruyama K. Clinical aspects of Kampo treatment for alcoholic liver disease. <i>Igaku no Ayumi (Journal of Clinical and Experimental Medicine)</i> 1993; 167: 811-4 (in Japanese).	RCT	N	323

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K73.2	Efficacy and safety of shosaikoto for chronic active hepatitis.	shosaikoto (小柴胡湯)	Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of sho-saiko-to in chronic active hepatitis. <i>Gastroenterologia Japonica</i> 1989; 24: 715-9.	DB-RCT	C&I	324
			Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. <i>Kan-Tan-Sui</i> 1990; 20: 751-9 (in Japanese).		I	
K73.2	Efficacy of shosaikoto for chronic active hepatitis.	shosaikoto (小柴胡湯)	Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis. Analysis of serum enzyme activities. <i>Kan-Tan-Sui</i> 1992; 25: 551-8 (in Japanese).	DB-RCT	I	325
K73.9	Efficacy and safety of saireito for chronic hepatitis.	saireito (柴苓湯)	Sasaki D, Sudoh T, Kunikane M, et al. Usefulness of Kanebo Saireito Extract Fine Granules for chronic hepatitis - a comparative study (with randomization carried out using the sealed-envelope method) - *. <i>Progress in Medicine</i> 1989; 9: 2923-37 (in Japanese).	RCT-envelope	I	326
K73.9	To evaluate the efficacy of liver protectors for preventing carcinogenesis in patients with chronic hepatitis C.	shosaikoto (小柴胡湯), juzentaihoto (十全大補湯)	Tarao K, Shibuya A, Ohkawa S, et al. Prevention of hepatocarcinogenesis by anti-inflammatory therapy: is combination anti-inflammatory therapy targeting an ALT level of under 80 units effective for hepatitis C virus-related cirrhosis (Child A)?: comparison with monotherapy*. <i>Kanagawa Cancer Center – Nenpo (Annual Report)</i> 2003; 19: 92 (in Japanese).	RCT	N	327
			Tarao K. Persistent inflammation and hepatocarcinogenesis in chronic hepatitis C and hepatitis C virus-related cirrhosis*. <i>Kanagawa Igakkai Zasshi (The Journal of the Kanagawa Medical Association)</i> 2006; 33: 115-8 (in Japanese).		N	
			Tarao K. Prevention of HCC by anti-inflammatory agents in patients with chronic hepatitis C. <i>Rinsho Shokaki Naika (Clinical Gastroenterology)</i> 2007; 22: 961-9 (in Japanese).		N	
K74.6	To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto administered for liver cirrhosis.	juzentaihoto (十全大補湯)	Higuchi K, Watanabe A. Study on liver cancer-preventive effect of juzentaihoto in patients with liver cirrhosis*. <i>Methods in Kampo Pharmacology</i> 2000; 5: 29-33 (in Japanese).	RCT-envelope	N	328
K74.6	To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto administered for liver cirrhosis.	juzentaihoto (十全大補湯)	Higuchi K, Shimizu Y, Yasumura S, et al. Preventive effect of liver carcinogenesis by juzuen-taiho-to in the patients with liver cirrhosis. <i>Kan-Tan-Sui</i> 2002; 44: 341-6 (in Japanese)	RCT-envelope	I	329
K75.9	Efficacy of shosaikoto for chronic non-A, non-B hepatitis in children.	shosaikoto (小柴胡湯)	Tajiri H, Kozaiwa K, Sawada A, et al. Efficacy of shosaikoto for chronic non-A, non-B hepatitis in children (non-A, non-B hepatitis in children and shosaikoto)*. <i>Nihon Shoni Toyo Igaku Kenkyukai Kaishi (Journal of the Japan pediatric society for oriental medicine)</i> 1996; 12: 12-7 (in Japanese).	RCT-envelope	N	330
K76.9	Efficacy of saikokeishito for liver dysfunction induced by chemotherapy for pulmonary tuberculosis.	saikokeishito (柴胡桂枝湯)	Mizutani Y, Imai S, Watanabe H, et al. Saiko-Keishi-To on patients with pulmonary tuberculosis: effect on liver dysfunction. <i>Donan Igakkaishi (Journal of the Medical Association of South Hokkaido)</i> 1994; 29: 247-9 (in Japanese).	RCT-envelope	N	331
K80.2	Effects of shosaikoto, goreisan, and tokishakuyakusan on the sphincter of Oddi.	goreisan (五苓散), tokishakuyakusan (当帰芍薬散), shosaikoto (小柴胡湯)	Seki M, Fujioka M, Hatano T, et al. Differences between the effects of sho-saiko-to, gorei-san, and toki-shakuyaku-san on the sphincter of Oddi - An intraoperative cholangiomanometric study -. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1993; 43: 395-402 (in Japanese with English abstract).	RCT	N	332

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K82.8	Efficacy of goreisan and tokishakuyakusan on urinary 6-keto-prostaglandin F1 α level in patients with gallbladder stones or polyps.	goreisan (五苓散), tokishakuyakusan (当帰芍薬散), shosaikoto (小柴胡湯)	Takagi S. Increase of urinary 6-keto-prostaglandin F1 α level by preoperative administration of gorei-san or toki-shakuyaku-san to the patients of gallbladder stones or polyps. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1992; 9: 32-9 (in Japanese with English abstract).	RCT	N	333
K83.1	Efficacy of inchinkoto for improving the bilirubin reduction rate after biliary drainage in patients with obstructive jaundice.	inchinkoto (茵陈蒿湯)	Okabayashi T, Tanaka N, Orita K. The effect of a Kanpo medicine, inchinko-to for the bilirubin reduction rate after biliary drainage on the patients with obstructive jaundice. <i>Nihon Rinsho Geka Gakkaishi (Journal of Japan Surgical Association)</i> 1998; 59: 2495-500 (in Japanese with English abstract).	RCT-envelope	I	334
K83.1	To evaluate the drug efficacy of inchinkoto (茵陈蒿湯) as a choleric drug on livers of patients with biliary obstruction due to bile duct carcinoma.	inchinkoto (茵陈蒿湯)	Watanabe S, Yokoyama Y, Oda K, et al. Choleric effect of inchinkoto, a herbal medicine, on livers of patients with biliary obstruction due to bile duct carcinoma. <i>Hepatology Research</i> 2009; 39: 247-55.	RCT	C&I	335
K91.0	To evaluate the effect of rikkunshito (六君子湯) on postoperative nausea and vomiting.	rikkunshito (六君子湯)	Okuno S, Hirayama K, Inoue J, et al. Effects of rikkunshito on the postoperative nausea and vomiting (PONV) after laparoscopic gynecological surgery. <i>Masui (Japanese Journal of Anesthesiology)</i> 2008; 57: 1502-9 (in Japanese with English abstract).	RCT	C	336
K91.3	Efficacy and safety of daikenchuto for ileus.	daikenchuto (大建中湯)	Kubo N, Uchida Y, Akiyoshi T, et al. Efficacy of daikenchuto for ileus - a multicenter study - *. <i>Progress in Medicine</i> 1995; 15: 1962-7 (in Japanese).	RCT-envelope	I	337
K91.3	To evaluate the efficacy of daikenchuto for the treatment of postoperative ileus and the improvement of postoperative conditions.	daikenchuto (大建中湯)	Itoh T, Yamakawa J, Mai M, et al. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. <i>The Journal of International Medical Research</i> 2002; 30: 428-32.	RCT	C	338
K91.8	Efficacy and safety of shosaikoto for postoperative liver dysfunction.	shosaikoto (小柴胡湯)	Okabayashi T, Mimura H, Orita K. Usefulness of Shosaikoto (TJ-9) in the treatment of postoperative liver dysfunction*. <i>Progress in Medicine</i> 1989; 9: 851-5 (in Japanese).	RCT-envelope	N	339
K91.8	Effect of shosaikoto on postoperative liver dysfunction.	shosaikoto (小柴胡湯)	Usuba A, Gao L. S., Motoki R. Effect of sho-saiko-to (xao-chai-hu-tang) on liver dysfunctions after surgery - the benefits of preoperative administration and the importance of diagnosis according to traditional Chinese logic -. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1992; 43: 1-12 (in Japanese).	RCT	N	340
K91.8	To evaluate the effectiveness and safety of daikenchuto (大建中湯) soon after colorectal cancer surgery.	daikenchuto (大建中湯)	Watanabe K. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* <i>Kampo Igaku (Science of Kampo Medicine)</i> 2010; 34: 346-7 (in Japanese). Fujii S. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* <i>Progress in Medicine</i> 2011; 31: 468-9 (in Japanese).	quasi-RCT	N N	335

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K91.9	To evaluate the effects of daikenchuto on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction.	daikenchuto (大建中湯)	Endo S, Nishida T, Nishikawa K, et al. Dai-kenchu-to, a Chinese herbal medicine, improves stasis of patients with total gastrectomy and jejunal pouch interposition. <i>American Journal of Surgery</i> 2006; 192: 9-13.	RCT-cross over	C	342
K91.9	To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.	daikenchuto (大建中湯)	Manabe N., Camilleri M, Rao A, et. al. Effect of Daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. <i>American Journal of Physiology. Gastrointestinal and Liver Physiology</i> 2010; 298: G970-5.	DB-RCT	C	343
K92.9	Efficacy and safety of keishikashakuyakuto combined with acarbose.	keishikashakuyakuto (桂枝加芍薬湯)	Hasebe K, Machida M, Yada M, et al. Clinical application of keishi-ka-syakuyaku-to for abdominal symptoms caused by α -glucosidase inhibitor acarbose. <i>Kiso to Rinsho (The Clinical Report)</i> 1997; 31: 3179-86 (in Japanese with English abstract).	quasi-RCT	I	344
K92.9	To evaluate the clinical effect of rikkunshito on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.	rikkunshito (六君子湯)	Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. <i>Biopsychosocial Medicine</i> 2007; 1: 21.	RCT	I	345
K92.9	To evaluate the effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by milnacipran, an antidepressant.	rikkunshito (六君子湯)	Oka T. Rikkunshito attenuates milnacipran-induced adverse gastrointestinal symptoms and potentiates its antidepressant effect. <i>Medical Tribune</i> 2008;41:82 (in Japanese).	RCT	N	346

12. Skin Diseases (16 abstracts, 17 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
L20.8	Efficacy and safety of shosaikoto for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.	shosaikoto (小柴胡湯)	Shimoda S, Hashizume S, Morita M, et al. Efficacy of TSUMURA Shosaikoto for atopic dermatitis*. <i>Hifuka ni okeru Kampo Chiryō no Genkyō</i> 1991; 2: 15-24 (in Japanese).	RCT	N	347
L20.9	To evaluate the efficacy and safety of hochuekkito (補中益気湯) in patients with <i>kikyo</i> (気虚, delicate constitution) associated with atopic dermatitis (AD).	hochuekkito (補中益気湯)	Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with “qi-kyo” – a multicenter, double-blind trial*. <i>Arerugi (Japanese Journal of Allergology)</i> . 2005; 54: 1020 (in Japanese). Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, hochu-ekki-to in the long-term management of kikyo (delicate constitution) patients with atopic dermatitis: A 6-month, multicenter, double-blind, randomized, placebo-controlled study. <i>Evidence-based Complementary and Alternative Medicine</i> 2008: 1-7. (2010; 7: 367-73.)	DB-RCT	N N	348
L20.9	To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) and goreisan (五苓散) for dampness-heat pattern in atopic dermatitis (AD) patients.	orengedokuto (黄連解毒湯) + goreisan (五苓散)	Choi I, Kim S, Kim Y, et al. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. <i>The Journal of Alternative and Complementary Medicine</i> 2012; 18: 576-82.	DB-RCT	N	349
L29.8	Efficacy and safety of orengedokuto and goshajinkigan for the treatment of senile pruritus.	orengedokuto (黄連解毒湯), goshajinkigan (牛車腎気丸)	Ohkawara A, Furuya K, Kurisu Y, et al. Experience with Orengedokuto (TJ-15) and Goshajinkigan (TJ-107) for the treatment of senile pruritus*. <i>Nishinohon Hifuka (The Nishinohon Journal of Dermatology)</i> 1991; 53: 1234-41 (in Japanese).	RCT-envelope	I	350
L29.8	Efficacy of tokiinshi combined with a bath preparation containing licorice extract in patients with senile xerosis.	tokiinshi (当帰飲子)	Iida T, Nishiyama C, Suzuki H. The effects of toki-inshi and a bath preparation containing licorice extract on patients with senile pruritus. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1996; 47: 35-41 (in Japanese with English abstract).	RCT	N	351

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
L29.8	Efficacy of hachimijogan for the treatment of senile pruritus.	hachimijogan (八味地黄丸)	Ishioka T, Aoi R. Comparative evaluation of hachimijogan and ketotifen fumarate on senile pruritus*. <i>Shinyaku to Rinsho (Journal of New Remedies and Clinics)</i> 1992; 41: 2603-8 (in Japanese).	RCT-cross over	N	352
L29.8	Efficacy of rokumigan and hachimijogan for the treatment of senile pruritus.	hachimijogan (八味地黄丸), rokumigan (六味丸)	Ishioka T. Comparative evaluation of rokumigan and hachimi-jogan on senile pruritus. <i>Therapeutic Research</i> 1995; 16: 1497-504 (in Japanese with English abstract).	RCT-cross over	N	353
L29.9	Effect on itching due to eczema and other skin disorders.	unseiin (温清飲)	Kusumoto M, Fujimura Y, Yamada H, et al. Evaluation of the effectiveness of various drugs for relieving itching due to eczema carried out by personnel in inpatient pharmacy practice: assessment based on "itching" score -. <i>Iyaku Journal (Medicine and Drug Journal)</i> 1993; 29: 973-6 (in Japanese).	RCT	N	354
L29.9	Efficacy of orengekuto and tokiinshi for the treatment of pruritus.	orengedokuto (黄連解毒湯) + tokiinshi (当帰飲子)	Ohkuma M. Treatment of pruritus by Chinese drugs. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1993; 10: 126-30 (in Japanese with English abstract).	RCT	N	355
L29.9	Efficacy of orengekuto, tokiinshi, external application, and oral antihistamine monotherapy or combination therapy for the treatment of pruritus.	orengedokuto (黄連解毒湯) + tokiinshi (当帰飲子)	Ohkuma M. Treatment of pruritus by Chinese drugs with external application and oral antihistamine. <i>Wakan Iyagakaku Zasshi (Journal of Traditional Medicines)</i> 1994; 11: 302-3 (in Japanese).	RCT	N	356
L30.9	Efficacy and safety of jumihaidokuto for the treatment of chronic eczema and atopic dermatitis.	jumihaidokuto (十味敗毒湯)	Kobayashi K, Ohkawara A. Therapeutic effect of jumihaidokuto on chronic eczema and atopic dermatitis*. <i>Hifuka ni okeru Kampo Chiryō no Genkyō (Current Situation of Kampo Therapy in Dermatology)</i> 1994; 5: 25-34 (in Japanese).	RCT-envelope	N	357
L40.9	Efficacy of saireito combined with topical steroid therapy for psoriasis.	saireito (柴苓湯)	Kukita A, Harada S, Fujisawa R, et al. The clinical efficacy of the herb medicine, TJ-114 (Sairei-to), on the topical steroid therapy of psoriasis vulgaris. <i>Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines)</i> 1991; 7: 927-36 (in Japanese with English abstract).	RCT-envelope	C&I	358
L50.9	Efficacy of kakkonto as an adjuvant for reducing adverse reactions to oxatomide.	kakkonto (葛根湯)	Tanaka M. Effects of oxatomide on urticaria. <i>Yakuri to Chiryō (Japanese Pharmacology and Therapeutics)</i> 1991; 19:5029-31 (in Japanese).	RCT	N	359
L70.0	Efficacy of jumihaidokuto and orengekuto for the treatment of acne vulgaris.	jumihaidokuto (十味敗毒湯), orengekuto (黄連解毒湯)	Ohkuma M. Treatment of acne by Chinese drugs and external application. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1993; 10: 131-4 (in Japanese with English abstract). Ohkuma M. Treatment of acne by Chinese drugs and external application - comparison with oral antibiotics -. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1993; 44: 173-7 (in Japanese).	RCT	N N	360
L89	Effects of juzentaihoto (十全大補湯) on pressure ulcers.	juzentaihoto (十全大補湯)	Nagai Y, Hasegawa M, Tago O, et al. Assessment of the therapeutic effect of juzentaihoto on pressure ulcer. <i>Kampo to Saishin-chiryō (Kampo & The Newest Therapy)</i> 2009; 18: 143-9.	RCT-envelope	I	361

13. Diseases of the Musculoskeletal System and Connective Tissue (20 abstracts, 19 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
M06.90	To evaluate the efficacy of saireito in the management of chronic rheumatoid arthritis in a controlled trial using lobenzarit, a western medicine with the established efficacy, as control.	saireito (柴苓湯)	Matsuura M. Efficacy of saireito in the management of chronic rheumatoid arthritis (RA)*. <i>Modern Physician</i> 1994; 14: 403-8 (in Japanese).	RCT-envelope	I	362
M06.90	Efficacy for reducing adverse effects of steroids in patients with chronic rheumatoid arthritis.	jiinkokato (滋陰降火湯)	Matsuta K, Gu XP, Ito K, et al. Evaluation of jiinkokato and steroid combination therapy for chronic rheumatoid arthritis*. <i>Kampo Igaku (Kampo Medicine)</i> 1995; 19: 50-2 (in Japanese).	RCT	N	363

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
M17.9	To compare the efficacy of Kampo medicines (boiogito and shuchibushimatsu with NSAIDs for improving analgesia, quality of life (QOL), and exercise capacity in patients with knee osteoarthritis.	boiogito (防已黄耆湯) + shuchibushimatsu (修治附子末)	Nishizawa Y, Nishizawa Y, Amenomori Y, et al. A comparison of the analgesic effect of non-steroid anti-inflammatory drugs (NSAIDs alminoprofen) and those of a Chinese traditional herbal medicine, boi-ogi-to and shuchi-bushi-powder on osteoarthritis of the knee joint in middle-aged and elderly patients with knee-joint osteoarthritis. <i>Itami to Kampo (Pain and Kampo Medicine) 1998; 8: 17-32</i> (in Japanese with English abstract).	RCT	I	364
M17.9	To evaluate the efficacy of boiogitokashuchibushimatsu for gonarthrosis.	boiogitoka shuchibushimatsu (防已黄耆湯加修治附子末)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Therapeutic effect of boiogitokashuchibushimatsu on gonarthrosis: a 10-year prospective randomized controlled trial with loxoprofen sodium*. <i>Pharma Medica 2007; 25: 15-21</i> (in Japanese).	RCT	I	365
M17.9	To evaluate the efficacy and safety of boiogito (防已黄耆湯), a Kampo medicine for gonarthrosis with joint effusion.	boiogito (防已黄耆湯)	Majima T, Inoue M, Kasahara Y, et al. Effect of the Japanese herbal medicine, boiogito, on the osteoarthritis of the knee with joint effusion. <i>Sports Medicine Arthroscopy Rehabilitation Therapy & Technology 2012; 4: 1-6</i> .	RCT	N	366
M35.0	To evaluate the efficacy and safety of bakumondoto therapy for dryness associated with primary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effects of traditional Chinese herbal medicine, mai-men-dong-tang (Japanese name: bakumondo-to) compared with bromhexine, hydrochloride on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group parallel comparative trial study with bromhexine. <i>Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society) 2002; 43: 62-6</i> .	RCT	I	367
M35.0	To evaluate the efficacy and safety of bakumondoto therapy for salivary hyposecretion associated with primary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effect of traditional Chinese herbal medicine, mai-men-don-tang on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group-parallel double-blinded study. <i>Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society) 2004; 45: 66-74</i> .	DB-RCT	N	368
M35.0	To evaluate the efficacy and safety of bakumondoto for treatment of secondary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Goto GH, et al. The Multicenter randomized comparative study of kampo herbal medicine, mai-men-dong-tang (Japanese name Bakumondo-to) compared with bromhexine on salivary secretion in secondary Sjögren's syndrome. <i>Itami to Kampo (Pain and Kampo Medicine) 2004; 14: 10-7</i> (in Japanese with English abstract).	RCT	I	369
M35.0	To evaluate the efficacy and safety of bakumondoto for treatment of dryness associated with secondary Sjögren's syndrome.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Improving effect of Chinese herb medicine mai-men-dong-tang (Japanese name: bakumondo-to) comparative with sicca syndrome in especial salivary patients with secondary Sjögren's syndrome in multicenter, well controlled, long-term comparative study. <i>Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society) 2003; 44: 65-70</i> .	RCT	N	370
M35.0	To evaluate the efficacy for Sjögren's syndrome.	bakumondoto (麦門冬湯), rokumigan (六味丸), hachimijogian (八味地黄丸), hochuekkito (補中益气湯)	Ohno S. The effect of Kampo medicine on salivary secretion in Sjögren's syndrome. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy) 2006; 15: 134-40</i> (in Japanese).	quasi-RCT	I	371

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
M48.02	To evaluate the efficacy of hachimijiogan, goshajinkigan, and shuchibushi powder for relief of residual symptoms after surgical treatment of cervical spinal stenosis.	hachimijiogan (八味地黄丸), goshajinkigan (牛車腎氣丸), goshajinkigan (牛車腎氣丸) + shuchibushimatsu (修治附子末)	Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. <i>Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)</i> 2004; 13: 232-6 (in Japanese).	RCT	I	372
M48.06	Efficacy and safety of hachimijiogan for lumbar spinal stenosis.	hachimijiogan (八味地黄丸)	Hayashi Y, Saito E, Takahashi O. Usefulness of hachimijiogan for lumbar spinal stenosis*. <i>Geriatric Medicine</i> 1994; 32: 585-91 (in Japanese).	quasi-RCT	N	373
M48.06	To evaluate the efficacy of goshajinkigan and shuchibushi powder for relief of chronic low back pain associated with lumbar spinal stenosis.	goshajinkigan (牛車腎氣丸), oshajinkigan (牛車腎氣丸) + shuchibushimatsu (修治附子末)	Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. <i>Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)</i> 2004; 13: 232-6.	RCT	I	374
M54.56	To evaluate the clinical effect of shakuyakuzantō on acute lumbago (so-called strained back).	shakuyakuzantō (芍薬甘草湯)	Tamakawa S, Ogawa H. The effect of shakuyaku-kanzo-to and goshakusan on lumbago. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 1997; 7: 83-5 (in Japanese with English abstract).	RCT	N	375
M54.56	To clinically evaluate the effects of keishibukuryogan and its combination with bushi on nonspecific lumbago in women during menopause.	keishibukuryogan (桂枝茯苓丸), keishibukuryogan (桂枝茯苓丸) + shuchibushimatsu (修治附子末)	Ohta H, Makita K. Lumbago - with emphasis on nonspecific lumbago, which obstetricians and gynecologists think is the most common form in women -. <i>Chiryō (The Journal of Therapy)</i> 1995; 77: 1646-57 (in Japanese).	RCT	N	376
M54.56	To evaluate the efficacy and safety of goshajinkigan in comparison with that of tiaramide hydrochloride for lumbago in the elderly.	goshajinkigan (牛車腎氣丸)	Nakamura T, Souza ACA, Ouchi Y, et al. Effects of goshajinkigan on lumbago*. <i>Dai 4 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu</i> 1989; 4: 24-9 (in Japanese).	RCT-envelope	N	377
M62.59	To evaluate the efficacy of jumentaihoto combined with hachimijiogan in patients with disuse syndrome.	jumentaihoto (十全大補湯), hachimijiogan (八味地黄丸)	Wang XD, Yoshida K, Honda K, et al. Study of the immunoregulatory activity of the combination therapy with jumentaihoto and hachimijiogan in patients with disuse syndrome*. <i>Kampo Igaku (Kampo Medicine)</i> 2006; 30: 65-7 (in Japanese).	RCT-envelope	I	378
M81.1	Combined effect of keishibukuryogan and vitamin D3 on osteopenia in women during menopause.	keishibukuryogan (桂枝茯苓丸)	Ohta H, Nemoto K. Effect of concurrent administration of active vitamin D ₃ and TSUMURA Keishibukuryogan on osteopenia following oophorectomy*. <i>Kampo Igaku (Kampo Medicine)</i> 1989; 13: 173-9 (in Japanese).	RCT	N	379
M81.1	Combined effect of keishibukuryogan or tokishakuyakusan and vitamin D3 on osteopenia in women during menopause.	keishibukuryogan (桂枝茯苓丸), tokishakuyakusan (当帰芍薬散)	Ohta H, Nemoto K. Preventive effect of 1 α -hydroxyvitamin D ₃ plus Kampo medicine combination therapy on osteopenia following oophorectomy - comparison between keishibukuryogan and tokishakuyakusan -. <i>Sanfujinka Kampo Kenkyū no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 1990; 7: 65-70 (in Japanese).	RCT	N	380
M81.9	Positive effects on menopause index, bone mass, and anemia in postmenopausal women with osteoporosis.	kamikihi (加味帰脾湯)	Kanai S. The effect of kami-kihi-to on the maintenance of bone mass in patients with osteoporosis. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1998; 49: 59-66 (in Japanese with English abstract).	quasi-RCT	N	381

14. Genitourinary Tract Disorders (including Climacteric Disorders) (37 abstracts, 43 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
N02.8	Efficacy and safety of saireito in childhood IgA nephropathy with focal/minimal mesangial proliferation.	saireito (柴苓湯)	Yoshikawa N, Ito H, Sakai T, et al. A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. <i>Nihon Jinzo Gakkaishi (The Japanese Journal of Nephrology)</i> 1997; 39: 503-6 (in Japanese with English abstract).	RCT-envelope	C	382

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
N02.8	Efficacy and safety of Kampo medicines for IgA nephropathy in adults.	saireito (柴苓湯)	Saruta T, Konishi K. Efficacy of Kampo medicines for renal diseases - with emphasis on saireito -*. <i>21 Seiki no Iryo to Kampo (Medical Care and Kampo in the 21st Century)</i> 1994; 157-65 (in Japanese).	RCT-envelope	N	383
N04.9	Efficacy of initial steroid therapy with saireito for preventing relapses in childhood steroid-responsive nephrotic syndrome.	saireito (柴苓湯)	Yoshikawa N, Ito H, Takekoshi Y, et al. Standard versus long-term prednisolone with sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: A prospective controlled study. <i>Nihon Jinzo Gakkaishi (The Japanese Journal of Nephrology)</i> 1998; 40: 587-90 (in Japanese with English abstract).	RCT-envelope	C&I	384
N20.9	Efficacy for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.	choreitogoshimotsuto (猪苓湯合四物湯) + shakuyakukanzoto (芍薬甘草湯)	Kinoshita H, Kanaya H, Yamamoto S, et al. Effects of Chinese herbal medicine in promoting the spontaneous discharge of upper urinary tract stones after ESWL. <i>Nishinohon Hinyokika (The Nishinohon Journal of Urology)</i> 1993; 55: 61-6 (in Japanese with English abstract).	RCT	N	385
N20.9	To evaluate the efficacy of low-dose tamsulosin and choreito for stone expulsion after extracorporeal shock wave lithotripsy (ESWL) in patients with ureteral stones.	choreito (猪苓湯)	Kobayashi M, Naya Y, Kino M, et al. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: Efficacy in Japanese male patients with ureteral stone. <i>International Journal of Urology</i> 2008; 15: 495-8.	RCT	I	386
N32.8	To evaluate the efficacy and safety of goshajinkigan and propiverine hydrochloride for overactive bladder.	goshajinkigan (牛車腎気丸)	Nishizawa Y., Nishizawa Y, Yoshioka H., et al. Efficacy and safety of Chinese traditional medicine, niu-che-shwn-qi-wan (Japanese name: goshajinki-gan) versus propiverine hydrochloride on health-related quality of life in patients with overactive bladder in prospective randomized comparative study. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 2007; 16: 131-42 (in Japanese).	RCT	I	387
N39.0	Efficacy of shosaikoto for improving immunity in the elderly.	shosaikoto (小柴胡湯)	Toba K. Role in host defense mechanisms and effect on prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation. <i>Taisha (Metabolism and Disease)</i> 1992; 29 suppl: 350-4 (in Japanese).	RCT-envelope	N	388
			Toba K. Role in host defense mechanisms and effect on the prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation'. <i>Dai 8 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu (Proceedings of the 8th Meeting of the Tokyo Society for Internal Kampo Medicine)</i> 1993; 8: 31-42 (in Japanese).			
N39.9	Efficacy of choreito and choreitogoshimotsuto for relieving nonspecific lower urinary tract complaints.	choreito (猪苓湯), choreitogoshimotsuto (猪苓湯合四物湯)	Ohkawa T, Ebisuno S, Watanabe T. Urological diseases and Kampo medicine*. <i>Dai 23 Kai Nihon Igakkai Sokai Sateraito Shinpojiumu Nihon Toyo Igakkai Rinsho Kampo Kenkyukai Koen Naiyo Shu (Proceedings of the Meeting for Clinical Kampo Medicine of the Japan Society for Oriental Medicine, the Satellite Symposium of the 23rd General Assembly of the Japan Medical Congress)</i> 1992: 22-39 (in Japanese).	RCT-envelope	N	389
N39.9	Efficacy of choreito and hachimijiogan for relieving urinary frequency, voiding pain, and incomplete emptying in patients without organic urinary tract disease.	hachimijiogan (八味地黄丸), choreito (猪苓湯)	Fuse H, Sakamoto M, Iwasaki M, et al. Effect of chorei-to and hachimi-jio-gan on unidentified complaints on urinary tract. <i>Hinyoki Geka (Japanese Journal of Urological Surgery)</i> 1995; 8: 603-9 (in Japanese).	RCT-envelope	N	390
N39.9	To evaluate the effect of single-dose administration of maobushisaishinto on urine flow.	maobushisaishinto (麻黄附子細辛湯)	Aoki Y, Ueda K, Tsutani K, et al. The influence of formula ma-huang-fu-zi-xi-xin-tang (mao-bushi-saishin-to; Mbst) on the results of urodynamic studies. <i>Journal of Traditional Medicine</i> 2001; 18: 203-9.	RCT-cross over	I	391
N40	Efficacy and safety for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.	Hachimijiogan (八味地黄丸), choreito (猪苓湯)	Sakamoto Y, Iwasaki M, Kazama T, et al. Study of effects hachimi-jio-gan and chorei-to on prostatic hypertrophy. <i>Dai 13 Kai Hinyokika Kampo Kenkyukai Koen Shu (Proceedings of the 13th Meeting of the Urological Society for Kampo Medicine)</i> 1996: 7-14 (in Japanese with English abstract).	RCT-envelope	N	392

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
N41.1	Efficacy and safety of goshajinkigan in the treatment of chronic prostatitis.	goshajinkigan (牛車腎気丸)	Horiba M, Kato S, Tanaka T, et al. Clinical validity of goshajinkigan in the treatment of chronic prostatitis - open comparative study with goshajinkigan vs ciprofloxacin -. <i>Gendai Toyo Igaku (The Journal of Traditional Sino-Japanese Medicine)</i> 1994; 15: 37-44 (in Japanese).	RCT-envelope	N	393
N41.1	To evaluate the efficacy and safety of goshajinkigan for relieving lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH) and concomitant overactive bladder (OAB).	goshajinkigan (牛車腎気丸)	Ishizuka O, Yamanishi T, Gotoh M, et al. LUTS: new evidence - clinical efficacy of Kampo formulations focusing on goshajinkigan -*. <i>Urology View</i> 2009; 7: 81-4.	RCT-cross over	I	394
N46	Positive effect on sperm profiles of male infertility patients.	saikokaryukotsuboreito (柴胡加竜骨牡蛎湯), hochuekkito (補中益気湯)	Hiramatsu M, Maehara I, Takahashi M, et al. Treatment experience with saikokaryukotsuboreito and hochuekkito in male infertility patients*. <i>Kampo Igaku (Kampo Medicine)</i> 1993; 17: 246-8 (in Japanese).	RCT	N	395
N46	Efficacy and safety of hochuekkito in the treatment of male infertility.	hochuekkito (補中益気湯)	Kazama T. Male infertility*. <i>Current Therapy</i> 1988; 6: 1683-6 (in Japanese).	RCT-envelope	N	396
N50.8	To evaluate the efficacy of androgen replacement therapy (ART) combined with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.	saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Sugimoto K, Shigehara K, Izumi K, et al. Effect of combination of saiko-ka-ryukotsu-borei-to with androgen replacement therapy for LOH syndrome. <i>Nihon Sei Kino Gakkai Zasshi (Japanese Journal of Sexual Medicine)</i> 2009; 24: 349-53 (in Japanese).	RCT	I	397
N64.9	Efficacy of kamishoyosan in the treatment of mastitis.	kamishoyosan (加味逍遙散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Kampo treatment for mastitis - kamishoyosan -*. <i>Kampo Igaku (Kampo Medicine)</i> 1994; 18: 238-41 (in Japanese).	RCT-envelope	N	398
N64.9	Efficacy of shigyakusan in the treatment of mastitis.	shigyakusan (四逆散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Kampo therapy for mastitis - shigyakusan -*. <i>Kampo Igaku (Kampo Medicine)</i> 1990; 14: 132-6 (in Japanese).	RCT-envelope	N	399
N64.9	Efficacy of tsudosan in the treatment of mastitis.	tsudosan (通導散), keishibukuryogan (桂枝茯苓丸)	Inoue M. Clinical study of effects of tsu-do-san on mastitis. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1993; 43: 517-21 (in Japanese).	RCT-envelope	N	400
N64.9	Efficacy of tokakujokito in the treatment of mastitis.	tokakujokito (桃核承気湯), keishibukuryogan (桂枝茯苓丸)	Inoue M. Clinical studies on effects of tokakujoki-to for fibro-cystic disease of the breast. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1992; 42: 415-8 (in Japanese).	RCT-envelope	N	401
N81.4	To evaluate the hachimijiogan-induced improvement in postoperative discomfort associated with surgery for uterine prolapse and quality of life (QOL).	hachimijiogan (八味地黄丸)	Oribe K, Nishida Y. Efficacy of hachimijiogan for discomfort after surgery for uterine prolapse. <i>Gekkan Kampo Ryoho (Monthly Journal of Kampo Medicine and Herbs)</i> 2006; 10: 282-8 (in Japanese).	RCT	N	402
N93.9	To evaluate the efficacy and safety of kyukikyogaito for menometrorrhagia.	kyukikyogaito (キユウ帰膠艾湯)	Iwabuchi S. Effect of kyuki-kyogai-to on stopping dysfunctional uterine bleeding - comparison with occidental hemostatic drugs -. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 2000; 50: 883-903 (in Japanese with English abstract).	quasi-RCT	I	403
N94.6	Double-blind study on pain-relieving effect of tokishakuyakusan on dysmenorrhea.	tokishakuyakusan (当帰芍薬散)	Kotani N, Oyama T, Sakai I, et al. Analgesic effect of a herbal medicine for treatment of primary dysmenorrhea - a double-blind study. <i>The American Journal of Chinese Medicine</i> 1997; 25: 205-12.	DB-RCT	C	404
N95.1	To compare the clinical effects of keishibukuryogan monotherapy with combined therapy (keishibukuryogan plus autonomic modulator).	keishibukuryogan (桂枝茯苓丸)	Tanaka E, Saito H, Hiroi M. Kampo treatment for nonspecific complaints in climacteric women - comparison of clinical efficacy of Kampo medicine alone versus Kampo medicine combined with tofisopam -*. <i>Kampo Shinryo</i> 1997; 16: 22-4 (in Japanese).	RCT	N	405

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.	
N95.1	Clinical effect on climacteric disorders.	tokishakuyakusan (当帰芍薬散), kojinmatsu (紅参末)	Samukawa K, Ogita S. Climacteric disorders and medicinal ginseng*. <i>Chiryogaku (Biomedicine & Therapeutics)</i> 1994; 28: 57-62 (in Japanese).	RCT-envelope	N	406	
N95.1	To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.	Kampo therapy (keishibukuryogan (桂枝茯苓丸), kamishoyosan (加味逍遥散), goshajinkigan (牛車腎気丸), etc.)	Ota H. Positioning of Kampo therapy and hormone replacement therapy in treatment of climacteric disorders*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2001; 18: 21-9 (in Japanese).	RCT	I	407	
N95.1	To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non- <i>sho</i> -based (非随証) Kampo medicines for gynecological disease.	kamishoyosan (加味逍遥散), tokishakuyakusan (当帰芍薬散), keishibukuryogan (桂枝茯苓丸), juzentaihoto (十全大補湯)	Takamatsu K, Musha C, Okano H, et al. Study of usefulness of Kampo therapy for climacteric disorders*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2002; 19: 111-6 (in Japanese).	quasi-RCT	I	408	
		tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遥散), keishibukuryogan (桂枝茯苓丸)	Takamatsu K. HRT and Kampo medicine*. <i>Nippon Konenki Igakkai Zasshi (The Journal of the Japan Menopause Society)</i> 2004; 12:155-7 (in Japanese).				N
			Takamatsu K, Makita K, Tanabe K, et al. HRT and Kampo medicine*. <i>Rinsho Kensa (Journal of Medical Technology)</i> 2004; 48: 877-84 (in Japanese).				N
			Takamatsu K, Tanabe K. Efficacy of Kampo medicine against climacteric disorders*. <i>Sanfujinka Chiryu (Obstetrical and Gynecological Therapy)</i> 2004; 89: 408-15 (in Japanese).				N
			Takamatsu K. Study of the usefulness of Kampo therapy for climacteric disorders – a randomized trial of three major Kampo medicines for treatment of gynecological disease*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2006; 23: 35-42 (in Japanese).				I
N95.1	To investigate the equivalence between non-extracted keishibukuryogan and keishibukuryogan extract.	keishibukuryogan (桂枝茯苓丸)	Ogita Y, Fujimoto S, Ushiroyama T, et al. Efficacy of formulation TK-061 for various climacteric symptoms – comparison with Teikoku Keishibukuryogan Extract Granules*. <i>Rinsho Fujinka Sanka (Clinical Gynecology and Obstetrics)</i> 2002; 56: 799-810 (in Japanese).	RCT	I	409	
			Ogita Y, Fujimoto S, Ushiroyama T, et al. Keishibukuryogan formulation TK-061 prepared with crude drug – verification of efficacy for various climacteric symptoms*. <i>Sanka to Fujinka (Obstetrics and Gynecology)</i> 2002; 69: 953-62 (in Japanese).				I
N95.1	To evaluate the efficacy of unkeito for climacteric disorders with depressive symptoms.	unkeito (温経湯), tokishakuyakusan (当帰芍薬散)	Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. <i>Clinical Neuropharmacology</i> 2004; 27: 157-62.	RCT-cross over	C	410	
N95.1	To evaluate effects of hormone replacement therapy (HRT) alone and in combination with kamishoyosan on climacteric disorders.	kamishoyosan (加味逍遥散)	Higuchi T, Tarakida A, Abe K, et al. Comparing the effects of hormone replacement therapy and kamishoyosan treatment on climacteric disorders*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2009; 26: 18-23.	RCT-envelope	I	411	
			Higuchi T, Iino K, Tarakida A, et al. A comparing the effects of kamishoyosan or HRT on climacteric disorders in postmenopausal women: results from a randomized controlled trial. <i>Nihon Josei Igaku Gakkai Zasshi (The Journal of Japan Society for Menopause and Women's Health)</i> 2012; 20: 305-12 (in Japanese).				N

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
N95.1	To evaluate the clinical effects of keishibukuryogan (桂枝茯苓丸) for hot flashes in menopausal American women.	keishibukuryogan (桂枝茯苓丸)	Plotnikoff GA, Watanabe K, Torkelson C, et al. The TU-025 Keishibukuryogan clinical trial for hot flash management in postmenopausal women: result and lessons for future research. <i>Menopause</i> 2011; 18: 886-92.	RCT	N	412
N95.1	To evaluate the effects of keishibukuryogan (桂枝茯苓丸) and kamishoyosan (加味逍遙散) on levels of circulating cytokines in patients with hot flashes.	keishibukuryogan (桂枝茯苓丸), kamishoyosan (加味逍遙散)	Yasui T, Matsui S, Yamamoto S, et al. Effects of Japanese traditional medicines on circulating cytokine levels in women with hot flashes. <i>Menopause</i> 2011; 18: 85-92	quasi-RCT	N	413
N95.1	To verify the efficacy of nyoshinsan (女神散) for female climacteric disorder.	nyoshinsan (女神散), tokishakuyakusan (当帰芍薬散), kamishoyosan (加味逍遙散), keishibukuryogan (桂枝茯苓丸)	Takamatsu K, Fujii E, Mizuno H, et al. An investigation of the usefulness of nyoshinsan for climacteric disorder. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2003; 20: 95-100 (in Japanese).	quasi-RCT	N	414
N95.8	To compare the efficacy of keishibukuryogan and hormone replacement therapy (HRT) for relief of hot flashes and chills.	keishibukuryogan (桂枝茯苓丸)	Ushiroyama T, Ikeda A, Sakuma K, et al. Comparing the effects of estrogen and an herbal medicine on peripheral blood flow in post-menopausal women with hot flashes: hormone replacement therapy and gui-zhi-fu-ling-wan, a Kampo medicine. <i>American Journal of Chinese Medicine</i> 2005; 33: 259-67.	RCT	C	415
N95.8	To evaluate the usefulness of Kampo medicine for treatment of depressive patients refractory to hormone replacement therapy (HRT).	unkeito (温経湯), tokishakuyakusan (当帰芍薬散)	Matsuo A, Koike K, Hoshina Y, et al. Study of the efficacy of unkeito for depressive and anxiety symptoms during menopause that are refractory to hormone replacement therapy. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2005; 22: 70-4 (in Japanese).	RCT-cross over	I	416
			Koike K. A slight advantage of Kampo treatment for gynecological disease 4: Menopausal depressed mood and the herbal medicine unkei-to. <i>Sanfujinka Chiryō (Obstetrical and Gynecological Therapy)</i> 2006; 92: 784-6 (in Japanese).		N	
N95.8	To compare the effects of unkeito and vitamin E on peripheral blood flow.	unkeito (温経湯)	Ushiroyama T, Sakuma K, Nosaka S. Comparison of effects of vitamin E and wen-jing-tang (unkei-to), an herbal medicine, on peripheral blood flow in post-menopausal women with chilly sensation in the lower extremities: a randomized prospective study. <i>The American Journal of Chinese Medicine</i> 2006; 34: 969-79.	RCT	C	417
N97.0	To compare the effects of clomiphene monotherapy with tokishakuyakusan and clomiphene combination therapy infrequent menses, anovular menstrual cycle, and amenorrhea.	tokishakuyakusan (当帰芍薬散)	Yasui T, Irahara M, Aono T. Studies on treatment with the combination clomiphene citrate and toki-shakuyaku-san. <i>Nippon Funin Gakkai Zasshi (Japanese Journal of Fertility and Sterility)</i> 1995; 40: 83-91 (in Japanese).	RCT-envelope	N	418

15. Ante/Post-partum Diseases (11 abstracts, 13 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
O12.0	To evaluate the effectiveness of saireito (柴苓湯) combined with either sojutsu (蒼朮, <i>Atractylodes Lancea</i> Rhizome) or byakujutsu (白朮, <i>Atractylodes Rhizome</i>) as constituent crude drugs for lower limb edema and functional dyspepsia-like gastrointestinal symptoms.	saireito (柴苓湯)	Takushima Y, Michigami F. Clinical study of saireito on gestational edema and upper gastrointestinal symptoms. <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2010; 64: 709-15 (in Japanese).	quasi-RCT	I	419

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
O20.0	To evaluate the efficacy of kyukikyogaito as a therapeutic drug for imminent abortion in patients with uterine hemorrhage.	kyukikyogaito (キユウ婦膠艾湯)	Ushiroyama T, Araki R, Sakuma K, et al. Efficacy of the kampo medicine xiong-gui-jiao-ai-tang, a traditional herbal medicine, in the treatment of threatened abortion in early pregnancy. <i>American Journal of Chinese Medicine</i> 2006; 34: 731-40.	RCT	C	420
			Ushiroyama T, Sakuma K, Nosaka S, et al. Clinical efficacy of kyukikyogaito for imminent abortion with uterine hemorrhage*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2006; 23: 100-3 (in Japanese).		I	
O47.0	Usefulness of tokishakuyakusan combined with ritodrine hydrochloride in the management of threatened premature delivery.	tokishakuyakusan (当帰芍薬散)	Mizuno M, Sato K, Mori T, et al. Clinical evaluation of TSUMURA Tokishakuyakusan and ritodrine hydrochloride combination therapy in the management of threatened premature delivery*. <i>Sanka to Fujinka (Obstetrics and Gynecology)</i> 1992; 59: 469-80 (in Japanese).	RCT-envelope	N	421
O90.9	To evaluate the usefulness of kyukichoketsuin for control of puerperium.	kyukichoketsuin (キユウ婦調血飲)	Takushima Y, Inoguchi H, Study on usefulness of kyukichoketsuin for control of puerperium – comparison with methylethylergometrine maleate (1st report) -*. <i>Progress in Medicine</i> 2001; 21: 1535-42 (in Japanese).	quasi-RCT	I	422
O90.9	To evaluate the efficacy and safety of kyukichoketsuin for puerperal psychosomatic disorder.	kyukichoketsuin (キユウ婦調血飲)	Sakuma K, Ushiroyama T, Akise D, et al. Clinical efficacy of kyukichoketsuin for regulation of puerperal psychosomatic functions. <i>Sanfujinka no Shinpo (Advances in Obstetrics and Gynecology)</i> 2002; 54: 80-6 (in Japanese with English abstract).	RCT-envelope	I	423
			Ushiroyama T, Sakuma K, Souen H, et al. Therapeutic effects of kyuki-chouketsu-in in restoring postpartum physical condition. <i>American Journal of Chinese Medicine</i> 2003; 31: 437-44.		C	
O90.9	To evaluate the clinical usefulness of kyukichoketsuin for “postpartum restoration”.	kyukichoketsuin (キユウ婦調血飲)	Wada H, Wada K, Motoyama K. Usefulness in postpartum control by kyukichoketsuin. <i>Sanfujinka no Sekai (World of Obstetrics and Gynecology)</i> 2003; 55: 1057-61.	RCT	I	424
O90.9	To evaluate the clinical usefulness of kyukichoketsuin during puerperium.	kyukichoketsuin (キユウ婦調血飲)	Narimatsu A., Ito A., Usefulness of kyukichoketsuin during puerperium. <i>Rinsho Iyaku (Journal of Clinical Therapeutics & Medicine)</i> 2001; 17: 1329-35 (in Japanese with English abstract).	RCT	I	425
O92.3	To evaluate the postpartum lactation-promoting effect and safety of kyukichoketsuin.	kyukichoketsuin (キユウ婦調血飲)	Ushiroyama T, Sakuma K, Souen H, et al. xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. <i>The American Journal of Chinese Medicine</i> 2007; 35: 195-202.	RCT-envelope	C	426
O92.5	To evaluate a Kampo medicine effective for relieving the feeling of lactation deficiency.	kakkonto (葛根湯), Juzentaihoto (十全大補湯), kyukichoketsuin (キユウ婦調血飲), and combination of these Kampo formulations	Kawakami S, Nishimura J, Umeki M, et al. Kampo therapy for feeling of lactation deficiency*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2003; 20: 140-3.	RCT	I	427
O99.0	To evaluate whether rikkunshito combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.	rikkunshito (六君子湯)	Fushiki H, Saeki A, Shiozaki A. Attempt to reduce adverse reactions associated with oral iron preparation for anemia in pregnancy by combination with Rikkunshito (TJ-43)*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2003; 20: 138-9 (in Japanese).	RCT	I	428
O99.3	To confirm the efficacy of kyukichoketsuin for the “maternity blues.”	kyukichoketsuin (キユウ婦調血飲)	Ushiroyama T, Sakuma K, Ueki M. Efficacy of the Kampo medicine xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, in the treatment of maternity blues syndrome in the postpartum period. <i>The American Journal of Chinese Medicine</i> 2005; 33: 117-26.	RCT-envelope	C	429

18. Symptoms and Signs (27 abstracts, 38 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
R05	To evaluate the efficacy of bakumondoto for persistent cough after infection in the elderly.	bakumondoto (麦門冬湯)	Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Beneficial effect of Chinese traditional herbal medicine, mai-men-don-tang (Japanese name: bakumondo-to) on acute pain in patients with acute internal medical disease: antitussive effect on elderly patients with post infectious persistent coughs, prospective, multicenter, randomized comparative trial between mai-men-dong-tang and forminoben hydrochloride. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 2003; 13: 12-21 (in Japanese with English abstract).	RCT	I	430
R05	To evaluate the efficacy of bakumondoto for relieving persistent cough after lung cancer surgery.	bakumondoto (麦門冬湯)	Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. <i>Kampo to Meneki Arerugi (Kampo and immuno-allergy)</i> 2008; 22: 43-55 (in Japanese with English abstract).	RCT-envelope	I	431
			Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form (SF-36) v2*. <i>Progress in Medicine</i> 2010; 30: 100-1 (in Japanese).		N	
R05.0	To evaluate the combined effects of bakumondoto (麦門冬湯) and a bronchodilator for prolonged cough following common cold.	bakumondoto (麦門冬湯)	Irifune K, Hamada H, Ito R, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients. <i>Phytomedicine</i> 2011; 18: 630-3.	RCT-envelope	C	432
R11	Effects of a Kampo suppository preparation on vomiting in children.	goreisan (五苓散)	Nishi K, Takata K, Asano S, et al. Effects of goreisan suppository on vomiting in children - comparison with domperidone suppository -. <i>Nihon Byoin Yakuzai Shikai Zasshi (Journal of Japanese Society of Hospital Pharmacists)</i> 1998; 34: 1173-6 (in Japanese).	quasi-RCT	N	433
R11	To evaluate the efficacy and safety of goreisan for vomiting in young children.	goreisan (五苓散), hochuekkito (補中益氣湯)	Yoshida M, Mizuno T, Mizoguchi F, et al. Efficacy of goreisan suppositories for vomiting in young children (2nd report) – a double-blind study of the hochuekkito suppository-. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1991; 7: 506-7 (in Japanese).	DB-RCT	N	434
			Yoshida M. Efficacy of goreisan suppository for vomiting in young children*. <i>Toyoigaku (Japanese Journal of Oriental Medicine)</i> 2000; 28: 36-8 (in Japanese).		I	
			Yoshida M. Efficacy of goreisan suppository*. <i>Nihon Syoni Toyo Igakkaishi (The Japan Pediatric Society for Oriental Medicine)</i> 2003; 19: 13-7 (in Japanese).		I	
R11.0	To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer	rikkunshito (六君子湯)	Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. <i>Kampo Igaku (Science of Kampo Medicine)</i> 2010; 34: 12-3 (in Japanese).	RCT	N	435
			Seike J, Sawada T, Kawakita N, et al. A new candidate supporting drug, rikkunshito, for the QOL in advanced esophageal cancer patients with chemotherapy using docetaxel/5-Fu/CDDP. <i>International Journal of Surgical Oncology</i> 2011; 2011: 1-7. DOI: 10.1155/2011/715623.		N	
R11.0	To verify the effects of rikkunshito (六君子湯) on cisplatin-induced anorexia in gastric cancer patients.	rikkunshito (六君子湯)	Ohno T, Yanai M, Ando H, et al. Rikkunshito, a traditional Japanese medicine, suppresses cisplatin-induced anorexia in humans. <i>Clinical and Experimental Gastroenterology</i> 2011; 4: 291-6.	RCT-cross over	N	436
R22.4	Efficacy and safety of saireito for posttraumatic or postoperative swelling in the lower extremities.	saireito (柴苓湯)	Igarashi I. Clinical study of traditional Chinese medicine therapy for post-operative or post-traumatic swelling in lower extremities. <i>Seikeigeka (Orthopedic Surgery)</i> 1993; 44: 127-31 (in Japanese).	RCT	N	437

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
R25.2	Efficacy and safety of shakuyakukanzoto for preventing muscle cramps in diabetic patients.	shakuyakukanzoto (芍薬甘草湯)	Yoshida M, Kitaoka H, Masui Y, et al. Effects of shakuyaku-kanzo-to on muscle cramp in diabetics. <i>Shinkei Chiryogaku (Neurological Therapeutics)</i> 1995; 12: 529-34 (in Japanese).	RCT-envelope	N	438
R25.2	To evaluate the efficacy and safety of shakuyakukanzoto for relief of muscle cramp.	shakuyakukanzoto (芍薬甘草湯)	Kumada T, Kumada H, Yoshiba M, et al. Effects of Shakuyaku-kanzo-to (Tsumura TJ-68) on muscle cramps accompanying cirrhosis in a placebo-controlled double-blinded parallel study. <i>Rinsho Iyaku (Journal of Clinical Therapeutics and Medicine)</i> 1999; 15: 499-523 (in Japanese with English abstract).	DB-RCT	I	439
		shakuyakukanzoto (芍薬甘草湯)	Kumada T, Kiriyaama I, Sone Y, et al. EBM-based Kampo therapy for gastrointestinal diseases 3. Efficacy of shakuyakukanzoto for “muscle cramps in the calves” associated with hepatic cirrhosis*. <i>Nihon Toyo Igaku Zasshi (Kampo Medicine)</i> 2003; 54: 536-8 (in Japanese).		N	
R25.2	To evaluate the efficacy and safety of shakuyakukanzoto for muscle cramps in the calves.	goshajinkigan (牛車腎気丸), shakuyakukanzoto (芍薬甘草湯)	Nishizawa Y, Nishizawa Y, Amemori Y, et al. A randomized paralleled group comparison in multicenter cooperation: analgesic effect and safety with gosha-jinki-gan and shakuyaku-kanzo-to in the treatment of painful muscle cramps in patients with cirrhosis. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 2000; 10: 13-8 (in Japanese with English abstract).	RCT	I	440
R31	Efficacy and safety of kyukikyogaito and saireito for essential microscopic hematuria.	kyukikyogaito (キユウ帰膠艾湯), saireito (柴苓湯)	Yoshikawa H, Ikeuchi T, Kai Y. Clinical effects of kyuki-kyogai-to and Sairei-to for essential microscopic hematuria. <i>Kampo to Saishin-chiryo (Kampo & the Newest Therapy)</i> 1997; 6: 55-8 (in Japanese).	RCT	N	441
R31	Clinical efficacy of saireito for essential hematuria.	saireito (柴苓湯)	Suzuki Y, Machida T, Onodera S, et al. Clinical effects of sairei-to for essential hematuria. <i>Hinyoki Geka (Japanese Journal of Urological Surgery)</i> 1994; 7: 325-7 (in Japanese).	RCT	I	442
R35.0	To evaluate the effectiveness of goshajinkigan (牛車腎気丸) for nocturnal polyuria with elevated B-type natriuretic peptide.	goshajinkigan (牛車腎気丸)	Shimizu Y, Yoshimura K, Soda T, et al. The effects of gosha-jinki-gan, a blended herbal medicine, and furosemide for nocturnal polyuria with elevated B-type natriuretic peptide: a crossover trial. <i>Neurourology and Urodynamics</i> 2010; 29: 833-4. Yoshimura K, Shimizu Y, Masui K, et al. Furosemide versus gosha-jinki-gan, a blended herbal medicine, for nocturnal polyuria: a randomized crossover trial. <i>Lower Urinary Tract Symptoms</i> 2012; 4: 77-81.	RCT-cross over	C N	443
R39.8	Effects of hachimijiogan and seishinrenshiin on anti-heat shock protein (HSP) 60 antibodies.	hachimijiogan (八味地黄丸), seishinrenshiin (清心レン子飲)	Sekiguchi Y, Miyai K, Noguchi K, et al. Study of effects of anti-heat shock protein 60 antibody by ba wei di huang wan and qing xin lian zi yin (II). <i>Wakan Iyagakugaku Zasshi (Journal of Traditional Medicines)</i> 1998; 15: 326-7 (in Japanese).	RCT-cross over	N	444
R51	Efficacy and safety of chotosan for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension.	chotosan (釣藤散)	Matsushita S, Ueda S, Ouchi Y, et al. Usefulness of Chotosan (TJ-47) for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension*. <i>Geriatric Medicine</i> 1995; 33: 1333-41 (in Japanese).	RCT-envelope	I	445
R51	Efficacy and safety of chotosan for relieving headache in patients with spinal cord injury.	chotosan (釣藤散)	Nishizawa Y, Nishizawa Y, Fushiki S. Analgesic effects on headache in patients with spinal cord injury. <i>Nippon Zutsu Gakkaiishi (Japanese Journal of Headache)</i> 1997; 25: 23-6.	DB-RCT	I	446

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
R51	To evaluate the efficacy and safety of goshuyuto for relieving chronic headache using keishininjinto as a control.	goshuyuto (呉茱萸湯), keishininjinto (桂枝人參湯)	Seki H, Tateyama M, Sahara M, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization using the sealed-envelope method)*. <i>Shinryo to Shinyaku (Medical Consultation & New Remedies)</i> 1991; 28: 573-6 (in Japanese).	RCT-envelope	I	447
			Seki H, Okita N, Takase S, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization carried out using the sealed-envelope method)*. <i>Pharma Medica</i> 1993; 11: 288-91 (in Japanese).			
R51	To evaluate the efficacy of goshuyuto for relief of chronic headache and to evaluate the associated adverse drug reactions.	goshuyuto (呉茱萸湯)	Odaguchi H, Hanawa Y. Complementary alternative medicine in headache treatment*. <i>Igaku no Ayumi (Journal of Clinical and Experimental Medicine)</i> 2005; 215: 1137-40 (in Japanese).	DB-RCT	C	448
			Odaguchi H, Wakasugi A, Ito H, et al. The efficacy of goshuyuto, a typical Kampo (Japanese herbal medicine) formula, in preventing episodes of headache. <i>Current Medical Research and Opinion</i> 2006; 22: 1587-97.			
R52.9	To evaluate the efficacy and safety of shakuyakukanzoto and L-glutamine for paclitaxel-induced myalgia and arthralgia.	shakuyakukanzoto (芍薬甘草湯)	Hasegawa K, Mizutani Y, Kuramoto H, et al. The Effect of L-glutamine and shakuyaku-kanzo-to for paclitaxel-induced myalgia/arthralgia. <i>Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)</i> 2002; 29: 569-74 (in Japanese with English abstract).	RCT-cross over	I	449
R53	To evaluate the efficacy of hochuekkito for the elderly with weakness.	hochuekkito (補中益氣湯)	Satoh N, Sakai S, Kogure T, et al. A randomized double blind placebo-controlled clinical trial of hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness N of one and responder restricted design. <i>Phytomedicine</i> 2005; 12: 549-54.	DB-RCT	C	450
R53.0	To evaluate the effectiveness of hochuekkito (補中益氣湯) for cancer-related fatigue.	hochuekkito (補中益氣湯)	Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: A pilot randomized clinical trial. <i>Integrative Cancer therapies</i> 2010; 9: 331-8.	RCT	N	451
R53.0	To evaluate the effect of hochuekkito (補中益氣湯) on lymphocytes.	hochuekkito (補中益氣湯)	Ohno S, Suzuki T, Asaoka T, et al. Effects of Oriental medicine on lymphoid cells. <i>Kampo to Meneki-Allergy (Kampo and Immunoallergy)</i> 1995; 9: 78-86 (in Japanese with English abstract).	quasi-RCT	C	452
R60.0	Efficacy of goreisan and saireito for mild edema of the dorsum of the foot in the elderly.	saireito (柴苓湯)	Ishioka T. Comparison of the efficacy of goreisan and saireito for mild edema of the dorsum of the foot in elderly subjects stratified by physical strength*. <i>Kampo no Rinsho (Journal of Kampo Medicine)</i> 1997; 44: 1091-5 (in Japanese).	RCT-cross over	N	453
R60.9	To investigate the efficacy and safety of saireito on postoperative edema and inflammation after total hip arthroplasty (THA).	saireito (柴苓湯)	Kishida Y, Miki H, Nishii T, et al. Therapeutic effects of Saireito (TJ-114), a traditional Japanese herbal medicine, on postoperative edema and inflammation after total hip arthroplasty. <i>Phytomedicine</i> 2007; 14: 581-6.	RCT	C	454
R68.8	To evaluate the efficacy of preoperative administration of hochuekkito (補中益氣湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.	hochuekkito (補中益氣湯)	Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). <i>Nihon Toyo Igaku Zasshi (Kampo Medicine)</i> 2010; 61: 78-83 (in Japanese with English abstract).	RCT	I	455

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
R73.0	To evaluate the efficacy and safety of bofutsushosan in obese Japanese women with impaired glucose tolerance.	bofutsushosan (防風通聖散)	Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san, an oriental herbal medicine, in obese Japanese women with impaired glucose tolerance. <i>Clinical and Experimental Pharmacology and Physiology</i> 2004; 31: 614-9. Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san in obese Japanese women with IGT. <i>Rinsho Kampo Yakuri Kenkyukai Kaishi (Journal of the Society for Clinical Kampo Pharmacology)</i> , 2004; 100th Memorial Issue: 19-22. Hioki C. Efficacy of bofutsushosan in obese women with IGT. <i>Pharma Medica</i> 2007; 25: 43-8. Hioki C, Arai M. Bofutsushosan use for obesity with IGT: search for scientific basis and development of effective therapy with Kampo medicine. <i>Journal of Traditional Medicines</i> 2007; 24: 115-27.	DB-RCT	C I I N	456

19. Injury, Poisoning, and Postoperative Pain (5 abstracts, 5 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
S93.4	To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.	jidabokuippo (治打撲一方)	Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. <i>Kampo to Rinsho (Journal of Kampo Medicine)</i> 2010; 1: 128–32 (in Japanese).	RCT	I	457
T88.5	Efficacy of goshuyuto and goreisan for post-spinal headache.	goshuyuto (呉茱萸湯), goreisan (五苓散)	Otake T, Kato I, Saito S, et al. The prophylactic effect of "goshiyuu-to" and "gorei-san" for post-spinal headache. <i>Pain Clinic</i> 1991; 12: 648-52 (in Japanese).	RCT	N	458
T88.8	Effects on pain and hyperhidrosis after thoracotomy.	keishikajutsubuto (桂枝加朮附湯), keishikajutsubuto (桂枝加朮附湯) + shakuyakukanzoto (芍薬甘草湯)	Isai H. Successful control of postoperative pain and hyperhidrosis by Kampo medicine after thoracotomy for pulmonary disease. <i>Itami to Kampo (Pain and Kampo Medicine)</i> 1997; 7: 29-32 (in Japanese with English abstract).	RCT	N	459
T88.8	To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) for pain after hemorrhoidectomy	shakuyakukanzoto (芍薬甘草湯)	Miyazaki M, Yasui M, Ikenaga M, et al. The effect of Shakuyaku-kanzo-to (Tsumura TJ-68) on pain after hemorrhoidectomy – a prospective randomized study –. <i>Journal of the Japan Society of Coloproctology</i> 2012; 65: 313–7 (in Japanese with English abstract).	RCT	I	460
T94.1	To evaluate the effectiveness and safety of saireito (柴苓湯) for keloid and hypertrophic scars following surgery, burn injury, and wound injury.	saireito (柴苓湯)	Watanabe Y, Asai S, Hida A, et al. Regarding the utility of saireito against keloid and hypertrophic scars following surgery and injury. <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2012; 67: 245–9 (in Japanese).	quasi-RCT	I	461

21. Others (34 abstracts, 38 references)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
Z01.8	To evaluate the effect of bakumondoto on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.	bakumondoto (麦門冬湯)	Saruwatari J, Hisaeda S, Higa Y, et al. The in-vivo effect of Bakumondo-to (TJ-29), a traditional Japanese medicine used for treatment of chronic airway disease, on cytochrome P450 1A2, xanthine oxidase and N-acetyltransferase 2 activity in man. <i>Journal of Pharmacy and Pharmacology</i> 2004; 56: 1171-7.	RCT-cross over	C	462

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
Z01.8	To evaluate the effect of shoseiryuto on blood carbamazepine concentration.	shoseiryuto (小青竜湯)	Ohnishi N, Yonekawa Y, Fumihara T. et al. Studies on interactions between traditional herbal and Western medicines, II. Lack of pharmacokinetic interaction between shoseiryu-to and carbamazepine in healthy volunteers. <i>TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)</i> 1999; 16: 399-404.	RCT-cross over	I	463
			Yonekawa Y, Ohnishi N, Kitano N, et al. Drug interaction with Kampo medicines (2): kinetic characteristics of carbamazepine combined with shoseiryuto in healthy volunteers. <i>TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)</i> 1999; 16: 191-2.		N	
Z01.8	To evaluate the effect of hachimijiogan on human central retinal artery.	hachimijiogan (八味地黄丸)	Isobe H, Yamamoto K, Cyong JC. Effects of hachimi-jio-gan (ba-wei-di-huang-wan) on blood flow in the human central retinal artery. <i>The American Journal of Chinese Medicine</i> 2003; 31: 425-35.	RCT-cross over	C	464
Z01.8	To assess the efficacy and safety of hochuekkito on antibody production after influenza vaccination.	hochuekkito (補中益氣湯)	Hamazaki K, Sawazaki S, Itomura M, et al. No effect of a traditional Chinese medicine, hochu-ekki-to, on antibody titer after influenza vaccination in man: a randomized, placebo-controlled, double-blind trial. <i>Phytomedicine</i> 2007; 14: 11-4.	DB-RCT	C	465
Z01.8	To evaluate the effect of maobushisaishinto on antibody titer after influenza vaccination.	maobushisaishinto (麻黃附子細辛湯)	Terashima Y, Hamazaki K, Itomura M, et al. Effect of a traditional Chinese medicine, maobushisaishinto, on the antibody titer after influenza vaccination: A randomized, placebo-controlled, double-blind trial. <i>Journal of Traditional Medicines</i> 2007; 24: 59-66.	DB-RCT	I	466
Z01.8	To elucidate the mechanism of bushirichuto activity in raising gut-regulated peptide levels.	bushirichuto (附子理中湯)	Sato Y, Katagiri F, Itoh H, et al. Bushi-richu-to raises calcitonin gene-related peptide, substance P, somatostatin, and vasoactive intestinal polypeptides levels in human plasma. <i>Journal of Health Science</i> 2007; 53: 615-21.	RCT-cross over	I	467
Z01.8	To evaluate effects of rokumigan on serum amino acid concentrations.	rokumigan (六味丸)	Takahashi H, Nakao R, Hirasaka K, et al. Effects of single administration of Rokumi-gan (TJ-87) on serum amino acid concentration of 6 healthy Japanese male volunteers. <i>Journal of Medical Investigation</i> 2007; 54: 91-8.	RCT-cross over	I	468
Z01.8	Interaction with the pharmacokinetics of acetaminophen.	kakkonto (葛根湯)	Qi J, Toyoshima A, Honda Y, et al. Pharmacokinetic study on acetaminophen: interaction with a Chinese medicine. <i>Journal of Medical and Dental Sciences</i> 1997; 44: 31-5.	RCT-cross over	C	469
Z01.8	Effects of kakkonto on the pharmacokinetics of phenacetin.	kakkonto (葛根湯)	Shimakura K, Mineshita S, Sanaka M, et al. Effects of kakkonto on the pharmacokinetics of phenacetin in human serum and saliva. <i>Rinsho Yakuri (Japanese Joournal of Clinical Pharmacology and Therapeutics)</i> 1994; 25: 229-30 (in Japanese).	RCT-cross over	N	470
Z01.8	Effects of saibokuto and saikokaryukotsuboreito on central nervous systems in humans.	saibokuto (柴朴湯), saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Fukushima M. Profiles of effects of traditional oriental herbal medicines on central nervous system in humans - assessment of Saiboku-to and Saiko-ka-ryukotsu-borei-to using EEG and pharmacokinetics of herbal medicine-derived ingredients as indices -. <i>Seishin Shinkeigaku Zasshi (Psychiatry et Neurologia Japonica)</i> 1997; 99: 355-69 (in Japanese with English abstract).	RCT	N	471
Z01.8	Effects on bioavailability of ofloxacin (OFLX) in healthy volunteers.	Shosaikoto (小柴胡湯), rikkunshito (六君子湯), saireito (柴苓湯)	Hasegawa T, Yamaki K, Nadai M, et al. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. <i>International Journal of Clinical Pharmacology and Therapeutics</i> 1994; 31: 57-61.	RCT-cross over	C	472

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
Z01.8	To evaluate the effects of shosaikoto, saibokuto, and saireito on prednisolone metabolism.	shosaikoto (小柴胡湯), saibokuto (柴朴湯), saireito (柴苓湯)	Niitsuma T, Fukuda T, Yamamoto S, et al. Effects of saibokuto and other <i>saiko-zai</i> (saiko-drugs) on prednisolone metabolism*. <i>Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)</i> 1993; 7: 43-52 (in Japanese).	RCT-cross over	N	473
			Homma M, Oka K, Ikeshima K, et al. Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. <i>Journal of Pharmacy and Pharmacology</i> 1995; 47: 687-92.			
Z01.8	Effect of coadministered Kampo medicine on the pharmacokinetics of levofloxacin (Cravit)	hochuekkito (補中益氣湯), rikkunshito (六君子湯), juzentaihoto (十全大補湯)	Hasegawa T, Yamaki K, Muraoka I, et al. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. <i>Antimicrobial Agents and Chemotherapy</i> 1995; 39: 2135-37.	RCT-cross over	C	474
Z01.8	To evaluate the effects of co-administered byakkokaninjinto on pharmacokinetics and renal excretion of antibiotics (tetracycline or ciprofloxacin).	byakkokaninjinto (白虎加人參湯)	Ohnishi M, Hitoshi K, Katoh M, et al. Effect of a Kampo preparation, byakkokaninjinto, on pharmacokinetics of ciprofloxacin and tetracycline. <i>Biological & Pharmaceutical Bulletin</i> 2009; 32: 1080-4.	RCT-cross over	C&I	475
Z01.8	To evaluate the antioxidative effect of bofutsushosan in healthy adults using the lag time of low-density lipoprotein (LDL) oxidation as the main yardstick.	bofutsushosan (防風通聖散)	Ogawa H, Xu F, Uebaba K, et al. Antioxidative potentiality of a Kampo formulation measured by an ex vivo study. <i>The Journal of Alternative and Complementary Medicine</i> 2009; 15: 267-74.	DB-RCT	N	476
Z01.8	To compare the effects of kamishoyosan and paroxetine in improving anxiety and depression as menopausal symptoms.	kamishoyosan (加味逍遙散)	Yasui T, Yamada M, Uemura H, et al. Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine. <i>Maturitas</i> 2009; 62: 146-52.	RCT	N	477
Z01.8	To evaluate the pharmacokinetic profiles of serum ephedrine and pseudoephedrine after oral administration of kakkonto (葛根湯), and changes in biokinetics after different administered doses.	kakkonto (葛根湯)	Inotsume N, Fukushima S, Hayakawa T, et al. Pharmacokinetics of ephedrine and pseudoephedrine after oral administration of kakkonto to healthy male volunteers. <i>Rinsho Yakuri (Japanese Journal of Clinical Pharmacology and Therapeutics)</i> 2009; 40: 79-83.	RCT-cross over	I	478
Z01.8	To analyze the blood kinetics of indicator components in daikenchuto (大建中湯).	daikenchuto (大建中湯)	Munekage M, Kitagawa H, Ichikawa K, et al. Pharmacokinetics of daikenchuto, a traditional Japanese medicine (Kampo) after single oral administration to healthy Japanese volunteers. <i>Drug Metabolism and Disposition</i> 2011; 39: 1784-8.	RCT	N	479
Z01.8	To evaluate the effect of daikenchuto (大建中湯) and abdominal thermotherapy on blood flow through the superior mesenteric artery.	daikenchuto (大建中湯)	Takayama S, Okitsu R, Iwasaki K, et al. The effect of warming the abdomen with herbal medicine or thermal therapy on superior mesenteric artery blood flow. <i>Kampo to Saishin Chiryō (Kampo & the Newest Therapy)</i> 2011; 20: 253-8 (in Japanese with English abstract).	RCT	I	480
Z03.8	Efficacy of shakuyakukanzoto for relieving pain during colonoscopy.	shakuyakukanzoto (芍藥甘草湯)	Arai M, Sato H, Shirota F. An investigation into the relief of colonoscopy pain provided by shakuyaku-kanzo-to. <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1994; 44: 385-90 (in Japanese with English abstract).	RCT	N	481
Z03.8	Efficacy of shakuyakukanzoto for relieving pain and complaints during preparation for barium enema.	shakuyakukanzoto (芍藥甘草湯)	Imazato S, Kai S, Koizumi K, et al. A clinical study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. <i>Therapeutic Research</i> 1997; 18: 5505-10 (in Japanese with English abstract).	RCT	N	482
			Imazato S, Kai S, Koizumi K, et al. A Clinical Study of shakuyaku-kanzo-to (Kampo) as a Preparation for Double Contrast Barium Enema. <i>Science of Kampo Medicine</i> 1998; 22: 87-92 (in Japanese).			
Z03.8	Efficacy of a new colon preparation using daiokanzoto.	daiokanzoto (大黃甘草湯)	Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). <i>Therapeutic Research</i> 1989; 10: 1637-43 (in Japanese with English abstract).	RCT	N	483

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
Z03.8	To evaluate the efficacy of shakuyakukanzoto combined with polyethylene glycol solution (PEG) in pretreatment for large bowel endoscopy.	shakuyakukanzoto (芍薬甘草湯)	Saida Y, Takase M, Okumura C, et al. Efficacy of combined use of shakuyakukanzoto in pretreatment for large bowel endoscopy – prospective randomized trial*. <i>Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)</i> 2003; 20: 34-7 (in Japanese).	RCT-envelope	I	484
Z03.8	To evaluate the efficacy of directly sprayed shakuyakukanzoto on large bowel spasm.	shakuyakukanzoto (芍薬甘草湯)	Ai M. Assessment of the antispasmodic effect of peppermint oil and shakuyaku-kanzon-to (TJ-68); a Chinese herbal medicine on the clonic wall. <i>Medical Tribune Online (Digestive Disease Week: DDW)</i> 2005; 10-1 (in Japanese).	RCT	N	485
Z03.8	To evaluate the efficacy of pretreatment with shakuyakukanzoto for upper gastrointestinal tract endoscopy.	shakuyakukanzoto (芍薬甘草湯)	Sugihara N. Effectiveness of shakuyaku-kanzo-to as a pretreatment for upper digestive tract endoscopic examination*. <i>Kampo Shinryo</i> 1999; 18: 17-9 (in Japanese).	quasi-RCT	N	486
Z03.8	To evaluate the efficacy of daikenchuto combined with polyethylene glycol solution (PG solution) in pretreatment for large bowel endoscopy.	daikenchuto (大建中湯)	Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, a herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. <i>Digestive Endoscopy</i> 2005; 17: 50-3.	RCT-envelope	C&I	487
Z03.8	To evaluate the efficacy and safety of direct spraying of shakuyakukanzoto on the colonic mucosa for suppression of bowel movement during colonoscopy.	shakuyakukanzoto (芍薬甘草湯)	Ai M, Yamaguchi T, Odaka T, et al. Objective assessment of the antispasmodic effect of Shakuyaku-kanzo-to (TJ-68), a Chinese herbal medicine, on the colonic wall by direct spraying during colonoscopy. <i>World Journal of Gastroenterology</i> 2006; 12: 760-4.	RCT	C	488
Z03.8	To evaluate the efficacy of shakuyakukanzoto solution in preparation for colonoscopy used with the water method of distension.	shakuyakukanzoto (芍薬甘草湯)	Mizukami T, Maruyama K, Yamauchi H, et al. Assessment of antispasmodic effect of herbal medicine, shakuyakukanzoto (TJ-68) on colonoscopy – Using colonoscopy insertion technique “collapsing method” –. <i>Kampo to Saishin-chiryō (Kampo & the Newest Therapy)</i> 2006; 15: 69-76 (in Japanese).	quasi-RCT	I	489
Z03.8	To evaluate the bowel cleansing effect of precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage solution (PG solution) combined with daikenchuto and mosapride.	daikenchuto (大建中湯)	Saida Y, Nagao J, Nakamura Y, et al. Dai-kenchu-to and mosapride in combination with precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. <i>Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)</i> 2005; 22: 145-8 (in Japanese).	RCT	I	490
Z03.8	To evaluate the effectiveness of daikenchuto in bowel preparation for barium enema X-ray study.	daikenchuto (大建中湯)	Arai J, Nakajima S, Fujinuma S, et al. A Comparative study of bowel preparation for barium enema using divided administrations of powdered magnesium citrate with mosapride or DAIKEN CHUTOU. <i>Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)</i> 2002; 19: 170-3 (in Japanese).	RCT	I	491
Z03.8	To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) as premedication for ERCP in suppressing duodenal peristalsis.	shakuyakukanzoto (芍薬甘草湯)	Fujinami H. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): randomized placebo-controlled trial. <i>Nikkei Medical (Supplement)</i> 2010; 8: 34 (in Japanese). Fujinami H, Kudo T, Nakayama Y, et al. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): a randomized, placebo-controlled trial. <i>Gastrointestinal Endoscopy</i> 2010; 71: AB227.	RCT	N N	492

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
Z04.8	To assess whether differences in ethical Kampo extract formulation dosage and dosing frequency have an effect on compliance and patient satisfaction.	Not described	Kita T, Sumino M. The effect of dosage frequency of ethical Kampo extract formulations on drug compliance – a comparison of twice a day and three times a day prescriptions. <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2011; 66: 117–22 (in Japanese).	RCT-cross over	I	492
Z22.8	To evaluate the effects of hochuekkito on prevention of MRSA carriage, prevention of <i>Pseudomonas aeruginosa</i> carriage, prevention of infection development, neutrophil count, and C-reactive protein (CRP) value.	hochuekkito (補中益気湯)	Ueda T, Yamashita K, Nakamori Y, et al. Study of the MRSA carriage-preventing effect of hochuekkito (TJ-41): 1st report*. <i>Progress in Medicine</i> 1999; 19: 1000-3 (in Japanese).	RCT	N	494
Z31.1	Effect of ovarian stimulation by tokishakuyakusan (used during in vitro fertilization and embryo transfer (IVF-ET) cycles) on follicular growth, luteal function, pregnancy rate, and abortion rate.	tokishakuyakusan (当帰芍薬散)	Fujii S, Fukushi Y, Yamaguchi E, et al. A study of the addition of tokishakuyakusan during in-vitro fertilization cycles*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 1997; 14: 121-5 (in Japanese).	RCT	N	495

<<A Structured Abstract describing Meta-analysis and the Reference Reporting It>>

15. Ante/Post-partum Diseases (1 abstract, 1 reference)

ICD-10	Research Question	Kampo Formula	Reference	Study Design	Source	Page No.
O90.8	To evaluate the efficacy of kyukichoketsuin in puerperal care in comparison with methylergometrine maleate by conducting a meta-analysis.	kyukichoketsuin (キユウ帰調血飲)	Koinuma M, Narikawa H, Kamei M, et al. Meta-analysis on the usefulness in postpartum control by kyukichoketsuin with methylergometrine maleate as control. <i>Nihon Toyo Igaku Zasshi (Kampo Medicine)</i> 2006; 57: 45-55 (in English with Japanese abstract).	Meta-analysis	I	497

2. Background

In an effort to disseminate evidence-based medicine (EBM) in oriental medicine, the Japan Society for Oriental Medicine (JSOM) established the Special Committee for Evidence Based medicine (EBM) in June 2001. In the Committee, led by Chairman Tetsuo Akiba, experts worked to organize clinical evidence of Kampo treatment. The achievements were the “EBM in Kampo 2002, Interim Report” (*Nihon Toyo Igaku Zasshi [Japanese Journal of Oriental Medicine]* 2002: 53(5), supplementary issue) issued in 2002, and “Evidence Reports of Kampo Treatment” (*Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2005: 56, EMB supplementary issue) in 2005 (in Japanese).

These reports covered the studies of Kampo formulations for prescription satisfying the new standards for Kampo formulations implemented in 1986, using the same prescription from the start through the end of the observation period in at least 10 subjects, and published between 1986 and 2002, including not only controlled trials but also case series (including records of academic or study meetings). References that satisfied the above criteria were selected from among the original database gathered and enumerated by the Japan Kampo Medicines Manufacturers Association (JKMA) and offered by the JKMA. In the final report, “Evidence Reports of Kampo Treatment,” 93 of 905 references offered by the JKMA were selected by the EBM Special Committee and compiled as structured abstracts consisting of five items, as follows: “participants,” “design (methods, period, and others),” “main results,” “from Kampo medicine perspective,” and “safety assessment in the article.” In addition, reference appraisal and recommendation ratings were made.

Preparation of this report was an epoch-making activity at that time, in terms of its basic procedures. However, some defects were pointed out; for example, whether a certain reference was not included because it was not found or because it was excluded in the selection process could not be distinguished

Okabe T. How much has the Kampo evidence been established to date? – the current state and future challenges based on the Evidence Reports. *Nihon Toyo Igaku Zasshi [Kampo Medicine]* –2007; 58(3): 435-41 [in Japanese].

Taking over predecessors’ achievements, the second phase of the JSOM EBM Special Committee, starting in 2005, adopted the systematic review approach, focusing on exhaustibility and transparency, to prepare structured abstracts limited to randomized controlled trials (RCTs) published in or after 1986 in accordance with worldwide standards.

Furthermore, in consideration of how the results could best be utilized, the results were to be published on the Japan Society for Oriental Medicine (JSOM) web site to improve accessibility, for the following reasons:

In a flood of medical information, it is not easy to make a right decision on which information would profit the patient. Dissemination of evidence-based medicine usually involves

four steps, as follows: step 1, identification of issues; step 2, information gathering; step 3, information review; and step 4, administration to patients. For busy clinicians, however, it is difficult to search various databases for available references, review all these references, and decide which reliable and appropriate medicines are. Especially for physicians not specialized in Kampo, it is even more difficult to judge which Kampo medicine should be used based on a search of general databases such as Medline.

In this context, it is desirable to develop a system to entrust the step 2 and step 3 procedures to a third party in advance so that information may be gathered and reviewed exhaustively and offered in an easy, accessible manner. Therefore, it was decided that the second phase of this activity would clearly focus on pre-appraisal and utilization of IT technology.

The outcomes of the activities after the second phase were sequentially published on the Society's website (<http://www.jsom.or.jp/medical/ebm/er/index.html>) according to version, as shown on page 2. The summary of the activities during the first 4-year period was reported in the Japan Society for Oriental Medicine 60th Annual Meeting (Tokyo) Forum "Transfer Kampo evidence," along with the activities of the Task Force for Clinical Practice Guidelines (CPG-TF) and the Task Force for Best Cases (BC-TF) (Abstracts of the Speeches in the Japan Society for Oriental Medicine 60th Annual Meeting, *Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2009; 60 suppl.: 157-72) (in Japanese).

The slides used by all ten speakers in the Forum were all published in book form along with the above abstracts of the speeches, and on the Society's website:

<http://www.jsom.or.jp/medical/ebm/doc/Forum2009.html>

Chaired by Kiichiro Tsutani MD, PhD, the third and fourth phases of the Committee for EBM (changed from Special Committee for EBM in June 2012), from April 2009 on, took over the activities of the previous phases. The second phase of the Task Force for Evidence Reports (ER-TF) and the Task Force for Clinical Practice Guidelines (CPG-TF) had activities and outcomes strongly associated with each other in nature, and were therefore combined in 2009 into the Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF) to carry on updating of the Evidence Reports and their English versions.

3. Purpose

The purpose was to exhaustively gather and review reports of randomized controlled trials of Kampo formulations, compile structured abstracts of them, and publish them on the website or in book form along with comments of third parties.

4. Steps for development of structured abstracts

(1) Criteria for reference selection

References that satisfied all of the following 3 criteria were included:

- 1) References using Kampo formulations approved for manufacture and sale in Japan (excluding in-house formulations such as decoctions, because of unknown quality of the medicines used)
- 2) Randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), crossover trials, and meta-analyses (including some with randomization procedure not fully indicated. Crossover trials are regarded as RCT)
- 3) References published in or after 1986
Those published in or after 1986 obviously using formulations of 1985 or previous quality, which differs from the current quality levels, were excluded throughout the study period.

(2) Search and screening

Searches were performed using the 3 databases listed below. Screening was performed in 2 steps: first, the references that obviously did not satisfy the criteria were excluded by the search staff; then, the remaining references were reviewed in the process of preparation of structured abstracts described below to finally decide which to include/exclude.

1) The Cochrane Library (C)

Kampo RCTs were searched using the Cochrane Central Register of Controlled Trials (CENTRAL), a worldwide RCT database organized by the Cochrane Collaboration. Since the CENTRAL covers all RCTs in the Medline, searches using the Medline were not performed.

On 26 November 2012, searches were performed by the following search formula, limited to publications in and after 1986:

#1 MeSH descriptor Medicine, East Asian Traditional explode all trees
#2 MeSH descriptor Medicine, Kampo explode all trees
#3 MeSH descriptor Medicine, Chinese Traditional explode all trees
#4 MeSH descriptor Drugs, Chinese Herbal explode all trees
#5 MeSH descriptor Herb-Drug Interactions explode all trees
#6 MeSH descriptor Herbal Medicine explode all trees
#7 MeSH descriptor Plants, Medicinal explode all trees
#8 MeSH descriptor Plant Structures explode all trees
#9 MeSH descriptor Plant Extracts explode all trees
#10 MeSH descriptor Materia Medica explode all trees
#11 MeSH descriptor Phytotherapy explode all trees
#12 (Kampo):ti,ab,kw

#13 (Kanpo):ti,ab,kw
#14 (Japanese):ti,ab,kw
#15 (Oriental):ti,ab,kw
#16 (Traditional):ti,ab,kw
#17 (East Asia):ti,ab,kw
#18 (East-Asia):ti,ab,kw
#19 (Herb*):ti,ab,kw
#20 (Chinese):ti,ab,kw
#21 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20), from 1986 to 2012
#22 (HS-EKAT)
#23 (#21 AND NOT #22)

In October 2011, of the RCT papers on Kampo formulations appearing EKAT 2010 under the “Reference(s)” of structured abstracts, those that had not been previously listed in CENTRAL were so listed and after HS-EKAT tagging, were linked to the EKAT SAs on the JSOM website. The present search excludes papers with “HS-EKAT” in the search formula, so as to exclude those papers related SAs.

Of 20,449 search hits, Kampo references were visually selected, resulting in 121 such references. Among Kampo references resulting from the CENTRAL search, 19 were overlapped with the Ichushi Web hits.

Kampo-related reports accounted for approx. 0.6% of the total hits.

Finally, of 121 references, 74 satisfying the inclusion criteria were compiled as structured abstracts, and 47 were not compiled as structured abstracts but cited as excluded references along with bibliographic items and the reason for exclusion.

2) *Igaku Chuo Zasshi* (I)

On 19 November 2012, randomized controlled trials of Kampo medicines were searched by the following search formula using *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicana* [JCRM], Ichushi) Web (in Japanese). Words in square brackets indicate equivalent English words.

Search formula:

(漢方薬 [Kampo medicine]/TH or 漢方 [Kampo]/AL) and (メタアナリシス [meta-analysis]/RD or ランダム化比較研究 [randomized controlled trial]/RD or 準ランダム化比較研究 [quasi-randomized controlled trial]/RD) and (DT=1986: 2012)

Since the Ichushi Web tags meta-analyses, randomized controlled trials, and quasi-randomized controlled trials, the present search targeted references that were tagged (メタアナリシス [meta-analysis]/RD or ランダム化比較研究 [randomized controlled trial]/RD or 準ランダム化比較研究 [quasi-randomized controlled trial]/RD), had “漢方薬

[Kampo medicine]” (漢方薬 [Kampo medicine]/TH) as a keyword (control term), or a title or abstract including the term “Kampo [漢方]” (漢方 [Kampo]/AL), and were published between 1986 and 2012 (DT=1986:2012).

As a result, 243 references were hit (19 of them were overlapped with CENTRAL hits). Of these references, 171 satisfying the inclusion criteria were selected and compiled as structured abstracts (170 RCTs and 1 meta-analysis). Of the references compiled as structured abstracts, 2 included 2 RCTs each, and were therefore compiled as structured abstracts separately for each RCT.

The Ichushi Web assigns the keyword “漢方 [Kampo]” to traditional Chinese medicines and food and Indian medicines as well. These references, combined with those with randomization not for evaluation of Kampo medicine, no-clinical articles, and citations of existing references, totaled 66, which were not compiled as structured abstracts but listed as excluded references along with bibliographic items and the reason for exclusion.

3) Database offered by the Japan Kampo Medicines Manufacturers Association (N)

The database offered by the Japan Kampo Medicines Manufacturers Association (JKMA) (unpublished) is the second database on Kampo and crude drugs, constructed by exhaustively searching existing databases including JST, JAPIC, Igaku Chuo Zasshi, Medline, and EMBASE with the keywords “漢方 [Kampo],” “東洋医学 [Oriental medicine],” “和漢 [Wakan],” “生薬 [crude drug],” “Kampo” and “Chinese Medicine,” and hand-searching several tens of Kampo-related journals. At present, the database includes approx. 100,000 references.

The database search on 19 November 2012 covered papers between 1986 and 2012 with the following search terms.

Search terms: the search terms are given in their original form (words in parentheses indicate search terms or hits in Roman characters, and the corresponding meanings in English):

メタアナリシス (meta-anarisisu, meta-analysis); メタ解析 (meta-kaiseki, meta-analysis); メタ分析 (meta-bunseki, meta-analysis); RCT; ランダム (randamu, random); 無作為, 無作意 (musakui, random); 封筒 (futo, envelope); 来院順 (rainjun, order of presentation); 受診順 (jushinjun, order of presentation); 診断順 (shindanjun, order of diagnosis); 割付, 割り付け (;waritsuke, allocation); ブラインド (buraindo, blind); 盲検, 盲験 (mouken, blind), 遮蔽, 遮へい, しゃへい (shahei, mask), マスク (masuku, mask); マスキング (masukingu, masking); クロスオーバー (kurosuoba,

crossover), 交叉, 交差 (kosa, crossover), 比較臨床 (hikaku rinsho, controlled clinical); random; cross over; meta analysis; envelope

The search included the terms メタ解析 (meta-kaiseki, meta-analysis); メタ分析 (meta-bunseki, meta-analysis); 来院順 (rainjun, order of presentation); 診断順 (shindanjun, order of diagnosis); and envelope, which were not used for EKAT 2010.

The 11,892 hits underwent primary visual screening, which resulted in 314 papers before SAs were prepared for 265 references that did not overlap with the results of CENTRAL or Ichushi Web searches. SAs were not prepared for 49 references that passed primary screening but did not exactly match the selection criteria. These SAs appear in the list of excluded references along with bibliographic information and the reasons for exclusion.

From these 3 databases combined, 653 references were identified, as shown in **Table 1**. Of these, SAs were prepared for 494, and 159 appear in the excluded references list along with bibliographic information.

Table 1 Number of references compiled as structured abstracts / excluded by database

Database	No. of hits	Visual refinement	Preparation of structured abstract	Exclusion
The Cochrane Library (C)	20,449 ¹⁾	121 ³⁾	74 ⁴⁾	47 ⁵⁾
Igaku Chuo Zasshi (I)	243 ¹⁾	237 ³⁾	171 ^{2), 4)}	66 ⁵⁾
Database offered by the Japan Kampo Medicines Manufacturers Association (N)	11,892 ¹⁾	314	265	49
Total, excluding overlapped references		653	494 ²⁾	159

¹⁾ Total number of search hits, ²⁾ including 1 meta-analysis, ³⁾ 19 references overlapped between (C) and (I),

⁴⁾ 16 references overlapped between (C) and (I), ⁵⁾ 3 references overlapped between (C) and (I)

(3) Preparation of structured abstracts

The references satisfying the inclusion criteria were compiled as structured abstracts (SA). Studies on SA started in the 1980s. Here, an 8-item structured abstract format of RCTs, as proposed by Altman, et al. and currently used worldwide, was employed.

Altman DG, Gardner MJ. More informative abstracts. *Ann Inter Med* 1987; 107(5): 790-1.

Aoki T. Kozoka shoroku no kiso-chisiki (Basic understanding in structured abstracts). In: Tsutani K, Yamazaki S, Sakamaki H (eds). *EBM no tameno joho senryaku – ebidensu wo tsukuru, tsutaeru, tsukau – (Information strategies for EBM – generate, transfer and use evidence–)*. Tokyo: Chugai-igakusha; 2000: 82-93 (in Japanese).

Here, 8 items are referred to as, (1) objectives, (2) design, (3) setting, (4) participants, (5) intervention, (6) main outcome measures, (7) main results, and (8) conclusions.

These 8 items are widely used in medical journals such as JAMA and secondary information journals such as Evidence Based Medicine, ACP Journal Club, as well as in secondary information journals on traditional medicine and complementary and alternative medicine, represented by *Focus on Alternative and Complementary Therapies (FACT)*. The acupuncture part of the journal is available in Japanese (Tsutani K [supervise-trans]. *Hari no ebidensu [Evidence for acupuncture – abstracts of articles on clinical evaluation of acupuncture–]*. Yokosuka: Ido-no-Nippon-sha; 2003 [in Japanese]. Thereafter, serialized in the journal “*IDO-NO NIPPON [The Japanese Journal of Acupuncture & Manual Therapies]*” [in Japanese]).

If one SA has been based on multiple references, all the bibliographic information for references used for the SA appears at the top of the SA, in order of publication, with the principle reference appearing in bold type.

Regarding (5) intervention, since the quality may differ among manufacturers, the brand name indicated in the original article was to be used as a rule. When the brand name was changed after the issue of the article for such reason as a change in manufacturer name, the brand name indicated in the article was used.

In the structured abstracts in the present “Evidence Reports of Kampo Treatment,” the following 4 items were added to the above world-standard 8 items: (9) from Kampo medicine perspective; (10) safety assessment in the article; (11) abstractor’s comments; and (12) abstractor and date. These are described below:

(9) “From Kampo medicine perspective” means how the unique diagnosis system of Kampo medicine is used. This is applied to 2 processes: design of a clinical trial and analysis after completion of the study. With RCT, this can be referred to as pre-randomization and post-randomization. In the former process of designing clinical trial design, “*sho* (証, pattern)” of Kampo medicine is indicated in the entry criteria and exclusion criteria of participants in the protocol in a manner that participating investigators can understand. The latter process involves stratified analysis, in which participants are stratified by “*sho*” (with *sho* or without *sho*), as well as by age and sex, etc. However, the stratified analysis is associated with “inference multiplicity”; that is, repeated testing of many strata produces false positive results, which indicates a difference when actually there is no difference. Among post-hoc approaches are adjustment for covariates.

(10) Safety assessment in the article” was incorporated since not only efficacy but also safety should always be considered in Kampo medicine as well. Here, the expression of “safety assessment in the article” was used rather than mere “safety assessment” because “safety assessment” is frequently misunderstood. RCTs usually use efficacy-related endpoints to determine appropriate sample sizes, and are not intended to assess safety. For instance, when no adverse drug

reactions occurred among 100 subjects receiving a Kampo medicine, the Kampo medicine is apt to be considered “safe because there are no adverse drug reactions when used in as many as 100 subjects.” Certainly, point estimation yields an incidence of 0%; however, interval estimation yields a 95% confidence interval (CI) for the incidence of 0-3%. Especially when a serious adverse drug reaction may infrequently occur, safety should be judged in consideration of the number of participants in the clinical trial in the article. From this perspective, the expression of “safety assessment in the article” was used.

Fig. 1 shows 95% CI in the absence of adverse events by the number of participants. The values are 0-26%, 0-14%, 0-6%, 0-3%, and 0-0.6% for 10, 20, 50, 100, and 500 subjects. The “law of 3” approximately holds around over 50 subjects. The confidence limit, values on both sides of a confidence interval, was constantly 0 on the left and $1-0.051/n$ on the right. For information, adverse event (AE) means “any untoward medical occurrence, whether or not related to the medical product,” and AE with “causal relationship with the medical product that cannot be ruled out” is referred to as adverse drug reaction (ADR).

Here, the above explanation including **Fig. 1** was based on the assumption that the incidence of AE was 0. When “AE occurred in m of n subjects,” however, the confidence interval can be determined by the equation below as a binominal distribution. This equation, which utilizes normal approximation of binominal distribution, produces larger error with smaller sample size ($n < 25$).

$$95\% \text{ confidence interval for event incidence} = p \pm 1.96\sqrt{p(1-p)/n}, \text{ where } p=m/n.$$

Although normal approximation was used for the above equation, there are other calculation systems easily available on the Internet, as represented by <http://www.ec.kagawa-u.ac.jp/~hori/delphistat/binom.html>.

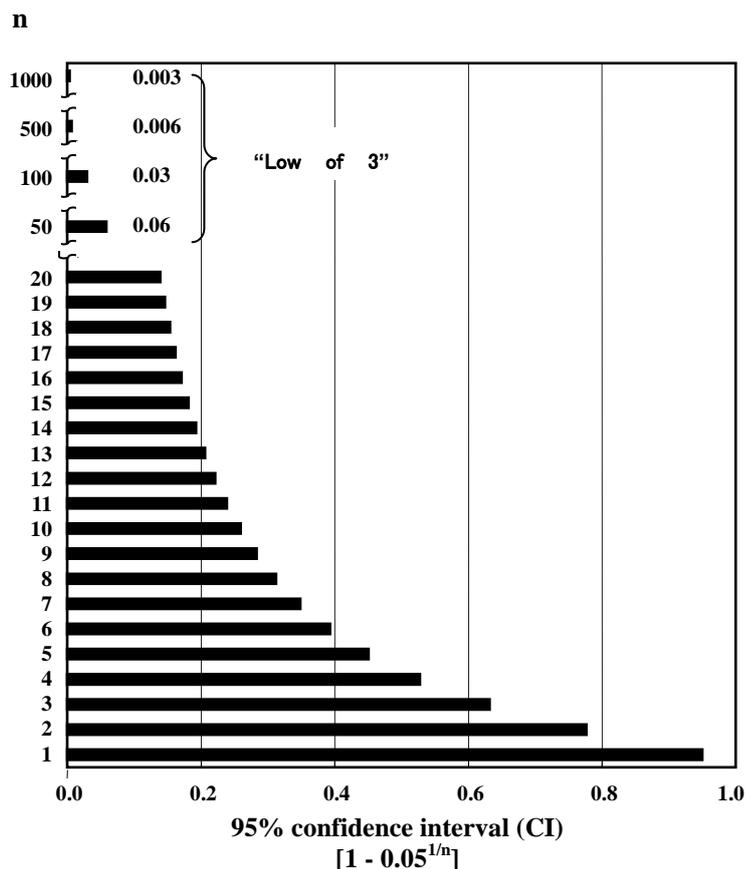


Fig. 1 Confidence interval for population mean of event incidence in the absence of events in any “n” subjects

(Tsutani K, et al. [eds] *EBM no tameno joho senryaku – ebidensu wo tsukuru, tsutaeru, tsukau – [Information strategies for EBM – generate, transfer and use evidence –]*. Tokyo: Chugai-igakusha; 2000: 26 [in Japanese])

In the present evidence report, indication as “safety assessment included in the article” was standardized as follows:

1) Without indication

When safety assessment was not performed or indicated, “none” was indicated.

2) With indication

When safety assessment was performed, even if only slightly, and revealed no adverse drug reactions, that effect was indicated. When adverse drug reactions were specifically indicated, the abstractor in charge indicated this according to the expression used in the reference. When the number of patients with adverse drug reactions was specified in the reference, it was indicated. Note that some indications of adverse drug reactions are not unified.

11) Abstractor’s comments” refers to objective comments on a reference presented as a structured abstract. This helps busy readers not used to critical appraisal correctly and easily judge

the value of the article. Abstractors were selected such that the abstractor did not belong to the same group of the authors concerned or have a master-student relationship, in consideration of conflict of interest (COI). How comments should be made was most actively discussed among members of the task force. With the aim of improving and standardizing comments, the 2nd Workshop of the Task Force for Evidence Report “To prepare appropriate comments” was held in conjunction with the Japan Society for Oriental Medicine 58th Annual Meeting held in Hiroshima on 17 Jun. 17, 2007.

Tsuruoka H, Okabe T, Tsutani K. Kampoyaku RCT no kozokashoroku niokeru komento kisai no kaizen — Dai 2-kai ebidensu repoto tasuku fosu wakushoppu hokoku — (Improvement of indication of comments in structured abstracts of RCTs on Kampo medicine—the Report of the 2nd Workshop of the Task Force for Evidence Report—. *Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2009; 60: 177-84 (in Japanese).

12) Abstractor and date” is intended to clarify the responsibility, which also concerns the abovementioned conflict of interest, and to show the temporary relationship between the comments and related studies and in consideration of the possibility of correction at a later date. When a structured abstract was revised, the date of revision was added.

Structured abstract preparation tasks were assigned to Task Force members in consideration of their specialties. However, since the specialties of members did not cover the whole field, some abstracts were prepared by non-specialized members.

Bibliographic items were indicated in the Vancouver style as a rule, with some modifications, including that the number of authors listed shall be up to 3 and that the name of a journal shall not be abbreviated.

Structured abstracts were arranged in the order of ICD10 (Version 2003) code of diseases. Those with the same code were arranged by date of publication of the main reference evaluated. When more than one ICD code was possible, the one seeming to be generally more understandable was selected. Similarly, excluded references were arranged in the order of ICD10 code. The names of Kampo formulae, etc. that could not be written in Chinese characters for daily use in Japan were written in Katakana. The names of ICD code diseases differ from general names and were therefore read as shown in **Table 2** to indicate them in this report.

Table 2 Expression of the disease classification in this report

	ICD10	Chapter title of ICD 10	Disease name in the reports
1	A00-B99	Certain infectious and parasitic diseases	Infections (including viral hepatitis)
2	C00-D48	Neoplasms	Cancer (condition after cancer surgery and unspecified adverse drug reactions of anti-cancer drugs)
3	D50-D89	Diseases of the blood and blood-forming organs, and certain disorders involving the immune mechanism	Blood diseases including anaemia
4	E00-E90	Endocrine, nutritional and metabolic diseases	Metabolism and endocrine diseases
5	F00-F99	Mental and behavioural disorders	Psychiatric/behavioral disorders
6	G00-G99	Diseases of the nervous system	Nervous system diseases (including alzheimer's disease)
7	H00-H59	Diseases of the eye and adnexa	Eye diseases
8	H60-H95	Diseases of the ear and mastoid process	Ear diseases
9	I00-I99	Diseases of the circulatory system	Cardiovascular diseases
10	J00-J99	Diseases of the respiratory system	Respiratory diseases (including influenza and rhinitis)
11	K00-K93	Diseases of the digestive system	Gastrointestinal, hepato-biliary-pancreatic diseases
12	L00-L99	Diseases of the skin and subcutaneous tissue	Skin diseases
13	M00-M99	Diseases of the musculoskeletal system and connective tissue	Diseases of the musculo skeletal system and connective tissue
14	N00-N99	Diseases of the genitourinary system	Genitourinary tract disorders (including climacteric disorders)
15	O00-O99	Pregnancy, childbirth and the puerperium	Ante/post-partum diseases
18	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Symptoms and signs
19	S00-T98	Injury, poisoning and certain other consequences of external causes	Injury, poisoning, and postoperative pain
21	Z00-Z99	Factors influencing health status and contact with health services	Others

In preparing structured abstracts, to maintain the quality, a Structured Abstract Preparation Manual was prepared, distributed to Task Force members, and updated as appropriate.

5. Included and excluded references

(1) Relations among included references, included studies, and excluded references

SAs were prepared for the 653 references selected. The 494 references included 55 cases of “2 papers for 1 study,” 10 cases of “3 papers for 1 study,” 3 cases of “4 papers for 1 study,” 2 cases of “5 papers for 1 study,” and also 2 cases of “1 paper for 2 studies,” resulting in 494 SAs (selected studies) (including 493 RCTs and 1 meta-analysis). The number of excluded references deviating from the inclusion criteria was 159 (**Table 3**).

Table 3 Relation between included references, included studies, and excluded references

No. of included references	494
1 study 2 papers	56
1 study 3 papers	10
1 study 4 papers	3
1 study 5 papers	2
2 studies 1 paper	2
No. of SAs (No. of studies)	403
No. of excluded references	159

Here, duplicate publication disclosed in the process of reference gathering for the present evidence report preparation is discussed. The guideline for manuscript submission, published by the International Committee of Medical Journal Editors (ICMJE), Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), has been employed by many journals in the world since its first issue in 1979. The revisions in and after 1984 mention duplicate publication and require that submission of already published study contents be approved by the editorial committee. The URM permits secondary publication for the following cases: editors of both journals concerned have accepted; the second publication targets different readers from those of the first publication; the second publication faithfully reflects the data and interpretations in the first publication; and the second publication specifies that it is a “secondary publication.”

Among references used for preparation of structured abstracts were some duplicate publications that did not specify that they were secondary publications. Submitting already published contents without permission of the editorial committee constitutes not only ethical but also copyright issues. With rising interests in publication-related ethics at home and abroad, consideration should be given to duplicate publication in papers on Kampo as well. These findings were published as study results in the following reference:

Kitagawa S, Tsutani K. Ebidensu repoto purojekuto: Kampo no RCT ronbun niokeru “Duplicate publication,” Dai 60-kai Nihon Toyo Igakkai Gakujutsusokai foramu “Kampo no ebidensu wo tsutaeru” (Evidence Report Project: “Duplicate publication” in Kampo RCT papers, the Japan Society for Oriental Medicine 60th Annual Meeting Forum “Transfer” Kampo evidence), 21 Jun. 2009, Tokyo. *Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2009; 60 suppl.: 162 (in Japanese).

Kitagawa M, Tsutani K. Duplicate publication cases in the field of Kampo (Japanese herbal medicine) in Japan. *Zhong Xi Yi Jie He Xue Bao (Journal of Chinese Integrative Medicine; 中西医结合学报)* 2011; 9(10): 1055-60.

In the following symposium, the issue of duplicate publication was addressed from the perspective of the above study:

Tsutani K. Publish or perish: Tajusyuppan ni tsuite (Publish or perish: duplicate publication). The Japanese Association of Medical Journal Editors (JAMJE) 2nd symposium (7 Jul. 2009, Tokyo) (in Japanese) (http://jams.med.or.jp/jamje/002jamje_06.html)

(2) Studies compiled as structured abstracts

For the studies shown in **Table 4**, structured abstracts were prepared.

Although two references termed “meta-analysis” were identified, one of them was not actually a meta-analysis and was therefore not compiled as a structured abstract, but instead listed as an excluded reference along with bibliographic items, resulting in a structured abstract prepared with only 1 reference.

Table 4 Studies prepared as structured abstracts

Meta-Analysis	1
Randomized Controlled Trial ¹⁾	361
Double blinded RCT: DB-RCT	35 ²⁾
Envelope method: RCT-envelope	103
Randomized Controlled Trial: RCT	177
RCT-cross over	46
Quasi-RCT: Controlled Clinical Trial (CCT) ³⁾	41
Total	403

1) Although it is possible to further sort RCTs using finer classifications, they have been sorted here into four classifications for convenience.

2) Including 1 DB-RCT-envelope and 3 DB-RCT-cross over.

3) Quasi-RCT: Quasi-RCT refers to randomization that is not complete, such as alternate assignment and assignment in the order of visit.

It is referred to as "Controlled Clinical Trial (CCT)" in MeSH of Medline.

For studies compiled as structured abstracts, the following items were indicated in the structured abstract and included the reference list: 1) SA No.; 2) ICD10 (2003 revision) code of disease; 3) research question; 4) name of Kampo formula; 5) bibliographic items of the reference; 6) study design; and 7) search source.

Research questions were supposed to be formulated with 4 items of patient, intervention, control, and outcome (PICO), but were simplified here.

(3) Preparation of excluded references list

The references not compiled as structured abstracts but listed as excluded references along with bibliographic items and the reason for exclusion were:

- 1) Clinical articles but not RCTs or meta-analyses
- 2) Those using formulations not approved for manufacture and sale in Japan as Kampo extract formulations (ex. Kampo decoctions, Chinese formulations)
- 3) Those using Kampo formulations in or before 1985 (with different quality from the current standards)
- 4) Citations of existing RCT articles.
- 5) Indicated with insufficient clarity to prepare the structured abstract
- 6) Others

Finally, 159 references were listed on the excluded references list.

6. Relation to other projects

The relation of this project to some other projects is described below.

(1) Scope

The research questions in controlled trials involve interventions and controls. This report includes a few studies comparing Kampo medicines, using several Kampo medicine groups as intervention or evaluating the system of Kampo medicine itself.

Further studies of this kind using Kampo formulations are desired.

In Kampo medicine in Japan, not only Kampo formulations but also decoctions are sometimes used. RCTs using decoctions are expected in future, but were listed as excluded references in this report. When a certain number of references are accumulated, their structured abstracts will be prepared.

For RCTs of crude drug therapies not based on Kampo formulae, preparation of structured abstracts and accessible forms of providing them are desired. Cooperation with other related organizations will also be a future challenge.

Although not limited to traditional medicine, the Japanese website Minds (<http://minds.jcqh.or.jp/>) has prepared and published free of charge Japanese translations of SAs in the Cochrane Library that are related to the Japanese treatment guidelines published on the Minds website. The Cochrane Library anticipated giving access to its abstracts in English, Spanish, Portuguese, Italian, Croatian, and Chinese, as well as Japanese by the end of 2013. Minds has also prepared Minds abstracts and published them on the website previously.

(2) Development in Japan and Korea of universal-style structured abstracts of RCTs in the fields of traditional medicine and complementary and alternative medicine

The first initiative to deliver SAs to people who require them was the *ACP Journal Club* in 1991. A further, similar initiative was taken by the *Evidence-Based Medicine*.

In the field of complementary and alternative medicine (CAM), there is the quarterly journal *FACT (Focus on Alternative and Complementary Therapies)* first published in 1996. Before long, an initiative was born in 2001 for Japanese translations on acupuncture, which have been serialized in the journal *Ido no Nippon (the Japanese Journal of Acupuncture & Manual Therapies)*, and a collection of all 50 translations since 1996 has been published as a book by Ido no Nipponsha as *Hari no Ebidensu (Evidence for Acupuncture (provisionally translated title))*. Further Japanese translations followed with each edition of *Ido no Nippon (the Japanese Journal of Acupuncture & Manual Therapies)* featuring translations, and with the cumulative total reaching 150, an enlarged and revised edition was published in 2009 with comments by Japanese.

Several other initiatives have followed in Japan that are modeled on EKAT.

First, in 2009, a research group within the Association for Health Economics Research and Social Insurance and Welfare (ASIW), called the Food for Special Dietary Uses and Nutrition Therapy Research Group (headed by Kiichiro Tsutani), published the “Tokubetsuyotoshokuhin oyobi Eiyoryoho no Ebidensuto ni Kansuru Joho no Syusyuseirigyomu: Heisei 20 Nendo Hokokusho” (Evidence Reports of Food for Special Dietary Uses [FSDU] and Nutrition Therapy 2008) (<http://www.shafuku.jp/healthfood/pdf/report.pdf>) (in Japanese).

Then in 2012, a Ministry of Health, Labour and Welfare (MHLW) scientific research grant entitled “Higashi Ajia Dento Igaku no Yukosei, Anzensei, Keizaisei no Shisutematic Rebu” (Systematic Review of the Effectiveness, Safety, and Economy of East Asian Traditional Medicine [Principal Researcher: Kiichiro Tsutani]) prepared a report entitled “Shinkyu Ebidensu Repoto 2011” (Evidence Reports of Japanese Acupuncture and Moxibustion 2011), “Anma Massagi Shiatsu (Amashi) Ebidensu Reporo 2011” (Evidence Reports of Anma-Massage-Shiatsu 2011), and “Kampoyaku no Keizaihyoukaryoiki no Ebidensu Repoto 2011” (Evidence Report of Economic Evaluation of Kampo Treatment 2011). The details are summarized below.

The researchers found 421 papers after searching Ichushi Web Ver. 4, The Cochrane Library (CENTRAL), the Japanese Acupuncture and Moxibustion RCT Database (JAC-RCT) by Tsutani and Suyama, the Acupuncture Clinical Trial Paper List (provisional name: JSAM-RDB) edited by members of the Japan Society of Acupuncture and Moxibustion, as well as a partly hand search of RCT papers. Subsequent screening found 53 papers meeting the selection criteria for which SAs were prepared. With third-party neutral comments, those SAs were compiled as “Nihon Shinkyu Ebidensu Repoto 2011 – 53 no RCT – (EJAM 2011)”. An English version was also prepared as “Evidence Reports of Japanese Acupuncture and Moxibustion 2011: 53 Randomized Controlled Trials (EJAM 2011)”.

In the field of Amashi, RCT papers were exhaustively gathered using Ichushi Web Ver. 4. SAs were prepared for 18 (19 papers) out of the 105 that fitted the criteria and these were compiled as Anma-Massaji-Shiatsu Ebidensu Repoto 2011 – 18 no RCT (EAMS 2011). An English version was also prepared: Evidence Reports of Anma-Massage-Shiatsu 2011: 18 Randomized Controlled Trials of Japan (EAMS 2011).

For the economic evaluation of Kampo medicines, a search was performed using Ichushi Web Ver. 5. After screening, 10 papers were identified as economic evaluations of Kampo medicines. SAs were prepared for these and were compiled as Kampo Chiryō no Keizai Hyōka Ebidensu Repoto (Evidence Report of Economic Evaluation of Kampo Treatment: [EREK] 2011).

In Korea, the Special Committee for EBM of the Korean Oriental Medicine Society (KOMS), with which JSOM has established an exchange agreement in 2009, published the Korean translation (근거중심의 한방처방 : 임상 근거를 만들고, 전달하며, 사용하는) of Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials (EKAT 2010) on 15 July 2011.

The Committee also used the same methods as for EKAT to prepare an evidence report on traditional Korean medicine, which was published on 20 January 2012 as 근거중심의 한의치료. The Committee prepared SAs in Korean after gathering and selecting 306 papers (including 134 RCTs), which include trials using designs other than RCT designs and were found by searching The Cochrane Library (CENTRAL), PubMed, the Korea Institute of Oriental Medicine (KIOM) database, and the websites of 17 sub-committees in the field of traditional Korean medicine. The SAs for the 134 RCTs were translated into English in “Heisei 22-23 nendo Kosei Rodo Kagakukenkyū Chiikiiryō Kibankaihatsu Suishin Kenkyūjigyo – Higashiajia Dentoigaku no Yukosei Anzensei Keizaisei no Shisutematikku Rebyū” (Systematic Review of the Effectiveness, Safety, and Economy of East Asian Traditional Medicine, a Research on Region Medical under the 2010/2011 Ministry of Health, Labour and Welfare Scientific Research grants) (Principal Researcher: Kiichiro Tsutani). The report is entitled “Evidence Reports of Korean Medicine Treatment 2010: 132 Randomized Clinical Trials (EKOM 2010)”. This evidence report contains 77 RCTs on acupuncture and moxibustion, 27 RCTS on herbal medicines, one RCT on both, and 27 RCTs on other traditional Korean medicine.

Of the above, SAs on Japanese acupuncture and moxibustion (in Japanese and English), Amashi (Japanese and English), traditional Korean medicine (English), economic evaluation of Kampo treatment (Japanese) can be accessed on the “Higashi Ajia Dento Igaku Ebidensu Repoto” (Evidence Reports of Traditional East Asian Medicine: ETEAM) website, which is searchable at <http://jhes.umin.ac.jp/team.html>. The website also has links to the EKATs.

(3) CONSORT Statement

With the aim of improving the quality of references of RCTs, the CONSORT statement was published in 1996 and revised in 2001 and 2010 (<http://www.consort-statement.org/>).

The 2010 version consists of a total of 25 items, and authors are requested to attach a checklist showing on which page the information on each item can be found. They are also requested to attach a flowchart representing subject disposition in case results might differ depending on the analysis population. These requirements not only control the quality of RCT articles but also improve the quality RCT themselves. The JSOM has added the statement that “RCT papers shall conform to revised CONSORT statement (2001)” to the instructions to authors its March 2008 revision (*Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2008; 59: 580-89). Currently CONSORT statement 2010 is required to use.

Two herbal extensions of the CONSORT statement have been published:

Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, et al. Reporting randomized controlled trials of herbal interventions: An elaborated CONSORT statement. *Annals of Internal Medicine* 2006; 144(5): 364-7. (Available in Japanese: Okabe T, Tsutani K [trans], Habu kainyu no randamuka hikakusiken hokoku: shosai na CONSORT seimei. In: Nakayama T, Tsutani K [supervise-eds] *Rinshokenkyu to Ekigakukenkyu notameno Kokusairuru-shu (International Rulebook for Clinical and Epidemiological Studies)*. Tokyo: Life Science Publishing Co., Ltd.; 2008: 156-63).

Bian ZX, Moher D, Dagenais S, Li YP, Wu TX, et al. Improving the quality of randomized controlled trials in Chinese herbal medicine, Part IV: applying a revised CONSORT checklist to measure reporting quality. *Journal of Chinese Integrative Medicine (Zhong Xi Yi Jie He Xue Bao)* 2006; 4(3): 233-42. (Available in Japanese: Tsutani K, Araki S [trans]. Chuyaku no randamuka Hikakushiken no Hokoku ni kansuru CONSORT seimei. In: Nakayama T, Tsutani K [supervise-eds], *Rinshokenkyu to Ekigakukenkyu notameno Kokusairuru-shu [International Rulebook for Clinical and Epidemiological Studies]*. Tokyo: Life Science Publishing Co., Ltd.; 2008: 164-9).

The former applies to plain herbs, while the latter to Chinese prescriptions. The former provides detailed explanation on how to describe “intervention” in consideration of the nature of crude drugs, and the latter gives consideration to the diagnosis system of Chinese traditional medicine and years of clinical experience.

In the third phase of the Special Committee for EBM starting 2009, the Task Force for KCONSORT (KC-TF) was established. A survey of the references compiled as structured abstracts in EKAT 2009 for compliance with the CONSORT statement demonstrated that few were good in quality. Particularly, the following defects were commonly noted: no indication that the study is an RCT in title/abstract; no indication of the study site or period; no indication of the name of the manufacturer of Kampo formulation or the daily dosing frequency; no indication of the methods and assurance of randomization; unclear numbers of enrolled patients, assigned patients, and analyzed patients; no indication of adverse events in the control group. In the future, Kampo RCTs

will also be required to be reported in compliance with the CONSORT statement. These findings were presented in the following meeting and published in *Nihon Toyo Igaku Zasshi (Kampo Medicine)* as study results.

Okabe T, Arai I, Tsutani K. Ebidensu repoto purojekuto: autorain to Kampo RCT no shitsu hyoka (Evidence Report Project [1] Outline and evaluation of Kampo RCTs). The Japan Society for Oriental Medicine 60th Annual Meeting Forum “Kampo no ebidensu wo tsutaeru (Transfer Kampo evidence),” 21 Jun. 2009, Tokyo. *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2009; 60 suppl.: 160 (in Japanese).

While it is recommended that RCTs be published in accordance with the CONSORT statement, the existing CONSORT statement and its extensions made it clear that it was not possible to correctly describe Kampo formulation interventions. To resolve that problem and to enable completion of the necessary information in the RCT paper methods field without needing to have a high degree of familiarity with Kampo formulations, the KCONSORT webpage was published in English in August 2011 by the Department of Pharmacognosy, Phytochemistry and Narcotics (DPPN), National Institute of Health Sciences (NIHS) of Japan, and the Research Center for Medicinal Plant Resources (RCMPR), National Institute of Biomedical Innovation (NIBIO) of Japan (<http://plaza.umin.ac.jp/~kconsort/>) under work collaboration of KC-TF and Japan Kampo Medicines Manufacturers Association (JKMA). The website is intended to replace the need for authors writing RCTs on Kampo preparations to complete detailed information in their papers relating to the Kampo preparations used in research, by including the web address of this website, which contains detailed information on Kampo preparations.

The CONSORT statement was extended to include various study designs such as epidemiological studies and systematic reviews, and further studies on above-mentioned complementary and alternative medicine (CAM). In this context, the “Equator Network” was established in June 2008 to cover the publication guidelines for all these studies for enhanced accessibility and to help prepare such guidelines in future [<http://www.equator-network.org>].

The Japanese version of these guidelines is included in the following:

Nakayama T, Tsutani K (eds). *Rinsho kenkyu to ekigaku kenkyu notameno kokusai ruru-shu (International Rulebook for Clinical and Epidemiological Studies)*. Tokyo: Life Science Publishing Co., Ltd.; 2008 (in Japanese).

(4) Clinical trial registry

In the Declaration of Helsinki revised in October 2008, a sentence “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject” was added in section 19. However, this requirement is not well known. Therefore, the discussion here

includes the historical background underlying the implementation of this requirement.

Awareness of the clinical trial registry (CTR) has increased since the 1990s, when evidence-based medicine (EBM) emerged. In particular, the problems became clearer after the Cochrane Collaboration, which plays a role in the EBM information infrastructure, was established in 1992 to fully implement systematic review (SR). SR is almost synonymous with meta-analysis (MA).

However, no matter how exhaustive the survey or search, how careful the assessment of quality, and how sophisticated the statistical method used for data consolidation, a problem of bias ("publication bias") arises when studies are not reported. This leads to flaws in decision making by health care providers, policy makers, medical consumers, etc. As a result, ineffective therapies, hazardous therapies, and therapies with poor cost-effectiveness are "used".

Table 5 gives an example of publication bias in the area of acupuncture. Search for papers with an abstract published between 1966 and 1995 by the Medline identified 108 of 109 papers published in China (99%) that have shown favorable results, that is, demonstrated the efficacy of acupuncture compared with control. The efficacy rate was 75% in England and similar to that in China in other countries including Japan. This has been attributed to failure to publish studies that do not show efficacy.

Table 5 Favorable results of controlled clinical trials of acupuncture interventions by country

Country of Publication	Abstracts Screened	Abstracts Included	Favoring Test Treatment	
			Number	Percent
China	196	109	108	99
England	329	107	80	75
Japan	317	120	107	89
Russia/USSR	150	29	28	97
Taiwan	78	40	38	95
Total	1100	405	361	89

Vickers A, et al. Do certain countries produce only positive results? A systematic review of controlled trials. *Controlled Clinical Trials* 1998; 19: 159-66

This situation was widely acknowledged by those involved in systematic review of these studies. Although some measures might avoid this bias, such as encouraging researchers to publish all studies, passing legislation mandating registry of all trials, and establishing a website to register planned or ongoing clinical trials, no specific measures were fully established.

In 2003, the National Library of Medicine (NLM) of the National Institutes of Health

(NIH) established "Clinical Trials.gov" (<http://clinicaltrials.gov/ct2/info/about>) with the aim of encouraging patients to access information on clinical trials of new drugs (therapies) intended for life-threatening disease. This is also an aim of the 1997 US-FDA Modernization Act. This system was not intended to avoid publication bias, but partially did a limited number of diseases including cancer, AIDS, and Alzheimer's disease.

The Glaxo SmithKline fraud scandal reported on the front page of the New York Times dated 3 June 2004 triggered a worldwide reaction. In a clinical trial of an anti-depressant in children, the company failed to properly report attempted suicide as an adverse event. The scandal prompted worldwide support for legislation requiring clinical trial registration and raised ethical issues such as the risk adverse events in similar clinical trials and abuse of the altruistic goodwill of participants.

In September 2004, the International Committee of Medical Journal Editors (ICMJE) issued a statement that no manuscript would be accepted in advance of registration of the clinical trial. Trials already in progress were given additional time to comply. The Cochran Colloquium in October 2004 issued the "Ottawa Statement." The WHO also supported these statements by holding the "WHO Technical Consultation on Clinical Trial Registration Standard Meeting" in its headquarters in Geneva in April 2005 to determine 20 items to be registered, etc.

This trend continued between 2004 and 2005 as indicated below:

- (1) Rinshoshiken no toroku to kekka no kokai (Clinical trial registry and publication of the results [regardless of whether or not results are positive or negative]). The 25th Annual Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics Symposium 12 (18 Sept. 2004, Shizuoka). *Rinsho Iyaku (Journal of Clinical Therapeutics Medicine)* 2005; 21(1): 3-62 (in Japanese).
- (2) Rinshoshiken toroku nikansuru "Ottawa seimei" to "Junebu kaigi" no doko ("Trend toward clinical trial registry as advocated by the "Ottawa Statement" and "Geneva Conference.>"). *Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)* 2005; 33(6): 543-66 (in Japanese).
http://www.lifescience.co.jp/yk/jpt_online/ottawa/index_ottawa.html
- (3) UMIN Clinical Trial Registry System Symposium (2 Feb. 2005)
<https://upload.umin.ac.jp/ctr/symposium20050202.htm>

In Japan, the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (June 2005-), the Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC-CTI) (July 2005-), and Japan Medical Association Center for Clinical Trials (JMA CCT) system (December 2005-) were launched. Subsequently, the Japan Primary Registries Network (JPRN) (October 2008-) of the National Health Science Institute consolidated these three

systems.

In 2007, the WHO established the International Clinical Trials Registry Platform (ICTRP, <http://www.who.int/ictrp/en/>) and opened a search portal (<http://apps.who.int/trialsearch/>) to facilitate access to all systems worldwide for searching.

Currently this site can be used to search for all registered trials, including trials of Kampo formulations in Japan.

In April 2007, interventional clinical studies supported by Health and Labour Sciences Research Grants were required to be registered. Also, in April 2009, the Ministry of Health, Labour, and Welfare “Ethical Guidelines for Clinical Research” required registry.

The intent of clinical trial registry has been discussed above from a historical perspective in some detail. Questions remain: how many RCTs and clinical studies are performed and what percentage of them is registered in Japan?

In a book summarizing the situation in various nations in the world released in 2006, it was estimated that 400 RCTs and 2,300 other clinical researches, for a total of 2,700, were performed at that time.

Matsuba H, Kiuchi T, Tsutani K, Uchida E, Ohashi Y. The Japanese perspective on registries and a review of the clinical trial process in Japan. In: Foote M ed. *Clinical trial registries: A practical guide for sponsors and researchers of medicinal product*. Basel: Birkhäuser, 2006.

According to the book, as of February 2006, the three systems combined had a total of 550 registries. UMIN-CTR was the first system in Japan, started in June 2005. A review in May 2010 found that the number of registries in 2006 was 259, 138 and 7 registries in UMIN-CTR, JAPIC-CTI and JMACCT, respectively. The total of 404 registries represented approx. 15% of all clinical studies (404/2,700).

A review showed that the number of registries in 2009 had risen to 1,311, 295 and 9, respectively, for a total of 1,615. Assuming that the number of clinical studies remained the same in 2009, i.e., approx. 2,700, registered studies accounted for approx. 60% (1,615/2,700) of all clinical studies.

The problem of publication bias was described above, citing the field of acupuncture in the period from 1966 to 1995 as an example. Is there currently publication bias in the reporting of studies on Kampo formulations?

Preliminary analysis of all 345 papers in EKAT 2010 revealed “favoring test treatment” results in 301 out of 308 trials (98%) (excluding those trials comparing only Kampo formulations with other Kampo formulation(s) as control). This result is consistent with the above-mentioned rate of publication bias in the reporting of acupuncture studies. In Japan, inasmuch as the percentage of

registered clinical trials is increasing, it is hoped that clinical trials of Kampo formulations are also being registered so as to provide true efficacy and safety evidence.

The global trend is toward requiring not only registry of ongoing clinical trials but also publication of the results. NIH-funded trials must fulfill these requirements. The situation relating to the publication of results from trials of Kampo formulations registered in Japan is described in the following article:

Arai I, Tsutani K. Kampoyaku no rinshoshikentoroku to kekka no kohyojokyo (Situation of registry of clinical trials of Kampo medicine and publication of the results). The Japan Society for Oriental Medicine 61st Annual Meeting (5 Jun. 2010, Nagoya), *Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2010; 61 suppl.: 244 (in Japanese).

Publication bias is considered to be more of a problem in CAM in broad sense than in conventional allopathic medicine. This is because CAM studies lack a regulatory framework, as many of these studies are conducted by physicians who are unfamiliar with clinical trial registry trends worldwide, including Japan. This is in contrast to clinical trials conducted by pharmaceutical companies.

The intent of this “Evidence Report” project, involving compilation of structured abstracts with third party’s neutral comments about RCTs in Japan, is to “tsutaeru (transfer)” users. Reducing bias is always considered as high priority in whole works of the project. However, publication bias cannot be prevented if the results of RCTs are not published.

We strongly recommend registration of all RCTs of Kampo formulations in Japan.

Furthermore, systems that allow for guarantees of quality and secondary analysis by accessing the raw data of clinical trials have been starting up since 2010 in the West and in Japan, and these should be extended to the field of CAM.

(5) The Cochrane Library (CENTRAL)

The Cochrane Library (CENTRAL) is a global RCT database platform, but includes only 67 of the 345 RCTs on Kampo formulations in EKAT 2010. The Center for Integrative Medicine, University of Maryland Medical School manages the compilation of RCTs on complementary therapies in CENTRAL. We have made contact with the Center and negotiated for the RCT papers compiled in EKAT to be added to CENTRAL. As a result, the Kampo RCT papers in EKAT 2010 will be included in CENTRAL, and it will have links to the English versions of JSOM’s EKAT SAs. When CENTRAL was updated in October 2011, additional EKAT papers were included. However, due to copyright issues, there are no links from the RCT papers on Kampo formulations that were originally included in CENTRAL. In any event, it is

now possible to access all the Kampo formulation RCTs from the Cochrane Library (CENTRAL). When evidence-based clinical practice guidelines (CPG) are produced, CENTRAL will be used most often to search for RCT papers. It is expected that this will facilitate Kampo formulation RCT searches, and that there will be no gaps in the evaluation of Kampo formulations for such CPGs.

The following paper describes the above in detail.

Wieland LS, Manheimer E, Sampson M, et al. Bibliometric and content analysis of the Cochrane Complementary Medicine Field specialized register of controlled trials. *Systematic Reviews* 2013, 2: 51 (<http://www.systematicreviewsjournal.com/content/2/1/51>)

(6) Clinical practice guidelines

Traditional medicines are already international commodities. From this perspective, Japan's Kampo formulations have fallen a little behind. If high quality SAs are prepared for Chinese and Korean traditional medicines, then it may become possible to reduce confusion in the debate through the publication of clinical practice guidelines (CPG) for traditional medicines, something that the WHO Office for the Western Pacific (WPRO) attempted to do in 2005 and 2006.

Motoo Y, Arai I, Hyodo I, Tsutani K. Current status of Kampo (Japanese herbal) medicines in Japanese clinical practice guidelines. *Complementary Therapies in Medicine* 2009; 17: 147-54.

Motoo Y, Tsutani K. Dento Igaku no Gurobaru Shinryo Gaidorain wa Kano ka? (Is it Possible to Realize Global Clinical Guidelines for Traditional Medicines?) *Nihon Toyo Igaku Zasshi [Kampo Medicine]* 2006; 57 (4): 465-75 (in Japanese).

Furthermore, the WHO/WPRO traditional medicine CPG project was discontinued at the 5th meeting in Hong Kong (2007) due to strong opposition from Japan and others. However, work was continued in China and the following three volumes were published in 2011.

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: TCM Internal Medicine (Chinese Edition) (中医循证临床实践指南 - 中医内科). Beijing. China Press of Traditional Chinese Medicine, 2011

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: Special disease (Chinese Edition) (中医循证临床实践指南 - 专科专病), Beijing. China Press of Traditional Chinese Medicine, 2011

China Academy of Chinese Medical Sciences ed. Chinese medicine evidence-based clinical practice guidelines: Acupuncture (Chinese Edition) (中医循证临床实践指南 - 鍼灸). Beijing. China Press of Traditional Chinese Medicine, 2011

The following paper includes details of the above.

Yanagawa T, Tsutani K. Chuyaku no Kokusaika to Hyojunka ni Kansuru Chugoku no Seisaku. Dai 5 kai Chui Shinryo ni Kansuru Gyokai Hyojun to Shinryo Gaidorain. (Chinese Policies on Internationalization and Standardization of Chinese Medicines. 5th Industry Standard and Clinical Practice Guidelines for Traditional Chinese Medicine Therapy) *Wakan'yaku* 2013; No.720: 3-10 (in Japanese).

7. Lists of Excluded References

(159 references)

Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).

Abbreviations: C, The Cochrane Library (CENTRAL); I, *Igaku Chuo Zasshi (Japan Centra Revuo Medicana, Ichushi)*; N, Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

Reasons for exclusion were classified as follows:

- 1) Clinical studies that were not RCTs or meta-analyses.
- 2) Studies using medicines that were not approved as Kampo preparations in Japan (Kampo tozai [decoctions], Chinese preparations, and others).
- 3) Studies using Kampo preparations manufactured before 1985 (their quality being different from that currently available).
- 4) Studies citing existing RCT papers.
- 5) Studies with unclear content.
- 6) Others (reasons are described in the list).

1. Infections (including Viral Hepatitis) (4 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
A09	Effects of Kampo prescriptions on inflammatory bowel disease (IBD)	Various prescriptions	Okumi H. An EBM evaluation of Kampo prescriptions related to inflammatory bowel disease (IBD). <i>Nihon Toyo Shinshin Igaku Kekkkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> . 2010; 25: 95-9 (in Japanese with English abstract).	4) RCT review	I
B08.1	Clinical efficacy for molluscum contagiosum	yokuinin extract powder	Clinical research group for coix seed (yokuinin) extract powder. Therapeutic effect of coix seed (yokuinin) extract powder on molluscum contagiosum – well-controlled double blind trials by multi-institutes compared with placebo-. <i>Hifu (Skin Research)</i> 1987; 29: 762-73.	2)	N
B18.2	Clinical evaluation for chronic hepatitis C	shosaikoto (小柴胡湯)	Gibo Y. Clinical evaluation of shosaikoto for chronic hepatitis C - long term comparison with no treatment group*. <i>Kampo Igaku (Kampo Medicine)</i> 1994; 18: 396-9.	1)	N
B34.9	Effects on immunocompetence in the elderly	hachimijiogan (八味地黄丸)	Yamamoto T, Tei M. Effects of Kampo medicine on immunocompetence in the elderly (III) - effects on the activity of the alternative complement pathway*. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1986; 3: 270-1.	3)	N

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs) (15 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C18.9	Efficacy of oxaliplatin combined with hydroxycamptothecin as an adjuvant therapy for colorectal cancer	Hydroxy-camptothecin	Yao Y, Zhao H, Sun Y, et al. Combined chemotherapy of hydroxycamptothecin with oxaliplatin as an adjuvant treatment for human colorectal cancer. <i>The Tohoku Journal of Experimental Medicine</i> 2008; 215: 267-78.	2)	I
C22.0	Preventive effect on hepatoma in patients with hepatic cirrhosis	shosaikoto (小柴胡湯)	Yamamoto S, Oka H, Kanno T, et al. Controlled prospective trial to evaluate syo-saiko-to for the prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. <i>Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)</i> 1989; 16: 1519-24.	1)	C
C22.0		shosaikoto (小柴胡湯)	Oka H. Chemoprevention of hepatocellular carcinoma with sho-saiko-to. <i>Rinsho Shokaki Naika (Clinical Gastroenterology)</i> 1998; 13: 1525-30.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Kobayashi K, Yamamoto S. Prevention of hepatoma with shosaikoto*. <i>Progress in Medicine</i> 1992; 12: 1196-200.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S. Controlled prospective study of prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. <i>Biotherapy</i> 1991; 5: 1867-73.		I
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S, Kuroki T, et al. Prospective study on chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). <i>Cancer</i> 1995; 76: 743-9.		C
C22.0		shosaikoto (小柴胡湯)	Oka H, Yamamoto S, Kanno T, et al. Controlled prospective evaluation of sho-saiko-to in prevention of hepatocellular carcinoma in patients with cirrhosis of the liver. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1989; 6: 40-4.		I
C22.0	Effects on hepatic cirrhosis and hepatoma	shosaikoto (小柴胡湯)	Yamauchi H, Nakayama S, Sato S, et al. Hepatic cirrhosis and hepatoma*. <i>Current Therapy</i> 1986; 4: 599-607.	3)	N
C22.0	Protective effect of jumentaihoto on hepatocarcinogenesis	jumentaihoto (十全大補湯)	Tsuchiya M, Kono H, Matsuda M, et al. Protective effect of juten-taiho-to on hepatocarcinogenesis is mediated through the inhibition of Kupffer cell-induced oxidative stress. <i>International Journal of Cancer</i> 2008; 123: 2503-11.	6) This was a basic study	C
C34.9	Effects on the adverse effects of chemotherapy for lung cancer	jumentaihoto (十全大補湯)	Okimoto N, Yoshida K, Tamada S, et al. Effects of TSUMURA Jumentaihoto on myelosuppression by anticancer agents*. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1993; 81: 2040-3.	1)	N
C55	Effects on the adverse effects of chemotherapy for gynecologic cancer	jumentaihoto (十全大補湯)	Matsui H, Takamizawa H. Effects of jumentaihoto on adverse effects of chemotherapy for gynecologic cancer*. <i>Sanfujinka Kampo Kenkyū no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 1993; 10: 104-9.	1)	N
C80	Effects on gastrointestinal complaints in postoperative patients with esophageal and lung cancer	Kampo medicines (rikunshito [六君子湯], ninjin'yoeito [人參養榮湯], bakumondoto [麥門冬湯], and saireito [柴苓湯])	Shikama T, Abo S. Usefulness of Kampo medicines in postoperative patients with esophageal and lung cancer - especially for gastrointestinal complaints*. <i>Roka to Shikkan (Ageing and Diseases)</i> 1996; 9: 103-6.	1)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
C80	Effects in postoperative patients with esophageal cancer	rikkunshito (六君子湯)	Li S, Nabeya K, Yamada T, et al. Experience with postoperative administration of rikkunshito*. <i>Dai-3-kai Rinsho WAKAN-YAKU Kenkyukai Koen Kirokusyu (Proceedings of the 3rd Meeting of the WAKAN-YAKU Medical and Pharmaceutical Society) 1986; 4-6.</i>	3)	N
C80.0	Usefulness for fatigue associated with cancer chemotherapy.	hochuekkito (補中益氣湯)	Motoo Y, Nakatani N, Shimasaki T, et al. Usefulness of hochuekkito for fatigue associated with cancer chemotherapy*. <i>Gan Chiryō no Ayumi (Advances in Cancer Treatment) 2009; 28: 39-43.</i>	5)	N
D25.9	Effects of kampo treatment and gonadotropin-releasing hormone on uterine leiomyoma in perimenopausal women	shakuyakukanzoto (芍藥甘草湯), keishibukuryogan (桂枝茯苓丸)	Sakamoto S, Mitamura T, Iwasawa M, et al. Conservative management for perimenopausal women with uterine leiomyomas using Chinese herbal medicines and synthetic analogs of gonadotropin-releasing hormone*. <i>In Vivo 1998; 12: 333-8.</i>	1)	C

3. Blood diseases including anaemia (2 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
D64.9	Influence of juzentaihoto on hemoglobin recovery during preoperative autologous blood donation and after hip surgery	juzentaihoto (十全大補湯)	Kishida Y, Nishii T, Inoue T, et al. Juzentaihoto (TJ-48), a traditional Japanese herbal medicine, influences hemoglobin recovery during preoperative autologous blood donation and after hip surgery. <i>International Journal of Clinical Pharmacology and Therapeutics 2009; 47: 716-21.</i>	1)	C
D64.9	Evaluation of the relation between the clinical effects of tokishakuyakusan and <i>Paeonia lactiflora</i> raw materials	tokishakuyakusan (當歸芍藥散)	Shimada K, Kawase M, Shibahara N, et al. The relation between clinical effects of tokishakuyakusan and the identity of <i>Paeonia lactiflora</i> materials. <i>Journal of Ethnopharmacology 2010; 132: 438-42.</i>	2)	C

4. Metabolism and Endocrine Diseases (12 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
E10.4	Therapeutic effect on numbness caused by diabetic neuropathy	goshajinkigan (牛車腎氣丸)	Sato Y. Diabetic complications and Kampo 1. Clinical effects of goshajinkigan for diabetic neuropathy. <i>Nihon Toyo Igaku Zasshi (Kampo medicine) 2003; 54: 500-3.</i>	4)	I
E11.0	Efficacy for insulin resistance in patients with type 2 diabetes	goshajinkigan (牛車腎氣丸)	Uno T, Ohsawa I, Tokudome M, et al. Effect of goshajinkigan on insulin resistance in patients with type 2 diabetes. <i>Diabetes Research and Clinical Practice 2005; 69: 129-35.</i>	1)	C
E11.6	Improvement effect of yidiyin on erectile dysfunction in diabetic patients	yindin	Feng X, Qin C, Leng J, et al. Yidiyin, a Chinese herbal decoction, improves erectile dysfunction in diabetic patients and rats through the NO-cGMP pathway. <i>Bioscience, Biotechnology, and Biochemistry 2012; 76: 257-63.</i>	2) Chinese decoction	I
E11.9	The anti-HSP antibody-reducing effect of rokumijogan and goshajinkigan in patients with noninsulin-dependent diabetes	rokumigan (六味丸) goshajinkigan (牛車腎氣丸)	Tomii M, Kobayashi T, Sekiguchi Y, et al. The effects of Kampo formulations on anti-hsp antibody titer of the non insulin depended diabetes mellitus (NIDDM) patients. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU) 1998; 15: 274-5.</i>	1)	N
E13.6	Effects on diabetic complications	goshajinkigan (牛車腎氣丸)	Sato Y. Measures and treatments for diabetic complications*. <i>Fukuoka Ishi Kampo Kenkyukai Kaiho 1988; 9: 1-36.</i>	4)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
E14.4	Effects on diabetic neuropathy	goshajinkigan (牛車腎気丸)	Tawata M, Kurihara A, Nitta K, et al. The effects of goshajinkigan, an herbal medicine, on subjective symptoms and vibratory threshold in patients with diabetic neuropathy. <i>Diabetes Research and Clinical Practice</i> 1994; 26: 121-8.	1)	C
E28.3	Effects on luteal phase deficiency	tokishakuyakusan (当帰芍薬散)	Usuki S, Nakauchi T, Higa S, et al. The improvement of luteal insufficiency in fecund women by tokishakuyakusan treatment. <i>American Journal of Chinese Medicine</i> 2002; 30: 327-38.	1)	C
E28.9	Effects on FSH, LH, and estradiol levels in women with amenorrhea	unkeito (温経湯)	Ushiroyama T, Hosotani T, Yamashita Y, et al. Effects of unkei-to on FSH, LH and estradiol in anovulatory young women with hyper- or hypo-functioning conditions. <i>American Journal of Chinese Medicine</i> 2003; 31: 763-71.	1)	C
E34.8	Effect of ninjin'yoeito on Werner's syndrome skin fibroblasts	ninjin'yoeito (人参養榮湯)	Uchiyama Y, Nakajima S, Ohno T, et al. The effect of ninjinyoeito on Werner's syndrome skin fibroblasts. <i>American Journal of Chinese Medicine</i> . 1992; 20: 295-305.	6) This was a basic study.	C
E66.9	Effect on body fat mass or distribution.	-	Goto T, Matsushita D, Takasuka Y, et al. Evaluation of improvement effect on obesity for the uptake of the tea product "Gokusen Shanhai Koucha". <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2004; 52: 349-58.	2)	I
E78.5	Combined effect of daisaikoto and probucol on hyperlipidemia associated with non-insulin-dependent diabetes mellitus (NIDDM)	daisaikoto (大柴胡湯)	Murakami T, Oku J, Kimura Y, et al. The effect of Oriental medicine (dai-sai-ko-to) with probucol on lipoprotein metabolism in non-insulin dependent diabetics with hypercholesterolemia. <i>Domyaku Koka (The Journal of Japan Atherosclerosis Society)</i> 1991; 19: 839-46.	1)	N
E88.9	Effect of keishibukuryogan on endothelial function in patients with metabolic syndrome	keishibukuryogan (桂枝茯苓丸)	Nagata Y, Goto H, Hikiami H, et al. Effect of keishibukuryogan on endothelial function in patients with at least one component of the diagnostic criteria for metabolic syndrome: a controlled clinical trial with crossover design. <i>Evidence-Based Complementary and Alternative Medicine</i> 2012; 2012: 1-10. doi: 10.1155/2012/359282	2) Homemade preparation	N

5. Psychiatric/Behavioral Disorders (21 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F01.9	Efficacy for vascular dementia	chotosan (釣藤散)	Itoh T, Shimada Y, Terasawa K. Efficacy of choto-san on vascular dementia and the protective effect of the hooks and stems of <i>Uncaria sinensis</i> on glutamate-induced neuronal death. <i>Mechanisms of Ageing and Development</i> 1999; 111: 155-73.	4)	C
F03	Effects on senile dementia	Yokukansanka-chimpihange (抑肝散加陳皮半夏)	Hayano T, Majima M, Kadomae S, et al. Effects of TSUMURA Yokukansankachimpihange extracts for various dementias (II)*. <i>Kampo Igaku (Kampo Medicine)</i> 1987; 11: 16-25.	1), 3)	I
F03		Yokukansanka-chimpihange (抑肝散加陳皮半夏)	Hayano T. Effects of yokukansankachimpihange in the treatment of senile dementia*. <i>Gendai Iryogaku</i> 1989; 5: 109-13.		I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F03	Effects of Kampo preparations in the treatment of senile dementia	hachimijiogan (八味地黄丸) shosaikoto (小柴胡湯) yokukansan (抑肝散)	Tei M, Yamamoto T. Effects of hachimijiogan on mental activity and performance status in elderly*. <i>Gendai Iryogaku</i> 1989; 5: 122-8.	3)	N
F05.1	Effects in the treatment of cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia and Lewy bodies	yokukansan (抑肝散)	Iwasaki K, Maruyama M, Tomita N, et al. Effects of the traditional Chinese herbal medicine yi-gan san for cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia with lewy bodies. <i>The Journal of Clinical Psychiatry</i> 2005; 66: 1612-3.	1)	C
F10.0	Preventive effects on hangover	orengedokuto (黃連解毒湯)	Shichido T, Arichi S. Preventive effects of Kampo medicine (orengedokuto) on hangover - a double-blind randomized pilot study*. <i>Igaku no Ayumi (Journal of Clinical and Experimental Medicine)</i> 1988; 145: 789-95.	3)	I
F17.2	The efficacy of smoking cessation education with collaboration between pharmacies and healthcare centers	Nicorette	Oguri S, Sakata K. The efficacy study of smoking cessation education with collaboration between pharmacies and healthcare centers*. <i>Nihon Miyou Shisutemu Gakkai zasshi (The Journal of Japan Miyou System Association)</i> 2009; 14: 199-201.	2)	I
F34.9	Effects of Kampo therapy on mood disorder and depression	saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯) etc.	Chijiwa T, Itoh T. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease 3) Mood disorder. <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2009; 24: 80-4 (in Japanese with English abstract).	4)	I
F41.1	Effects on the adverse effects of anticancer agents in patients with ovarian cancer	kamikihito (加味帰脾湯)	Ikeda A, Higashio S, Ushiroyama T, et al. Experience with administration of kamikihito with chemotherapy and palliative care in patients with gynecologic cancer*. <i>Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)</i> 2003; 20: 152-5.	1) Although this was a randomized study, Kampo medicine use was not randomized.	I
F45.3	Therapeutic effect of Kampo medicine on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯)	Yamagiwa M. Effects of Kampo medicine on abnormal sensation in the throat of neurotic patients <i>Jibi Inkoka Rinsho (Practica Otologica)</i> 1998; 98 suppl: 52-5.	1) ,3)	N
F45.3	Effects on depressive pharyngolaryngeal paresthesia	saibokuto (柴朴湯)	Yamagiwa M. Effects of saibokuto in patients with depressive pharyngolaryngeal paresthesia*. <i>Kampo Igaku (Kampo Medicine)</i> 1998; 22: 19-22.	1) ,3)	N
F45.3	Therapeutic effect on depressive pharyngolaryngeal paresthesia	saibokuto (柴朴湯)	Furukawa K, Ishii T. Therapeutic effect of saibokuto vs. placebo on depressive pharyngolaryngeal paresthesia*. <i>Jibiinkoka Tenbo (Oto-rhino-laryngology, Tokyo)</i> 1988; 31: 1111-21.	3)	I
F45.3	Therapeutic effect on pharyngolaryngeal paresthesia	bukuryoingohange kobokuto (茯苓飲合半夏厚朴湯)	Kobayashi H, Soma M, Takano S, et al. Therapeutic effects of bukuryoingohangekobokuto on pharyngolaryngeal paresthesia*. <i>Jibiinkoka Tenbo (Oto-rhino-laryngology, Tokyo)</i> 1986; 29 suppl: 309-13.	3)	N
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯) saireito (柴苓湯)	Yamagiwa M. Effects of Kampo medicine on abnormal sensation in the throat of neurotic patients. <i>Kampo to Saishin Chiryō (Kampo & The Newest Therapy)</i> 1998; 7: 153-6.	1) , 3)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯) saireito (柴苓湯)	Yamagiwa M. Effect of saiboku-to on throat discomfort of patients with psychological symptoms. <i>Kampo to Saishin Chiryō (Kampo & The Newest Therapy)</i> 1999; 7: 353-8.	1)	N
F45.3	Effects on pharyngolaryngeal paresthesia	Saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯) saireito (柴苓湯)	Yamagiwa M. The role of Kampo preparations in treating pharyngolaryngeal paresthesia*. <i>Nihon Toyo Shinshin Igaku Kenkyū (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2001; 16: 36-8 (in Japanese with English abstract).	1), 3)	N
F45.9	Evaluation of Kampo therapy for unidentified complaints.	"keishibukuryogan (桂枝茯苓丸) + orengekuto (黃連解毒湯) kamishoyosan (加味逍遙散) tokishakuyakusan (當歸芍藥散) + ninjinto (人參湯)"	Terasawa K, Kumagai A, Arichi S, et al. Research on Kampo therapy - study overview of clinical controlled trial of Kampo treatments of unidentified complaints*. <i>Chiryogaku (Biomedicine and Therapeutics)</i> 1986; 16 suppl: 54-5.	3)	N
F45.9	Therapeutic effect on unidentified complaints associated with circulatory insufficiency	rokushingan (六神丸)	Kato H, Yano S, Hanasaki N, et al. Clinical evaluation of rokushin-gan on unidentified clinical complaints with circulatory insufficiencies – double blind comparative study of traditional and modified prescriptions in many hospitals-. <i>Therapeutic Research</i> 1988; 9: 785-800.	2)	I
F48.0	Effectiveness of Kampo medicines on fatigue and chronic fatigue syndrome	Various prescriptions	Chijiwa T, Itoh T. Fatigue and chronic fatigue syndrome. <i>Journal of Japanese Association of Oriental Psychosomatic Medicine</i> 2010; 25: 90-4.	4) RCT review	I
F48.9	Unidentified complaints with tendency to neurosis (stress disease)	orengokuto (黃連解毒湯)	Yamada K. 3. Kampo treatment in psychiatry. In: Role of Kampo medicines on the stress-related disorders in a modern society. <i>Nihon Toyo Igaku Zasshi (Kampo Medicine)</i> 1999; 49: 774-80.	5)	N
F60.3	Efficacy in the treatment of borderline personality disorder	yokukansan (抑肝散)	Miyaoka T, Furuya M, YasudaH, et al. Yi-gan san for the treatment of borderline personality disorder: an open-label study. <i>Progress in Neuro Psychopharmacology & Biological Psychiatry</i> 2008; 32: 150-4.	1)	C

6. Nervous System Diseases (including Alzheimer's Disease) (8 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
G24.0	Efficacy in the treatment of neuroleptic-induced tardive dyskinesia	yokukansan (抑肝散)	Miyaoka T, Furuya M, YasudaH, et al. Yi-gan san for the treatment of neuroleptic-induced tardive dyskinesia: an open-label study. <i>Progress in Neuro Psychopharmacology & Biological Psychiatry</i> 2008; 32: 761-4.	1)	C
G30.9	Effects on cognitive function in Alzheimer-type dementia	kamiuntanto (加味温胆湯)	Maruyama M, Tomita N, Iwasaki K, et al. Benefits of combining donepezil plus traditional Japanese herbal medicine on cognition and brain perfusion in Alzheimer's disease: a 12-week observer-blind, donepezil monotherapy controlled trial. <i>Journal of the American Geriatrics Society</i> 2006; 54: 869-71.	2)	C
G40.2	Clinical benefits for patients with partial epilepsy	shosaikotogokeishi kashakuyakuto (小柴胡湯合桂枝加芍藥湯)	Nakane Y, Yamauchi T, Onuma T, et al. Clinical utility of TJ-960 in patients with localization related epilepsy – late phase II study: multicenter, double-blind study in comparison with placebo. <i>Rinsho Hyoka (Clinical Evaluation)</i> 1999; 26: 419-52.	2)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
G40.9	Clinical application in arteriosclerosis, neurasthenia, nervous palpitation, epilepsy, and chronic kidney disease	saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯)	Sato J. Clinical application of saikokaryukotsuboreito in arteriosclerosis, neurasthenia, nervous palpitation, epilepsy, and chronic kidney disease*. <i>Atsugi Byoin ishi (Atsugi Medical Journal)</i> 1991; 11: 52-3.	1)	N
G40.9	Effects on epilepsy	shosaikotogokeishi kashakuyakuto (小柴胡湯合桂枝加芍薬湯)	Nagakubo S, Niwa S, Kumagai N, et al. Effects of TJ-960 on Sternberg's paradigm results in epileptic patients. <i>The Japanese Journal of Psychiatry and Neurology</i> 1993; 47: 609-20.	2)	C
G62.9	Preventive effect of goshajinkigan on peripheral neurotoxicity of FOLFOX therapy	goshajinkigan (牛車腎気丸)	Kono Toru, Mishima H, Shimada M, et al. Preventive effect of goshajinkigan on peripheral neurotoxicity of FOLFOX therapy: a placebo-controlled double-blind randomized phase II study (the GONE study). <i>Japanese Journal of Clinical Oncology</i> 2009; 39: 847-9.	5)	C&I
G90.9	Effects of ninjin, oriental bezoar, and kanzo powder combination capsules on autonomic nerve activity	ninjin (人參), oriental bezoar (牛黄), and kanzo powder combination capsule (甘草末配合カプセル)	Zheng A, Moritani T. Effect of the combination of ginseng, oriental bezoar and glycyrrhiza on autonomic nervous activity as evaluated by power spectral analysis of HRV and cardiac depolarization-repolarization process. <i>Journal of Nutritional Science and Vitaminology</i> 2008; 54: 148-53.	2)	I
G90.9	Effects of ninjin, oriental bezoar, and kanzo powder combination capsules on autonomic nerve activity and the immune system	ninjin (人參), oriental bezoar (牛黄), and kanzo powder combination capsule (甘草末配合カプセル)	Zheng A, Moritani T. Effect of the combination of ginseng, oriental bezoar and glycyrrhiza on autonomic nervous activity and immune system under mental arithmetic stress. <i>Journal of Nutritional Science and Vitaminology</i> 2008; 54: 244-9.	2)	I

8. Ear Diseases (1 reference)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
H65.9	Efficacy for secretory otitis media in children	saireito (柴苓湯)	Ikeda K, Takasaka T. Treatment of secretory otitis media with kampo medicine. <i>Archives of Otorhinolaryngology</i> 1988; 245: 234-6.	1)	C

9. Cardiovascular Diseases (6 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
I25.9	Effects on blood rheology in patients with coronary heart disease	-	Wu X, Harada T, Ishizaki F, et al. Study on the effect of xinnaotongluo liquid on hemorheology in patients with coronary heart disease. <i>International Medical Journal</i> 2005; 12: 129-31.	2)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
I67.9	Therapeutic effect of keishibukuryogan and trapidil on microcirculatory hemodynamics in patients with cerebrovascular accident	keishibukuryogan (桂枝茯苓丸)	Itoh T, Terasawa K, Kohta K, et al. Effect of keishi-bukuryo-gan and trapidil on the microcirculation in patients with cerebro-spinal vascular disease. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1992; 9: 40-6.	2)	I
I67.9		keishibukuryogan (桂枝茯苓丸)	Itoh T, Terasawa K, Kohta K, et al. Effects of keishi-bukuryo-gan and Trapidil on the microcirculation in patients with cerebro-spinal vascular disease. <i>Toyama Kenritsu Chuo Byoin Igaku Zasshi (The Medical Journal of Toyama Prefectural Central Hospital)</i> 1993; 16: 74-80.		N
I69.8	Effects on sequelae of cerebrovascular accidents	orengedokuto (黄連解毒湯)	Araki G. Effects of TSUMURA Orengekuto for sequelae of cerebrovascular accident*. <i>Geriatric Medicine</i> 1991; 29: 1587-99.	1)	N
I67.9	Effectiveness and safety of hachimijiogan in patients with hypertension or cerebrovascular disease and concomitant symptoms	hachimijiogan (八味地黄丸)	Ito K, Yamamoto H, Saibara T, et al. The usefulness of Kanebo Hachimijiogan in patients with hypertension or cerebrovascular disease [excluding acute phase symptoms] and their concomitant symptoms: a multicenter, double-blind, crossover study. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1988; 76: 1096-114 (in Japanese)	3) Included in EKAT 2010, but excluded due to likelihood that pre-1985 Kampo preparations were used.	I
I73.0	Usefulness of TSUMURA Ninjin'yoeito for Raynaud's symptoms	ninjin'yoeito (人參養榮湯)	Tanabe E. Usefulness of TSUMURA Ninjin'yoeito for Raynaud's symptoms*. <i>Hifuka ni Okeru Kampo Chiryō no Genkyō</i> 1990; (1): 113-24.	1)	N

10 Respiratory Diseases (including Influenza and Rhinitis) (8 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
J00	Effects on common cold syndrome and acute bronchitis	maobushisaishinto (麻黄附子細辛湯)	Yamamoto T, Ounishi M, Yoshida K. Meta-analysis about effectiveness of mao-bushi-saishin-to in treating common cold syndrome. <i>Health science</i> 2001; 17: 94-9.	1)	I
J00	Therapeutic effect on cough in patients with common cold syndrome	maobushisaishinto (麻黄附子細辛湯)	Nishizawa Y, Tomiyo N, Mayumi Y, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and Western drugs for cold in common patients with allergic cold syndrome. <i>Kampo to Meneki Arerugi (Kampo and Immuno-Allergy)</i> 2005; 18: 56-67.	5)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
J10.1	Comparison of the effects of oseltamivir and maoto on pediatric influenza A	maoto (麻黄湯)	Suzuki E, Ichihara K. Impact of Japanese herbal medicine, mao-to, compared to oseltamivir on fever course in children with Influenza type A. <i>Gairai Shonika (The Journal of Ambulatory and General Pediatrics)</i> 2011; 14: 248-53.	1) Not an RCT The choice of drugs was basically left up to parents/guardians, and only if there was no specific preference were the drugs administered alternately in order of examination. The fact that the drugs were administered in order of examination lends it to being described as a quasi-RCT, however, that fact, and the fact that the drugs were administered according to parents'/guardians' preferences, mean it does not fit the description of an RCT.	I
J12.8	Effects of integrated Chinese and western medicine on QOL in convalescent-phase SARS patients	-	Bian Y, Qi W, Song Q, et al. Effects of integrated Chinese and western medicine on QOL in convalescent-phase SARS patients*. <i>Toho Igaku (Eastern Medicine)</i> 2003; 19: 51-5.	2)	I
J18.2	Effect on aspiration pneumonia	seihaito (清肺湯)	Mantani N, Kasahara Y, Kamata T, et al. Effect of seihai-to, a Kampo medicine, in relapsing aspiration pneumonia-an open label pilot study. <i>Phytomedicine</i> 2002; 9: 195-201.	2)	C
J30.1	Outcomes of patients treated with mao-preparations for spring pollinosis	ryokankyomishingeninto (苓甘姜味辛夏仁湯), eppikajutsuto (越婢加朮湯), daiseiryuto (大青竜湯), keimakakuhanto (桂麻各半湯), gokoto (五虎湯), and maobushisaishinto (麻黄附子細辛湯)	Mori H, Shimasaki M, Kurata F, et al. Outcome after six-year treatment with mao-preparations for spring pollinosis*. <i>Progress in Medicine</i> 2003; 23: 1925-9.	4)	I
J44.8	Therapeutic effect on diffuse panbronchiolitis (DPB)	hochuekkito (補中益氣湯)	Sugiyama Y. Kampo therapy on diffuse panbronchiolitis. <i>Kampo to Saishin Chiryō (Kampo & The Newest Therapy)</i> 1997; 6: 263-7.	1)	N
J45.9	Effect on cough thresholds in asthmatic patients compared with emedastine difumarate	bakumondoto (麥門冬湯)	Watanabe N, Gang C, Fukuda T. Comparison of traditional Chinese-Japanese herbal medicine bakumondo-to with emedastine difumarate on asthmatic patients with increase cough sensitivity. <i>Journal of the World Allergy Organization</i> 2003; suppl 1: 52 P-2-28.	1)	C

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases (16 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K11.7	Recovery effects against psychotropic drug-induced xerostomia	ninjin'yoeito (人參養榮湯), byakkokaninjinto (白虎加人參湯)	Hara R, Yamagishi H, Okubo M, et al. The Effects of Kampo medicine against drug-induced xerostomia. <i>Journal of Dental Research</i> 2000; 79: 1239 No.36.	6) This was a basic study.	C
K29.5	Therapeutic effect on chronic gastritis	orento (黃連湯)	Nakajima O, Sone M. Treatment with TSUMURA Orento for chronic gastritis*. <i>Progress in Medicine</i> 1994; 14: 1713-9.	5)	N
K30.0	Evaluation of Kampo preparations for functional dyspepsia	rikkunshito (六君子湯)	Okumi H, Sekiya N, Terasawa K. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease 1) EBM evaluation of Kampo preparations for functional dyspepsia. <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2009; 24: 70-75 (in Japanese with English abstract)	4)	I
K59.0	Laxative effects	hyakudoku-kudashi (百毒下し)	Sugimoto K, Ohta H. Comparison of Hyakudoku-kudashi® with Colac® or Withone® in drug-taking satisfactory -Characteristic effect of Hyakudoku-kudashi® as a herbal laxative-. <i>Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)</i> 2006; 56: 367-76.	2)	I
K59.0	The effect on bowel movement and its safety	young barley leaf powder	Matsui N, Yamamoto K, Yamamoto S, et al. Safety and effect of young barley leaf powder on defecation. <i>Nihon Rinsho Eiyō Gakkai Zasshi (Journal of Japanese Society of Clinical Nutrition)</i> 2008; 29: 406-13.	2)	I
K59.0	Evaluation of the safety and improvement in bowel habits of young barley leaf powder	young barley leaf powder (大麦若葉粉末)	Matsui N, Yamamoto S, Nagao M, et al. Bowel Habit-improving Effect and safety of a young barley leaf powder-containing diet in male and female adult volunteers with low fecal frequency: a dose-finding study and an efficacy confirmation study. <i>Journal of Japanese Society of Clinical Nutrition</i> 2011; 32: 243-51.	2)	I
K71.9	Preventive effect on danazol-induced hepatic damage	shosaikoto (小柴胡湯)	Yaginuma T, Okamura T, Takeuchi T, et al. Preventive effect of traditional herbal medicine, shosaiko-to, on danazol-induced hepatic damage. <i>International Journal of Gynaecology & Obstetrics</i> 1989; 29: 337-41.	1)	C
K72.9	Efficacy and safety for removal of plasma ammonia in hepatectomized patients	daikenchuto (大建中湯)	Kaiho T, Tanaka T, Tsuchiya S, et al. Effect of the herbal medicine dai-kenchu-to for serum ammonia in hepatectomized patients. <i>Hepato-Gastroenterology</i> 2004; 52: 161-5.	1)	C
K73.0	Effect on chronic hepatitis	shosaikoto (小柴胡湯)	Mizuta M, Murata K, Morimoto T, et al. Therapeutic evaluation of shosaikoto on chronic hepatitis – study on double-blind test -. <i>Kan Tan Sui</i> 1986; 12: 155-68.	3)	I
K73.9	Therapeutic effect on chronic active hepatitis	shosaikoto (小柴胡湯)	Jia K, Chen N, Peng X, et al. The study of shosaikoto as treatment for chronic active hepatitis*. <i>Progress in Medicine</i> 1992; 12: 1180-3.	2)	N
K73.9	Effect on the adverse effects of IFN in patients with chronic hepatitis	maoto (麻黃湯) daiseiryuto (大青竜湯)	Kainuma M, Hayashi J, Sakai S, et al. The efficacy of herbal medicine (Kampo) in reducing the adverse effects of IFN-β in chronic hepatitis C. <i>American Journal of Chinese Medicine</i> 2002; 30: 355-67.	1), 2)	C
K73.9	Effect on the adverse effects of IFN in patients with chronic hepatitis	maoto (麻黃湯)	Kainuma M, Sakai S, Sekiya N, et al. The effects of a herbal medicine (mao-to) in patients with chronic hepatitis C after injection of IFN-beta. <i>Phytomedicine</i> 2004; 11: 5-10.	1), 2)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
K74.6	Usefulness in the treatment of hepatic cirrhosis	saireito (柴苓湯)	Ohkubo H, Shiota A, Amaki S, et al. Oriental medicine in liver cirrhosis: effect of "sairei-tou" in liver cirrhosis with controlled study. <i>Kampo to Saishin Chiryō (Kampo & the Newest Therapy)</i> 1994; 3: 121-7.	1)	N
K76.9	Effect on immune abnormality in liver disease	shosaikoto (小柴胡湯)	Mizoguchi Y, Sakagami Y, Kodama C, et al. Immune abnormality in liver disease and oriental medicine therapy*. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1987; 4: 227-30.	6) This was a basic study.	I
K83.1	Effects in postoperative patients with biliary obstruction	inchinkoto (茵陳蒿湯)	Kobayashi H, Horikoshi K, Yamataka A, et al. Beneficial effect of a traditional herbal medicine (inchin-ko-to) in postoperative biliary atresia patients. <i>Pediatric Surgery International</i> 2001; 17: 386-9.	1)	C
K91.3	Effects on bowel movements after colonic and rectal surgery	keishibukuryogan (桂枝茯苓丸) + daikenchuto (大建中湯)	Suehiro T, Matsumata T, Shikada Y, et al. The effect of the herbal medicines dai-kenchu-to and keishi-bukuryo-gan on bowel movement after colorectal surgery. <i>Hepato-Gastroenterology</i> 2005; 52: 97-100.	1)	C

12. Skin Diseases (6 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
L20.9	Evaluation of Kampo therapy for atopic dermatitis	shosaikoto, etc. (小柴胡湯ほか)	Toyoda M. Kampo therapy and atopic dermatitis - An EBM evaluation of Kampo therapy for atopic dermatitis. <i>Hifu no Kagaku (Skin Research)</i> 2010; 9: suppl. 15: 22-7	4)	I
L30.9	Effects on atopic dermatitis and chronic eczema	shosaikoto (小柴胡湯)	Morohashi M, Toyoda M. Evaluation of efficacy of an evidence-based Kampo therapy for atopic dermatitis. <i>Hifu no Kagaku (Skin Research)</i> 2003; 2: 44-8.	4)	I
L65.9	Clinical evaluation in the treatment of male pattern baldness	Taiho HR-2 preparation (大宝HR-2製剤)	DABAO HR-2Study Group. Topical DABAO HR-2in the treatment of male pattern alopecia – a randomized double-blind trial - <i>Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines)</i> 1988; 4: 1955-67.	2)	I
L65.9	Evaluation of kampo treatment for alopecia	hangekobokuto (半夏厚朴湯)	Ohkuma M. Treatment of alopecia by Chinese drug, hange-koboku-to combined with liquid nitrogen application and PUVA – the second report- . <i>Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)</i> 1998; 15: 422-3.	1)	C
L70.0	Effects on acne vulgaris	jumihaidokuto (十味敗毒湯) seijobofuto (清上防風湯)	Hayashi N, Kawashima M. The usefulness of chemical peeling with 30% glycolic acid (ph 1.5) for acne vulgaris. <i>Rinsho Hifuka (Japanese Journal of Clinical Dermatology)</i> 2003; 57: 1213-6.	6) Although used in combination, Kampo medicines were not evaluated.	I
L70.9	Clinical efficacy of chemical peels for the treatment of acne	seijobofuto (清上防風湯) jumihaidokuto (十味敗毒湯)	Kishioka A, Yamamoto Y, Miyazaki M, et al. Clinical evaluation of chemical peeling with glycolic acid for acne. <i>Aesthetic Dermatology</i> 2004; 14: 195-202.	6) Although used in combination, Kampo medicines were not evaluated.	I

13. Diseases of the Musculoskeletal System and Connective Tissue (4 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
M06.9	Effects of Kampo medicines on rheumatoid arthritis patients receiving methotrexate	keishinieppiryojut subu (桂枝二越婢苓朮附)	Kogure T, Tatsumi T, Sato H, et al. Traditional herbal medicines (Kampo) for patients with rheumatoid arthritis receiving concomitant methotrexate: a preliminary study. <i>Alternative Therapies in Health and Medicine</i> 2009; 16: 46-51.	1) , 2)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
M35.0	Effects on Sjögren's syndrome	bakumondoto (麦門冬湯)	Doi Y, Suzuki T, Ono S. Effects of bakumondoto on Sjögren's syndrome*. <i>Gendai Toyo Igaku (The Journal of Traditional Sino-Japanese Medicine)</i> 1991; 12 suppl 1: 229-31.	1)	N
M35.2	Effects on Behçet's disease	unseiin (温清飲)	Kaneko F. Clinical use of unseiin for Behçet's disease. <i>Progress in Medicine</i> 1986; 6: 384-6.	3)	N
M35.9	Effects of Kampo medicines in treating collagen disease	saireito, etc. (柴苓湯ほか)	Ohno S. Roles of Kampo medicine in treating rheumatic diseases. <i>Journal of Traditional Medicines</i> 2007; 24: 73-80.	4)	C

14. Genitourinary Tract Disorders (including Climacteric Disorders) (11 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
N02.8	Clinical efficacy for the treatment of IgA nephropathy in children	shosaikoto (小柴胡湯)	Takahashi Y, Uemura M. Clinical efficacy of shosaikoto for the treatment of IgA nephropathy in children*. <i>Kampo Igaku (Kampo Medicine)</i> 1986; 10: 27-30.	3)	N
N18.9	Improvement of creatinine levels in chronic renal failure with yojinkodakuto	yojinkodakuto (養腎降濁湯)	Nagasaka K, Fukuda H, Hashimoto M, et al. Yozinkodakuto, a traditional Chinese (Japanese Kampo) medicine, improves the creatinine level in chronic renal failure. <i>Journal of Traditional Medicines</i> 2007; 24: 87-9.	1), 2)	C
N20.9	Effects on excretion of calculi after extracorporeal shock wave lithotripsy (ESWL)	choreito (猪苓湯)	Takada M, Yano H, Kanbara N, et al. Effect of chorei-to on spontaneous discharge of urinary stones after extracorporeal shock wave lithotripsy (ESWL). <i>Hinyokika Kiyo (Acta Urologica Japonica)</i> 1997; 43: 311-4.	1)	C
N20.9	Evaluation of the effects on calcium oxalate crystal formation in human urine	choreito (猪苓湯) goreisan (五苓散)	Yoshimura K, Miyake O, Okuyama A, et al. Effect of chorei-to and gorei-san on calcium oxalate crystallization in human urine. <i>Hinyokika Kiyo (Acta Urologica Japonica)</i> 1998; 44: 13-6.	1)	C
N28.9	Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction	anisodamine	Wang Y, Fu X, Wang X, et al. Protective effects of anisodamine on renal function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. <i>The Tohoku Journal of Experimental Medicine</i> 2011; 224: 91-7.	2)	I
N41.1	Combined effects of hachimijiogan and trimethoprim-sulfamethoxazole on chronic prostatitis	hachimijiogan (八味地黄丸)	Kaneko S, Akiyama T, Kurita T. Combined treatment of chronic prostatitis with sulfamethoxazole-trimethoprim. <i>Hinyokika Kiyo (Acta Urologica Japonica)</i> 1988; 34: 1091-5.	3)	N
N46	Effects in patients with idiopathic male infertility	ninjin'yoeito (人參養榮湯)	Oeda F, Ichikawa T, Ozawa H, et al. Clinical experience of ninjin-yoei-to on male sterility. <i>Shinyaku to Rinsho (Journal of New Remedies & Clinics)</i> 1994; 43: 2197-203.	1)	I
N50.8	Clinical efficacy for the treatment of urologic disease	saireito (柴苓湯)	Shida K, Imamura K, Katayama T, et al. Clinical efficacy of sairei-to in various urinary tract diseases centering on fibrosis. <i>Hinyokika Kiyo (Acta Urologica Japonica)</i> 1994; 40: 1049-57.	1)	C
N74	Effects on infectious vaginal discharge	-	Nazar H, Usmanhani K, Hannan A. Clinical evaluation of unani medicine for infective vaginal discharge. <i>Journal of Traditional Medicines</i> 2005; 22: 301-7.	2)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
N95.1	Effects in climacteric patients with depression	kamishoyosan (加味逍遙散)	Ushiroyama T, Ikeda A, Sakuma K, et al. Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients. <i>American Journal of Chinese Medicine</i> 2004; 32: 621-9.	1)	C
N97.9	Effects on infertility due to ovarian dysfunction	kamishoyosan (加味逍遙散)	Kano T, Ito C, Kasamatsu H, et al. Clinical study of prognosis of 200 deliveries after kampo-treatment for ovarian dysfunctional infertilities and tocolysis. <i>Nihon Funin Gakkai Zasshi (Japanese Journal of Fertility and Sterility)</i> 1991; 36: 612-20.	1)	N

15. Ante/Post-partum Diseases (2 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
O12.0	Clinical benefits for patients with gestational edema	saireito (柴苓湯)	Iura T, Kuwahara S, Takabayashi H, et al. Clinical benefits of saireito treatment for gestational edema*. <i>Rinsho Fjinka Sanka (Clinical Gynecology and Obstetrics)</i> 1994; 48: 355-8.	1)	N
O92.3	Clinical efficacy for postpartum galactostasis	kakkonto (葛根湯)	Aisaka K, Kokuho K, Tawada T, et al. Study of the clinical efficacy of kakkonto (EK-1) for treatment of postpartum galactostasis*. <i>Sanfujinka no Sekai (The World of Obstetrics and Gynecology)</i> 1990; 42: 289-93.	1)	N

18. Symptoms and Signs (18 references)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R10.4	Effects on lower abdominal pain after surgery	tokishigyakuka-goshuyushokiyoto (当帰四逆加呉茱萸生姜湯)	Nishizawa Y, Amakata Y. The clinical effect of tokishigakukagoshuyushokiyoto on abdominal pain following to lower abdominal operation. <i>Toyo Igaku to Pain Clinic (Oriental Medicine and the Pain Clinic)</i> 1988; 18: 138-44.	1)	N
R13	Effects on swallowing reflex	hangekobokuto (半夏厚朴湯)	Iwasaki K, Wang Q, Nakagawa T, et al. The traditional Chinese medicine banxia houpo tang improves swallowing reflex. <i>Phytomedicine</i> 1999; 6: 103-6.	1)	C
R19.8	Anomalous abdominal relaxation in Shakuju therapy	-	Takahashi K, Matsuzawa T, Hara O, et al. Research into anomalous abdominal relaxation in Shakuju therapy. <i>Toyo Ryoho Gakko Kyokai Gakkai Shi (The Journal of Japan College Association of Oriental Medicine)</i> 2012; 35: 81-3.	2)	I
R20.8	Effects on diabetic neuropathy	goshajinkigan (牛車腎気丸)	Sakamoto N, Sato Y, Goto Y, et al. Treatment of diabetic neuropathy with oriental medicines - comparison between goshajinkigan and mecobalamin*. <i>Tonyobyo (Journal of the Japan Diabetes Society)</i> 1987; 30: 729-36.	3)	I
R20.8	Effects on diabetic peripheral neuropathy	goshajinkigan (牛車腎気丸)	Toba K, Orimo H. Diabetic peripheral neuropathy*. <i>Shindan to Chiryō (Diagnosis and Treatment)</i> 1986; 74: 2330-4.	3)	N
R25.2	Usefulness in the treatment of muscle cramp associated with hepatic cirrhosis	hachimijiogan (八味地黄丸), goreisan (五苓散), shakuyakukanzoto (芍薬甘草湯)	Takamori S, Ando T. A study of the effect of hachimi-jio-gan on painful muscle cramps (komuragaeri). <i>Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)</i> 1994; 45: 151-7.	1)	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R42.0	Efficacy and safety in the treatment of chronic dizziness	saikokaryukotsu-boreito (柴胡加竜骨牡蠣湯) ryokeijutsukanto (苓桂朮甘湯)	Komatsuzak A, Sakata E, Kamei T, et al. Clinical study of chai-hu-gia-long-gu-nu-li tang and ling-gui-zhu-gan tang on chronic dizziness cares. <i>Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)</i> 1986; 14: 4479-90.	3)	I
R42.0	Efficacy in the treatment of dizziness	takushato (沢瀉湯)	Yoneta Y, Hashiguchi K, Takiguchi Y, et al. Clinical efficacy of takushato a Kampo (Japanese herbal) medicine, in the treatment of refractory dizziness and vertigo: Comparison between standard and triple dose. <i>Journal of Traditional Medicines</i> 2009; 26: 68	2)	I
R42	QOL improvement with combination of hochuekkito and vestibular rehabilitation for patients with dizziness and depression tendency	hochuekkito (補中益気湯)	Arai M, Goto F, Hosaka T. Study of Combination Therapy of Vestibular Rehabilitation and Hochuekkito for Intractable Dizziness. <i>Shinshin Igaku (Japanese Journal of Psychosomatic Medicine)</i> 2012; 52: 221-8 (in Japanese)	1)	I
R50.9	Effects of on postoperative nonspecific fever	shosaihoto (小柴胡湯)	Ochiai K, Kobayashi S, Shimizu Y, et al. Effect of Chinese medicine for nonspecific fever after operation. <i>Nippon Sanka Fujinka Gakkai Tokyo Chiho Bukai Kaishi (Tokyo Journal of Obstetrics and Gynecology)</i> 1986; 35: 279-82.	3)	N
R51.0	Usefulness for treating chronic headache	keishininjinto (桂枝人參湯) chotosan (釣藤散)	Matsumoto H, Kashiwagi M, Matsuya M, et al. Study of the usefulness of keishininjinto and chotosan for treating chronic headache*. <i>Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)</i> 1995; 72: 1299-303.	1)	N
R51.0	Effects of Kampo therapy on primary headache (other than migraine)	chotosan, etc. (釣藤散ほか)	Chiba N, Oka T, Tsuji S. Japanese Association of Oriental Psychosomatic Medicine, EBM Team Report: Kampo therapy evidence for psychosomatic disease and stress-related disease - Primary headache (non-migraine). <i>Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)</i> 2009; 24: 85-8 (in Japanese with English abstract).	4)	I
R52.9	Effects on postoperative abdominal pain	tokishigyakuka-goshuyushokiyoto (当帰四逆加呉茱萸生薑湯)	Nishizawa Y, Amakata Y. The analysis of the effect of tokishigyakukagoshuyushokiyoto on the abdominal pain after lower abdominal operation. <i>Toyo Igaku to Pain Clinic (Oriental Medicine and the Pain Clinic)</i> 1988; 18: 102-8.	1)	I
R52.9	Effects on postoperative abdominal pain	tokishigyakuka-goshuyushokiyoto (当帰四逆加呉茱萸生薑湯)	Nishizawa Y, Amakata Y. The clinical effect of tokishigyakukagoshuyushokiyoto on abdominal pain following to abdominal operation. - III Clinical effectiveness in each class of CMI classification-. <i>Toyo Igaku to Pain Clinic (Oriental Medicine and the Pain Clinic)</i> 1988; 18: 50-7.	1)	I
R52.9	Efficacy as a prophylactic for myalgia and arthralgia following carboplatin and paclitaxel combination chemotherapy in patients with non-small cell lung cancer	shakuyakukanzoto (芍薬甘草湯)	Yoshida T, Sawa T, Ishiguro T, et al. The efficacy of prophylactic shakuyaku-kanzo-to for myalgia and arthralgia following Carboplatin and Paclitaxel combination chemotherapy for non-small cell lung cancer. <i>Support Care Cancer</i> 2009; 17: 315-20.	1)	N
R53	Effects on chronic fatigue	various kinds of decoctions (煎劑)	Sekiya N, Shimada Y, Shintani T, et al. Reduction of perception of chronic fatigue in an observational study of patients receiving 12 weeks of Kampo therapy. <i>The Journal of Alternative and Complementary Medicine</i> 2005; 11: 895-901.	1), 2)	C

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
R68.8	Effects on "oketsu" score and erythrocyte deformability in patients with multiple lacunar infarction	keishibukuryogan (桂枝茯苓丸)	Hikiyama H, Goto H, Sekiya N, et al. Comparative efficacy of keishi-bukuryo-gan and pentoxifylline on RBC deformability in patients with "oketsu" syndrome. <i>Phytomedicine</i> 2003; 10: 459-66.	1), 2)	C
R68.8	Effects on indefinite complaints including coldness and shoulder stiffness	NT21 fine granules (keishibukuryogan [桂枝茯苓丸] + vitamin E)	Sato N, Takei N, Ikejima K, et al. Effects of a combination preparation of guizhi fuling wan and vitamin E on indefinite complaints such as stiffness of shoulder and cold feeling. <i>Toho Igaku (Eastern Medicine)</i> 2004; 19: 23-43.	2)	I

19. Injury, Poisoning, and Postoperative Pain (2 reference)

ICD-10	Research Question	Kampo Formula	Reference	Reason for Exclusion	Source
T65.8	Effects on yusho (油症)	hochuekkito (補中益気湯) keigairenyoto (荊芥連翹湯) goshajinkigan (牛車腎気丸) bakumondoto (麦門冬湯)	Tokunaga S. Kampo therapy for yusho. Research on the effect of the heating medium on humans, and its therapeutic effects*. <i>Kosei Rodosho Kagaku Kenkyuui Hojokin Shokuhin no Anshin Anzen Kakuho Suishin Kenkyu Jigyo Heisei 19 Nendo Sokatsu Buntan Kenkyu Hokokusho (Ministry of Health, Labour and Welfare, Science Research Grant, Food Safety and Security Promotion Research Project, Summary and Working-group Research Report Fiscal Year 2006)</i> 2008; 65-72.	1)	N
T75.2	Combined effects of balneotherapy with other therapies	tokishigyakugos huto (当帰四逆加呉茱萸湯), goshajinkigan (牛車腎気丸), bushimatsu (ブシ末)	Wang H, Eboshida A, Kagamimori S. Balneotherapy in combination with other therapies. <i>The Journal of the Japanese Society of Balneology, Climatology and Physical Medicine</i> 2010; 73: 143-58.	4)	I

21. Others (23 reference)

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Effects on plasma levels of gut-regulatory peptides in healthy subjects	keishininjinto (桂枝人參湯)	Sato Y, Katagiri F, Inoue S, et al. Effect of a single treatment with keishininjinto on plasma levels of gut-regulatory peptides in healthy subjects. <i>Journal of Health Science</i> 2007; 53: 220-5.	1)	I
Z01.8	Effects on gastrointestinal peptide concentrations in the plasma of healthy subjects	shohangeka-bukuryoto (小半夏加茯苓湯)	Katagiri F, Itoh H, Takeyama M. Effect of sho-hange-ka-bukuryo-to on gastrointestinal peptide concentrations in the plasma of healthy human subjects. <i>Biological & Pharmaceutical Bulletin</i> 2004; 27: 1674-8.	1)	C
Z01.8	Effects on human plasma adrenocorticotrophic hormone and cortisol levels in patients exposed to continual stress	shohangeka-bukuryoto (小半夏加茯苓湯) nichinto (二陳湯)	Katagiri F, Inoue S, Sato Y, et al. Comparison of the effects of sho-hange-ka-bukuryo-to and nichin-to on human plasma adrenocorticotrophic hormone and cortisol levels with continual stress exposure. <i>Biological & Pharmaceutical Bulletin</i> 2004; 27: 1679-82.	1)	C
Z01.8	Effects on plasma neuropeptide levels in healthy subjects	daikenchuto (大建中湯)	Sato Y, Inoue S, Katagiri F, et al. Effects of pirenzepine on dai-kenchu-to-induced elevation of the plasma neuropeptide levels in humans. <i>Biological & Pharmaceutical Bulletin</i> 2006; 29: 166-71.	1)	I

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Effects on plasma levels of calcitonin gene-related peptides and substance P in healthy subjects	ninjinto (人参湯)	Sato Y, Katagiri F, Inoue S, et al. Effects of ninjin-to on levels of calcitonin gene-related peptide and substance P in human plasma. <i>Biological & Pharmaceutical Bulletin</i> 2004; 27: 2032-4.	1)	C
Z01.8	Immunological effects in bedridden elderly patients	hochuekkito (補中益氣湯) kanzo powder (甘草末) hochuekkito (補中益氣湯) + kanzo powder (甘草末)	Oide H, Okuda C. Evaluation of immunological effects of hochuekkito and kanzo powder in bedridden elderly patients*. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1988; 5: 555.	5)	N
Z01.8	Changes in serotonin and vasoactive intestinal peptides in human plasma	daikenchuto (大建中湯)	Nagano T, Itoh H, Takeyama M. Effect of dai-kenchu-to on levels of 5-hydroxytryptamine (serotonin) and vasoactive intestinal peptides in human plasma. <i>Biological & Pharmaceutical Bulletin</i> 2000; 23: 352-3.	1)	C&I
Z01.8	Effects on plasma levels of brain-gut peptides (motilin, vasoactive intestinal peptide, gastrin, and somatostatin)	ninjinto (人参湯)	Naito T, Itoh H, Nagano T, et al. Effects of ninjin-to on levels of brain-gut peptides (motilin, vasoactive intestinal peptide, gastrin, and somatostatin) in human plasma. <i>Biological & Pharmaceutical Bulletin</i> 2001; 24: 194-6.	1)	C&I
Z01.8	Improvement in QOL of patients undergoing bowel preparation for colonoscopy	daikenchuto (大建中湯) shakuyakukanzoto (芍薬甘草湯)	Saida Y. Efficacy of daikenchuto combination in bowel preparation for colonoscopy — 6 prospective study*. <i>Progress in Medicine</i> 2005; 25: 3058-9.	5)	N
Z01.8	Effects on corticosteroids	hachimijiogan (八味地黄丸)	Itoh T, Tanaka N, Shibahara N, et al. Effect of hachimi-jio-gan on adrenal corticosteroids. <i>Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)</i> 1998; 15: 155-60.	2)	I
Z01.8	Pharmacokinetics of (-) epicatechin 3-O-gallate, glycyrrhetic acid, and rhein in healthy subjects after unpito administration	unpito (温脾湯)	Takizawa Y, Mizuhara Y, Morita T, et al. Pharmacokinetics of (-) epicatechin 3-o-Gallate, glycyrrhetic acid and rhein in healthy male volunteers after a single dose administration of TJ-8117 (Unpito), a Japanese traditional medicine for renal failure. <i>Rinsho Yakuri (Japanese Journal of Clinical Pharmacology and Therapeutics)</i> 2006; 37: 33-40.	2)	I
Z01.8	Effects on serum triglyceride levels in healthy young women	azukiyu (azuki bean juice)	Maruyama C, Araki R, Kawamura M, et al. Azuki bean juice lowers serum triglyceride concentrations in healthy young women. <i>Journal of Clinical Biochemistry and Nutrition</i> 2008; 43: 19-25.	2)	I
Z01.8	Serum aconitine concentrations after bushi powder administration	shuchibushimatsu (修治ブシ末) bushi powder (ブシ末)	Nakae H, Fujita Y, Igarashi T, et al. Serum aconitine concentrations after taking powdered processed Aconiti tuber. <i>Biomedical Research</i> 2008; 29: 225-31.	2) An herbal preparation was used.	C
Z01.8	Effect of bushimatsu on blood plasma serotonin and interleukin 18 levels	bushimatsu (ブシ末)	Nakae H. Plasma serotonin and interleukin 18 levels after taking powdered processed aconiti tuber. <i>Journal of Complementary and Integrative Medicine</i> 2010; 7: 1-9.	2) A herbal preparation was used.	N
Z01.8	Effect of bushimatsu on degree of oxidation and antioxidative activity	shuchibushimatsu (修治ブシ末), bushimatsu (ブシ末)	Nakae H. Clinical Evaluation of oxidative stress after taking powdered processed Aconiti Tuber. <i>Nihon Toyo Igaku Zasshi (Kampo Medicine)</i> 2010; 61: 15-8 (in Japanese with English abstract).	2) A herbal preparation was used.	N

ICD-10	Research Question	Kampo Formula	References	Reason for Exclusion	Source
Z01.8	Physical property of glycyrrhizin contained in kampo extracts and change in the blood levels of glycyrrhetic acid	shoseiryuto (小青竜湯), shosaikoto (小柴胡湯)	Miyamura M, Ono M, Kyotani S, et al. Properties of glycyrrhizin in Kampo extracts including licorice root and changes in the blood concentration of glycyrrhetic acid after oral administration of Kampo extracts. <i>Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan)</i> 1996; 116: 209-16.	1)	C
Z01.8	Comparison of differences in human gene expression induced by tokishakuyakusan containing different grades of crude drug	tokishakuyakusan (当帰芍薬散)	Hayasaki T, Katoh A, Shojo M, et al. Differences in human gene expression induced by tokishakuyakusan containing different grades of Angelica radix. <i>Journal of Traditional Medicines</i> 2010; 27: 166-78.	1)	I
Z01.8	Comparison of GLP-1 response and postprandial blood sugar and insulin level to evaluate the effects of the traditional Japanese medicine rikkunshito on postprandial glucose and lipid metabolism	rikkunshito (六君子湯)	Tanaka K, Urita Y, Nara K, et al. Effects of the traditional Japanese medicine rikkunshito on postprandial glucose and lipid metabolism. <i>Hepato-Gastroenterology</i> 2011; 58: 1112-8.	6) This is an RCT-cross over paper, however, the RCT-cross over outcomes were not described in the results.	N
Z01.9	Effects on plasma levels of brain-gut peptides (motilin, gastrin, and somatostatin)	hangeshashinto (半夏瀉心湯)	Naito T, Itoh H, Yasunaga F, et al. Hange-shashin-to raises levels of somatostatin, motilin, and gastrin in the plasma of healthy subjects. <i>Biological & Pharmaceutical Bulletin</i> 2002; 25: 327-31.	1)	I
Z02.9	Augmentative effect on acupuncture anesthesia	shakuyakukanzoto (芍薬甘草湯)	Kitade T, Jinno H, Hyodo M, et al. Experimental study of the augmentative effect of shakuyakukanzoto on acupuncture anesthesia*. <i>Kiso to Rinsho (The Clinical Report)</i> 1986; 20: 3309-14.	3)	I
Z22.8	Effects of <i>hozai</i> (補劑, formulations with tonic effects) on carriers of methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) undergoing neurosurgery	juzentaihoto (十全大補湯) hochuekkito (補中益氣湯)	Karibe H, Kumabe T, Ishibashi Y, et al. The effect of Japanese herbal medicine on MRSA carrier in neurosurgery. <i>No Shinkei Geka (Neurological Surgery)</i> 1997; 25: 893-7.	1)	C
-	Pharmacoeconomic analysis	Various prescriptions	Koinuma M, Kamei M, Matsumoto K, et al. Feasibility study for the pharmacoeconomic analysis of Kampo Medicines. <i>Nihon Toyo Igaku Zasshi (Kampo medicine)</i> 2005; 56: 813-22.	6) This was not a clinical study.	I
-	Effects of abdominal examination practice with simulated patients on acupuncture and moxibustion students	None	Okuno Y, Taniguchi M. Effects of abdominal examination practice with simulated patients on acupuncture and moxibustion students (No. 1) Communication ability among sighted students. <i>Education of Acupuncture and Manual Therapy</i> 2010; 6: 10-5.	6) This was a study of acupuncture and moxibustion	I

8. Conflict of interests

Based on the “Guidelines for conflict of interests (COI) in medical research” (January 27, 2013) by the Japan Society for Oriental Medicine, COI during the period between January 1, 2013 and December 31, 2013 to be disclosed by current members of the EBM Committee and abstractors is as follows. Belonging of the abstractors to laboratories endowed by companies etc. during the period of the second, third and fourth phases of the project (June 2005 – December 2013) is separately described.

- (1) COI (except for belonging to laboratories endowed by companies) during the period between January 1, 2013 and December 31, 2013 to be disclosed based on the “Guidelines for conflict of interests (COI) in medical research”

Ichiro ARAI, Compensation (TSUMURA Co. Ltd.); Makoto ARAI, Lecture fee etc. (TSUMURA Co. Ltd.), scholarship/grant donation etc. (TSUMURA Co. Ltd.); Takahisa USHIROYAMA, Lecture fee etc. (TSUMURA Co. Ltd.); Tetsuro OIKAWA, No potential COI; Tetsuro OKABE, No potential COI; Yukio KANEKO, No potential COI; Masamichi KITAGAWA, No potential COI; Toshiaki KOGURE, No potential COI; Hirozo GOTO, No potential COI; Hiroki TAKUMA, Compensation (Hogen Pharmacy, Ltd.); Kiichiro TSUTANI, No potential COI; Koki TSURUOKA, None; Hideyuki NAKATA, No potential COI; Takao NAMIKI, scholarship/grant donation etc. (TSUMURA Co. Ltd.); Michio FUJISAWA, No potential COI; Etsuo HOSHINO, Lecture fee etc. (TSUMURA Co. Ltd.) and manuscript fee (TSUMURA Co. Ltd.); Shin-ichi MURAMATSU, Lecture fee etc. (TSUMURA Co. Ltd.) and scholarship/grant donation etc. (TSUMURA Co. Ltd.); Yoshiharu MOTOO, scholarship/grant donation etc. (TSUMURA Co. Ltd.)

- (2) Belonging to laboratories endowed by companies etc. (June 2005 – December 2013)

Makoto ARAI	Belongs to endowed lab, TSUMURA Co. Ltd. (June 2005 – March 2013)
Takahisa USHIROYAMA	Belongs to endowed lab, PARAMOUNT BED, Fujitsu, FUJIFILM Medical Systems, The Zenitaka Corporation, KSK Co. Ltd., NIPPON TELEGRAPH AND TELEPHONE WEST CORPORATION, MEDICEO CORPORATION, Asami Co. Ltd., ROHTO Pharmaceutical Co. Ltd., Godotoho Co. Ltd., Kuraya Sanseido Inc., PARATECHNO Co. Ltd., Kracie Pharmaceutical Ltd., Konishi Medical Instruments Co. Ltd., and 4 personal contributions (June 2009 –)
Tetsuro OKABE	Belongs to endowed lab, TSUMURA Co. Ltd. (June 2005 – March 2013)
Toshiaki KOGURE	Belongs to endowed lab, TSUMURA Co. Ltd. (June 2005 – March 2010)
Hirozo GOTO	Belongs to endowed lab, TSUMURA Co. Ltd. (June 2005 – March 2006)
Hiroki TAKUMA	Belongs to endowed lab, Japan Pharmaceutical Manufacturers Association (JMPA) (June 2005 – March 2006)
Kiichiro TSUTANI	Belongs to endowed lab, JMPA (June 2005 – March 2006) Belongs to endowed lab, Towa Pharmaceutical (April 2006 – December 2013)
Hideyuki NAKATA	Belongs to endowed lab, TSUMURA Co. Ltd. (July 2005 – March 2008)
Takao NAMIKI	Belongs to endowed lab, TSUMURA Co. Ltd. (October 2005 – May 2010)

9. Japan Society for Oriental Medicine EBM Committee members (participants)

Second Phase (June 2005 – May 2009) Task Force for Evidence Reports (ER-TF) Special Committee for Evidence-based Medicine (EBM) The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of May 2009, and may differ from the current status.

Chair:

Tetsuro OKABE Department of Integrated Traditional Medicine, Graduate School of Medicine, University of Tokyo

Members (12 persons, order of the Japanese syllabary):

Makoto ARAI Department of Oriental Medicine, Tokai University School of Medicine
Takahisa USHIROYAMA Health Science Clinic, Osaka Medical College
Tetsuo OIKAWA Department of Clinical Research, Oriental Medicine Research Center, Kitasato University
Masamichi KITAGAWA Main Library, Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE Department of Japanese Oriental Medicine, Gunma Central General Hospital
Hirozo GOTO Department of Japanese Oriental (KAMPO) Medicine, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama
Hiroki TAKUMA Social and Administrative Pharmacy Science Unit, College of Pharmacy, Nihon University
Koki TSURUOKA Tsurukame Clinic, and Division of Community and Family Medicine, Jichi Medical University
Hideyuki NAKATA Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Takao NAMIKI Department of Frontier Japanese-Oriental (Kampo) Medicine, Graduate School of Medicine, Chiba University
Michio FUJISAWA Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO Department of Gastroenterology, Cancer Institute Ariake Hospital
Yoshiharu MOTOO Department of Medical Oncology, Kanazawa Medical University

Observers (2 persons, order of the Japanese syllabary):

Ichiro ARAI Subcommittee to Assess the Efficacy of Kampo Medicines, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Sen SHINOHARA Safety Committee, Japan Kampo Medicines Manufacturers Association

Trustee in charge of Special Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Tetsuo AKIBA AKIBA Clinic of Traditional Medicine, Department of Kampo Medicine, Keio University School of Medicine

(16 Jun. 2001 – 15 Jun. 2007)

Mitsugi SUGIYAMA Advanced Critical Care and Emergency Center, Yokohama City University School of Medicine

(15 Jun. 2007 – 9 Mar. 2009)

Chairperson, Special Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

Third Phase (June 2009 – May 2013)
Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of May 2013, and may differ from the current status.

Chair:

Tetsuro OKABE Department of Integrated Traditional Medicine, Graduate School of
Medicine, University of Tokyo

Members (10 persons, order of the Japanese syllabary):

Masamichi KITAGAWA Academic Information Center, the Jikei University School of Medicine
Takahisa USHIROYAMA Health Science Clinic, Osaka Medical College
Toshiaki KOGURE Department of Japanese Oriental Medicine, Gunma Central and General
Hospital
Hirozo GOTO Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA Acupuncture and Physical Therapy Teacher Training School, University of
Tsukuba
Koki TSURUOKA Graduate School of Social Service Management, Japan College of Social
Work
Hideyuki NAKATA Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Michio FUJISAWA Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO Division of Kampo Support, Cancer Institute Ariake Hospital
Yoshiharu MOTOO Department of Medical Oncology, Kanazawa Medical University

Observers (2 persons, order of the Japanese syllabary):

Ichiro ARAI Sub Committee to Assess the Efficacy of Kampo Formulations, Committee
on Kampo Formulations for Prescription, Japan Kampo Medicines
Manufacturers Association
Yutaka OHTANI Medical Media Center, Toho University

**Chairperson, Committee for EBM, Japan Society for Oriental Medicine (JSOM) / Trustee in charge of
Committee for EBM, JSOM:**

Kiichiro TSUTANI Department of Drug Policy and Management, Graduate School of
Pharmaceutical Sciences, University of Tokyo

Fourth Phase (June 2013 –)
Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

Notes: The information below is as of December 31, 2013.

Chair and chairperson of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo
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Members (12 persons, order of the Japanese syllabary):

Ichiro ARAI	Sub Committee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
Takahisa USHIROYAMA	Health Science Clinic, Osaka Medical College
Tetsuro OKABE	The University of Tokyo Hospital
Masamichi KITAGAWA	Academic Information Center, The Jikei University School of Medicine
Toshiaki KOGURE	Department of Japanese Oriental Medicine, Gunma Central General Hospital
Hirozo GOTO	Department of Kampo Medicine, Hokusei Hospital
Hiroki TAKUMA	Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba
Koki TSURUOKA	Graduate School of Social Service Management, Japan College of Social Work
Hideyuki NAKATA	Kampo Internal Medicine/Health Medical Center, Nerima General Hospital
Michio FUJISAWA	Division for Health Service Promotion, University of Tokyo
Etsuo HOSHINO	Division of Kampo Support, Cancer Institute Ariake Hospital
Yoshiharu MOTOO	Department of Medical Oncology, Kanazawa Medical University

Trustee in charge of Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Shin-ichi MURAMATSU	Division of Oriental Medicine, Center for Community Medicine, Jichi Medical University (vice-president of JSOM, and trustee in charge of Committee for EBM, JSOM)
Yukio KANEKO	Kaneke Clinic (vice-trustee in charge of Committee for EBM)

10. Acknowledgements

Special thanks to the members of the Study Subcommittee to Assess the Efficacy of Kampo Medicines, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association, Miyuki Minari, Ichiro Utaka, Reiko Saijo, Miho Shibahara, Masayo Taira, Tomoe Hirata, Keiji Mori, Madoka Usami, Masaaki Oshiro, Tsuneo Kawashima, and Masayuki Takezaki for their cooperation in gathering references and the members of the Japan Medical Abstract Society for showing how to gather references and select randomized controlled trials.

11. Contact point

We would appreciate your comments on this report. Please send your comments to the address below. Comments from the authors of the included references would also be welcome. If you find that the references that should be included are not included, please inform us. We will reflect your comments in the final report.

ebm-er@jsom.or.jp

12. Structured Abstracts

(402 abstracts describing RCTs)

- Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).
- Each bibliographic item is followed by its ID No. from a particular searched database (CENTRAL ID, PubMed ID, or Ichushi web ID).
- Articles published on the Web are indicated along with the site.

(free of charge)

J-STAGE:

Japan Science and Technology Agency—Electronic Journal Publication/Dissemination Center

<http://www.jstage.jst.go.jp/browse/-char/ja>

CiNii:

National Institute of Informatics Scholarly and Academic Information Navigator

<http://ci.nii.ac.jp/>

(payment required)

MOL:

Medical Online

<http://www.meteo-intergate.com/>

Subscription is needed for viewing.

MOL-Lib:

Medical Online Library

<http://www.meteo-intergate.com/library/>

Institutions that subscribe to the Medical Online Library have access to articles via the above URL.

1. Infections (including Viral Hepatitis)**References**

Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection * . *Nihon Shonika Rinsho (Japanese Journal of Pediatrics)*. 1992; 45: 1889-91 (in Japanese).

Yoshiya K, Nakazawa S. A controlled study of TSUMURA Saireito (柴苓湯) for rotavirus infection * . *Dai 9-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku Nihon Shoni Toyo Igakkaishi (Proceedings of the 9th meeting of the Japan Pediatric Society for Oriental Medicine)* 1993; 9: 20-3 (in Japanese).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) for rotavirus infection.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

No mention of participating centers (the authors are from the Department of Pediatrics, Kobe Teishin Hospital), Japan.

4. Participants

Forty infants diagnosed with rotavirus infection using Rotalex.

5. Intervention

Patients were allocated alternately to the two treatment groups in the order of consultation.

Arm 1: one intestinal infusion of powdered TSUMURA Saireito Extract Granules (0.3 g/kg body weight) dissolved in 20 mL of warmed saline solution administered by soft catheter immediately after rotavirus diagnosis (n=20).

Arm 2: no treatment (n=20).

6. Main outcome measures

Number of days with diarrhea and total number of vomiting episodes compared before and after administration and between groups; number of transfusion cases and number of hospitalized cases compared between groups.

7. Main results

The mean number of days with diarrhea (1.3–3.4 in arm 1 and 1.1–3.6 in arm 2) was not significantly different between groups. The mean number of vomiting episodes decreased significantly from 3.6 before administration to 0.6 after administration in arm 1 ($P < 0.01$), but not in arm 2 (the numbers being 3.3 and 2.8, respectively). There was no significant between-group difference in the number of transfusion cases (8 in arm 1 and 14 in arm 2) and number of hospitalized cases (2 in arm 1 and 6 in arm 2).

8. Conclusions

Saireito administered by intestinal infusion for rotavirus infection effectively decreases the number of vomiting episodes.

9. From Kampo medicine perspective

Saireito was used because it is a combination of shosaikoto (小柴胡湯), which is effective for inflammation, and goreisan (五苓散), which is effective for vomiting.

10. Safety assessment in the article

No adverse effects from saireito intestinal infusion were observed.

11. Abstractor's comments

This clinical study investigated the efficacy of saireito for vomiting and diarrhea due to rotavirus infection. Given the difficulties of following up acute infection after examination, it is a valuable study because it does follow up 40 participants with no dropouts. However, the authors do not mention whether the blood sample taken at initial consultation or the blood sample taken after drug administration was tested, making it unclear whether the presented test results were included to compare severity between groups, or to indicate there is no safety issue with saireito. It is also unclear whether the intestinal infusion itself had any effect on vomiting because the authors did not carry out intestinal infusion using saline solution alone in arm 2, although this is pointed out in the paper. Yet, the authors have devised a possibly groundbreaking therapy, which appears to have relatively few adverse effects, for a disease that has lacked a good therapy, even though it affects many infants each year in winter. A future clinical study with a better defined control group is anticipated.

12. Abstractor and date

Goto H, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Miyazaki R, Tomita H. A study of the efficacy of keihito for diarrhea in children*. *Kampo no Rinsho (Journal of Kampo Medicine)* 1996; 43: 217-23 (in Japanese).

1. Objectives

To determine the efficacy of keihito (啓脾湯) for diarrhea in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Two clinics, Japan.

4. Participants

Thirty-four children (25 boys and 9 girls; age, 4 months – 12.5 years; weight, 7 – 32 kg) with diarrhea that did not respond to 4-day treatment with intestinal remedies (albumin tannate, multidrug-resistant lactobacillus preparation, and loperamide hydrochloride) followed by fosfomycin (50 mg/kg/day) plus antipyretics as needed.

5. Intervention

Arm 1: treatment with TSUMURA Keihito Extract Granules (啓脾湯) 1.5–2.0 g/10 kg/day (n=18).

Arm 2: treatment with western medicines (control group; n=16).

6. Main outcome measures

Rate of relief of diarrhea, rate of improvement in appetite, and mean number of days to diarrhea resolution.

7. Main results

Mean number of days to diarrhea resolution was significantly lower in arm 1 (6.6±2.0 days) than in arm 2 (8.2±1.7 days) ($P<0.05$). Rates of relief of diarrhea and improvement in appetite were not significantly different between arms 1 and 2.

8. Conclusions

For children with diarrhea unresponsive to 4-day treatment with the usual western medicines, keihito is an effective prescription inasmuch as it reduces the number of days to diarrhea resolution.

9. From Kampo medicine perspective

After the completion of the study, retrospective evaluation of responders and non-responders in the keihito group revealed that two non-responders had residual cold symptoms including fever and were not considered to have *tai-in-byo* (太陰病, greater yin disease) *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

None.

11. Abstractor's comments

Diarrhea in children can be classified roughly into disease caused by viral or bacterial infection and disease resulting from noninfectious causes such as hypersensitivity to foods and enzyme abnormalities. Most cases are caused by viral infections. For this type of disease, western medicine is not specific and Kampo therapy might be indicated. In the present study, prespecified exclusion of children with bacterial infection, which increases the risk of severe disease, is appreciated. Some problems remain, such as the lack of identification of the cause of diarrhea in participants, the wide variation in age and weight, and the lack of an assessment of safety. In addition, medical economics evaluation would make the study more interesting.

12. Abstractor and date

Arai M, 17 October 2008, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Miura Y, Yamagishi Y, Mikamo H, et al. Investigation into the effects of Kampo therapy for infectious diarrhea*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2011; 28: 102–4 (in Japanese). Ichushi Web ID: 2011211647

1. Objectives

To evaluate the effectiveness of Kampo therapy for infectious diarrhea.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT - envelope).

3. Setting

Izumi Ladies' Clinic, Japan.

4. Participants

Thirty-three patients who presented with watery diarrhea between September 2007 and March 2009 and were diagnosed with infectious gastroenteritis caused by norovirus, identified from stool samples using a rapid testing method.

5. Intervention

Arm 1: goreisan (五苓散) (manufacturer not identified) 2.5 g t.i.d. (n=11).

Arm 2: goreisan (五苓散) (manufacturer not identified) 2.5 g t.i.d. + Shakuyakukanzoto (芍薬甘草湯) (manufacturer not identified) 2.5 g t.i.d. (n=11).

Arm 3: no Kampo therapy (n=11).

6. Main outcome measures

Time to dissipation of vomiting, diarrhea, and abdominal pain.

7. Main results

Time until vomiting dissipated was 79.1 ± 27.5 minutes in Arm 1 (mean \pm S.D. and the same below), 83.6 ± 20.1 minutes in Arm 2, and 1701.8 ± 377.2 minutes in Arm 3. Time until diarrhea dissipated was 110.0 ± 30.0 minutes in Arm 1, 129.5 ± 28.6 minutes in Arm 2, and 1728.2 ± 352.0 minutes in Arm 3. Time until abdominal pain dissipated was 122.3 ± 26.5 minutes in Arm 1, 105.0 ± 16.0 minutes in Arm 2, and 1813.6 ± 357.1 minutes in Arm 3.

8. Conclusions

Goreisan and shakuyakukanzoto are effective for vomiting, diarrhea, and abdominal pain due to infectious diarrheal disease caused by norovirus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial investigated the therapeutic effects of goreisan and shakuyakukanzoto for infectious diarrheal disease caused by norovirus. It is difficult to assess the therapeutic effects of Kampo medicines on acute-stage diseases, particularly because patients do not return for examination after improvement. In that sense, this is a valuable clinical study as it elucidates the effectiveness of Kampo medicines for an acute-stage disease. Yet, notwithstanding that this written report has the form of an academic article, no mention is made of patient background (age and gender, etc.), the period between onset and examination, and the number (if any) of dropouts. Furthermore, time until dissipation of symptoms are clearly different between the Arms (goreisan, goreisan and shakuyakukanzoto, and no Kampo medicine), but the statistics are not analyzed, meaning there is no mention of significant differences. It is a worthwhile clinical study, so, the authors should have included these details in their article. Yet, the study can rightly be considered excellent because acute-stage disease cannot be easily monitored following therapy, and because it focuses attention on the question of whether Kampo medicines are effective for norovirus infection, a disease without very effective treatment. Hopefully this study will lead to others that examine larger numbers of cases.

12. Abstractor and date

Goto H, , 31 December 2012.

1. Infections (including Viral Hepatitis)**References**

Watanabe A, Hasegawa S. Effect of combined Kampo medicines as adjuvant therapy for pulmonary tuberculosis. *Nippon Iji Shinpo (Japan Medical Journal)* 1992; (3553): 76-7 (in Japanese).

Watanabe A, Takahashi N, Uchida Y, et al. Efficacy of hochuekkito as adjuvant therapy for pulmonary tuberculosis. *JAMA (Japanese version)* 1992; 13 (6) suppl: 20-1 (in Japanese)

1. Objectives

To determine the effect of hochuekkito (補中益気湯) and shosaikoto (小柴胡湯) on improving appetite and host defense in patients undergoing chemotherapy for pulmonary tuberculosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

One hundred and one hospitalized patients with sputum positive for tubercle bacilli and were treated with rifampicin, isoniazid, and streptomycin during a 5-year period from January 1987 to December 1991.

5. Intervention

Arm 1: chemotherapy alone (n=40).

Arm 2: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day (n=31).

Arm 3: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day and TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day (n=30).

6. Main outcome measures

Body weight, degree of sputum smear positivity (on the Gaffky scale), erythrocyte sedimentation rate (ESR), and number of peripheral blood lymphocytes.

7. Main results

After admission, body weight began to increase 2 months after the start of the study treatment in all three arms. The gain was greater in arm 3 than in arm 1 at 3 months and greater in arms 2 and 3 than in arm 1 at 5 months. The weight gain [in kg] at 5 months in arms, 1, 2, and 3 was 3.2, 4.7, and 5.3, respectively. The number of peripheral blood lymphocytes was increased in all 3 arms during the course of treatment and there were no significant between-arm differences. In the subgroup with decreased number of peripheral blood lymphocytes on admission, weight gain was markedly greater in arms 2 and 3 than in arm 1. Furthermore, weight gain was more remarkable in elderly patients aged 60 or older (a total of 45 patients) who received Kampo medicine(s)-combined therapy than in all the patients, including younger patients, who received the combination.

8. Conclusions

Although they affected body weight and the number of peripheral blood lymphocytes but not ESR and sputum smear positivity, Kampo medicines are presumed to be a useful adjunct to antituberculosis therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Hepatic dysfunction occurred and treatment was discontinued in 2 patients of arm 1. In contrast, mild hepatic dysfunction occurred but treatment was continued in arms 2 and 3, indicating the possibility that Kampo medicines help prevent hepatic dysfunction.

11. Abstractor's comments

At the time when this comparative study was conducted, most tuberculosis patients who excreted bacilli had to be hospitalized for treatment. Recently, the number of tuberculosis patients has decreased and, thanks to early detection, most patients present mild disease. Yet some patients with severe disease still require long-term hospitalization. If the lifestyle characteristics of the patients and the severity of their disease had been clearly described, this paper would be helpful today. It is said that shosaikoto or something else was used as treatment for tuberculosis before the war. The both papers were published around the same time as the present paper. It included arms 1 and 2 of the present study and highlights the efficacy of hochuekkito.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013

1. Infections (including Viral Hepatitis)**References**

Shijubo N, Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis – the reducing effect on hepatic dysfunction occurring as an adverse drug reaction–. *Kampo Igaku (Kampo Medicine)* 1993; 17: 241-3 (in Japanese).

Nakanishi F. Experience with hochuekkito in the short-course intensified chemotherapy for pulmonary tuberculosis. *Nikkei Medical* 1994; 23 (12): 24-5 (in Japanese).

1. Objectives

To determine the efficacy of hochuekkito (補中益気湯) for reducing hepatic dysfunction and improving digestion and malabsorption in tuberculosis patients undergoing chemotherapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Eighty hospitalized patients with tuberculosis who had no history of liver disease and no hepatic dysfunction on admission.

5. Intervention

Anti-tubercular agents were RFP+INH+SM (EB) for patients who excreted tubercle bacilli and RFP+INH for patients who tested negative for tubercle bacillus excretion and vomicae.

Arm 1: chemotherapy + treatment with TSUMURA Hochuekkito (補中益気湯) Extract Granules 2.5 g t.i.d. between meals (n=40).

Arm 2: chemotherapy alone (n=40).

6. Main outcome measures

Hepatic dysfunction and body weight.

7. Main results

Abnormal glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and GOT and/or GPT levels were observed in 10%, 10%, and 13% of patients in arm 1 and 23%, 28%, and 30% in arm 2. Obviously, the occurrence of hepatic dysfunction was decreased in arm 2. The rate of weight gain began to increase at 1 month in arm 1 and at 2 months in arm 2.

8. Conclusions

Coadministration of hochuekkito reduces hepatic dysfunction resulting from RFP/INH-based chemotherapy and stimulates body weight gain, which is an indicator of improved *hiiqikyo* (impaired digestion and absorption), but does not normalize C-reactive protein level or prevent tuberculosis bacillus excretion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

GOT and GPT levels increased to 200 IU/L or higher and treatment discontinuation was required in 2 patients of arm 1.

11. Abstractor's comments

Nakanishi (1994) adds 16 participants to the paper by Shijubo et al. (1993). Hepatic dysfunction due to anti-tubercular agents increased slightly for the first one to two months of administration, but in most cases it gradually improved even with continued use. However, in some cases, hepatic dysfunction was severely aggravated and required regular monitoring. This RCT provides some interesting outcomes in terms of reducing the occurrence of hepatic dysfunction.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Seki T, Matsumoto T, Deguchi H, et al. Evaluation of the efficacy of hochuekkito in preventing MRSA colonization and infection. *Kampo Igaku (Kampo Medicine)* 1999; 23: 196-7 (in Japanese). Ichushi Web ID: 2000068588

1. Objectives

To evaluate whether hochuekkito has efficacy in preventing colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Traumatology and Critical Care Medicine, Dokkyo Medical University Koshigaya Hospital, Japan

4. Participants

Ninety-five patients admitted to the above hospital.

5. Intervention

Arm 1: treatment with hochuekkito (補中益気湯) (2.5 g, t.i.d.) per os (p.o.) or using a nasogastric tube; every day from the third day of hospitalization.

Arm 2: no treatment with hochuekkito.

6. Main outcome measures

From all patients, nasal, throat, and urine specimens were cultured for MRSA on the second hospital day, one week later, and then once a week. Sputum was also cultured from patients who underwent endotracheal intubation or tracheotomy and from those who were able to provide sputum. Similarly wound cultures were performed for patients with wound infection. When at least one culture of any specimen was positive for MRSA, the patient was considered to be MRSA-positive.

7. Main results

A total of 63 patients - 30 of 48 in arm 1 and 33 of 47 in arm 2 - withdrew from the study. Among these withdrawals, 25 patients in arm 1 and 32 in arm 2 were transferred to other wards or died, 3 received no hochuekkito, and 3 underwent no laboratory follow-up (cultures). Thus, 18 patients in arm 1 and 14 in arm 2 were examined and compared. The most common disease was trauma, followed by cerebrovascular disorder. There was no significant difference in MRSA positivity between arm 1 (8 of 18 patients) and arm 2 (9 of 14 patients). Among the trauma patients, however, there was a trend toward lower MRSA positivity in hochuekkito-treated patients (5 of 11 [45.5%] being positive), compared with hochuekkito-untreated patients (5 of 7 [71.4%] being positive). A similar trend toward lower MRSA positivity in hochuekkito-treated patients was found among patients who required mechanical ventilation.

8. Conclusions

It is suggested that administration of hochuekkito can prevent MRSA infection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors deserve praise for conducting this RCT in an emergency care setting. Given the setting, it is not surprising that many patients (66%) withdrew from the study. But the authors' reasons for the withdrawals provide readers with very useful information. They also described gown use and hand washing by medical personnel and visitors, reflecting their consideration of bias and confounding factors. Unfortunately, this study included only a small number of patients. If it had employed a blinded, placebo-controlled design, the report would have been more reliable. The development of future studies is expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)**Reference**

Suzuki J, Arata S, Sugiyama M. Improvement of immunity and nutrition by hochuekkito in immuno-compromised hosts – for the control of MRSA –*. *Progress in Medicine* 2002; 22: 1362-3 (in Japanese). Ichushi Web ID: 2002261757 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate whether hochuekkito (補中益気湯) can improve immune and nutritional status in immuno-compromised hosts.

2. Design

Randomized controlled trial (RCT).

3. Setting

Critical Care and Emergency Center, Yokohama City University Medical Center, Japan.

4. Participants

Twenty-six immuno-compromised patients who were admitted to the above center. Of these, 13 patients received hochuekkito or placebo for three weeks or longer.

5. Intervention

Arm 1: oral or enteral administration of hochuekkito (補中益気湯) (2.5 g t.i.d.) in 7 patients (all males; mean age 53.3±5.6 years).

Arm 2: administration of the same amount of lactose (placebo) in 6 patients (4 males and 2 females; mean age 53.0±7.7 years).

6. Main outcome measures

Serum albumin level and peripheral lymphocyte count (at baseline, 1, 2, 3, and 4 weeks after the start of the treatment).

Change in prognostic nutrition index (PNI=[albumin level]×10+[peripheral lymphocyte count]×0.005).

7. Main results

There was no significant difference between the two arms in serum albumin level and peripheral lymphocyte count. In placebo-treated patients, PNI increased 1 week after the start of treatment, but decreased in the following week, then increased again. PNI was significantly higher in hochuekkito-treated patients than in placebo-treated patients ($P<0.05$).

8. Conclusions

PNI value is significantly increased by hochuekkito treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors deserve praise for attempting the RCT in an emergency care setting. Since PNI is a surrogate outcome measure, future trials focusing on outcomes that involve the presence or absence of infection and quantity of nutrition, as mentioned in the last part of the present results, are anticipated. Although the number of patients in this study is small, future studies are expected to be larger and confirmatory. In the results of this paper, MRSA infection was identified in 4 of 9 previously non-infected patients in the lactose arm and only 1 of 8 in the hochuekkito arm.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 May 2009, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Higuchi K, Arakawa T, Ando K, et al. Eradication of *Helicobacter pylori* with a Chinese herbal medicine without emergence of resistant colonies. *American Journal of Gastroenterology* 1999; 94: 1419-20. CENTRAL ID: CN-00162864, Pubmed ID: 10235237

1. Objectives

To evaluate the efficacy and safety of triple therapy with proton pump inhibitor, antibiotic, and goshuyuto (呉茱萸湯) for *Helicobacter pylori* (*H. pylori*) infection.

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the authors belong to the Third Department of Internal Medicine, Osaka City University Medical School, Japan.

4. Participants

Sixty-three patients infected with *H. pylori*.

5. Intervention

Arm 1: treatment with omeprazole (40 mg/day), amoxicillin (1,500 mg/day), and goshuyuto (呉茱萸湯) (7.5 g/day), n=32.

Arm 2: treatment with omeprazole (40 mg/day) and amoxicillin (1,500 mg/day), n=31.

The duration of treatment was 2 weeks.

6. Main outcome measures

Histologic evaluation of gastric biopsy specimen and rapid urease test were performed.

The outcomes were evaluated at 4 weeks after the treatment.

7. Main results

H. pylori eradication rates were 60% in the double therapy arm and 80% in the triple therapy arm. There was no emergence of goshuyuto- or amoxicillin-resistant bacteria even in cases where treatment failed to eradicate *H. pylori*.

8. Conclusions

The novel triple therapy containing goshuyuto improves the eradication rate without increasing incidences of adverse effects and treatment resistance by *H. pylori*. This therapy is a useful tool for eradicating *H. pylori*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were similar in arm 1 (4 patients with diarrhea) and in arm 2 (4 patients with diarrhea and 1 with abdominal pain). No serious adverse effects were observed.

11. Abstractor's comments

In this study, goshuyuto was used differently from its original application of Kampo medicine. This article, as a Letter to the Editor, lacks adequate descriptions, so the submission as an original article is desired.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)**References**

Taniguchi S, Terai T, Kono T, et al. The effect of hochuekkito on postherpetic neuralgia*. *Hifu no Rinsho (Clinical Practice of Dermatology)* 1999; 41: 601-3 (in Japanese)

Taniguchi S, Kono T, Terai T. Preventive effect of hochuekkito on postherpetic neuralgia*. *Progress in Medicine* 2002; 22: 863-5 (in Japanese). Ichushi Web ID: 2002176936 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate whether hochuekkito (補中益気湯) has a preventive effect on postherpetic neuralgia (PHN).

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one department of dermatology), Japan.

4. Participants

Fifty-seven patients with acute-phase herpes zoster.

5. Intervention

Arm 1: oral administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) for 12 weeks (42 patients: 12 males and 30 females; mean age, 69.2 years).

Arm 2: no treatment with hochuekkito (補中益気湯) (15 patients: 5 males and 10 females; mean age, 66.9 years).

6. Main outcome measures

Pain intensity was evaluated by visual analogue scale (VAS) at baseline, and 12 and 24 weeks after the start of treatment. Obtained data are expressed as median (25 percentile, 75 percentile).

7. Main results

VAS score in the hochuekkito arm and control arm was respectively 7.1 (6.5, 7.4) and 6.9 (5.5, 7.9) at baseline, 4.1 (3.0, 5.4) and 3.5 (1.7, 5.1) at 12 weeks, 1.4 (0.5, 2.3) and 2.9 (1.7, 4.2) at 24 weeks. The ratio of VAS score at 24 weeks to that at baseline (rVAS) was significantly different between the hochuekkito arm (0.20 [0.09, 0.30]) and control arm (0.42 [0.33, 0.53]).

8. Conclusions

During the acute phase of herpes zoster, 12-week oral administration of hochuekkito significantly controlled PHN at 24 weeks. Hochuekkito therefore has a preventive effect on PHN.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In one of the 42 hochuekkito-treated patients, transient stomach discomfort developed, which did not interfere with continuation of the treatment.

11. Abstractor's comments

Many patients suffer from PHN for years. This study provides valuable insight. Although the authors found no between-group difference in age, affected area, number of days with symptoms, underlying disease, and concomitant medications, there was a between-group difference in the number of cases. This problem is related to the incidence of PHN, so an examination of the influence of incidence of PHN on the study results is needed. The outcomes of these studies are clinically relevant, and results of further studies are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 12 October 2011, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Sata M, Amagase H, Koga S, et al. Therapeutic effect of IFN- β (Feron) plus shosaikoto combination therapy on chronic active hepatitis B*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1994; 71: 814-20 (in Japanese). Ichushi Web ID: 1994141311

1. Objectives

To evaluate the therapeutic effect of interferon (IFN)-beta plus shosaikoto (小柴胡湯) on chronic active hepatitis B.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

Nine university hospitals and 15 general hospitals, Japan.

4. Participants

Sixty-two patients who presented with chronic active hepatitis on liver biopsy histology (obtained within a year of symptom onset) and were positive for both HBsAg and HBeAg.

5. Intervention

Arm 1: treatment with IFN- β (total dose 102×10^6 IU) for 8 weeks + shosaikoto (小柴胡湯) (manufacturer, not specified) 2.0 g or 2.5 g t.i.d. for 8 weeks and 6 months (n=28).

Arm 2: treatment with IFN- β alone (total dose 102×10^6 IU) for 8 weeks (n=34).

6. Main outcome measures

Blood levels of HBsAg, HBeAg, HBeAb, and HBV-DNA-polymerase (DNA-P), blood biochemistry, and urinalysis. These variables were examined 4 weeks before the start of the treatment; on day 1 and weeks 1, 2, and 4 of the treatment, at the end of the treatment, and 1, 2, 3, 4, 5, 6, 9, and 12 months after the completion of the treatment.

7. Main results

Treatment was discontinued in 3 patients in arm 1 and 8 patients in arm 2. After the IFN- β therapy, there were no significant between-arm differences in DNA-P reduction, clearance rate, other changes over time, clearance of HBeAg, rate of HBeAg seroconversion (SC), and time course of serum ALT and AST levels. In 12 patients who cleared HBeAg at 12 months after the completion of IFN- β therapy, AST level tended to be lower in the shosaikoto-combined group. There were no significant between-arm differences in blood biochemistry findings.

8. Conclusions

IFN plus shosaikoto and IFN alone had similar efficacy for chronic hepatitis B.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Treatment was not discontinued due to adverse drug reactions in either arm. Hematemesis developed in one patient in the IFN alone group but resolved with antiulcer drug treatment. The causal relationship between this event and the intervention is not clear. The event may be attributed to NSAIDs (non-steroidal anti-inflammatory drugs) use.

11. Abstractor's comments

The authors of this study deserve praise for conducting an RCT in a multicenter setting. The report would have been more informative if it included evaluation of subjective symptoms and long-term outcomes, in addition to the results of virological examinations.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)**Reference**

Sato S, Ishikawa K, Chiba T. Efficacy of sho-saiko-to on chronic type B hepatitis. *Shokakika (Gastroenterology)* 1991; 15: 39–49 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) in the treatment of chronic hepatitis B.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Six university hospitals and 15 general hospitals, Japan.

4. Participants

Forty-four patients who met the following criteria: liver biopsy within a year of symptom onset, in principle; Hepatitis (H)Be antigen-positive; abnormal baseline glutamic-pyruvic transaminase (GPT) requiring treatment. However, those who received any immunostimulant agent such as antiviral agents (IFN, Ara-A, etc.) within 12 weeks of recruitment were excluded.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules at a dose of 7.5 g/day for 24 weeks (n=28).
Arm 2: common hepatoprotective agents (Proheparum, etc.) for 24 weeks (n=16).

6. Main outcome measures

HBe antigen/anti-HBe antibody and GPT were continuously monitored and rated on a 6-grade scale: seroconversion (SC), seronegative (SN), decreased antigen titer, unchanged antigen titer, increased antigen titer, and substantially worsened antigen titer.

7. Main results

Decrease in the HBe antigen titer was not significantly different between the two groups at Week 24. The anti-HBe antibody titer was significantly higher in arm 1 than in arm 2 at Weeks 4 ($P<0.05$) and 24 ($P<0.01$). GPT was not significantly different between the two groups at Week 24 or 48. A comparison of the percentage of patients with unchanged or higher HBe antigen titer and the percentage of patients with decreased HBe antigen titer between the two groups revealed a tendency for HBe antigen titer to decrease in arm 1 at Week 24 ($P<0.1$) but revealed no significant between-group difference at Week 48.

8. Conclusions

Compared to the hepatoprotective agents, shosaikoto tends to decrease HBe antigen titer and significantly increase anti-HBe antibody titer.

9. From Kampo medicine perspective

Nothing special.

10. Safety assessment in the article

Not evaluated.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted. However, the difference in the percentage of patients with SC or SN was not significant. Thus, caution should be used in prescribing this intervention.

12. Abstractor and date

Kogure T, 8 August, 2008, 1 June 2010, 31 December 2013.

1. Infections (including Viral Hepatitis)**References**

Shiraki K, Tanimoto K, Togashi T, et al. A study of the efficacy of shosaikoto in children with HBe antigen-positive chronic hepatitis B*. *Shonika Rinsho (Japanese Journal of Pediatrics)* 1991; 44: 2146–51 (in Japanese).

Shiraki K, Tanimoto K. Clinical Evaluation of the efficacy of TSUMURA Shosaikoto in children with chronic hepatitis B*. *Dai 7-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 7th meeting of the Japan Pediatric Society for Oriental Medicine)* 1991; 7: 18–22 (in Japanese)

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of HBe antigen-positive children with chronic hepatitis B.

2. Design

Randomized controlled trial (RCT).

3. Setting

Nine university hospitals, Japan.

4. Participants

Forty-three HBe antigen-positive children with chronic hepatitis B.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules was administered before breakfast and dinner according to age (n=23).

Arm 2: no treatment (n= 20).

Follow-up was 6–24 months; mean treatment duration was 18.6± 5.5 months.

6. Main outcome measures

Hepatic function test and effect on the HBe antigen-antibody system (SC: seroconversion, SN: seronegative).

7. Main results

ALT and AST levels tended to progressively decrease from the baseline in arm 1 but not to change in arm 2. The percentage of patients with SC or SN at Month 6, Month 12, and final follow-up was 30.4%, 34.8%, and 43.5% in arm 1, and 5.0%, 10.0%, and 25.0% in arm 2, respectively. The percentage of patients with SC at Month 6, Month 12, and final follow-up was 17.4%, 17.4%, and 30.4% in arm 1, and 0%, 10.0%, and 20.0% in arm 2, respectively.

8. Conclusions

Shosaikoto improves hepatic function and promotes SC from HBe antigen to anti-HBe antibody in children with chronic hepatitis B.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient treated with shosaikoto had epigastric discomfort.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted and showed the efficacy and safety of shosaikoto in children with chronic hepatitis B. Interestingly, hepatic function was normalized in all patients with SC in the shosaikoto group. The result of a statistical between-group comparison will provide stronger evidence.

12. Abstractor and date

Kogure T, 8 August 2008, 12 October 2011, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Hatakeyama S, Ueki J, Ishizuka M, et al. Comparative study of ursodeoxycholic acid and shosaikoto as treatment for chronic liver diseases type C. *Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)* 1994; 22: 3295-305 (in Japanese). Ichushi Web ID: 1995069962

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) for type C chronic liver diseases.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One general hospital, Japan.

4. Participants

A total of 55 patients (27 with chronic hepatitis C [CH] and 28 with type C compensated liver cirrhosis [cLC]).

5. Intervention

Arm 1: treatment with ursodeoxycholic acid (UDCA) 200 mg t.i.d. for 6 months (n=26).

Arm 2: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. orally before meals for 6 months (n=29).

6. Main outcome measures

Liver functions and serum bile acid fractions.

7. Main results

Three UDCA-treated and 2 shosaikoto-treated patients withdrew from the study. The percent decrease in GOT and GPT at 6 months was significantly greater in arm 1 than in arm 2 for both CH and cLC patients. γ -GTP and γ -globulin also decreased significantly more in arm 1 than in arm 2. Albumin increased significantly more in arm 1 than in arm 2. The glycine-conjugated UDCA fraction increased significantly while the glycine-conjugated cholic acid (CA) and chenodeoxycholic acid (CDCA) fractions decreased significantly in arm 1. There were no variations in serum bile acid level in arm 2.

8. Conclusions

The efficacy of shosaikoto for type C chronic liver diseases is not clear, and UDCA is more effective than shosaikoto.

9. From Kampo medicine perspective

Not specifically mentioned. The authors commented that UDCA might be a better choice when *sho* (証, pattern) is not a consideration.

10. Safety assessment in the article

One UDCA-treated patient developed pruritus and withdrew from the study. Two shosaikoto-treated patients withdrew due to abnormally high levels of GPT.

11. Abstractor's comments

The authors of this study deserve praise for conducting an RCT using UDCA as a control. Longer-term follow-up and inclusion of virological examination results would enhance the clinical significance of this study.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)**Reference**

Nakajima O, Sone M. Interferon plus shosaikoto combination therapy for chronic hepatitis C (the first report) - effectiveness in reducing adverse effects of interferon-*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)*. 1993; 70: 2994-3002 (in Japanese). Ichushi Web ID: 1994049432

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for reducing the adverse effects of interferon in patients with chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (National Okura Hospital; current National Center for Child Health and Development), Japan.

4. Participants

Forty-eight patients with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha 6 million units daily for 2 weeks, then three times weekly + Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 2 g t.i.d. (n=24).

Arm 2: treatment with interferon alone (n=24).

Duration of treatment: at least 12 months.

6. Main outcome measures

Subjective symptoms including fever and laboratory findings including blood cell counts.

7. Main results

Both the severity and frequency of fever were significantly lower in arm 1. Leukopenia at 1 month was significantly reduced in arm 1. There was no significant between-arm difference in the occurrence of other adverse drug reactions.

8. Conclusions

Shosaikoto may reduce adverse effects of interferon.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is the first report on a clinical trial of interferon plus shosaikoto combination therapy for chronic hepatitis C, summarizing only the part related to the occurrence of adverse drug reactions. Interestingly, shosaikoto, which is also used for treating *sho-kan* (傷寒, cold damage), reduces the “*sho-kan* -like” adverse effects of interferon.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

1. Infections (including Viral Hepatitis)**References**

Sone M, Nakajima O. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1995; 72: 3193-7 [in Japanese]. Ichushi Web ID: 1996190408 [MOL](#), [MOL-Lib](#)

Nakajima O, Sone M. Evaluation of the usefulness of shosaikoto in the treatment of chronic hepatitis C after interferon therapy - the second report-*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1998; 75: 1883-8 (in Japanese). Ichushi Web ID: 1999004032 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in chronic hepatitis C after interferon (IFN) therapy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

One hundred and one patients with chronic active hepatitis C who completed IFN therapy.

5. Intervention

Arm 1: IFN therapy (for 6 months) and then administration of liver protector (for 6 months), followed by treatment with Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 2.0 g t.i.d. 30 minutes before meals for 24 months (n=49).

Arm 2: IFN therapy and then administration of liver protector, followed by continued treatment with liver protector for 24 months (n=52).

6. Main outcome measures

Liver function test, time course of hepatitis C virus (HCV)-RNA level, time course of platelet and white blood cell counts.

7. Main results

Alanine aminotransferase (ALT) level was not significantly different between arms 1 and 2 at 24 months. Aspartate aminotransferase (AST) level and HCV-RNA level were significantly reduced in arm 1 compared with arm 2 at 24 months ($P<0.05$).

8. Conclusions

Shosaikoto is effective as maintenance therapy following IFN treatment for chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Platelet count was significantly different between arms 1 and 2 ($P<0.05$); it was reduced compared with the baseline level in arm 2. White blood cell count was also significantly different between arms 1 and 2; it was reduced, but not significantly different from the baseline level in arm 2. The tendency toward pancreatic dysfunction after the IFN therapy was improved earlier in arm 1 than in arm 2.

11. Abstractor's comments

This is a clinically, highly significant study in that long-term follow-up was conducted in an RCT. Furthermore, between-arm comparisons were sufficient. This study provides high-level evidence.

12. Abstractor and date

Kogure T, 8 August 2008, 31 December 2013.

1. Infections (including Viral Hepatitis)**Reference**

Nakajima O, Sone M, Kurokawa K, et al. The Complementary treatment for chronic hepatitis C. *Kagaku Ryoho Kenkyusho Kiyo (Bulletin of the Institute of Chemotherapy)* 2003; 34: 40-51 (in Japanese with English abstract). Ichushi Web ID: 2004188041

1. Objectives

To confirm the efficacy of shosaikoto (小柴胡湯) for interferon-resistant chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and general hospitals, Japan.

4. Participants

One hundred patients with chronic active hepatitis C who completed interferon therapy.

5. Intervention

Arm 1: treatment with squalene 1500 mg/day.(n=33)

Arm 2: treatment with cepharanthine (1 mg/kg body weight per day). (n=33)

Arm 3: treatment with shosaikoto (小柴胡湯) 6.0 g/day. (n=34)

In all arms, study drugs were orally administered in three divided daily doses before meals for 5 years.

6. Main outcome measures

Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), procollagen III peptide (PIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. Main results

AST and ALT showed overall significant decreases, except for transient elevations after 6 and 30 months of treatment. Type IV collagen, PIIP, and HCV-RNA also decreased significantly in all arms. No significant differences in these variables were observed among the three arms. AST and ALT were significantly decreased at 50 months in arm 3, but not in arms 1 and 2. Choline esterase (Ch-E) did not change in arm 3, but decreased significantly in arms 1 and 2. Type IV collagen and HCV-RNA decreased significantly in arm 3 and increased significantly in arms 1 and 2. Changes in PIIP were similar to those of type IV collagen.

8. Conclusions

Shosaikoto is effective for the treatment of chronic hepatitis C and its efficacy is equivalent to that of squalene or cepharanthine.

9. From Kampo medicine perspective

One patient with “*in-sho* (陰証, yin pattern)” and “*kyo-sho* (虚証, deficiency pattern)” was excluded before the allocation, and the study was actually conducted in 99 patients.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

1. Infections (including Viral Hepatitis)**Reference**

Nakajima O, Sone M, Onishi H, et al. Preventive effect of shosaikoto on the progression of chronic hepatitis C to cirrhosis*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1999; 76: 1008-16 (in Japanese). Ichushi Web ID: 1999207089 [MOL](#), [MOL-Lib](#)

1. Objectives

To confirm the efficacy of shosaikoto (小柴胡湯) for chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

Multiple general hospitals, Japan.

4. Participants

Ninety-nine patients with chronic active hepatitis C who completed interferon therapy.

5. Intervention

Arm 1: oral administration of Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules 6 g/day, t.i.d.(n=49)

Arm 2: oral administration of one of the commonly used liver protectors.(n=50)

Patients were followed for 50 months in both arms.

6. Main outcome measures

Level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), choline esterase (Ch-E), procollagen III peptide (PIIIP), type IV collagen, and hepatitis C virus (HCV)-RNA.

7. Main results

AST and ALT were significantly decreased at 50 months in arm 1, but not in arm 2. Ch-E did not change in arm 1, but decreased significantly in arm 2. Type IV collagen and HCV-RNA decreased significantly in arm 1, and increased significantly in arm 2. Changes in PIIIP were similar to those of type IV collagen.

8. Conclusions

Shosaikoto is effective for the treatment of chronic hepatitis C, and its prevention of the progression to cirrhosis is implied.

9. From Kampo medicine perspective

Patients with “*in-sho* (陰証, yin pattern)” and “*kyo-sho* (虚証, deficiency pattern)” were excluded before the allocation.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study confirmed the efficacy of shosaikoto for the treatment of chronic hepatitis C.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

1. Infections (including Viral Hepatitis)**Reference**

Tanaka N, Matsuzaki Y, Osuga T, et al. A comparative study of IFN monotherapy versus IFN plus TJ-9 Shosaikoto combination therapy in patients with chronic hepatitis C (interim report)*. *Progress in Medicine* 1993; 13: 2868-72 (in Japanese).

1. Objectives

To evaluate the efficacy of interferon (IFN) plus shosaikoto (小柴胡湯) combination therapy for chronic hepatitis C.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Three hospitals including Tsukuba University Hospital, Japan.

4. Participants

Thirty-six patients aged under 65 years with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha (or -beta) 6 million units daily for 2 weeks, then 3 times weekly for 23 weeks + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=15) for 1.5 year.
Arm 2: treatment with interferon alone for 23 weeks (n=21).

6. Main outcome measures

Alanine aminotransferase (ALT) level.

7. Main results

There was no significant difference in the time course of ALT levels between arms 1 and 2.

8. Conclusions

At the time of this interim report, the shosaikoto and IFN combination did not provide an enhanced therapeutic efficacy for chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This is an interim report on a clinical trial of interferon plus shosaikoto combination therapy for chronic hepatitis C, summarizing data from 36 patients who completed treatment, out of more than 100 patients who enrolled. Efficacy of this therapy was not demonstrated. But this is only an interim report and a final report is anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

1. Infections (including Viral Hepatitis)**Reference**

Isai H. Efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C*. *Shindan to Chiryō (Diagnosis and Treatment)* 1996; 84: 1505-9 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of Kampo formulations for reducing adverse effects of interferon therapy in patients with chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Hokkaido Kosei-ren Mukawa Kosei Hospital), Japan.

4. Participants

Twelve patients with chronic hepatitis C.

5. Intervention

Arm 1: treatment with interferon-alpha 6 million units daily on days 1–3 and 10 million units daily on days 4–14, then 10 million units 3 times weekly for 12 weeks + Kampo formulation (TSUMURA Keishito [桂枝湯] Extract Granules 5 g, TSUMURA Maoto [麻黄湯] Extract Granules 5 g, and TSUMURA Kojinmatsu [紅参末] 4 g) daily from the first day of interferon therapy and continuing for 4 weeks (n=6).

Arm 2: treatment with interferon alone (n=6).

6. Main outcome measures

Body temperature, subjective symptoms, blood biochemistry, and usage of diclofenac sodium suppository.

7. Main results

During first 4 weeks, usage of diclofenac sodium suppository was significantly lower in arm 1. Significantly fewer patients complained of anorexia or arthralgia in arm 1.

8. Conclusions

Kampo formulations may have efficacy for reducing the adverse effects of interferon therapy in patients with chronic hepatitis C.

9. From Kampo medicine perspective

Kojinmatsu was added in hope that its immunostimulatory activity would be coupled with the effects of keimakakuhanto (桂麻各半湯).

10. Safety assessment in the article

One patient in arm 1 discontinued treatment because of gastrointestinal symptoms on day 9 of Kampo formulation treatment and was excluded from further evaluation. Another patient complained of nausea/vomiting on day 9 of Kampo formulation treatment. Despite continuation of treatment, the symptoms disappeared after 5 days allowing further continuation of this patient's treatment.

11. Abstractor's comments

This paper describes an attempt to evaluate the efficacy of Kampo formulations against the adverse effects of interferon therapy in patients with chronic hepatitis C. The author's original formula was used and it is suggested that *happyozai* (發表劑, exterior-effusing formula) has certain efficacy for reducing influenza-like adverse effects of interferon. Unfortunately, the number of patients was very small, so future studies including a large number of patients are anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010, 12 October 2012.

1. Infections (including Viral Hepatitis)**Reference**

Fukue H, Hagiwara T, Yoshida S, et al. Efficacy of high-dose shosaikoto for HIV infection*. *HIV Kansensha Hassho Yobo, Chiryō ni kansuru Kenkyūhan Heisei 7 Nendo Kenkyū Hokokusho (Research Report by the Study Group on Prevention and Treatment of HIV Infection)* 1996: 203–10 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of human immuno-deficiency virus (HIV) infection.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

No study site was specified (authors belonged to the Department of Diagnostic Pathology, Tokyo Medical University; National Institute of Health; Department of Public Health, Yokohama City University; and Division of Theoretical Epidemiology, Department of Epidemiology, Institute of Public Health), Japan.

4. Participants

Nineteen patients with acquired immunodeficiency syndrome (AIDS) related complex or asymptomatic carriers with 200–500 CD4-positive cells/ μ L.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules at a dose of 7.5 g t.i.d. for 12 weeks.
Arm 2: placebo.

6. Main outcome measures

Immunology (absolute number of CD4-positive cells, CD4/CD8, and lymphocyte stimulation test), virology (P24 antigen, branched DNA assay), and clinical symptoms.

7. Main results

A total of 15 patients (7 in arm 1 and 8 in arm 2) were included in the analysis. After treatment, no statistically significant between-arm difference was found in the absolute number of CD4-positive cells, CD4/CD8, and results of the lymphocyte stimulation test. Virologically, no analysis could be performed because many patients lacked detectable virus.

8. Conclusions

Shosaikoto may be ineffective for HIV infection.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

In the shosaikoto group, 1 patient was withdrawn from treatment owing to hepatic dysfunction. Two patients in each of the groups had slight gastrointestinal symptoms.

11. Abstractor's comments

This clinical trial suggested that shosaikoto is ineffective for HIV infection. Nonetheless, it is desirable to conduct another trial to overcome the following drawbacks of the present trial as cited by the authors: small sample size and lack of antiviral efficacy evaluation because no virus was detectable.

12. Abstractor and date

Okabe T, 17 September 2008, 1 June 2010.

2. Cancer (Postoperative Cancer Patients, Unspecific Adverse Reactions to Anticancer Agents)**Reference**

Konno H, Maruo Y, Baba S, et al. Improvement of host-immunity by adding juzen-taiho-to to the postoperative adjuvant chemotherapy for patients with gastric cancer. *Biotherapy* 1997; 11: 193-9 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) in host-immunity in gastric cancer patients undergoing postoperative adjuvant uracil+tegafur (UFT, 300 mg/day).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT- envelope).

3. Setting

One university hospital (Second Department of Surgery, Hamamatsu University School of Medicine) and two other hospitals, Japan.

4. Participants

Twenty-three patients who underwent macroscopic curative resection of gastric cancer (stage I-III).

5. Intervention

Arm 1: UFT 300 mg/day + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. from 2 to 14 weeks after surgery (n=11).

Arm 2: UFT 300 mg/day alone (n=12).

6. Main outcome measures

Hematology (hemoglobin, white blood cell count, lymphocyte count, suppressor T cell %, cytotoxic T cell %): 1, 3, 6, and 12 months after the start of treatment.

Scores of subjective symptoms (performance status [PS], anorexia, general malaise): once a month.

7. Main results

There were no between-arm differences in hemoglobin level, white blood cell count, and lymphocyte count. Suppressor T cells (%) tended to be decreased for 3 months and were significantly lower in arm 1 only at Month 1 ($P<0.05$). Cytotoxic T cells (%) tended to be increased in arm 1 only at Month 1 ($P=0.076$).

Subjective symptoms such as anorexia and general malaise (especially anorexia) improved markedly but not significantly in arm 1. Statistical analysis could not be performed because of a small sample size.

8. Conclusions

Juzentaihoto is useful in gastric cancer patients undergoing postoperative adjuvant UFT.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Decreased white blood cell and granulocyte counts were observed in 1 patient in Arm 1 and 1 patient in Arm 2.

11. Abstractor's comments

The authors concluded that juzentaihoto used in combination with the anticancer agent (UFT) is useful in improving host-immunity and reducing adverse reactions to the anticancer agent. However, the only statistically significant difference was in the suppressor T cell % at Month 1 (significantly lower in the juzentaihoto combination group than in the control group). Otherwise, there was no significant difference between the two groups in suppressor T cell % at any other time points or in cytotoxic T cell % throughout the follow-up period, indicating that their conclusion was unjustified. Throughout the follow-up, white blood cell count and lymphocyte % tended to be higher in the combination group, indicating that the absolute lymphocyte count may have been significantly higher in the combination group. In addition, anorexia improved more in the combination group suggesting greater improvement in its nutritional status (but no significance could be demonstrated because of a small sample size). Difference in body weight gain % may have been significant although changes in body weight were not assessed. The data in this article needs re-analysis and re-interpretation.

12. Abstractor and date

Hoshino E, February 15 2009, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Sugimachi K. A study of the usefulness of ninjin'yoeito in the postoperative adjuvant chemotherapy for gastric cancer*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1995; 72: 454–8 (in Japanese). Ichushi Web ID: 1995168756 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人參養榮湯) for reducing adverse effects and improving performance status (PS) in patients undergoing postoperative adjuvant chemotherapy (fluoropyrimidine anticancer drug) for gastric cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Three university hospitals (2nd Department of Surgery, Kyushu University, 2nd Department of Surgery, Fukuoka University, 2nd Department of Surgery, University of Occupational and Environmental Health) and 19 other hospitals, Japan.

4. Participants

Forty-six postoperative patients with stage I-IV gastric cancer undergoing gross curative resection.

5. Intervention

Arm 1: fluoropyrimidine anticancer drug + KANEBO Ninjin'yoeito (人參養榮湯) Extract Granules 2.5 g t.i.d. from 2 to 14 weeks postoperatively (n=27).

Arm 2: fluoropyrimidine anticancer drug alone (n=19).

6. Main outcome measures

Hematological measures (white blood cell [WBC], red blood cell [RBC], and platelet counts), body weight, PS, subjective symptoms (appetite, nausea/vomiting, and diarrhea) at 14 weeks after the start of administration.

7. Main results

Change in body weight, PS: no significant difference between arms.

Decrease in RBC count, platelet count: a smaller decrease in arm 1, although not significantly smaller.

Decrease in WBC count: no significant between-arm difference.

Degree of improvement in subjective symptoms: no significant between-arm difference.

8. Conclusions

Ninjin'yoeito (人參養榮湯) tends to suppress the decreases in RBC count and platelet count but not the decrease in WBC count and does not improve PS in patients undergoing postoperative adjuvant fluoropyrimidine-based chemotherapy for gastric cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions in arm 1 did not occur, and adverse events in arm 2 were not mentioned.

11. Abstractor's comments

The authors concluded that ninjin'yoeito combined with the anticancer drug (fluoropyrimidine) has therapeutic usefulness. However, given that the physicians were not blinded to the patient's clinical information and medical status, the finding that the intervention was effective may have been biased. It is problematic that the extent of intraoperative progression and invasion varied between patients and that patients were included who had early-stage and advanced gastric cancer; differentiated and undifferentiated gastric cancer; partial, subtotal, and total gastrectomy; and stage I to IV disease. The fluoropyrimidine drugs also varied. Comparison should have been made between groups of patients with homogeneous baseline characteristics. Such heterogeneity may have contributed to the failure to show a significant improvement in subjective symptoms. Use of a protocol designed to optimally rather than uniformly administer ninjin'yoeito or to select the optimal Kampo medicine [*hozai* (補劑, formulations with tonic effects)] (i.e., hochuekkito, juzentaihoto, or ninjin'yoeito) would have resulted in a significant difference.

12. Abstractor and date

Hoshino E, 15 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yamada T. Randomized controlled trial of the efficacy of Juzentaihoto (TJ-48) combined with oral 5-FU for gastric cancer*. *Progress in Medicine*. 2004; 24: 2746-7 (in Japanese)

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯; TJ-48) combined with oral 5-FU as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifteen hospitals associated with Gifu University, Japan.

4. Participants

Ninety-four patients with surgically treated gastric cancer satisfying the following 8 criteria were included: (1) curability A or B; (2) no serious complications; (3) no preoperative treatment; (4) no double or multiple cancer; (5) WBC $\geq 3,000/\text{mm}^3$, Plt $\geq 70,000/\text{mm}^3$, total protein $\geq 6.0\text{g/dL}$, AST/ALT $\leq 60\text{ IU/L}$, and urinary protein (-), before the start of chemotherapy; (6) no possibility of pregnancy; (7) performance status of grade 0 or 1; (8) receipt of consent to participate in the study from patient or family member.

5. Intervention

Arm 1: combination therapy group; continuous treatment with 5-FU tablets (200 mg/day) combined with TSUMURA Juzentaihoto (十全大補湯) Extract Granules (TJ-48; 7.5 g/day) for 2 years starting 2 weeks after surgery; 43 patients.

Arm 2: monotherapy group; continuous treatment with 5-FU tablets (200 mg/day) for 2 years starting 2 weeks after surgery; 51 patients.

6. Main outcome measures

Five-year survival rate, 5-year survival rate by clinical stage.

7. Main results

Five-year survival rate was 74.3% in arm 1 and 73.5% in arm 2, indicating no significant difference between arms. By clinical stage, patients with stage I or II had 2-year and 5-year survival rates of 92% and 90%, respectively, in arm 1 (n=42), and 91% and 83%, respectively, in arm 2 (n=35), indicating no significant difference between arms. In contrast, patients with stage III or IV had 2-year and 5-year survival rates of 22% and 0%, respectively, in arm 1 (n=9), and 87% and 25%, respectively, in arm 2 (n=8), with median survival of 35.1 months in arm 2 and 14.2 months in arm 1, demonstrating significantly extended survival of patients treated with juzentaihoto.

8. Conclusions

Combination of juzentaihoto with oral 5-FU is effective for patients with surgically treated stage III or IV gastric cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The finding that the combination with juzentaihoto extends the postoperative survival of patients with surgically treated gastric cancer is clinically very impressive. The adverse drug reactions (ADRs) associated with this anticancer treatment are also of interest. Also, some information on study design (such as blinding) is lacking, making further evaluation difficult. Publication of the original paper is awaited.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Toda T, Matsuzaki K, Kawano T, et al. Preoperative and postoperative combination therapy with slow-release tegafur capsules and juzen-taiho-to in patients with colorectal cancer - Tissue concentrations and thymidine phosphorylase activity -. *Gan no Rinsho (Japanese Journal of Cancer Clinics)* 1998; 44: 317-23 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To elucidate the mechanism by which juzentaihoto (十全大補湯) reduces the adverse reaction to treatment with 5-fluorouracil (5-FU) (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Forty-four patients with colorectal cancer who received the anti-cancer drug tegafur (slow-release capsules, 800 mg/day) preoperatively and postoperatively.

5. Intervention

Arm 1: combination of juzentaihoto (十全大補湯) (manufacturer unknown) 7.5 g/day with slow-release tegafur capsules for 7–20 days preoperatively (n=24).

Arm 2: administration of slow-release tegafur capsules alone for 7–20 days preoperatively (n=20).

As postoperative adjuvant chemotherapy, the treatment was continued as long as possible in both arms.

6. Main outcome measures

Tegafur and 5-FU concentrations in peripheral blood, tegafur and 5-FU concentrations and thymidine phosphorylase (TP) activity in surgical specimen tissues (tumor and normal tissues), amount of tegafur converted to 5-FU per TP activity unit in tumor and normal tissues, tumor/normal tissue ratio of the amount of tegafur converted to 5-FU per TP activity unit, hematology/liver function test/total protein at start and completion of administration.

7. Main results

The 5-FU concentration in non-tumor tissues was higher in arm 2 than in arm 1 ($P<0.05$). There were no significant between-arm differences in tegafur and 5-FU concentrations in peripheral blood and tumor tissue, or in tegafur concentration in normal tissues. The common adverse drug reactions to slow-release tegafur (anorexia, nausea/vomiting, and diarrhea) occurred later in arm 2 (9/23) than in arm 1 (6/28). The change in glutamic pyruvic transaminase (GPT) between the start and completion of administration was not significant in arm 1 but it was significant in arm 2 ($P<0.01$), suggesting that juzentaihoto may suppress development of liver dysfunction. Thymidine phosphorylase (TP) activity was higher in tumor tissues than in normal tissues both in arm 1 ($P<0.01$) and arm 2 ($P<0.05$). Conversion of tegafur to 5-FU per TP activity unit was higher in tumor tissues than in normal tissues in arm 1. The ratio of the conversion to 5-FU per TP activity unit in tumor tissue to that in normal tissue was higher in arm 1 than in arm 2 ($P<0.05$).

8. Conclusions

Administration of juzentaihoto in patients receiving slow-release tegafur capsules increases 5-FU concentration in tumor tissues but decreases 5-FU concentration in normal tissues, enhancing the tumor selectivity of tegafur. This effect may be partly due to the modulation by juzentaihoto of TP activity in tissues and of cytochrome P-450 (CYP).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It is attractive to suppose that a Kampo medicine modulates the effect of a drug-metabolizing enzyme to increase the tumor selectivity of an anti-cancer drug. Identification of the active component(s) of the Kampo medicine may pave the way for development of novel anti-cancer drugs. However, given the large standard error of the mean (SEM), it is unreasonable to conclude from higher GPT values at the completion of treatment that juzentaihoto suppresses hepatopathy associated with slow-release tegafur capsules. It would be more reasonable to attribute the higher GPT values to discontinuation of treatment in a few patients who developed hepatopathy.

12. Abstractor and date

Hoshino E, 26 April 2009, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Sasaki K, Takashima K, Kitagawa K, et al. Immunostimulation and suppression of liver metastasis by Kampo medicines in postoperative patients with colorectal cancer*. *Progress in Medicine* 1992; 12: 1652–5 (in Japanese).

1. Objectives

To evaluate the suppression of liver metastasis and stimulation of the immune response by shosaikoto (小柴胡湯) in postoperative patients with colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (1st Department of Surgery, Sapporo Medical College), Japan.

4. Participants

Twenty postoperative patients with colorectal cancer on chemotherapy.

5. Intervention

Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day started 3–4 weeks postoperatively (n=10).

Arm 2: administration of Krestin (polysaccharide Kureha: PSK) 3 g/day started 3–4 weeks postoperatively (n=10).

6. Main outcome measures

Peripheral blood white blood cell (WBC) count, lymphocyte count, CD3-, CD4-, CD8-, CD57-, CD16-positive cells (%), and phytohemagglutinin (PHA)-stimulated lymphocyte proliferation, measured at baseline, 2, 4, and 12 weeks after administration as immunological indices. Patient prognosis (observation for 3 years and 6 months to 4 years and 4 months) in both arms.

7. Main results

CD4/CD8 ratio: There was no difference between arms.

CD57: At week 2, the percent increase was significantly larger in arm 1 than in arm 2. At week 4, a significant increase from baseline was noted in both arms.

CD16: At weeks 4 and 12, a significant increase from baseline was noted in both arms.

PHA-stimulated lymphocyte proliferation: A significant increase from baseline was noted at weeks 2, 4, and 12 in arm 1 and at week 12 in arm 2.

Prognosis: In arm 1, there was 1 patient with tumor recurrence in the abdominal wall who survived after re-operation and 1 death. In arm 2, there was 1 patient with liver metastasis who died and 1 patient with local recurrence who survived after re-operation.

8. Conclusions

Saiko agents increased PHA-stimulated lymphocyte proliferation and NK cell activity, evaluated by CD57 and CD16, suggesting its immunostimulating effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The above immunological findings were in patients on chemotherapy started 3–4 weeks postoperatively. Generally, the immune system is compromised postoperatively because of trauma and malnutrition. Cellular immunity is thought to be reduced for 2–4 weeks postoperatively and restored to preoperative level in 6 weeks. Therefore, it is impossible to conclusively attribute the increase in PHA lymphocyte proliferation and NK activity at 2–12 weeks postoperatively to the effect of shosaikoto or PSK without a no treatment control. Also, there is a wide distribution of disease stages, making it impossible to discuss prognosis. It is necessary to compare two groups of patients with stage III–IV on specified chemotherapy after confirmation of sufficient recovery from surgery: one group treated with Kampo medication and one group without such treatment.

12. Abstractor and date

Hoshino E, 26 April 2009.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Araki Y, Tanaka T, Ogata Y, et al. Immunological evaluation of the efficacy of Kampo prescription for postoperative patients with colorectal cancer*. *Shinyaku to Rinsho (Journal of New Remedies and Clinic)* 1992; 41: 1670–6 (in Japanese).

1. Objectives

To evaluate the immunostimulation and improvement of nutritional status by ninjin'yoeito (人参養榮湯) in postoperative patients with colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (1st Department of Surgery, Kurume University), Japan.

4. Participants

Twenty-three postoperative patients with colorectal cancer on chemotherapy.

5. Intervention

Arm 1: TSUMURA Ninjin'yoeito (人参養榮湯) Extract Granules 9.0 g/day from the start of postoperative oral feeding (n=12).

Arm 2: no treatment (n=11).

6. Main outcome measures

Peripheral blood white blood cell (WBC) count, lymphocyte count, percentage of T cells (%), phytohemagglutinin (PHA) lymphocyte transformation, lymphocyte surface markers (CD4, CD8, and CD25), NK cell activity (%), and interleukin (IL)-2 responsiveness, measured preoperatively, and at postoperative week 2 and months 3 and 6 as indices of immunological status. Patient prognosis (observation for 3 years and 6 months to 4 years and 4 months) in both arms. Prognostic nutritional index (PNI).

7. Main results

Percent change in lymphocyte count: greater in arm 1 than arm 2 at postoperative week 2 and month 3 ($P<0.05$).

Change in the T cell number (in %): greater in arm 2 than arm 1 ($P<0.05$) at postoperative week 2, but greater in arm 1 than arm 2 ($P<0.05$) at postoperative months 3 and 6.

Percent change in PHA-stimulated lymphocyte proliferation: greater in arm 1 than arm 2 at postoperative month 6 ($P<0.05$).

Change in NK cell activity (in %) and prognostic nutritional index (PNI): no significant difference between arms.

Change in the number of CD4- and CD8-positive cells (in %) and IL-2 responsiveness ratio: all tended to be greater in arm 1 than arm 2 at postoperative week 2 and month 3.

IL-2 receptor-positive cell ratio: tended to be greater in arm 1 than arm 2 at postoperative week 2 and month 6. At postoperative month 6, there was a significant reduction from preoperative value in arm 1 ($P<0.05$).

8. Conclusions

Ninjin'yoeito significantly promotes improvement of lymphocyte count and PHA-stimulated lymphocyte proliferation in postoperative patients with colorectal cancer, suggesting its role as a possible biological response modifier.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study demonstrated that administration of ninjin'yoeito increased lymphocyte count, the percentage of T lymphocytes, and PHA-stimulated lymphocyte proliferation but had no effect on NK cell activity, IL-2 responsiveness ratio, or IL-2 receptor-positive cell ratio (indices of unknown immunological significance), or nutritional state (PNI). (Although the authors concluded that NK cell activity was enhanced, a similar increase was noted in the control group; thus, it is impossible to conclude that NK cell activity was enhanced by the Kampo medicine.) However, certain cellular immune functions may have been stimulated one of the mechanisms underlying Kampo medicine activity.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**References**

Sasaki K, Ezoe E, Araya J, et al. Effects of Kampo medicine on the immune functions in gastrointestinal gastroenteric cancer patients— utility from the perspective of immunity. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 2006; 15: 9-14 (in Japanese).

Sasaki K, Takasaka H, Furuhata T, et al. Effect of Kampo medicine on the cancer chemotherapy of cancer. *Geka Chiryō (Surgical Therapy)* 2007; 97: 504-10 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the clinical efficacy of juzentaihoto (十全大補湯) for the prevention of postoperative recurrence of colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

The First Department of Surgery of Sapporo Medical University and other institutions (their names, unspecified), Japan.

4. Participants

One hundred and sixty-eight patients (mean age, 65 years) with stage II or III colorectal cancer who received curative resection and adjuvant chemotherapy between July 2001 and March 2005.

5. Intervention

Arm 1: treatment with oral 5-FU and juzentaihoto (十全大補湯) (manufacturer, not specified) 7.5 g/day, n=86.

Arm 2: treatment with oral 5-FU, n=82.

6. Main outcome measures

Recurrence rate, time to recurrence, and survival time.

7. Main results

Mean postoperative follow-up was 38.6 months. Recurrence rate for patients with stage II disease was slightly, though not significantly, more favorable in arm 1 (6.9%) than in arm 2 (14.0%). Mean times to recurrence were 18.2 months in arm 1 and 16.9 months in arm 2. The 3-year recurrence-free survival rate was slightly, though not significantly, better in arm 1: 92.2% in arm 1 and 85.9% in arm 2 for patients with stage II disease, and 67.5% and 62.9%, respectively, for patients with stage III disease.

8. Conclusions

Juzentaihoto may have a metastasis-suppressive effect, but since these are interim reports, the follow-up is still ongoing.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

These two papers are interim reports on a multicenter clinical study that evaluated the clinical efficacy of juzentaihoto for the prevention of postoperative recurrence of colorectal cancer. The data from slightly less than 100 patients in each arm were analyzed. At this point, no clear difference is observed between the juzentaihoto-treated arm and the control arm, although the outcomes tend to be slightly more favorable in the former. A final report is anticipated. This abstract summarized mainly data from the second, recently published, paper mentioned above.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Nishimura G. Evaluation of clinical efficacy of hochuekkito in improving nutritional/immune status in patients with surgery for large intestine carcinoma*. *Progress in Medicine*. 2009; 29: 84-85. [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of 1-week preoperative treatment with hochuekkito (補中益気湯) for improving pre- and postoperative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital (Kanazawa Red Cross Hospital), Japan.

4. Participants

Twenty patients scheduled to undergo laparotomy for large intestine carcinoma.

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules at a dose of 2.5 g t.i.d. from 7 days to 1 day before the operation (n=10).

Arm 2: not treated (n=10).

6. Main outcome measures

Height, body weight (body mass index [BMI]), white blood cell count, and levels of C-reactive protein (CRP), total protein, albumin, prealbumin, and immunological parameters (IL-6, CD4, CD8) were determined before and after administration preoperatively and 1, 3, and 7 days postoperatively.

7. Main results

One patient in arm 1 dropped out. The remaining 19 patients (9 in arm 1 and 10 in arm 2) were included in the analysis. There was no between-arm difference in the age, sex, affected site, duration of the operation, blood loss, or percentage of patients who received blood transfusion and no significant between-arm difference in body weight (BMI), white blood cell count, CRP, total protein, or albumin. Mean prealbumin level tended to be higher in arm 1 than in arm 2 from the day before surgery to 7 days after surgery, with a significant difference observed only 3 days after surgery ($P=0.02$). IL-6 tended to be lower in arm 1 than in arm 2 on postoperative day 1.

8. Conclusions

Preoperative treatment with hochuekkito may be useful for early recovery from surgery for large intestine carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events: one patient in arm 1 dropped out because he/she refused the treatment due to “no Kampo medicine was accepted constitutionally.”

11. Abstractor's comments

Administering hochuekkito for 1 week prior to surgery for large intestine carcinoma to improve perioperative nutritional/immune status and reduce complications and thereby to reduce hospital stay and medical costs is an interesting issue. In revitalization therapy, hochuekkito is an *hozai* (補劑; formulations with tonic effects) that is focused on “*qi* (気虚, *qi* deficiency)” and on improving anorexia, general malaise, sleep disorder, etc. Prealbumin is a short-lived protein that reflects recent protein intake. Hochuekkito may have acted by reducing the patient's anxiety and thus preventing loss of appetite before surgery. Appetite, sleep, bowel movement, etc., which were not followed in this study, should also be monitored. It would be desirable to confirm the usefulness of hochuekkito in randomized controlled trials using other *hozai* (juzentaihoto and ninjin'yoeito) or anxiolytics as controls.

12. Abstractor and date

Hoshino E, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto*. *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai (5th Annual Meeting of the Japanese Gastroenterological Association) (Workshop 5) 2009: 9-10.*

1. Objectives

To evaluate the reduction in the number of days to postoperative flatulence and the anti-inflammatory efficacy of daikenchuto (大建中湯) in patients who underwent laparotomy for large intestine carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Tokushima University Hospital), Japan.

4. Participants

Thirty postoperative patients with large intestine carcinoma.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules postoperatively (dose and duration of treatment, unknown; n=15 including 8 with rectal cancer and 7 with colon cancer).

Arm 2: not treated with daikenchuto (大建中湯) postoperatively (n=15, including 6 with rectal cancer and 9 with colon cancer).

6. Main outcome measures

In addition to the number of days to postoperative flatulence, white blood cell count, lymphocyte count, and levels of C-reactive protein (CRP), β -D glucan, and *Candida* antigen were determined before and 1, 3, 5, and 7 days after the operation.

7. Main results

There were between-arm differences in age, sex, stage, duration of the operation, blood loss, etc. but no mention of their significance. The lymphocyte count was not described. There was no significant between-arm difference in the white blood cell count, β -D glucan level, or *Candida* antigen level. CRP level (5.1 ± 2.3 vs. 7.7 ± 4.7 ; $P < 0.05$) and the number of days to postoperative flatulence (1.7 ± 0.4 vs. 2.9 ± 0.8 ; $P < 0.05$) were significantly lower in arm 1 than in arm 2 on postoperative day 3.

8. Conclusions

Daikenchuto is useful in promoting flatulence and inhibiting inflammation after surgery for large intestine carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Reduction in the time to resumption of intestinal peristalsis and inhibition of postoperative inflammation (CRP) after surgery for large intestine carcinoma in order to reduce medical costs and hospital stay are interesting issues. To explain the early postoperative anti-inflammatory effect of daikenchuto, the author referred to daikenchuto-mediated inhibition of inflammatory cytokine production, intestinal mucosal villous damage, and bacterial translocation demonstrated in a fasted rat model. Further analysis of the effects of daikenchuto on the general condition (appetite, sleep, bowel movement, hot flushes, etc.) of postoperative patients will be needed before treatment of all patients with daikenchuto is deemed appropriate.

12. Abstractor and date

Hoshino E, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Takagi K, Nagata H, Horie T, et al. Effect of the preventive herbal therapy using dai-kenchu-to on intestinal obstruction following curative resection for colorectal cancer: prospective, randomized study. *Kampo Kenkyu (Kampo Research)* 2007; (429): 270-1 (in Japanese). Ichushi Web ID: 2008028028

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on intestinal obstruction following colorectal cancer surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Second Department of Surgery, Dokkyo University School of Medicine, Japan.

4. Participants

One hundred and seventy-five patients who underwent surgery for colorectal cancer (cecal colon [n=119] or rectal [n=56] cancer).

5. Intervention

Arm 1: treatment with daikenchuto (大建中湯) (manufacturer, not specified) 27 g/day (n=86).
Arm 2: no treatment (n=87).

6. Main outcome measures

The percentage of patients who postsurgically developed each of the following: ileus, abdominal pain, abdominal distention, and irregular bowel movements.

7. Main results

The between-arm difference in the percentage of patients who developed ileus in arms 1 (1.16%) and 2 (5.75%) or who experienced abdominal distention in arms 1 (2.33%) and 2 (6.90%) was not significant. A significantly smaller percentage of patients in arm 1 developed abdominal pain (1.16% vs 9.20% [for arm 2]; $P=0.042$) or experienced irregular bowel movements (3.49% vs 13.79% [for arm 2]; $P=0.033$).

8. Conclusions

Daikenchuto extract fine granules do not prevent ileus following colorectal cancer surgery, but do result in the reduction of postoperative abdominal pain and irregular bowel movements.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The description of the study method in the present paper is extremely inadequate, and the protocol itself is problematic. Details, such as duration of treatment with daikenchuto extract fine granules, outpatient or inpatient setting, length of follow-up, and definitions of abdominal pain, abdominal distention, or irregular bowel movement are not given. Significant results would have been obtained if the authors had defined these specifics. Therefore, I recommend a rewrite of this paper after these details are clarified and the results are reviewed.

12. Abstractor and date

Hoshino E, 17 March 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Nagatomo H, Shigehira M. Efficacy of TSUMURA Juzentaihoto for reducing the adverse effects of the anticancer drug cisplatin. *Kampo Igaku (Kampo Medicine)* 1992; 16: 116–9 (in Japanese).

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) for reducing adverse effects of Spongel + Lipiodol + phosphatidyl choline + cisplatin treatment in transarterial embolization (TAE) for hepatocellular carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty patients undergoing transarterial embolization with Spongel + Lipiodol + cisplatin 100 mg + phosphatidyl choline 300 mg for hepatocellular carcinoma. On the day of TAE, Primperan 1 mg/kg and Solu-Cortef 200 mg were administered for anti-emesis.

5. Intervention

Grouping by block randomization.

Arm 1: TSUMURA Juzendaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. (from 3 days before through 5 days after TAE) (n=10).

Arm 2: no administration of juzendaihoto (十全大補湯) (n=10).

6. Main outcome measures

Gastrointestinal symptoms: number of nausea/vomiting episodes until 24 hr after TAE, number of days until recovery of food intake.

Renal disorder: blood urea nitrogen, creatinine (comparison between 7 days before and 7 days after TAE)

Nutritional state: albumin, total cholesterol, choline esterase (comparison between 7 days before and 7 days after TAE), number of weeks until recovery of body weight to pre-TAE level.

7. Main results

The number of nausea/vomiting episodes was significantly decreased in Arm 1 compared with Arm 2, but changes in the renal function and nutrition status indices were similar in both arms.

8. Conclusions

Juzentaihoto significantly suppresses nausea/vomiting after transarterial embolization (TAE) with Spongel + Lipiodol + phosphatidyl choline + cisplatin for hepatocellular carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The authors concluded that juzentaihoto administered before and after TAE for hepatocellular carcinoma relieved nausea/vomiting for 24 hr after TAE. However, whether juzentaihoto should have been administered within the timeframe 3 days before through 5 days after TAE has no basis and should have been investigated before beginning the controlled trial. Traditionally, juzentaihoto is not used to suppress nausea/vomiting. Therefore, a clinical study of the antiemetic use of this Kampo medicine should not have been performed in patients with advanced hepatocellular carcinoma who are not indicated for surgery and who are “relatively *kyosho* (虚証, deficiency pattern).” The traditional Kampo antiemetic medicines (shohangekabukuryoto [小半夏加茯苓湯], bukuryoin [茯苓飲], shinbuto [真武湯], and kankyoninjinhangegan [乾姜人參半夏丸]) should have been investigated first.

12. Abstractor and date

Hoshino E, 15 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Ayukawa K, Sato T, Nagase S, et al. Preventive effect of shosaikoto on liver carcinogenesis*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1994; 71: 1874–6 (in Japanese). Ichushi Web ID: 1995019997

1. Objectives

To evaluate the preventive effect of shosaikoto (小柴胡湯) on the progression of cirrhosis to liver cancer.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One university hospital (3rd Department of Internal Medicine, Kyushu University) and 8 other hospitals, Japan.

4. Participants

Ninety-five patients with cirrhosis diagnosed by laparoscopy, liver biopsy, and laboratory examination.

5. Intervention

Randomization based on whether the birth month is odd or even.

Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 5.0–7.5 g/day (n=52).

Arm 2: no administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules (n=43).

6. Main outcome measures

Incidence of liver cancer during the 3-year period, alpha-fetoprotein (AFP) level, and blood biochemistry.

7. Main results

There was no significant difference in 3-year incidence of liver cancer between arms. AFP tended to be lower in arm 1, although not significantly lower. GOT was significantly lower in arm 1 only at weeks 12 and 15.

8. Conclusions

While not significant, the Shosaikoto treatment tends to lower the incidence of liver cancer and AFP.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events in arm 1 did not occur and adverse events in arm 2 were not mentioned.

11. Abstractor's comments

This study is a sequel of the study by Oka et al. (Oka H, Yamamoto S. Controlled prospective study of prevention of hepatocellular carcinoma of the liver. *Shokakika (Gastroenterology)* 1991; 15: 71-8.) and may have failed to demonstrate significant differences because the follow-up period of 3 years was too short and the doses of TSUMURA Shosaikoto Extract Granules (5.0–7.5 g) were too low. Thereafter, shosaikoto was contraindicated for cirrhosis in principle, further compromising the usefulness of this study.

12. Abstractor and date

Hoshino E, 22 February 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yoshikawa K. Evaluation of anti-inflammatory efficacy of daikenchuto*. *Dai 5 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai (5th Annual Meeting of the Japanese Gastroenterological Association) (Workshop 5) 2009: 9-10.*

1. Objectives

To evaluate the anti-inflammatory efficacy of daikenchuto (大建中湯) in postoperative patients with liver carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Tokushima University Hospital), Japan.

4. Participants

Twenty patients who underwent hepatectomy.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (dose and duration of treatment, unknown; n=11).

Arm 2: not treated with daikenchuto (大建中湯) (n=9).

6. Main outcome measures

In addition to the number of days to postoperative flatulence, white blood cell count, lymphocyte count, C-reactive protein (CRP) level, β -D glucan level, and *Candida* antigen level were determined before and 1, 3, 5, and 7 days after the operation.

7. Main results

There were between-arm differences in age, sex, stage, duration of the operation, blood loss, etc., but no mention of their significance. The number of days to postoperative flatulence, white blood cell count, lymphocyte count, or *Candida* antigen level was not described. The CRP and β -D glucan levels were significantly lower in arm 1 than in arm 2 on postoperative day 3 ($P<0.05$).

8. Conclusions

Daikenchuto may be useful in inhibiting early postoperative inflammation after surgery for liver carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Inhibition of postoperative inflammation after surgery for liver carcinoma to reduce medical costs and hospital stay is an interesting issue. β -D glucan, a fungal cell wall component, is measured to determine fungal infection. In this study, no mechanism has been offered to explain the transient increase in β -D glucan after surgery for liver carcinoma in arm 2 (the control group). Transient bacterial translocation is unlikely after only a few days of postoperative fasting. To explain the early postoperative anti-inflammatory effect of daikenchuto, the author referred to daikenchuto-mediated inhibition of inflammatory cytokine production, intestinal mucosal villous damage, and bacterial translocation demonstrated in a fasted rat model. Further analysis of the effects of daikenchuto after abdominal surgery on the general condition (appetite, sleep, bowel movement, hot flushes, etc.) of postoperative patients will be needed before its use in treatment is deemed appropriate.

12. Abstractor and date

Hoshino E, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yamagata T, Ajimura K, Yukawa S. Effect of juzentaihoto on myelosuppression during lung cancer chemotherapy. *Therapeutic Research* 1998; 19: 705-8 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the preventive effect of juzentaihoto (十全大補湯) on myelosuppression in patients undergoing chemotherapy (carboplatin + etoposide) for primary lung cancer (squamous cell carcinoma, adenocarcinoma, or small cell carcinoma).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (third Department of Internal Medicine, Wakayama Medical University), Japan.

4. Participants

Thirty-six patients with stage III-IV primary lung cancer (25 with small-cell carcinoma, 6 with squamous cell carcinoma, and 5 with adenocarcinoma) receiving carboplatin on day 1 + etoposide 40 mg/m² on days 1-5.

5. Intervention

Arm 1: administration of the above-mentioned anti-cancer drugs + juzentaihoto (十全大補湯) (manufacturer unknown) 7.5 g/day (7 days before through 21 days after the start of administration of the anti-cancer drugs) (n=20).

Arm 2: the above-mentioned anti-cancer drugs alone (n=16).

6. Main outcome measures

Changes in platelet, white blood cell (WBC), and red blood cell (RBC) counts, and hemoglobin value during treatment, and change in each item between pre- and post-treatment.

7. Main results

Because baseline platelet and WBC counts were significantly lower in arm 1, there were no significant between-arm differences in their minimum values. However, decrements in these values from pre- to post-treatment were significantly smaller in arm 1 (platelet count, $P < 0.01$; WBC count, $P < 0.05$). The decrement in RBC count was significantly smaller in arm 1 ($P < 0.05$), although there was no significant between-arm difference in hemoglobin value.

8. Conclusions

Juzentaihoto extract helps reduce the severity of myelosuppression in patients on chemotherapy (carboplatin + etoposide) for primary lung cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions in arm 1 (adverse events in arm 2, not indicated).

11. Abstractor's comments

The authors concluded that combination of juzentaihoto with anti-cancer drugs (carboplatin + etoposide) is effective for reducing myelosuppression associated with anti-cancer drug treatment, and thus useful in administering potent chemotherapy and improving quality of life. However, the significant differences in pre-treatment platelet and WBC counts between arm 1 and arm 2 as well as the conclusion drawn from comparison of the degree of decrements were problematic.

12. Abstractor and date

Hoshino E, 22 February 2009, 6 January 2010, 22 October 2011, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Inui H, Yamagata T, Minakata Y, et al. Prevention of side effects during lung cancer chemotherapy by Hochuekkito. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 1993; 2: 56–60 (in Japanese).

1. Objectives

To evaluate the preventive and relieving effect of hochuekkito (補中益氣湯) on general malaise in patients undergoing chemotherapy (including cisplatin for 5 days) for advanced primary lung cancer.

2. Design

Cross over randomized controlled trial (RCT-cross over).

3. Setting

One hospital, Japan.

4. Participants

Nine patients with advanced (stage III–IV) lung cancer (small cell [n=4] and non-small cell [n=5]) who underwent gross curative resection and postoperative cisplatin + etoposide and postoperative cisplatin + mitomycin + vindesine, respectively.

5. Intervention

Arm 1: hochuekkito (補中益氣湯) (manufacturer unknown) 2.5 g t.i.d. in combination in the first course and anticancer drugs alone in the second course.

Arm 2: anticancer drugs alone in the first course and hochuekkito (補中益氣湯) (manufacturer unknown) 2.5 g/day in combination in the second course.

Comparison between anticancer drugs alone and hochuekkito (補中益氣湯) (manufacturer unknown) 2.5 g t.i.d. in combination.

6. Main outcome measures

Subjective symptoms (appetite, mood, sleep, general malaise, daily life, and face scale) with and without hochuekkito rated on a 5-point scale and recorded in a quality of life diary for 3 weeks. CD4/8 and NK activity before and after administration of hochuekkito.

7. Main results

General malaise, mood, and appetite showed a tendency for improvement during administration of hochuekkito. There were no significant between-arm differences in CD4/8 or NK activity.

8. Conclusions

Hochuekkito administered during chemotherapy for lung cancer relieves and improves mood and general malaise.

9. From Kampo medicine perspective

The *sho* (証, pattern) concept was not used as a rationale for inclusion or exclusion and was not discussed, although “calculation based on the Kampo score questionnaire revealed 7 patients with *kyosho* (虚証, deficiency pattern) and 2 patients with *chukansho* (中間証, intermediate pattern).”

10. Safety assessment in the article

None.

11. Abstractor’s comments

Despite the lack of statistically significant differences, the authors concluded that hochuekkito may be used to relieve and improve adverse reactions to anticancer drugs (cisplatin + α). The bar chart showing the severity of each symptom is meaningless. Although “the data were compared by sign test,” the analysis seems to be incorrect.

12. Abstractor and date

Hoshino E, 24 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Kato S, Kishiro I, Machida S, et al. Combined effects of hochu-ekki-to (*bu-zhong-yi-qi-tang*) and clarithromycin on Lung Carcinoma. *Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)* 1999; 13: 83-8 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) combined with clarithromycin (CAM) for improvement in the prognosis of lung cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Department of Internal Medicine, Dokkyo Medical University Hospital), Japan.

4. Participants

Thirty-five patients with primary lung cancer lesions that responded to chemotherapy or radiotherapy either partially or completely (21 males, 14 females; mean age, 63.2±6.7 years; performance status [P.S.] 0-2; baseline clinical stage Ia [n=5], Ib [n=21], and II [n=9]; squamous cell carcinoma [n=14], adenocarcinoma [n=21]).

5. Intervention

Arm 1: combination therapy group; 400 mg/day of CAM + 7.5 g/day of hochuekkito (補中益気湯) extract granules administered to 17 patients (10 males, 7 females; mean size reduction of the primary lesion, 62.8 ± 11.2%).

Arm 2: monotherapy group; 400 mg/day of CAM administered to 18 patients (11 males, 7 females; mean size reduction of the primary lesion, 66.7±8.6%).

6. Main outcome measures

Tumor markers, NK cell activity (at baseline, and 2 and 12 months after the start of treatment), and 1-year survival.

7. Main results

Serum levels of tumor markers were significantly elevated in both treatment groups compared with the control group. In patients surviving 1 year after the start of treatment, NK cell activity, representing immunoreactivity, was elevated in both treatment groups, and was significantly higher in the combination therapy group than the control group.

8. Conclusions

The combination (hochuekkito plus CAM) seems to be effective for maintaining the efficacy of chemotherapy and radiotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study deserves praise for attempting to conduct RCT targeting a difficult-to-treat pathology of lung cancer prognosis. Regrettably, however, it is unclear whether "the control group" mentioned here refers to the CAM monotherapy group or yet another group, or to a before-after comparison in the same group. Clarification of the study is expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Mori K, Saito Y, Tominaga K. Utility of hochu-ekki-to in general malaise accompanying lung cancer chemotherapy. *Biotherapy* 1992; 6: 624–7 (in Japanese with English abstract). Ichushi Web ID: 1993020654

1. Objectives

To evaluate the efficacy of hochuekkito (補中益気湯) for the prevention and relief of general malaise related to chemotherapy for primary lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma).

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Forty-one patients with stage III–IV lung cancer receiving (cisplatin 25 mg/m² for 5 days) + (vindesine 3 mg/m² at days 1 and 8 or etoposide 100 mg/m² at days 1, 3, and 5) every 3 or 4 weeks.

5. Intervention

A table of random numbers was used for group assignment.

Arm 1: TSUMURA Hochuekkito (補中益気湯) Extract Granules 7.5 g/day (beginning from 7 or more days before the start of anticancer drug treatment) (n=21).

Arm 2: no administration of hochuekkito (補中益気湯) (n=20).

6. Main outcome measures

Subjective symptoms (general malaise, mood, appetite, and nausea/vomiting) after 1–4 cycles of chemotherapy in arm 1 or 2–4 cycles in arm 2, recorded in a health diary for comparison.

7. Main results

General malaise, mood, and appetite were significantly improved in arm 1 ($P < 0.01$), but there was no significant between-arm difference in the severity of nausea/vomiting.

8. Conclusions

Hochuekkito is useful for prevention of general malaise and improvement of mood and appetite in patients on chemotherapy (including cisplatin) for primary lung cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions in arm 1, and none was mentioned in arm 2.

11. Abstractor's comments

The authors concluded that hochuekkito combined with anticancer drugs (cisplatin + α) is useful for prevention of general malaise and improvement of mood and appetite. Symptoms were graded ensuring objectivity to some degree, although the study was not blinded. However, improvement was not rated at the same time point in arm 1 (after 1–4 cycles) and arm 2 (after 2–4 cycles). Improvement should have been evaluated over time in both arms after a fixed number of chemotherapy cycles.

12. Abstractor and date

Hoshino E, 6 May 2009, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Nagao K, Nishimura R, Matsuda M, et al. Clinical evaluation of the combined effect of tegafur and *hozai* (補劑; formulations with tonic effects) *. *Toho Igaku (Eastern Medicine)* 1998; 14: 63-71 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hochuekkito (補中益氣湯) or ninjin'yoeito (人參養榮湯) for reducing adverse drug reactions and improving quality of life (QOL) in breast cancer patients undergoing postoperative (after curative resection or initial treatment) Sunfral S (800 mg/day).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Patients with breast cancer receiving the anti-cancer drug Sunfral S (800 mg/day) postoperatively (21 of 26 were evaluated).

5. Intervention

Arm 1: Sunfral S 400 mg/day b.i.d.+ Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules 2.5 g t.i.d. for at least 5 months (n=13).

Sunfral S 400 mg/day b.i.d. + Kanebo Ninjin'yoeito (人參養榮湯) Extract Fine Granules 2.5 g t.i.d. for at least 5 months (n=1).

Arm 2: Sunfral S 400 mg/day b.i.d. alone (n=12).

6. Main outcome measures

Adverse drug reactions; white blood cell (WBC), lymphocyte, and red blood cell (RBC) counts; carcinoembryonic antigen (CEA) evaluated before treatment and at 2, 4, and 6 months after treatment; immunological indices including CD2 CD4, CD8, CD16, and NK cell counts, and lymphocyte stimulation index; and duration of administration.

7. Main results

The Kampo medicines did not significantly reduce adverse drug reactions associated with tegafur/uracil (UFT). There were no between-arm differences in WBC, lymphocyte, or RBC counts (statistical analysis not performed). CEA was increased in 0/5 patients in arm 1 and 4/7 patients in arm 2 (not determined in all patients, statistical analysis not performed). Among patients with adverse drugs reactions to Sunfral S, those in arm 1 received Sunfral S for a longer duration.

8. Conclusions

In patients with adverse drug reactions to postoperative Sunfral S (800 mg/day) for breast cancer, hochuekkito was immunostimulatory (according to percent change noted in the lymphocyte stimulation index) and Sunfral S could be administered for a longer period than the control group.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no differences in the incidence or severity of adverse events between arm 1 and arm 2 (statistical analysis not performed).

11. Abstractor's comments

The authors concluded that combination of hochuekkito with the anti-cancer drug (Sunfral S) was immunostimulatory, as indicated by the increase in lymphocyte stimulation index, and thereby facilitated long-term treatment with anti-cancer drugs. This conclusion is however not supported by evidence that the lymphocyte stimulation data reflect the degree of immunostimulation, considering that there were no significant differences in the percent changes in tumor immunity-related markers including lymphocyte surface markers (helper T/suppressor T/NK cell activities). Furthermore, changes in CEA were not evaluated in the total population, and the evaluation depended on an unsound criterion (i.e., change by 1 µg/mL or more). Moreover, arm 1 in this study included more than one Kampo medicine; 13 patients receiving hochuekkito and 1 patient receiving ninjin'yoeito, and thus the amount of data available for statistical analysis was insufficient and a meaningful conclusion cannot be drawn from these findings.

12. Abstractor and date

Hoshino E, 23 April 2009, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**References**

Adachi I. Supporting therapy with shi quan da bu tang in advanced breast cancer patients. *Biomedical Research* 1990; 11 suppl: 25–31.

Adachi I, Watanabe T, Chen JY, et al. Supportive therapy of oriental medicine for patients with advanced breast cancer. *Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)* 1989; 16: 1538–43 (in Japanese with English abstract). CENTRAL ID: CN-00060398, Pubmed ID: 2730051, Ichushi Web ID: 1990185338

Adachi I. Juzen-taiho-to as a supporting therapy in advanced breast cancer. *Biotherapy* 1989; 3: 782–8. Ichushi Web ID: 1991039494

1. Objectives

To evaluate the efficacy of supportive therapy with juzentaihoto (十全大補湯) for advanced breast cancer patients.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not mentioned (Dr. Adachi belongs to the faculty of the National Cancer Center), Japan.

4. Participants

A total of 119 patients were included in the study. Inclusion criteria: 1) advanced breast cancer with metastasis; 2) 6-month or longer survival expected; 3) no history of gastrointestinal surgery; 5) ability to take drugs orally; 6) no cancer other than breast cancer; and 7) use of anticancer drugs for breast cancer but no use of other Kampo medicines.

5. Intervention

Arm 1: chemotherapy + hormone therapy + juzentaihoto (十全大補湯) (manufacturer unknown) 5–7.5 g (n=58).

Arm 2: chemotherapy + hormone therapy (n=61).

6. Main outcome measures

Significance test using Kaplan-Meier survival curve.

7. Main results

There were no significant differences in survival and biochemistry between the control group and juzentaihoto group; however, when the juzentaihoto group was stratified by Kampo diagnosis (diagnostic criteria not mentioned), a significant difference was noted in survival ($P<0.05$).

8. Conclusions

If used appropriately, supportive therapy with juzentaihoto is effective for patients with breast cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Within 2 weeks of treatment initiation, edema and skin pruritus appeared in 2 patients, one of whom withdrew from treatment.

11. Abstractor's comments

This study evaluated the efficacy of juzentaihoto as supportive therapy for breast cancer. The conclusion that use of juzentaihoto as supportive therapy should be based on Kampo diagnosis is very suggestive. Considering the significance of this point, the rationale for diagnostic criteria for juzentaihoto-indicated patients should be specified.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Mizuno M, Yoshikawa H, Taketani Y, et al. Clinical effects of ninjin'yoeito on performance status (PS) and recovery of physical strength in patients following gynecologic cancer treatment – comparison with no-treatment controls*. *Sanka to Fujinka (Obstetrics and Gynecology)* 1993; 60: 1533–45 (in Japanese). Ichushi Web ID: 1994139265 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人參養榮湯) for relieving subjective symptoms and improving activities of daily living in patients following gynecologic cancer surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokyo Hospital, National Hospital Organization Medical Center, and 21 other facilities, Japan.

4. Participants

Inclusion criteria: gynecologic cancer (uterine cervical, uterine corpus, ovarian, etc.); more than 1 month since the completion of the initial treatment or treatment for recurrence; outpatient with at least one of the following subjective symptoms: anorexia, fatigue/malaise, decreased physical strength, cold limbs, night sweats, and lightheadedness; age, 15–75 years; Eastern Cooperative Oncology Group (ECOG) performance status (P.S.) ≤2; and no recurrence of cancer.

5. Intervention

Arm 1: oral administration of Kanebo (currently Kracie) Ninjin'yoeito (人參養榮湯) Extract Fine Granules 2.5 g t.i.d. for 12 weeks (n=46).

Arm 2: no administration for 12 weeks (n=44).

6. Main outcome measures

Improvement in subjective symptom scores was used to measure efficacy.

7. Main results

Ten patients were excluded. Global improvement rating was significantly higher in arm 1. Stratified analysis revealed no significant between-arm difference for patients only receiving surgery, and significantly higher efficacy in arm 1 for patients also receiving chemotherapy and radiotherapy.

8. Conclusions

Ninjin'yoeito is expected to be useful for relieving subjective symptoms such as fatigue/malaise and regaining ability to perform activities of daily living following gynecologic cancer surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study evaluated the efficacy of ninjin'yoeito for relieving subjective symptoms and improving activities of daily living after surgery to remove a gynecologic cancer. Considering that patients can be expected to value a therapy that relieves subjective symptoms such as fatigue/malaise and restores their ability to perform activities of daily living following gynecologic cancer surgery, a study report like this one is very meaningful. It would be interesting to investigate prognosis.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Hasegawa K, Fukunishi H, Kiyoshige K, et al. Clinical usefulness of Kampo medicines (ninjin-yoei-to, juzen-taiho-to) for side effects in gynecologic cancer chemotherapy – Effects on reducing side effects by CDDP in CAP therapy–. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 181–7 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of combination of ninjin'yoeito (人参養榮湯) and juzentaihoto (十全大補湯) for reducing adverse effects of cyclophosphamide, adriamycin, cisplatin (CAP) chemotherapy including myelosuppression, renal impairment, and gastrointestinal symptoms.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Hyogo Medical Center for Adults, Department of Obstetrics and Gynecology, Kobe National Hospital (currently National Hospital Organization Kobe Medical Center), Department of Obstetrics and Gynecology, Kobe City Medical Center West Hospital, and another 4 facilities, Japan.

4. Participants

Thirty-two patients with ovarian, uterine cervical, or uterine corpus cancer undergoing CAP therapy.

5. Intervention

Arm 1: oral administration of Kanebo (currently Kracie) Ninjin'yoeito (人参養榮湯) Extract Fine Granules 2.5 g t.i.d and Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. for 5 weeks from 1 week before to 4 weeks after administration of anticancer drugs (n=19).

Arm 2: no administration (n=13).

6. Main outcome measures

Pre- and post-treatment myelosuppression and nephrotoxicity evaluated by hematology (blood counts, urea nitrogen, serum creatinine), and subjective symptoms (general malaise, anorexia, and vomiting) evaluated on a 4-point scale using a standard questionnaire.

7. Main results

Kampo medicine treatment did not significantly affect decreases in white blood cell (WBC), red blood cell (RBC), and platelet counts but tended to promote their reversal. Kampo medicine also reduced nephrotoxicity (i.e., normalized blood urea nitrogen [BUN] level and reduced creatinine fluctuation). Subjective gastrointestinal symptoms were not improved.

8. Conclusions

The combination of ninjin'yoeito and juzentaihoto is effective for reducing myelosuppression and nephrotoxicity associated with anticancer drug administration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse drug reactions worth special mention.

11. Abstractor's comments

This study investigated the possible efficacy of combination of ninjin'yoeito and juzentaihoto for relieving myelosuppression and nephrotoxicity, which are important factors affecting completion of anticancer drug treatment. Further investigation is expected. While reduction in subjective symptoms by ninjin'yoeito has been reported, the present study did not demonstrate such an effect. This may be attributable to the increased amount of jio and toki resulting from the combination of ninjin'yoeito with juzentaihoto, given that one-third of patients failed to take the full dose of 7.5 g. It would be interesting to investigate this point in the future.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yamamoto T, Fujita H, Okada H, et al. Clinical evaluation of the effects of ninjin'yoeito on subjective and objective symptoms and bone-marrow function during chemotherapy or radiotherapy in female patients with genital cancer. *Oncology & Chemotherapy* 1994; 10: 126–34.

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人參養榮湯) against subjective and objective symptoms and myelosuppression due to postoperative chemotherapy or radiotherapy in female patients with genital cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, and 8 related facilities, Japan.

4. Participants

Forty patients undergoing cancer chemotherapy or radiotherapy (excluding those with serious complications or Eastern Co-operative Oncology Group (ECOG) performance status (PS) 4 at entry, or those judged by the investigator to be ineligible).

5. Intervention

Arm 1: chemotherapy + Kanebo (currently Kracie) Ninjin'yoeito (人參養榮湯) Extract Fine Granules 2.5 g t.i.d (n=11).

Arm 2: chemotherapy + cepharanthine 2 tablets t.i.d. (n=12).

Arm 3: radiotherapy + Kanebo (currently Kracie) Ninjin'yoeito (人參養榮湯) Extract Fine Granules 2.5 g t.i.d (n=10).

Arm 4: radiotherapy + cepharanthine 2 tablets t.i.d. (n=7).

Duration of administration: at least 2 weeks (more than 4 weeks if possible)

6. Main outcome measures

Four performance status items evaluated on a 5-point scale, nausea/vomiting evaluated on a 4-point scale, hematology (blood counts, biochemistry), and urinalysis (protein, glucose, and urobilinogen).

7. Main results

Kampo medicine treatment significantly improved myelosuppressive symptoms but not subjective and objective symptoms associated with anticancer drug administration. It also improved anorexia and fatigue/malaise during radiotherapy.

8. Conclusions

Ninjin'yoeito is effective for reducing myelosuppression associated with anticancer drug administration and radiotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient had acute hepatitis with unknown causal relationship to ninjin'yoeito.

11. Abstractor's comments

This study investigated the possible efficacy of ninjin'yoeito for relieving myelosuppression caused by anticancer drugs. Ninjin'yoeito improved anticancer drug-caused myelosuppression but not severe anorexia, consistent with other papers. A future report on its efficacy in patients treated with three or more cycles of chemotherapy is also awaited.

12. Abstractor and date

Nakata H, 1 January 2009 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**References**

Oda T. My prescription – clinical application of ninjin'yoeito during chemotherapy for gynecologic cancer: the preventive effect on bone marrow suppression*. *WE* 2004; 9: 5-6 (in Japanese). Ichushi Web ID: 2006050757

Oda T, Ohnuki T, Kihara K, et al. A clinical study of a traditional Chinese herbal medicine, ninjin-yoei-to in bone marrow suppression due to chemotherapy in gynecologic cancer. *Yamagata Kenritsu Byoin Igaku Zasshi (The Yamagata Journal of Medicine)* 2004; 38; 6-9 (in Japanese). Ichushi Web ID: 2004222295

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人參養榮湯) for reducing myelosuppression due to chemotherapy for gynecologic cancer.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital, Japan.

4. Participants

Eight patients who underwent surgery for gynecologic cancer (ovarian [n=6], uterine [n=1], or fallopian tube [n=1] cancer) and received granulocyte colony-stimulating factor (G-CSF) for neutropenia during the first cycle of chemotherapy (CAP: cyclophosphamide, Farmorubicin [epirubicin], cisplatin).

5. Intervention

Arm 1: treatment with Kanebo Ninjin'yoeito (人參養榮湯) Extract Fine Granules (7.5 g/day in two divided doses) continuously from 1 to 2 weeks prior to the start of the second cycle of chemotherapy (n=4).

Arm 2: no treatment with ninjin'yoeito (n=4).

6. Main outcome measures

The following measures during the second and third cycles of chemotherapy: nadir leukocyte and neutrophil counts, the length of time for neutrophil count to fall below 1,000/ μ L, total dose of G-CSF, duration of neutrophil counts under 1,000/ μ L, and nadir hemoglobin level and platelet count.

7. Main results

There were no significant between-arm differences in nadir leukocyte, neutrophil, and platelet counts or in the length of time for the neutrophil count to fall below 1,000/ μ L. Duration of neutrophil count under 1,000/ μ L tended to be shorter in arm 1 than in arm 2 during the second cycle, and became significantly shorter during the third cycle. Total dose of G-CSF tended to be lower in arm 1 than in arm 2 during the second cycle, and became significantly lower during the third cycle. Nadir hemoglobin level during the second cycle, compared with that during the first cycle, was significantly lower in arm 1, but not in arm 2.

8. Conclusions

It is strongly suggested that Kanebo Ninjin'yoeito Extract Fine Granules may exert neutropenia-preventing effects by inducing pluripotent stem cells to multiply and differentiate and by increasing the activity of G-CSF.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Because of the small sample size (only four in each arm), it seems difficult to address the statistical significance of differences observed in this study. Furthermore, although G-CSF administration affects "total dose of G-CSF" and "duration of neutrophil counts under 1,000/ μ L," administration criteria for G-CSF are not described. Thus the data are not objective. The significant decrease in hemoglobin level in arm 1 may indicate that Kanebo Ninjin'yoeito Extract Fine Granules is effective against neutrophil suppression, but not against suppression of erythropoietic cells. It is necessary to include more patients and to investigate not only the efficacy, but also the adverse events induced by G-CSF.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Fukui I, Gotoh S, Kihara K, et al. Adjuvant chemotherapy for invasive bladder cancer. Multicenter study. *Nippon Hinyokika Gakkai Zasshi (Japanese Journal of Urology)* 1992; 83: 1633-9 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of postoperative adjuvant chemotherapy for bladder cancer on survival (the efficacy of the combination with jumentaihoto (十全大補湯) was assessed in patients stratified into 3 groups).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Tokyo Medical and Dental University) and 9 other institutions, Japan.

4. Participants

Forty-eight patients undergoing total cystectomy for bladder cancer.

5. Intervention

Arm 1: chemotherapy + TSUMURA Jumentaihoto Extract Granules (十全大補湯) 7.5 g/day (n=16).

Arm 2: chemotherapy + Picibanil (OK432) (n=15).

Arm 3: chemotherapy only (n=17).

Patients received chemotherapy with one of three cis-platinum-based combinations (5-fluorouracil + adriamycin + cis-platinum [FAP], cyclophosphamide + vincristine + methotrexate [COM] alternating with FAP, or ifosfamide + 5-fluorouracil + cis-platinum [IFP]) for at least 3 cycles, and 6 to 8 cycles if possible.

6. Main outcome measures

Survival.

7. Main results

There was no significant difference between groups.

8. Conclusions

The combination with jumentaihoto for patients with bladder cancer had no effect on their survival.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Since the main objective of this multicenter study was to examine the effect of adjuvant chemotherapy for invasive bladder cancer, main analysis was not conducted on the combination with or without jumentaihoto, and the sample size was too small (17 patients) to draw firm conclusions on the efficacy of jumentaihoto. Investigation with a larger sample size is expected.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Ohkawa T, Ebisuno S, Watanabe T, et al. Clinical evaluations of saireito, a herbal drug, for the urological side-effects of cancer chemotherapy. *Biotherapy* 1990;4:1445–60 (in Japanese with English abstract). Ichushi Web ID: 1991149339

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for relieving the adverse urological effects of anticancer drugs.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The departments of urology of 12 university hospitals including those of Wakayama Medical University, Nara Medical University, and Osaka University School of Medicine; and the departments of urology of 16 non-university affiliated hospitals, Japan.

4. Participants

Two-hundred and seventeen patients with urological cancer treated or to be treated with anticancer drugs.

5. Intervention

Arm 1: anticancer drug maintenance therapy + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d for at least 12 weeks (n=42).

Arm 2: anticancer drug maintenance therapy without administration of Kampo medicine (n=44).

Arm 3: intermittent anticancer therapy + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d for at least 2 courses (n=38).

Arm 4: intermittent anticancer therapy without administration of Kampo medicine (n=33).

6. Main outcome measures

Subjective symptom score (with subscales including general condition, anorexia, general malaise, nausea, vomiting, diarrhea, stomach discomfort, and stomatitis), hematological parameters, and blood biochemistry.

7. Main results

Of 217 patients, 60 were excluded from the analyses. There were no significant differences in subjective symptoms between those receiving saireito (arm 1 and arm 3) and those not receiving saireito (arm 2 and arm 4). The decrease in serum creatinine level after 4 weeks was greater in arm 1 than in arm 2, and was significantly greater after 3 courses in arm 3 than in arm 4.

8. Conclusions

Saireito is not effective for relieving the adverse effects of anticancer drugs, except for decreasing serum creatinine level.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions occurred in 7 patients (6%): 5 in arm 1 and 2 in arm 3. Treatment was discontinued in 4 of the 5 patients in arm 1 and 1 of the 2 patients in arm 2. Adverse drug reactions included vomiting, diarrhea, anorexia, and stomach pain.

11. Abstractor's comments

Although reduction in the adverse effects of anticancer drugs by Kampo formulations has frequently been observed in clinical settings, few full-fledged controlled clinical trials have been conducted. The present study is a valuable multicenter RCT investigating whether saireito relieves the adverse urological effects of anticancer drugs. Although allocation by the envelope method is likely to lead to incomplete randomization, the study found that saireito did not relieve the adverse effects of anticancer drugs. However, saireito did suppress elevation in serum creatinine level suggesting it improves renal function, raising expectations for future studies.

12. Abstractor and date

Okabe T, 15 August 2008, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**References**

Kosaka A, Hojyo M, Osaku M, et al. The value of TSUMURA Juzentaihoto (TJ-48) in reducing adverse effects of anticancer drugs from the perspective of QOL improvement*. *Progress in Medicine* 1993; 13: 1072-9 (in Japanese).

Kosaka A, Kamiya T, Sumiyama M, et al. Usefulness of TSUMURA Juzentaihoto (TJ-48) for reducing adverse effects of anticancer drugs and improving QOL*. *Progress in Medicine* 1994; 14: 2259-64 (in Japanese).

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) for reducing adverse effects and improving quality of life (QOL) in postoperative patients undergoing chemotherapy (tegafur-uracil [UFT] 4 capsules/day) for gastric, colorectal, or breast cancer (curative resection/non-curative resection).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Twelve hospitals, Japan.

4. Participants

Two-hundred and eighty-four postoperative patients undergoing chemotherapy for at least 3 months for gastric, colorectal, or breast cancer.

5. Intervention

Arm 1: UFT 4 capsules/day + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day (n=124).

Arm 2: UFT 4 capsules/day alone (no administration of juzentaihoto (十全大補湯)) (n=127).

Arm 3: surgical excision alone (n=33)

6. Main outcome measures

Presence or absence of adverse drug reactions to the anticancer drug. QOL, evaluated using an interview sheet preoperatively, and 2 weeks, 1, 3, and 6 months postoperatively.

7. Main results

Adverse drug reactions to UFT: arm 1 < arm 2 for colorectal cancer; arm 1 = arm 2 for gastric cancer; arm 1 > arm 2 for breast cancer (data not analyzed statistically, no definite differences).

QOL: significantly improved in breast cancer patients only for disease symptoms 2 weeks postoperatively and only for adverse drug symptoms and social life 6 weeks postoperatively and not significantly improved in patients with any other cancer for any symptoms, mood, and social life at any time point.

8. Conclusions

Juzentaihoto reduces the number of adverse drug reactions and improves QOL in postoperative patients on chemotherapy (UFT 4 capsules/day) for gastric, colorectal, or breast cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events were vomiting and difficulty taking medications in 1 and 3 patients with colorectal cancer, respectively, in Arm 1.

11. Abstractor's comments

The authors wrongly conclude that combination of juzentaihoto with the anticancer drug (UFT) reduces adverse drug reactions and improves QOL, since there was almost no statistically significant difference. The conclusion should be guided by the correct interpretation of the results. Since the study failed to demonstrate the hypothesized usefulness of juzentaihoto, the authors should have discussed in the paper why postoperative patients with cancer receiving UFT did not respond to juzentaihoto. The possible reasons include: patients with cancer on postoperative chemotherapy may not be indicated for a *hozai* (補劑, formulations with tonic effects); may have a *sho* (証, pattern) indicated for a *hozai* other than juzentaihoto; or may respond to different *hozai* depending on cancer type. Even before that, this study should have begun with confirmation that the participants suffered from adverse drug reactions to UFT, had reduced QOL, did not respond to western medicine, and required treatment with Kampo medicine.

There is another report by the same first author of a study limited to one center (Kosaka et al [1993]). This study was then expanded to a multicenter trial with a larger sample size and produced similar results.

12. Abstractor and date

Hoshino E, 28 April 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**References**

Tanaka Y, Hashimoto S. Effects of TSUMURA Juzentaihoto on various complaints occurring as adverse reactions during radiotherapy*. *JAMA* (Japanese version) 1988; (6) suppl: 70-1 (in Japanese).

Hashimoto S, Tanaka Y. Adverse reactions to cancer radiotherapy*. *Sanfujinka no Sekai (World of Obstetrics and Gynecology)* 1990; 42 suppl: 176-84 (in Japanese).

1. Objectives

Efficacy and safety of juzentaihoto (十全大補湯) for reducing adverse reactions during cancer radiotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Multi-center study involving 9 institutions: 6 university hospitals and 3 community hospitals, Japan.

4. Participants

Eighty-three patients who underwent radiotherapy of the chest or abdomen (the irradiated area was about 100 cm² and exposure dose was 50–60 Gy).

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. (n=43).

Arm 2: no treatment (n=40).

6. Main outcome measures

Subjective symptoms: anorexia, general malaise, nausea and vomiting, and diarrhea.

White blood cell, red blood cell, and platelet counts, and blood biochemical values.

7. Main results

Before radiotherapy, there was no significant between-group difference. For anorexia, a trend towards improvement in the treatment group was observed after 4–6 weeks and the difference was significant after 5 weeks ($P<0.05$). There were also between-group differences in general malaise after 4 weeks, in nausea and vomiting after 5 weeks, and in diarrhea after 3–5 weeks. There were no differences in white blood cell, red blood cell, and platelet counts, and in blood biochemical values.

8. Conclusions

Juzentaihoto for adverse reactions during cancer radiotherapy reduced the symptoms of anorexia, general malaise, nausea and vomiting, and diarrhea.

9. From Kampo medicine perspective

This study did not take into account *sho* (証, pattern), according to the related article indicated below.

10. Safety assessment in the article

Juzentaihoto has few adverse effects, according to the related article.

11. Abstractor's comments

The present study was a multicenter RCT based on a previous single-center open trial and controlled trial examining the effect of juzentaihoto for GI side-effects during cancer radiotherapy. The study is valuable in that it was carefully planned for many years.

Although almost the same number of patients assigned to each group, the study included more women (male:female ratio = 1:3). Therefore, further investigation is required to determine whether the observed improvements in symptoms are related to the treatment of only female-related cancer or all cancers. Investigation taking into consideration *sho* to amplify the effect is also expected in the future.

The paper by Tanaka et al (1988) described the allocation method using sealed envelopes, which is not stated in the main article by Hashimoto et al (1990), and also described that mainly patients with breast or uterine cancer were included.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yamada T. Clinical study of juzen-taiho-to administration for postoperative esophageal carcinoma, gastric carcinoma, and colorectal carcinoma – Influence of surgical intervention and postoperative chemotherapy on cell mediated immunity–. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1992; 9: 157-64 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of juzentaihoto (十全大補湯) on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Kyorin University Hospital), Japan.

4. Participants

One hundred seventy-four postoperative patients with esophageal, gastric, or colorectal cancer.

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day beginning 2 weeks after surgery (n=75).

Arm 2: no treatment (n=99).

Patients in arms 1 and 2 who received anticancer agents within 1 month after surgery were considered to be separate groups, i.e., combination therapy groups (cf., arm 3 and arm 4), and their data were analyzed separately.

Arm 3: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day + anticancer agents beginning 2 weeks after surgery (n=49).

Arm 4: no treatment with juzentaihoto (十全大補湯) + anticancer agents (n=55).

The duration of treatment was 6 months.

6. Main outcome measures

Hemoglobin, white blood cell count, lymphocyte count, and levels of serum albumin, CD3, CD4, CD8, phytohemagglutinin (PHA) lymphocyte proliferation, and NK-cell activity.

7. Main results

In patients undergoing total gastrectomy in arm 3, hemoglobin and red blood cell count increased significantly and the white blood cell count decreased significantly. Immune function as indicated by PHA-induced lymphocyte proliferation and NK-cell activity was enhanced in patients with esophageal cancer or total gastrectomy in arm 3.

8. Conclusions

Juzentaihoto postoperatively administered for treatment of esophageal, gastric, or colorectal cancer may act as a biological response modifier (BRM).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study evaluates the change in cell-mediated immunity in response to postoperative administration of juzentaihoto in patients with esophageal, gastric, or colorectal cancer. The data suggest that juzentaihoto may act as a BRM. This study included a variety of cancers, operative procedures, and medical conditions. Investigation (including survival analysis) with a larger sample size in limited populations is expected.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Ohara T, Onda M, Futagawa S, et al. Clinical evaluation of the combined effect of bu-zhong-yi-qi-tang (Japanese name, hochu-ekki-to) or ren-shen-yang-rong-tang (Japanese name, ninjin-yoei-to) and the anticancer drug tegafur. *Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)* 1993; 21: 4423–34 (in Japanese). CENTRAL ID: CN-00546092, Ichushi Web ID: 1994154383 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the clinical effects of hochuekkito (補中益気湯) and ninjin'yoeito (人参養栄湯) in patients undergoing chemotherapy (tegafur).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fourteen university hospitals (3rd Department of Surgery, University of Tokyo, 1st Department of Surgery, Nippon Medical School, 2nd Department of Surgery, Juntendo University, etc.) and 11 other hospitals, Japan.

4. Participants

One-hundred and seventy-eight patients with cancer receiving an anticancer drug (tegafur 400 mg/day or 600 mg/day). The cancer types were gastric cancer (n=91), colorectal cancer (n=63), breast cancer (n=18), and other cancers (n=6). The efficacy analysis population consisted of 162 patients who could receive the above treatment for at least 1 month.

5. Intervention

Arm 1: Kanebo Hochuekkito (補中益気湯) Extract Fine Granules 2.5 g t.i.d. for 6 months (n=57).

Arm 2: Kanebo Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. for 6 months (n=56).

Arm 3: Tegafur alone for 6 months (n=49).

6. Main outcome measures

Subjective symptoms (appetite, nausea/vomiting, etc.), objective symptoms (performance status [PS], body weight, blood pressure, etc.), hematology (blood counts, carcinoembryonic antigen, and immunosuppressive acidic protein), and biochemistry at baseline and after 2, 4, and 6 months of treatment.

7. Main results

Subjective symptom improvement (comparison between pre- and post-dose): Appetite was significantly improved in arm 1, while nausea/vomiting, bowel movement abnormality, motivation, and fatigue/malaise were significantly improved in arm 2. In arm 3, no symptoms were improved. Overall, improvement was noted in 21/57 patients (36.8%) in arm 1, 19/56 patients (33.9%) in arm 2, and 7/49 patients (14.3%) in arm 3, with significant differences in the percentage of patients showing improvement between arm 1 and arm 3 and between arm 2 and arm 3.

Objective symptom improvement: Overall, improvement was noted in 21/57 patients (36.8%) in arm 1, 22/56 patients (39.3%) in arm 2 and 10/49 patients (20.4%) in arm 3, with significant differences in the percentage of patients showing improvement between arm 1 and arm 3 and between arm 2 and arm 3.

Hematology: There were no significant differences between any 2 of the 3 arms.

Cancer type: Only in patients with gastric cancer, the percentage showing improvement in both subjective and objective symptoms was significantly greater in arm 1 than arm 3 and greater in arm 2 than arm 3. For colorectal cancer, there were no significant differences between any 2 of the 3 arms.

8. Conclusions

Combination of either hochuekkito or ninjin'yoeito is useful in patients on chemotherapy with tegafur.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no significant difference in the incidence of adverse events between arm 1 (2/57 patients) and arm 2 (7/56 patients).

11. Abstractor's comments

Kampo medicine combined with anticancer drug treatment is intended to maintain quality of life (QOL), suppress adverse events during treatment, and potentiate the action of the anticancer drug. In this study, Kampo medicine treatment and anticancer drug treatment were both started at the same time. In this case, the endpoint should be either 1) time-course of QOL score including PS during the treatment period rather than significance of the difference in the percentage of patients showing improvement or 2) differences in QOL score and adverse events between groups treated with the anticancer drug alone and treated with the anticancer drug/Kampo drug combination. The results of this study are based on a comprehensive evaluation of various symptoms. However, the patient's physician may partially bias the findings because of lack of blinding. Regarding the safety evaluation, adverse events can be caused by either the anticancer drug itself or the Kampo medicine (when combined with the anticancer drug). Therefore, some thought is required to distinguish between the causes for these adverse events.

12. Abstractor and date

Hoshino E, 23 April 2009, 1 June 2010.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Saito S, Iwagaki H, Kobayashi N, et al. Effects of a Japanese herbal medicine (TJ-41) on surgical stress of patients with gastric and colorectal cancer*. *Nihon Rinsho Geka Gakkai Zasshi (Journal of Japan Surgical Association)* 2006; 67: 568-74 (in Japanese). Ichushi Web ID: 2006114494, [J-STAGE](#)

1. Objectives

To evaluate whether preoperative administration of hochuekkito (補中益氣湯) relieves surgical stress in patients with gastric or colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Okayama University, and six other institutions, Japan.

4. Participants

Forty-eight patients who underwent surgery for gastric (n=10) or colorectal (n=38) cancer.

5. Intervention

Arm 1: treatment with TSUMURA Hochuekkito (補中益氣湯) Extract Granules 2.5 g, t.i.d. for 1 week prior to surgery (n=22).

Arm 2: no preoperative treatment (n=26).

6. Main outcome measures

The levels of cortisol, soluble tumor necrosis factor receptor (sTNF-R), and soluble interleukin-2 receptor (sIL-2R) measured right before surgery and on postoperative day 1; total and differential white blood cell counts measured preoperatively and postoperatively at days 1 and 7; C-reactive protein level measured preoperatively and postoperatively at days 1, 3, and 7; postoperative course of body temperature and pulse rate; length of postoperative stay; the number of patients who received therapeutic antibiotics after surgery.

7. Main results

There were no significant between-arm differences in total and differential white blood cell counts, CRP level, and rates of increase in sTNF-R and sIL-2R from before to after surgery. The rate of increase in cortisol from before to after surgery was significantly lower in arm 1. The body temperature from postoperative day 6 was significantly lower in arm 1. The pulse rate on postoperative days 6 and 7 was significantly lower in arm 1. The number of patients who received therapeutic antibiotics after surgery was significantly smaller in arm 1 (3/22) than in arm 2 (11/22).

8. Conclusions

Preoperative administration of TSUMURA Hochuekkito Extract Granules reduces the response to surgical stress and may be helpful for accelerating postoperative recovery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events: no adverse drug reactions occurred in arm 1.

11. Abstractor's comments

The authors postulate that preoperative administration of hochuekkito improves quality of life, helps control body temperature and heart rate, and reduces therapeutic administration of antibiotics in patients during postoperative recovery, and thus may lead to reduction of medical costs. They also suggest that the mechanism underlying these effects may involve Kampo medicine-induced attenuation of the increase in cortisol blood level. The principle of this treatment is similar to that of "immunonutrition," which involves omega-3 fatty acids, arginine, and nucleic acids. These approaches attempt to reduce postoperative surgical complications by means of preoperative nutritional supplementation. Cancer patients before surgery are in a state of *qikyo* (氣虛, qi deficiency) with various anxieties, and at the same time in a relatively mild state of *kekkyo* (血虛, blood deficiency) if they are operable. Hochuekkito and other comparable *hozai* (補劑; formulations with tonic effects) seem to be suitable for these patients. The investigation of hochuekkito combined with the immunonutritional approach and further elucidation of the mechanism are anticipated in the future.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010, 31 December 2013.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)**Reference**

Yamamoto K, Hirano F, Ikoma N, et al. Efficacy of keishibukuryogan for hysteromyoma/uterine adenomyosis*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2003; 20: 135-7 (in Japanese). Ichushi Web ID: 2004068783

1. Objectives

To evaluate the anti-tumor effect of keishibukuryogan (桂枝茯苓丸) in patients with hysteromyoma/uterine adenomyosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Department of Obstetrics and Gynecology, Sakai Hospital, Kinki University School of Medicine), Japan.

4. Participants

The 24 patients seen at the above institution and diagnosed with hysteromyoma or uterine adenomyosis were randomized into two arms: 1) the gonadotropin-releasing hormone (GnRH) analogue + keishibukuryogan arm (mean age, 45.9 years; mean tumor diameter, 35.7 mm) and 2) the GnRH analogue arm (mean age, 46.3 years; mean tumor diameter, 34.1 mm).

5. Intervention

Arm 1: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months + oral administration of a sachet of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (2.5 g) t.i.d (before meals) for 12 months (n=14).

Arm 2: subcutaneous injection of a GnRH analogue (1.88 mg) once monthly for 4 consecutive months (n=10).

6. Main outcome measures

Tumor response was evaluated on a 3-point scale: tumor diameter reduction: remarkably effective, $\geq 50\%$; effective, $>0 - 50\%$; not effective, 0% . Evaluation was performed at baseline, 4, 8, and 12 months after intervention.

7. Main results

Four months after treatment, complete response was achieved in 42.9% (6/14) of arm 1 and 10% (1/10) of arm 2, showing that GnRH + keishibukuryogan tended to have a higher anti-tumor effect although there were no between-group differences in tumor size reduction 8 or 12 months after treatment. Analysis limited to hysteromyoma revealed that 4-month treatment produced complete response in a significantly higher percentage of arm 1 (50%) than arm 2 (0%) ($P=0.012$). When the analysis was limited to the GnRH analogue leuprorelin, 4-month treatment produced a significantly higher complete response rate in arm 1 (62.5%) than in arm 2 (0%) ($P=0.016$). GnRH + keishibukuryogan exerted clinical efficacy in the short-term but not in the long-term (8 or 12 months after treatment).

8. Conclusion

Keishibukuryogan increases the efficacy of standard GnRH therapy for tumor size reduction in 4-month, short-term treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

As the contents of this paper have also been described in several previous case reports and clinical studies, the present study provided additional supportive evidence. Nevertheless, the present results are not sufficient to conclude that the effect can be generalized beyond the study sample because of the small sample size, but it will serve as a helpful reference in determining the future direction of research. Although the measure of tumor response (use of a 3-point scale) was rather crude, further accumulation of cases may enable more reliable determination — for clinical practice — of mean tumor reduction and differences in tumor reduction with time after administration.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Akase T, Akase T, Onodera S, et al. A comparative study of the usefulness of tokishakuyakusan and an oral iron preparation in the treatment of hypochromic anemia in cases of uterine myoma. *Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan)* 2003; 123: 817-24. CENTRAL ID: CN-00457950, Pubmed ID: 14513774, Ichushi Web ID: 2004068366 [J-STAGE](#)

1. Objectives

To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for hypochromic anemia in patients with uterine myoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Outpatient Department of Obstetrics and Gynecology, Kitasato University Hospital), Japan.

4. Participants

Twenty-three patients having hypochromic anemia associated with uterine myoma visiting the above institution between August 1999 and the end of January 2000. Mean age: 45.4±1.99 years in the tokishakuyakusan group; 42.9 ± 1.68 years in the oral iron preparation group. Range of blood hemoglobin concentration: 8 – 12 g/dL.

5. Intervention

Arm 1: oral administration of a sachet of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (2.5 g) t.i.d. (before meals) for 3 months.

Arm 2: oral administration of a tablet containing sodium ferrous citrate (50 mg) q.d or b.i.d. (after meals) for 3 months.

6. Main outcome measures

Laboratory: hematology (RBC, hemoglobin, hematocrit, etc.), blood chemistry (serum iron, ferritin concentration, etc.), blood coagulation function (PT, APTT), evaluated at baseline, and 4 and 8 weeks after dosing. Improvement in subjective symptoms, including pallor, dizziness on standing up, and dizziness/vertigo, evaluated on a 5-point scale at baseline, and 4 and 8 weeks after dosing. Adverse drug reactions (ADRs): incidences of heartburn, nausea/vomiting, diarrhea, etc. during 8-week administration.

7. Main results

Although there was no between-group difference in blood profile, subjective symptoms such as cold, pallor, spoon nail, and dizziness/vertigo were significantly improved with tokishakuyakusan ($P<0.05$). In particular, cold was improved significantly efficiently in the tokishakuyakusan group (score at 8 weeks: 0.3±0.2 for tokishakuyakusan, 2.0±0.6 for oral iron; $P<0.05$). ADRs occurred in 80% of patients receiving the oral iron preparation (heartburn and nausea noted with the highest incidences of 46.7% each) but in no patients receiving tokishakuyakusan.

8. Conclusions

Three-month treatment with tokishakuyakusan is more effective in improving subjective symptoms and is safer than an oral iron preparation for mild to moderate anemia in women with uterine myoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

ADRs occurred in none of 10 patients receiving tokishakuyakusan, while in 12 (80%) of 15 patients receiving the oral iron preparation.

11. Abstractor's comments

If clinicians designed a noninvasive antianemic treatment plan for the present study population, i.e., patients with anemia (defined as blood hemoglobin concentration, 8–12 g/dL) and uterine myoma, the oral iron preparation would be the treatment of choice. However, in the present study, tokishakuyakusan had higher efficacy for subjective symptom improvement. In addition, tokishakuyakusan was clinically more efficacious and safer (i.e., had no ADRs). However, since tokishakuyakusan (unlike the oral iron preparation) did not improve the blood profile, a combination of these drugs might be more efficacious. A new research protocol to investigate the efficacy of Kampo formulations combined with oral iron to reduce the severity of anemia is expected in the future.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Yanagihori A, Miyagi M, Hori M, et al. Efficacy of ninjin'yoeito for iron deficiency anemia*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1995; 72: 2605-8 (in Japanese). Ichushi Web ID: 1996162428, [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人参栄養湯) for iron deficiency anemia due to menorrhagia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Toho University Sakura Medical Center, Japan.

4. Participants

Thirty-nine patients diagnosed with iron deficiency anemia (hemoglobin, 9.0 mg/dL or less) due to menorrhagia and metrorrhagia associated with uterine myoma, uterine adenomyoma, endometrial polyp, etc.

5. Intervention

Arm 1: Kanebo (currently Kracie) Ninjin'yoeito (人参栄養湯) Extract Granules 5 g/day + ferrous citrate (Ferromia) 100 mg/day for 4 weeks (n=21).

Arm 2: ferrous citrate (Ferromia) 100 mg/day for 4 weeks (n=18).

6. Main outcome measures

Changes in hematological values, including serum iron and ferritin and subjective symptoms (general malaise, shortness of breath, and palpitation) from pre- to post-dose.

7. Main results

Elevation in hemoglobin value from pre- to post-dose was significantly higher in arm 1 ($P<0.01$). Palpitation and shortness of breath and symptoms for which ninjin'yoeito should be effective (anorexia, night sweats, and cold limbs) were similarly improved in both arms.

8. Conclusions

Ninjin'yoeito combined with an iron preparation is effective for iron deficiency anemia due to menorrhagia.

9. From Kampo medicine perspective

The effects of the components of ninjin'yoeito (*ninjin* [人参], *byakujutu* [白朮], and *onji* [遠志]) on bone marrow are suggested.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study investigated the hematopoietic effect of ninjin'yoeito on anemia due to menorrhagia. Given accumulated clinical reports supporting the efficacy of ninjin'yoeito for myelosuppression associated with anticancer drug treatment, its effect on iron deficiency anemia was expected. Lack of improvement in the symptoms for which ninjin'yoeito should be effective other than anemia, such as night sweats and cold limbs, may warrant review of the Kampo criteria for application of ninjin'yoeito, as pointed out by the authors in the text. Future reports are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Aoe H, Takada K, Kawahara N, et al. Effectiveness of erythropoietin and ninjin'yoeito in preoperative autologous blood donation*. *Jikoketsu Yuketsu (Journal of Japanese Society of Autologous Blood Transfusion)* 1997; 10: 145–51 (in Japanese).

1. Objectives

Combined effect of erythropoietin and ninjin'yoeito (人参養榮湯) on anemia after autologous blood donation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Himeji Red Cross Hospital, Japan.

4. Participants

Patients who donated 800 mL or more of blood for autologous transfusion between January 1994 and December 1996. The control group (iron preparation only) consisted of patients who donated blood for autologous transfusion between June 1992 and December 1993; treatment assignment was not randomized.

5. Intervention

Arm 1: iron preparation monotherapy (intravenous administration of 80 mg three times a week) (n=10).
 Arm 2: iron preparation (intravenous administration of 80 mg three times a week) + Epogin (6000 units three times a week) (n=37).
 Arm 3: iron preparation (intravenous administration of 80 mg three times a week) + Epogin (6000 units three times a week) + TSUMURA Ninjin'yoeito (人参養榮湯) Extract Granules (9 g/day) (n=26).

6. Main outcome measures

Blood tests (red blood cell count, hemoglobin, hematocrit, reticulocyte count, white blood cell count, and serum iron) before blood donation and before surgery.

7. Main results

Compared to patients in arm 1, patients in arm 3 but not arm 2 had significantly increased red blood cell count, hemoglobin, and hematocrit at the time of preoperative blood collection.

8. Conclusions

The addition of ninjin'yoeito to iron and erythropoietin preparations is considered to be effective in raising red blood count, hemoglobin, and hematocrit of blood donated for autologous transfusion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper describes the hematopoietic effect of ninjin'yoeito, which appears to be useful for improving the quality of blood units donated for autologous transfusion. Although significant differences were observed between arms 1 and 3 but not between arms 2 and 3, it may not simply be concluded that the addition of ninjin'yoeito is effective. However, considering the increasing numbers of patients who are undergoing autologous blood transfusion, this attempt should be appreciated. Including postoperative results in the evaluation of ninjin'yoeito would enhance another efficacy of this formulation. Further results are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 1 June 2010.

3. Blood Diseases including Anaemia

Reference

Aoe H, Sumida Y, Kawahara N, et al. Efficacy of an erythropoietin preparation and Kampo medicines in preoperative autologous blood donation in cancer patients*. *Jikoketsu Yuketsu (Journal of Japanese Society of Autologous Blood Transfusion)* 1999; 12: 100-4 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) and ninjin'yoeito (人参養榮湯) combined with an erythropoietin (EPO) preparation in preoperative autologous blood donation in cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single hospital (Department of Obstetrics and Gynecology, Japanese Red Cross Society Himeji Hospital), Japan.

4. Participants

Ninety patients with gynecologic malignant tumors who visited the above institution between January 1992 and the end of November 1997 and preoperatively donated 800 mL or more of autologous blood.

5. Intervention

Intravenous administration of an iron preparation to patients with hemoglobin concentration of ≥ 14 g/dL. Randomization of patients with hemoglobin concentration of < 14 g/dL to receive intravenous iron preparation + Kampo formulation + EPO or intravenous iron preparation + EPO.

Arm 1: intravenous administration of an iron preparation (240 mg weekly) from the day of the first donation through the day before the operation.

Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation.

Arm 3: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of TSUMURA Juzentaihoto (十全大補湯) Extract Granules or Ninjin'yoeito (人参養榮湯) Extract Granules 2.5 g t.i.d (before meals), from the day of the first donation through the day before the operation.

6. Main outcome measures

Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).

Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).

Hemoglobin increment: pre-donation hemoglobin concentration \times volume of donated blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin volume).

7. Main results

The increase in reticulocyte count from the time of donation to the time of operation was larger in the Kampo group (n=36) and EPO group than in the iron group (n=15). The increase in hemoglobin level was larger in the EPO group (1.73 ± 1.30 g/dL) than the iron group (0.92 ± 0.70 g/dL), and significantly ($P < 0.05$) larger in the Kampo group (2.33 ± 1.11 g/dL) than the EPO group.

8. Conclusions

Combining a Kampo formulation with an iron preparation plus EPO enhances the clinical effectiveness of preoperatively donated autologous blood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The finding that adding juzentaihoto or ninjin'yoeito to the preoperative donation management protocol enhances the increase in blood hemoglobin concentration suggests that the hematological profile of donated autologous blood is better after use of the combination than after use of only the iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study is expected including an examination of the possibility that complementary medicines promote cancer cell growth.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 31 December 2013.

3. Blood Diseases including Anaemia

References

Aoe H, Matsuo T, Ebisutani M, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation in cancer patients*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2000; 17: 67-71 (in Japanese)

Aoe H, Ota M, Kawahara N, et al. Efficacy of using juzentaihoto to augment preoperative autologous blood donation*. *Rinsho Kensa (Journal of Medical Technology)* 2003; 47: 395-9 (in Japanese). Ichushi Web ID: 2003251978

Aoe H. Effect of Juzen-taiho-to on haematological recovery from predeposit autologous blood donation. *Pharma Medica* 2007; 25: 11-4. Ichushi Web ID: 2008070612 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of using juzentaihoto (十全大補湯) to augment preoperative autologous blood donation in cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not identified (but the abstractor infers a Department of Obstetrics and Gynecology in each of the following three facilities: Japanese Red Cross Society Himeji Hospital, Fukuyama City Hospital, and Chugoku Central Hospital), Japan.

4. Participants

One-hundred and twenty patients who visited the above institutions within the past 5 years and 2 months and donated 800 mL or more autologous blood before undergoing surgery for gynecologic malignant tumors. Patients receiving preoperative chemotherapy and patients with collagen disease were excluded.

5. Intervention

Arm 1: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly, from the day of the first donation through the day before the operation in patients with pre-donation Hb value of < 14 g/dL, n=52.

Arm 2: intravenous administration of an iron preparation (240 mg weekly) + intravenous drip infusion of 6000 units of EPO three times weekly + oral administration of a sachet (2.5 g) of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d (before meals), from the day of the first donation through the day before the operation in patients with pre-donation Hb value of < 14 g/dL, n=51.

Arm 3: intravenous administration of an iron preparation (240 mg weekly), n=17.

6. Main outcome measures

Hematological profile: RBC count, hemoglobin, hematocrit, reticulocyte count, etc., measured before donation (before administration) and preoperatively (immediately after completion of administration).

Serum biochemical profile: total protein, albumin, and iron concentrations, determined before donation (before administration) and preoperatively (immediately after completion of administration).

Hemoglobin increment: pre-donation hemoglobin concentration × volume of donation blood/volume of circulating blood – (pre-donation hemoglobin concentration – preoperative hemoglobin concentration).

7. Main results

Decrements in RBC count and hematocrit after donation were significantly smaller in the EPO combination groups than in the iron monotherapy group, and significantly smaller in the juzentaihoto and EPO combination group than in the EPO combination group ($P<0.05$). There was also a significant difference in hemoglobin increment between arms ($P<0.05$).

8. Conclusions

An iron preparation combined with EPO and additionally with juzentaihoto enhances the clinical efficacy of preoperatively donated autologous blood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study demonstrated that adding juzentaihoto to the preoperative donation management protocol successfully suppresses reductions in RBC count and hematocrit after donation and enhances the increase in blood hemoglobin concentration. This suggests that the hematological profile of donated autologous blood is better after use of this combination than after use of only an iron preparation plus EPO. Thus, this finding is clinically significant. With the accumulation of more cases, a safety study, including an examination of the possibility that complementary medicines promote cancer cell growth, is expected.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 19 December 2008, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Motoo Y, Mouri H, Ohtsubo K, et al. Herbal medicine ninjinyoeito ameliorates ribavirin-induced anemia in chronic hepatitis C: a randomized controlled trial. *World Journal of Gastroenterology* 2005; 11: 4013-7. CENTRAL ID: CN-00522971, Pubmed ID: 15996025

1. Objectives

To evaluate the efficacy and safety of ninjin'yoeito (人参養榮湯) for ribavirin-induced anemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-three chronic hepatitis C patients treated with interferon alpha-2b and ribavirin. Five of them withdrew from the study.

5. Intervention

Arm 1: designated "the NY group" and treated with IFN α -2b and ribavirin plus TSUMURA Ninjin'yoeito (人参養榮湯) Extract Granules (9 g, orally), n=10.

Arm 2: designated "the control group" and treated with interferon alpha-2b (IFN α -2b) and ribavirin, n=13

IFN α -2b was administered for a total of 24 weeks at a dose of 10 MU intramuscularly, 6 days per week for the first 2 weeks and 3 days per week for the following 22 weeks. Ribavirin was orally administered for 24 weeks at a dose of 800 mg/day (if the patient's body weight was \geq 60 kg) or 600 mg/day (body weight < 60 kg).

6. Main outcome measures

Maximum increase in red blood cell count (max Δ RBC), maximum increase in hemoglobin level (max Δ Hb) minimum hemoglobin level (min Hb), white blood cell count (WBC), platelet count (Plt), T-helper 1 cell (Th1) count, T-helper 2 cell (Th2) count, Th1/Th2, and glutathione peroxidase level in peripheral blood.

7. Main results

Peripheral max Δ Hb and min Hb were significantly improved in the NY group ($P=0.026$ and $P=0.079$, respectively). No between-group differences were observed in max Δ RBC, WBC count, Plt count, Th1 count, Th2 count, Th1/Th2, and glutathione peroxidase level. Antiviral effects were not different, either.

8. Conclusions

Ninjin'yoeito is an effective and safe treatment for ribavirin-induced anemia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions specific to ninjin'yoeito were not observed.

11. Abstractor's comments

This study showed the efficacy of ninjin'yoeito for ribavirin-induced anemia. The authors speculated that the mechanism of action of this drug is the activation of undifferentiated erythroid cells and antioxidation.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Nakamaoto H, Mimura T, Honda N. Orally administrated Juzen-taiho-to/TJ-48 ameliorates erythropoietin (rHuEPO)-resistant anemia in patients on hemodialysis. *Hemodialysis International* 2008; 12: S9-14. CENTRAL ID: CN-00667345, Pubmed ID: 18837771

1. Objectives

To evaluate the efficacy and safety of juzentaihoto (十全大補湯) for erythropoietin-resistant anemia in patients on hemodialysis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital and 1 general hospital, Japan.

4. Participants

Forty-two patients on hemodialysis with erythropoietin-resistant anemia.

5. Intervention

Arm 1: TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. for 12 weeks (n=22).

Arm 2: not treated with TSUMURA Juzentaihoto (十全大補湯) Extract Granules (n=20).

Patients in the two groups were on the same dietary regimen and dialysis program.

6. Main outcome measures

Hemoglobin level.

7. Main results

While Hb level increased nonsignificantly from 8.3±0.7 to 8.5±0.5 g/dL in arm 2, it increased significantly from 8.4±1.1 to 9.5±1.3 g/dL in arm 1 ($P=0.0272$).

8. Conclusions

Treatment with TSUMURA Juzentaihoto Extract Granules is effective for erythropoietin-resistant anemia in patients on hemodialysis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse event (complication, abnormality in blood chemistry) was reported in the juzentaihoto group.

11. Abstractor's comments

This RCT was conducted in many patients with erythropoietin-resistant anemia and using a double-blind design. However, it is questionable that this trial was not placebo-controlled and no statistical analysis was mentioned. Given the decrease in serum C-reactive protein (CRP) level and negative correlation between serum CRP and Hb levels in the juzentaihoto group (and the absence of a decrease in serum CRP level and negative correlation in the non-treatment group), the authors assume that juzentaihoto may act, at least in part, as an anti-inflammatory agent. This is an interesting assumption that may suggest a basic research question.

12. Abstractor and date

Kogure T, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Seki M. Efficacy of goreisan for preventing thrombocytopenia and activating vascular endothelial cells after cholecystectomy*. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1990; 7: 510–1 (in Japanese).

1. Objectives

To evaluate the efficacy of goreisan (五苓散) and shosaikoto (小柴胡湯) for thrombocytopenia after cholecystectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Forty-seven female patients who underwent cholecystectomy for gallbladder stones or polyps.

5. Intervention

Arm 1: administration of TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. until the day before surgery for a mean of 8.4 ± 6.0 days (n=14).

Arm 2: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. until the day before surgery for a mean of 6.5 ± 3.4 days (n=12).

Arm 3: bed rest in the hospital for a mean of 8.5 ± 3.7 days (n=21).

6. Main outcome measures

Blood counts and urinary excretion of prostaglandin E1 (PGE1) and F1 alpha (6-keto-PGF1 α).

7. Main results

Platelet counts were significantly higher on postoperative day 1 in arms 1 and 2 than in arm 3. Excretion of urinary PGE1 was significantly higher in arm 1 on postoperative days 1, 5, 6, and 7 and in arm 2 only on postoperative day 1 than in arm 3. Excretion of urinary 6-keto-PGF1 α was significantly higher on postoperative days 1, 5–7, and 8–14 in arm 1, and on postoperative day 1 in arm 2, than in arm 3.

8. Conclusions

Goreisan is effective for consumptive thrombocytopenia after cholecystectomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study showed that administration of goreisan before cholecystectomy reduced postoperative thrombocytopenia.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

3. Blood Diseases including Anaemia**Reference**

Mori T, Tauchi K, Yokoyama S, et al. Effects of sho-saiko-to (xiao-chai-hu-tang) on thrombocytopenia bei therapy with anti-cancer drugs. *Sanfujinka Chiryō (Obstetrical and Gynecological Therapy)* 1992; 65: 102–5 (in Japanese).

1. Objectives

To evaluate the effects of preoperative administration of shosaikoto (小柴胡湯) on thrombocytopenia in gynecologic cancer patients receiving anti-cancer drugs.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Department of Gynecology and Obstetrics, Kyoto University Hospital) and 12 other hospitals, Japan.

4. Participants

Eighty-nine gynecologic cancer patients receiving anti-cancer drugs (ovarian cancer, 68; endometrial cancer, 16; cervical cancer, 5; choriocarcinoma, 1; uterine sarcoma, 1).

5. Intervention

Arm 1: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day for 14 days after white blood cell (WBC) count fell below 3000 (n=49).

Arm 2: no administration of Kampo medicines after WBC count fell below 3000 (n=40).

6. Main outcome measures

Peripheral blood leukocytes, platelet count, IgG, IgA, IgM, OKT 4, OKT 8, and NK cell activity before administration of anti-cancer drugs, on the day the WBC fell below 3000 and 14 days after the WBC count fell below 3000, as well as days to recovery of the WBC count to ≥ 3000 .

7. Main results

Days to recovery of the WBC count to ≥ 3000 : no significant difference between groups.

Increase in platelet count for 14 days: greater in arm 1 than arm 2 ($P < 0.05$).

IgG, IgA, IgM, OKT 4, OKT 8, and NK cell activity: no significant difference between groups.

8. Conclusions

Administration of shosaikoto in patients with leukopenia associated with anti-cancer therapy leads to the recovery of platelet count.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned in the article.

11. Abstractor's comments

The authors reported that shosaikoto was effective in raising the platelet count in patients with thrombocytopenia associated with anti-cancer drugs. However, the platelet counts had decreased to within the normal range and these decreases might not be due to myelosuppression. The platelet count reduction was therefore not by definition indicative of "thrombocytopenia associated with anti-cancer drugs." Shosaikoto was started at the time the WBC count had fallen below 3000. Inasmuch as lymphocyte count may be decreased by undernutrition, granulocyte count should be used as a measure of myelosuppression. There is a lack of consistency in terms of endpoints, that is, for the WBC count, it was the time to recovery to ≥ 3000 , while for the platelet count, it was the difference in values at the time and 14 days after the WBC count fell below < 3000 . It is also not clear why the duration of treatment with shosaikoto is two weeks. An appropriate strategy for analysis would be to perform serial WBC and platelet counts beginning just after the start of shosaikoto, and analyze these measurements.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia

Reference

Inoue S, Kuwahara H, Kato Y, et al. Thrombopoietic and leukopoietic effects of a traditional Chinese herbal medicine, formula reverti lienalis compositae (Japanese name: *Kami-kihi-to TJ-137*) in cancer patients. *Biotherapy* 1998; 12: 1071-6 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effect of kamikihito (加味帰脾湯) on thrombocytopenia and leukopenia in patients receiving anti-cancer drugs.

2. Design

A randomized cross-over controlled trial (RCT-cross over).

3. Setting

Two hospitals, Japan.

4. Participants

Six patients with gynecological cancer (four with ovarian cancer, one with endometrial cancer, and one with cervical cancer) receiving cisplatin-based anti-cancer therapy.

5. Intervention

Since allocation of patients to treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen. Cycles of anti-cancer therapy up to the fourth cycle in each patient were randomly assigned to either treatment or no treatment with TSUMURA Kamikihito (加味帰脾湯) Extract Granules (7.5 g/day) (Granisetron was administered to all patients for antiemetic purposes, and granulocyte colony-stimulating factor (G-CSF) was prophylactically administered in all cycles in all 6 patients except 1.

Arm 1: administration of TSUMURA Kamikihito (加味帰脾湯) Extract Granules 7.5 g/day during the treatment period (n=6, 11 cycles).

Arm 2: no administration of kamikihito (加味帰脾湯) (n=6, 12 cycles).

6. Main outcome measures

Peripheral blood platelet and white blood cell (WBC) counts, minimum value of hemoglobin, severity of adverse drug reactions (WHO grade), decrease in area under the platelet-time curve (area of the platelet-time curve below the lower limit of the normal range [$130,000/\mu$]), dose of G-CSF.

7. Main results

The minimum platelet count was higher in treated cycles (arm 1) than in untreated cycles (arm 2) in 5 of 6 patients ($P=0.0127$). The area of the decrease in platelet count was smaller in arm 1 than in arm 2 ($P=0.0126$). The minimum value of WBC count was higher in arm 1 than in arm 2 ($P=0.0025$).

The dose of G-CSF was lower in arm 1 than in arm 2 (significance of difference not tested).

There was no significant difference in the minimum value of hemoglobin between arms.

8. Conclusions

Kamikihito is expected to prevent thrombocytopenia and leukopenia associated with anti-cancer drugs.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Although this report is attractive in that a Kampo medicine can suppress or reverse thrombocytopenia, leukopenia (granulocytopenia), and anemia associated with anti-cancer drugs, establishment of the criteria for patient entry requires careful consideration. The present study failed to consider platelet count at the baseline of each cycle. Baseline platelet count was higher in kamikihito-treated cycles in all 6 patients except 1, and quite different between arms. Naturally, decrements due to anti-cancer treatment are smaller when baseline platelet count (and probably WBC count as well) is higher. Even though cycles were randomly assigned to Kampo treatment or no treatment, the evidence in this report is not sufficiently convincing, given that the differences in background values between arms were not considered in the analysis of the results.

12. Abstractor and date

Hoshino E, 26 April 2009, 6 January 2010, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Suzuki S, Abe R, Nomizu T, et al. Effect of Juzentaihoto (TJ-48) on leukopenia in patients receiving cancer chemotherapy. *Progress in Medicine* 1995; 15: 1968-71 (in Japanese). Ichushi Web ID: 1996098925

1. Objectives

To evaluate the effects of juzentaihoto (十全大補湯) on leukopenia in patients receiving cancer chemotherapy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four university and community hospitals, Japan.

4. Participants

Ninety patients who received chemotherapy for cancer.

5. Intervention

Arm 1: treatment with TSUMURA Juzentaihoto (十全大補湯) Extract Granules 7.5 g/day (n=47 patients, including 17 with gastric, 20 with colorectal, and 10 with breast cancer).

Arm 2: no treatment (n=43 patients, including 16 with gastric, 19 with colorectal, and 8 with breast cancer).

Duration of treatment: 12 months.

6. Main outcome measures

Leukocyte count was measured before and after 1, 2, 3, and 4 weeks of treatment, then monthly for 12 months. The frequency and time course of leukopenia (defined as a leukocyte count less than 4,000 cells/m³) were also evaluated during the follow-up.

7. Main results

Leukocyte counts were not significantly different between the two arms. Significantly fewer patients developed leukopenia (<4,000mm³) in arm 1 (30 patients) than in arm 2 (38 patients). The onset of leukopenia was significantly delayed and the time from onset to nadir was significantly increased in arm 1. There was no between-arm difference in the time from nadir to recovery. Juzentaihoto had a beneficial effect on leukopenia in gastric or colorectal cancer patients, but not in breast cancer patients.

8. Conclusions

Juzentaihoto delays the onset of leukopenia and also increases the time from onset to nadir in patients receiving chemotherapy for gastric or colorectal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper demonstrates the usefulness of prophylactic administration of juzentaihoto for leukopenia, which is one of the serious adverse reactions to cancer chemotherapy in patients with gastric or colorectal cancer. The authors explored the factors influencing the effects in detail and demonstrated that juzentaihoto delayed the onset of leukopenia, increased the time from onset to nadir, but had no influence on the time to recovery, thereby reducing the number of patients who developed leukopenia. Recently, even more severe cases of leukopenia have become treatable with granulocyte colony-stimulating factor (G-CSF). Nevertheless, oral administration of juzentaihoto as a prophylaxis is valuable. Although the evaluation based on cancer type failed to find an effect in breast cancer patients, it was a secondary objective of this study and therefore reexamination in those patients is needed. Also, studies taking into account the Kampo concept of *sho* (証, pattern) are anticipated.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

3. Blood Diseases including Anaemia

Reference

Okawa T, Hashimoto S, Sakamoto S, et al. Ninjin-yoei-to in the treatment of leukopenia and symptoms associated with radiotherapy of malignant tumors. *Gan no Rinsho (Japanese Journal of Cancer Clinics)* 1995; 41: 41–51 (in Japanese with English abstract). Ichushi Web ID: 1995174288 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the improvement in subjective symptoms and leukopenia after ninjin'yoeito (人参養栄湯) administration in patients undergoing radiotherapy for thoracoabdominal tumors.

2. Design

Randomized controlled trial (RCT).

3. Setting

Thirteen university hospitals (Tokyo Women's Medical University [Department of Radiology], Keio University School of Medicine [Department of Radiology], Tohoku University School of Medicine [Department of Radiology], and 10 other universities) and 9 other hospitals, Japan.

4. Participants

One hundred sixteen patients with thoracoabdominal tumors undergoing radiotherapy (lung cancer: 42, esophageal cancer: 19, breast cancer: 9, rectal cancer: 7, cervical cancer: 33, and other cancers: 16).

5. Intervention

Arm 1: administration of Kanebo ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. during radiotherapy (n=63).

Arm 2: radiotherapy only (without ninjin'yoeito [人参養栄湯]) (n=63).

6. Main outcome measures

Subjective symptoms (anorexia, general malaise, diarrhea, coldness, nausea, and vomiting) were evaluated weekly on a 4-point scale. Hematological parameters (white blood cell [WBC], differential WBC, platelet, red blood cell, and reticulocyte counts, hemoglobin, and hematocrit), body weight, and blood pressure were measured weekly. Biochemical values (glutamic-oxaloacetic transaminase [GOT], glutamic-pyruvic transaminase [GPT], albumin, total protein, cholinesterase [Ch-E], blood urea nitrogen [BUN], Cr, Na, K, and Cl) were measured biweekly. Primary physicians evaluated the response of patients based on the above measures on a 4-point scale (marked, moderate, mild, or none).

7. Main results

There were no between-group differences in the mean WBC counts at baseline and at weeks 1–4. The proportion of patients with WBC count >3000 at the end of the treatment (weeks 4–8) was higher in arm 1 (51/56) than in arm 2 (42/60) ($P=0.005$).

Improvement in subjective symptoms (at least mild response) was observed more frequently in arm 1 (44/56) than in arm 2 (6/60) ($P=0.0001$).

Improvement in laboratory test results (at least mild response) was observed more frequently in arm 1 (43/56) than in arm 2 (23/60) ($P=0.0003$).

8. Conclusions

Ninjin'yoeito may prevent subjective symptoms and leukopenia associated with radiotherapy.

9. From Kampo medicine perspective

After the study, a retrospective analysis based on *sho* (証, pattern) was conducted, and *sho* was determined from an assessment of subjective symptoms (anorexia, general malaise, cold hands and feet, and night sweats). However, no correlation between *sho* and effectiveness was found.

10. Safety assessment in the article

Adverse events: 4 patients in arm 1 had, respectively, drug eruption, abdominal discomfort, abdominal pain + diarrhea, and diarrhea.

11. Abstractor's comments

It would be interesting to know whether Kampo medicines can prevent leukopenia associated with radiotherapy. In this study, although the mean WBC counts were similar in both arms, the proportion of patients with WBC counts >3000 was significantly higher in arm 1 than in arm 2 at the end of the treatment (weeks 4–8). The reason should be considered. The WBC count is the only laboratory test result shown. The granulocyte and platelet counts, hemoglobin level, and the biochemical test results are not reported. It was also unclear which subjective symptom was improved. The reliability of this study remains questionable because each result was a composite evaluation by physicians using a 4-point scale and this was an open trial. In the discussion of results, “overall improvement” based on physician's judgment was considered the gold standard. In addition, they just compare “overall improvement” with patient characteristics and test data in the stratified analysis. In this kind of open trial, objectivity is not assured unless the presence and degree of each subjective symptom as well as the test data are recorded sequentially and are compared between groups.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia**Reference**

Hatano T. Mitigation of postoperative lymphopenia and protection of T cells by preoperative administration of xial-chai-hu-tang. *Saitama Ika Daigaku Zasshi (Journal of Saitama Medical School)* 1990; 17: 357–63 (in Japanese with English abstract).

1. Objectives

To evaluate the preventive effect of preoperative administration of shosaikoto (小柴胡湯) on postoperative lymphopenia in female patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Second Department of Surgery, Saitama Medical Center, Saitama Medical School), Japan.

4. Participants

Hundred and twenty-two postoperative female patients (breast cancer, 37; cholecystolithiasis, 65; gastric cancer, 20).

5. Intervention

Arm 1: preoperative administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for a mean of 7.3 days in breast cancer patients, 5.4 days in cholecystolithiasis patients, and 9.0 days in gastric cancer patients (n=27: breast cancer, 9; cholecystolithiasis, 14; gastric cancer, 4).

Arm 2: no administration of Kampo medicines (n=95).

6. Main outcome measures

(1) Lymphocyte counts and subsets (OKT3, OKT4, OKT8, OKIA, and Leu 7).

These were measured before and after preoperative administration of shosaikoto and on 14 consecutive postoperative days.

(2) Assessment of the impact of surgery (blood loss, duration of surgery, anesthesia, postoperative stay, and complications).

7. Main results

(1) Lymphocyte counts: only the mean value was plotted on a line chart, standard deviation (error) was not shown. No significance test between arms was performed.

(2) Comparison of lymphocyte counts and subsets before and after preoperative administration of shosaikoto: in cholecystolithiasis patients, no significant differences between arms were observed.

(3) Lymphocyte subsets at 1 day after surgery (in cholecystolithiasis patients): OKT3 and OKT4 decreased significantly in arm 2, while no significant decrease was observed in arm 1. No significance test between arms was performed.

(4) Impact of surgery: blood loss, duration of surgery, anesthesia, and postoperative stay, and complications did not differ significantly between arms.

8. Conclusions

Preoperative administration of shosaikoto attenuates postoperative lymphopenia. This effect is supposed to be due to protection of the biomembranes of mature cells, especially helper/inducer T-cells.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In the Method section, the authors noted that the number of peripheral blood lymphocytes and the number of lymphocyte subsets were sequentially measured beginning before surgery and ending on postoperative day 14. However, the available results do not include lymphocyte counts for postoperative days 8–13 and show only mean lymphocyte count at each measurement day without standard deviation (error). The tests might not have been performed for all patients included. Moreover, lymphocyte subsets in breast or gastric cancer patients are not provided. Since statistical tests between arms for disease-specific lymphocyte counts were not performed, it cannot be concluded that “preoperative administration of shosaikoto attenuated postoperative lymphopenia.” Besides, a clinical trial (like an animal study) should not collect blood postoperatively for 14 consecutive days to sequentially measure lymphocyte counts and subsets.

12. Abstractor and date

Hoshino E, 26 April 2009, 1 June 2010.

3. Blood Diseases including Anaemia**Reference**

Fujiwara M, Koumoto Y. Effect of jumentaihoto on myelosuppression due to chemotherapy for gynecologic malignant tumor*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 1998; 15: 86-9 (in Japanese).

1. Objectives

To evaluate the effect of combined jumentaihoto (十全大補湯) on myelosuppression during chemotherapy in patients with gynecologic cancers.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Obstetrics and Gynecology, Kawasaki Medical School Hospital.

4. Participants

Ten patients who underwent chemotherapy following surgery for gynecological malignancies at the Department of Obstetrics and Gynecology, Kawasaki Medical School Hospital, Japan.

5. Intervention

Arm 1: Jumentaihoto (十全大補湯) 7.5 g/day administered for 21 days beginning the day before administration of the anticancer drug in the odd-day cycle and no administration in the even-day cycle (n=5 patients with odd numbers).

Arm 2: Jumentaihoto (十全大補湯) 7.5 g/day administered for 21 days beginning the day before administration of the anticancer drug in the even-day cycle and no administration in the odd-day cycle (n=5 patients with even numbers).

In both arms, chemotherapy consisted of intraabdominal administration of carboplatin (CBDCA) at 500 mg/m² and parenteral administration of cyclophosphamide (CPA) at 450 mg/m².

6. Main outcome measures

White blood cell (WBC) count, neutrophil count, red blood cell (RBC) count, hemoglobin value, platelet count, and use of granulocyte colony-stimulating factor (G-CSF).

7. Main results

The jumentaihoto and non-jumentaihoto groups completed 20 courses of treatment.

Decrements in WBC, neutrophil, and RBC counts were significantly smaller in arm 1 ($P<0.01$, $P<0.05$, and $P<0.01$, respectively), as was the number of G-CSF units used ($P<0.05$). Hemoglobin value was significantly increased in arm 1 ($P<0.05$). There was no significant between-arm difference in platelet count.

8. Conclusions

Jumentaihoto is highly effective in reducing subjective/objective adverse drug reactions during cancer chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes the preventive effect of jumentaihoto on myelosuppression during chemotherapy. It is meaningful that the use of G-CSF was almost halved by jumentaihoto treatment.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

3. Blood Diseases including Anaemia**References**

Inagaki M, Nakazawa T, Michimata H, et al. Treatment experience with TSUMURA Keishikajutsubuto for pulmonary sarcoidosis*. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1990; 7: 316–7 (in Japanese).

Inagaki M. Effectiveness of Kampo medicine in relieving complaints associated with chronic intractable diseases*. *Kampo Shinryo* 1993; 12: 1–3 (in Japanese)

1. Objectives

To evaluate the effects of Keishikajutsubuto (桂枝加朮附湯) on the levels of angiotensin-converting enzyme and lysozyme in sarcoidosis patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Nine patients with ophthalmic manifestations whose sarcoidosis was confirmed by bronchoscopic lung biopsy. Corticosteroid was used in five of these patients. Chest X-ray showed lymphadenopathy only in six patients, lymphadenopathy and lung field lesions in one, and lung field lesions only in two.

5. Intervention

Keishikajutsubuto (桂枝加朮附湯) was administered for at least 1 year.

Arm 1: TSUMURA Keishikajutsubuto (桂枝加朮附湯) extract granules 2.5 g t.i.d. (n=4).

Arm 2: no treatment (n=5).

6. Main outcome measures

The levels of angiotensin converting enzyme (ACE) and lysozyme.

7. Main results

At the end of the follow-up period, the levels of ACE and lysozyme were decreased in all patients in both arms 1 and 2, including participants using steroids. At the end of the follow-up period, the levels of ACE and lysozyme were decreased in both arms. The decrease in ACE was greater in arm 1. In nonusers of steroids, the decreases in ACE and lysozyme were also greater in arm 1.

8. Conclusions

TSUMURA Keishikajutsubuto, with or without steroids, reduces the levels of ACE and lysozyme in sarcoidosis patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

ACE and lysozyme are referred to as markers for sarcoidosis activity and diagnosis. This paper does not mention improvement on chest X-rays, which suggests there were no changes. Sarcoidosis follow-up takes a long time, so a long-term study with accumulated cases would be more interesting. Furthermore, the sample size in this study was small (four participants in arm 1 and five in arm 2), which makes interpretation of the statistical analysis difficult. Hopefully the authors will conduct an RCT with greater statistical power and an adequate sample size. Inagaki's study (1993) included a large number of cases. Keishikajutsubuto was chosen because sarcoidosis patients often complain of symptoms such as fatigability, cold hands and feet, or joint pain; however, knowing the frequency of such complaints would improve the paper.

12. Abstractor and date

Fujisawa M, 31 March 2009, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Azuma M, Motomiya M, Toyota T. Effects of Seishin-renshi-in (TJ-111) on blood sugar levels of patients with non-insulin-dependent diabetes mellitus. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1994; 45: 339-44 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the efficacy and safety of seishinrenshiin (清心蓮子飲) in the treatment of glucose tolerance.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three community hospitals, Japan.

4. Participants

Eighteen patients with non-insulin-dependent diabetes mellitus.

5. Intervention

Arm 1: TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules 2.5 g t.i.d. for 2 weeks (n=12; male:female = 8:4).

Arm 2: no treatment (n=6; all males).

Patients were allowed to continue only an antidiabetic agent that had been taken at baseline.

6. Main outcome measures

Blood tests: HbA1, HbA1c, diurnal variation in blood glucose (once a week), fasting blood glucose (every other day), and other common blood tests.

Severity was classified into 3 grades based on HbA1 level. Efficacy was assessed in 5 grades based on blood glucose level.

Subjective symptoms: thirst, pollakiuria, pain in arms/legs, numbness in arms/legs, blurred vision, dizziness/orthostatic dizziness, heaviness of the head, and general malaise.

7. Main results

There was a significant difference between groups in glucose tolerance. In arm 1, four patients had improvement, four had mild improvement, and four had no improvement, while, in arm 2, no patient had improvement.

8. Conclusions

Seishinrenshiin is an effective and safe treatment for glucose tolerance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patient in the seishinrenshiin arm had adverse reactions. Although one in seishinrenshiin arm had increased dizziness, orthostatic dizziness, and heaviness of head (symptoms that had been observed before treatment), their direct association with seishinrenshiin was not clear. In addition, one had mild increase in total cholesterol and triglyceride, and another had mild increase in BUN and creatinine, but the association of these events with seishinrenshiin was uncertain.

11. Abstractor's comments

This meaningful article describes the efficacy and safety of seishinrenshiin in treating glucose tolerance. However, the problems of this study are the short duration of treatment as well as allocation bias, that is, all members of the no treatment group were male and there were between-group differences in diabetic history and treatment at baseline. So the reliability of the assessment should be considered. Recently, treatment of metabolic abnormalities such as metabolic syndrome has received attention. Further evaluation of the effectiveness of seishinrenshiin in improving glucose tolerance is expected.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Ikeda A, Sakai M, et al. Effects of unkei-to, a herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion. *The Journal of Reproductive Medicine* 2001; 46: 451-6. CENTRAL ID: CN-00355871, Pubmed ID: 11396371

1. Objectives

To evaluate the efficacy of unkeito (温経湯) for reducing high luteinizing hormone (LH) levels and improving ovulation disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital (Osaka Medical College Hospital), although not mentioned, Japan.

4. Participants

One-hundred patients with ovulation disorder and an LH level of ≥ 10 mIU/mL, aged 21 to 32 years. Of these 100 patients, 38 were diagnosed with polycystic ovarian syndrome (PCOS).

5. Intervention

Arm 1: oral administration of a sachet (2.5 g) of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d, 30 min before meals, for 8 weeks, n=52.

Arm 2: clinical observation (without administration of placebo granules) for 8 weeks, n=48.

6. Main outcome measures

Comparison of plasma LH level.

Comparison of ovarian follicle size evaluated by ultrasonography.

7. Main results

Of 52 patients receiving unkeito, 34 showed decreased LH level, and 28 showed improved menstrual cycle regularity. In addition, ovulation was confirmed in 11 patients. Decreased LH level was significant in patients without PCOS.

8. Conclusions

Unkeito improves ovulation disorder by normalizing the high level of LH in patients with ovulation disorder. It also increases E2 hormone level in non-PCOS patients. Control patients remained unchanged. Thus, unkeito is an effective treatment for ovulation disorder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is highly significant in that it demonstrated the ovulation disorder-improving effect of unkeito at the hormonal level. However, the underlying mechanism of this improvement is not explained. Further investigation to determine, for example, why some patients do not respond to unkeito, is awaited. Nevertheless, it can be concluded that unkeito contributes to normalization of the menstrual cycle and stimulation of ovulation.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Hosotani T, Mori K, et al. Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. *The American Journal of Chinese Medicine* 2006; 34: 177-87. CENTRAL ID: CN-00563518, Pubmed ID: 16552830

1. Objectives

To evaluate the efficacy of switching to unkeito (温経湯) from treatment based on the traditional diagnostic criterion “eight-principle pattern identification” in women with polycystic ovary syndrome (PCOS).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine, Japan.

4. Participants

Sixty-four patients who visited the outpatient department and were diagnosed with PCOS between 1993 and 2004.

5. Intervention

Sixty-four patients were randomly assigned to one of 2 groups using the diagnostic criterion “*in-yo* (陰陽, yin and yang), *kyo-jitsu* (虚実, excess or deficiency), *hyo-ri* (表裏, interior and exterior), *kan-netsu* (寒熱, cold and heat)” to receive 8-week preliminary administration of either “keishibukuryogan (桂枝茯苓丸)” or “tokishakuyakusan (当帰芍薬散).” Then, 54 non-ovulating patients were further assigned via the RCT-envelope method to receive either a continuation of the same treatment (the continuous treatment group; n = 27) or unkeito (温経湯) (the unkeito group; n = 27) for 8 weeks.

Arm 1: TSUMURA Unkeito (温経湯) Extract Granules 7.5 g/day group, n = 27.

Arm 2: continuous administration group (TSUMURA Keishibukuryogan Extract Granules 7.5 g or TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 7.5 g), n = 27.

6. Main outcome measures

Blood follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels and ovulation status.

7. Main results

Switching to unkeito decreased blood LH level and significantly stimulated ovulation.

8. Conclusions

Unkeito has an ovulatory inductive effect, regardless of conventional “*sho*”(証, pattern) identification.

9. From Kampo medicine perspective

Although eight-principle pattern identification is an important criterion for treatment selection, it was not used for the selection unkeito, which was found to stimulate ovulation. Traditional diagnosis based on clinical findings, pathology, and hematology can be an important guide to the selection of Kampo formulae.

10. Safety assessment in the article

No special problems noted.

11. Abstractor’s comments

This paper indicates that switching to unkeito after treatment based on traditional “*sho*” identification improves outcome. The requirement for more objective criteria to make a Kampo diagnosis is extremely important. Other Kampo formulae beside keishibukuryogan and tokishakuyakusan should be considered to treat PCOS. It is of interest to determine whether monotherapy with unkeito would be more effective than monotherapy with other formulae. Future research is expected.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Ushiroyama T, Ikeda A, Higashino S, et al. Unkei-to for correcting luteal phase defects. *The Journal of Reproductive Medicine* 2003; 48: 729-34. CENTRAL ID: CN-00458287, Pubmed ID: 14562640

1. Objectives

To evaluate the efficacy of unkeito (温経湯) for luteal phase deficiency.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not mentioned (the authors belong to a clinic of the Department of Obstetrics and Gynecology, Osaka Medical College), Japan.

4. Participants

One-hundred and ninety-seven patients with a luteal phase of <10 days or a luteal-phase blood progesterone concentration of <10 ng/mL, who had not received hormone therapy for the past 12 months.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Unkeito (温経湯) Extract Granules (TJ-106) t.i.d (daily dose 7.5 g), n=103.

Arm 2: untreated control group, n=94. (88 included for analysis)

(Note) During 2 to 8 days after ovulation, 5,000 IU of human chorionic gonadotropin (hCG) was injected three times in 71 of 103 patients in arm 1 and all 94 patients in arm 2.

6. Main outcome measures

Ovarian follicle size, endometrial thickness, and luteal function improvement rating (prolongation of luteal phase or elevation in progesterone value).

7. Main results

During days 14 to 18 of the menstrual cycle, most of the unkeito group showed significant improvement in both ovarian follicle size and endometrial thickness (83/103 patients in arm 1 vs. 13/88 patients in arm 2). Luteal functions were also significantly improved by unkeito treatment

8. Conclusions

Unkeito improves luteal phase defect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned

11. Abstractor's comments

This paper is a follow-up of "Effects of unkeito, an herbal medicine, on endocrine function and ovulation in women with high basal level of luteinizing hormone secretion (*The Journal of Reproductive Medicine* 2001; 46: 451-6.) by Ushiroyama T, Ikeda A, Sakai M, et al." In addition to the previously reported efficacy of unkeito for ovulation disorder, the present paper reports its luteal phase-stabilizing effects including thickening of the endometrium and elevating progesterone value. Although the mechanism of action of unkeito remains unclear, this report provides further details of the effects of unkeito.

12. Abstractor and date

Nakata H, 1 April 2008.

4. Metabolism and Endocrine Diseases

Reference

Namiki T. Basic and clinical investigation of the effect of Kampo medicines on arteriosclerosis*. *Uehara Kinen Seimei Kagaku Zaidan Kenkyu Hokokushu (Research Reports of Uehara Memorial Foundation)* 2007; 21: 60-3 (in Japanese). Ichushi Web ID: 2008156867

1. Objectives

To evaluate the anti-obesity effect of bofutsushosan (防風通聖散) extract granules in obese patients and the course of high-sensitivity C-reactive protein (HS-CRP) as an arteriosclerosis-promoting factor.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The outpatient department of internal medicine at a general hospital, Japan.

4. Participants

Patients who were obese (body mass index [BMI] of 25 or greater), hypertensive (diastolic blood pressure of 90 mmHg or higher and/or a systolic blood pressure of 140 mmHg or higher), treatment-naïve or taking oral antihypertensives, and aged ≥ 20 to < 80 years were included after giving written informed consent. Exclusion criteria were: 1) serious complications (cardiac disease, renal disease, malignancy, etc.); 2) use of medications that might affect the outcome of this trial; 3) pregnant, lactating, or likely to become pregnant; and 4) considered ineligible by the investigator.

5. Intervention

Arm 1: bofu group: conventional therapy plus oral administration of bofutsushosan (防風通聖散) extract granules (manufacturer, not specified) 7.5 mg/day before or between meals for 12 weeks in 25 patients (16 males and 9 females; mean age, 63.3 ± 12.3 years).

Arm 2: control group: continuation of conventional therapy in 30 patients (19 males and 11 females; mean age, 64.2 ± 10.3 years).

6. Main outcome measures

1) Body weight, BMI, blood pressure, pulse; 2) levels of fasting blood glucose, hemoglobin a1c (Hba1c), and insulin; 3) levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride; 4) visceral fat (measured by computed tomography [CT]); and 5) blood biochemistry including HS-CRP level, hepatic and renal functions, and electrolyte levels. 1) to 3) were measured at weeks 0, 4, 12, and 24; 4) at weeks 0 and 24; and 5) at weeks 0, 4, 8, 12, and 24.

7. Main results

Body weight was reduced by 1.16 kg (-1.5%) (from 77.82 ± 17.53 kg at week 0 to 76.63 ± 17.66 kg at week 24) in the bofu group, in contrast to the reduction of 1.49 kg (-2.8%) (from 71.79 ± 10.16 kg at week 0 to 70.30 ± 10.36 kg at week 24) in the control group. But the between-group difference was not significant. BMI was decreased by 1.6% (from 30.62 ± 5.81 at week 0 to 30.14 ± 5.78 at week 24) in the bofu group and 2.1% (from 27.80 ± 2.56 at week 0 to 27.22 ± 2.79 at week 24) in the control group.

HS-CRP was 1199.00 ± 1040.46 $\mu\text{g/dL}$ at week 0, then gradually increased by 914.54 $\mu\text{g/dL}$ to 2113.54 ± 4524.08 $\mu\text{g/dL}$ at week 24 in the control group, while it was 2918.17 ± 4239.03 $\mu\text{g/dL}$ at week 0, transiently increased to 5229.26 ± 11066.85 $\mu\text{g/dL}$ at week 4, then decreased to 2694.92 ± 3606.66 $\mu\text{g/dL}$ at week 24 (decrease of 223.25 $\mu\text{g/dL}$ from the week 0 level) in the bofu group.

8. Conclusions

Although body weight and BMI were higher in the bofu group than in the control group, HS-CRP at week 24 was decreased in the bofu group and increased in the control group.

9. From Kampo medicine perspective

As a basic evaluation, the anti-arteriosclerosis effect of keishibukuryogan is also described in this paper.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is an RCT that used HS-CRP as an outcome measure to evaluate arteriosclerosis. The study is very interesting in that it used a novel approach to assess a Kampo medicine. Although results on body weight and BMI were negative, further studies are expected to reveal some positive effects.

12. Abstractor and date

Tsuruoka K, 26 January 2009, 1 June 2010.

4. Metabolism and Endocrine Diseases

References

Takashima T, Ohmori K, Higuchi N, et al. Combination therapy with probucol and daisaikoto (a Kampo medicine) - Effects of daisaikoto on HDL metabolism -. *Domyaku Koka (The Journal of Japan Atherosclerosis Society)* 1993; 21: 47-52 (in Japanese with English abstract).

Yamamoto K. A study of the hepatic triglyceride (TG)-lowering effects and antioxidant capacity of various Kampo preparations *. *Proceedings of the 4th Kampo Treatment Seminar at Kyoto University* 1995: 48-56 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) combined with probucol in patients with hyperlipidemia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Ten institutions (1 university hospital, 7 hospitals, and 2 clinics), Japan.

4. Participants

Ninety-six patients with untreated hyperlipidemia (28 to 81 years of age) (33 with type IIa, 26 with type IIb, and 37 with type IV, according to WHO classification).

Patients with total cholesterol ≥ 220 mg/dL and triglyceride ≥ 500 mg/dL were excluded.

5. Intervention

Arm 1: probucol 500 mg/day for 16 weeks (n=35).

Arm 2: TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day for 16 weeks (n=36).

Arm 3: combination of probucol 500 mg/day and TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day for 16 weeks (n=25).

6. Main outcome measures

Blood level of fasting total cholesterol (T-CHO), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), apoprotein A-I, A-II in the early morning, and B before treatment and at week 4, 8, and 16.

7. Main results

T-CHO and HDL-C decreased significantly in Arm 1 and 3. In Arm 2, T-CHO and TG showed a trend toward decrease, while HDL-C showed no change. Apoprotein A-I decreased in Arm 1, increased in Arm 2, and tended to decrease in Arm 3. There was no change in Apoprotein A-II and B in any group. Analysis according to disease type revealed that 1) for patients with type IIa hyperlipidemia, T-CHO decreased significantly in Arm 1 and 3 and HDL-C did not decrease in Arm 2 and 3; 2) for patients with type IIb and IV hyperlipidemia who had high TG levels, T-CHO decreased significantly in Arm 1 and 3 and tended to decrease in Arm 2 (-8.5% at week 16), while TG decreased significantly in only Arm 3.

8. Conclusions

The combination of daisaikoto and probucol for patients with hyperlipidemia is effective in inhibiting the reduction of HDL-C and reducing TG.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In patients with high T-CHO, probucol monotherapy decreases not only T-CHO but also HDL-C (i.e., "good" cholesterol). In this study, the combination with daisaikoto in these patients suppressed the reduction of HDL-C. In hyperlipidemic patients with high TG, their TG levels were decreased significantly by only the combination therapy. Therefore, the benefit of combination therapy with daisaikoto was shown in both types of hyperlipidemia. In addition to probucol, a number of statins with HDL-C-elevating ability have been developed, lessening the importance of inhibiting the reduction of HDL-C. However, HDL-C-increasing and TG-lowering effects, which are less with statin, are still useful. From this perspective, the combination therapy with statins and daisaikoto may still be significant and worthy of further evaluation.

The article by Yamamoto (1995) also describes a basic study using human cultured hepatocytes to evaluate the reducing effect of daisaikoto on lipid levels.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Sasaki J, Matsunaga A, Handa K, et al. Effect of daisaikoto on hyperlipidemia - comparison with clonofibrate - . *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1991; 68: 3861-71 (in Japanese). Ichushi Web ID: 1992128245

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) in patients with hyperlipidemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

University hospitals and community hospitals, Japan.

4. Participants

Sixty patients with fasting serum total cholesterol ≥ 220 mg/dl and/or triglyceride ≥ 150 mg/dl.

5. Intervention

Arm 1: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2.5 g t.i.d. for 16 weeks (n=27).

Arm 2: administration of clonofibrate 200 mg t.i.d. for 16 weeks (n=18).

Arm 3: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2.5 g t.i.d. plus clonofibrate 200 mg t.i.d. for 16 weeks (n=15).

6. Main outcome measures

Levels of serum lipids (including total cholesterol, LDL cholesterol, HDL cholesterol, and serum triglyceride), and apoprotein.

7. Main results

There was a significant reduction in serum triglyceride ($P < 0.05$), apo A-1 ($P < 0.05$), apo E ($P < 0.05$), and lipid peroxide ($P < 0.01$) in the daisaikoto monotherapy group. In contrast, there was no significant change in the clonofibrate monotherapy and clonofibrate with daisaikoto groups.

8. Conclusions

Daisaikoto monotherapy was effective for hyperlipidemia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although no patient had severe adverse effects, five had diarrhea and loose stool, one had tachycardia and menorrhagia, and one had the elevation of γ -GTP level in the daisaikoto monotherapy group. One in clonofibrate with daisaikoto group had mild adverse effects including diarrhea and abdominal pain.

11. Abstractor's comments

The low follow-up rate (20 of 60 enrolled patients dropped out of the study, leaving only 40 included in the analysis) is a limitation of this study.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

Reference

Muramatsu N, Okayasu M. Clinical study on hyperlipidemia at bezafibrate and da-chai-hu-tang (dai-saiko-to) for the combination therapy (Clinical study of hyperlipidemia after combination therapy with bezafibrate and da-chai-hu-tang (dai-saiko-to)). *Shigaku (Odontology)* 1993; 81: 94-9 (in Japanese with English abstract).

1. Objectives

Efficacy and safety of daisaikoto (大柴胡湯) combined with bezafibrate in patients with hyperlipidemia.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Ten patients with hyperlipidemia (mean age, 55.4 years) (3 with type IIa and 7 with type IIb according to WHO classification, and 4 with *jitsu-sho* [実証, excess pattern] and 6 with *chukan-sho* [中間証, intermediate pattern]).

5. Intervention

Arm 1: combination of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 7.5 g/day and bezafibrate 400 mg/day for 12 weeks (n=5).

Arm 2: bezafibrate 400 mg/day for 12 weeks (n=5).

6. Main outcome measures

Total cholesterol (TC) and triglyceride (TG) were measured every 4 weeks and their rate of decline was calculated.

7. Main results

The rate of decline in TC was not different between arms and that in TG tended to be greater in arm 1 than arm 2.

8. Conclusions

Daisaikoto (大柴胡湯) enhances the blood TG-lowering effect of bezafibrate.

9. From Kampo medicine perspective

Deficiency-Excess Pattern Identification according to *jitsu-sho* score was adopted as a patient characteristic; 3 and 1 patient in arm 1, and 1 and 4 patients in arm 2, had *jitsu-sho* and *chukan-sho*, respectively. However, the article does not discuss *sho* (証, pattern).

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

This study compared the efficacy of bezafibrate monotherapy with that of bezafibrate and daisaikoto combination therapy. For lowering TG, the combination therapy may be more effective than monotherapy; however, this study was small and no statistical analysis was performed. Since there are few effective agents for lowering TG by a mechanism of action different from that of bezafibrate, investigation of combination therapy with such agents (e.g., daisaikoto) would be meaningful. Studies with larger sample size are needed.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

Reference

Yamano S, Sawai F, Hashimoto T, et al. Comparative effects between dai-saiko-to and elastase on lipid metabolism and cerebral circulation in patients with hyperlipidemia. *Kampo to Saishin-chiryō (Kampo & The Newest Therapy)* 1995; 4: 309-13 (in Japanese).

1. Objectives

To evaluate the effects of daisaikoto (大柴胡湯) on serum lipid level and cerebral circulation.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Sixty-five outpatients with hyperlipidemia (i.e., serum cholesterol \geq 200 mg/dL or serum triglyceride \geq 150 mg/dL) on 3-month diet therapy.

5. Intervention

Arm 1: administration of TSUMURA Daisaikoto (大柴胡湯) Extract Granules 2 g t.i.d. for 12 months (n=27).

Arm 2: administration of elastase 5,400 elastase unit (EL.U.) per day for 12 months (n=38).

Arm 3: healthy controls matched for age and sex (n=27).

6. Main outcome measures

Determination of serum lipids (including total cholesterol [TC], high density lipoprotein-cholesterol [HDL], and triglyceride [TG] levels) before treatment and after 6 and 12 months.

Hemodynamic parameters in the common carotid artery were also measured.

7. Main results

In within-group comparisons, in arm 1, TC and TG levels decreased significantly after 6 and 12 months and HDL level increased significantly after 12 months, relative to baseline (pretreatment level). In arm 2, TC and HDL showed no change but TG decreased significantly. In between-group comparisons, improvement in TC was greater in the daisaikoto arm than the elastase arm (245.2 ± 64.5 ng/dL vs. 228.5 ± 48.7 ng/dL), whereas between-arm improvements in HDL and TG were similar. Hemodynamic parameters of the common carotid artery, blood pressure, and heart rate were unaffected in both arms.

8. Conclusions

In patients with hyperlipidemia, daisaikoto and elastase improves serum cholesterol but not cerebral circulation. The effect of daisaikoto is greater than that of elastase.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The control group consisted of healthy subjects (matched for age and sex). This study was therefore a randomized controlled trial with two arms.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

4. Metabolism and Endocrine Diseases

References

Takagi S. Mitigation of hyponatremia after operation for cholelithiasis or gallbladder polyp by preoperative administration of wu-ling-san. *Saitama Ikadaigaku Zasshi (Journal of Saitama Medical School)* 1990; 17: 145-50 (in Japanese with English abstract).

Seki M, Fujioka M, Hatano T, et al. Analysis of regulatory effects of gorei-san on circulatory, metabolic and diuretic function - especially in relation to endothelial activation and increase of urinary 6-keto-prostaglandin F₁α level-. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1992; 42: 313-22 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of goreisan (五苓散) in the treatment of postoperative hyponatremia for cholelithiasis or gallbladder polyps.

2. Design

Randomized controlled trial (RCT).

3. Setting

A university hospital (Saitama Medical University Hospital), Japan.

4. Participants

Fifty-eight females undergoing surgery for cholelithiasis or gallbladder polyps (without evidence of inflammation).

5. Intervention

Arm 1: administration of TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. on an empty stomach for a mean treatment duration of 7.9 days before surgery (n=17).

Arm 2: administration of TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. on an empty stomach for a mean treatment duration of 6.3 days before surgery (n=13).

Arm 3: control group, bed rest in the hospital (n=28).

6. Main outcome measures

Morning fasting levels of blood sodium (Na), potassium (K), and chloride (Cl), white blood cell, red blood cell, and platelet counts, 24-hour urinary prostaglandin (PGE1), and 24-hour urinary excretion of 6-keto prostaglandin F1 alpha (6-keto-PGF1α) were assessed beginning before administration to 14 days after surgery.

Blood urea nitrogen (BUN) was also measured in the related article indicated below.

7. Main results

At postoperative days 0 and 1, blood sodium (Na) but not K and Cl was higher in Arm 1 than in Arms 2 and 3. There was no among-group difference in white blood cell count, whereas at postoperative days 8–14, red blood cell count was lower in Arm 1 than in Arm 3, and at postoperative day 1, platelet count was higher in Arms 1 and 2 than in Arm 3. There was no among-group difference in PGE1. But 6-keto-PGF1α increased significantly in only Arm 1 for up to 14 days after surgery.

8. Conclusions

In patients planned for gallbladder surgery, preoperative administration of goreisan significantly increased postoperative urinary PGF1α and urine output. In addition, postoperative hyponatremia was mitigated and associated with a shorter duration.

9. From Kampo medicine perspective

No significant among-group difference was observed in the number of patients with *netsu-sho* (熱証, heat pattern) or *kan-syo* (寒証, cold pattern) according to Kampo diagnosis.

10. Safety assessment in the article

Goreisan has no adverse effects, according to the related article indicated below.

11. Abstractor's comments

The interim report of this study described the effect of preoperative administration of goreisan on edema in patients planned for gallbladder surgery. This study further examined that effect in terms of its mechanism. Notably, the diuretic effect of preoperatively administered goreisan persisted after surgery. The authors speculate that this effect was caused by increased production of PGI2 (associated with an increase in urine PGF1α, a 6-keto-PGI2 metabolite), which in turn resulted in renal vasodilatation and the anti-ADH effect of 6-keto-PGF1α leading to increased diuresis. Therefore, the administration before common elective surgery (not just gallbladder surgery) may result in significant increase of urine volume or reduced postoperative hyponatremia, as well as shorten duration of hospitalization. Further evaluation of goreisan may expand its applicability to other surgeries in the future.

The article by Takagi (1990) is the interim report of the article by Seki et al (1992).

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

4. Metabolism and Endocrine Diseases

References

Uebaba K, Xu F. Association between the SNP in sympathetic β 3-adrenergic receptor gene and the efficacy of bofutsushosan* *Nihon Toyo Igaku Zasshi (Kampo medicine)* 2003; 54: S225.

Kamohara S, Kawakami T, Uebaba K, et al. A study on the development of individualized medicine for the prevention, diagnosis, and treatment of metabolic syndrome using an integrative approach*. *Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (Research Papers of the Suzuken Memorial Foundation)* 2009; 26: 399–403.

Xu FH, Uebaba K, Ogawa H, et al. Personalized effects of a Kampo herbal formulation on metabolism — A randomized, double-blind, placebo controlled study of bohutusei-san — *Toho Igaku (Eastern Medicine)* 2012; 28: 37-59 (in Japanese).

1. Objectives

To evaluate whether bofutsushosan (防風通聖散) reduces obesity.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Medical institutions in Toyama Prefecture, Japan.

4. Participants

Invitation letters were sent to 2000 residents aged 55–65. Totally 120 subjects without diarrhea, cardiac disease, and serious hepatic or renal disease (as determined by history-taking, blood test, and electrocardiography data) were selected from obese individuals (BMI \geq 25) who consented to participate.

5. Intervention

Arm 1: Kanebo Bofutsushosan (防風通聖散) Extract Fine Granules 3.75 g b.i.d. at least 1 hour after meals for 2 months (n=70).

Arm 2: Indistinguishable placebo containing 5% Kanebo Bofutsushosan (防風通聖散) Extract Fine Granules with the same taste, smell, and color, and administered in the same manner as arm 1 (n=50).

6. Main outcome measures

WHOQOL-26, Oriental medicine questionnaire, serum biochemical indices, IRI (immunoreactive insulin), and homeostasis model assessment-insulin resistance (HOMA-R) were measured at baseline, 2, 4, and 8 weeks.

7. Main results

The data from 112 subjects (67 in arm 1 and 45 in arm 2) who completed the study were included in the analysis. The male/female ratio was 19/48 and 11/34 for arms 1 and 2, respectively. A total of 36 subjects (18 in arm 1 and 18 in arm 2; 32.1%) had a single nucleotide polymorphism (SNP) in β 3-adrenergic receptor gene (18 Arg hetero in arm 1 and 15 Arg hetero and 3 Arg homo in arm 2). There was a significant between-arm difference ($P<0.05$) with demonstrated weight loss of 0.8 kg in arm 1 versus 0.1 kg in arm 2. Comparison of the responders (15 subjects: weight loss \geq 1.5 kg) with the non-responders (16 subjects: weight loss \geq 0.1 kg) in arm 1 demonstrated higher blood pressure and serum total protein before administration in arm 1 than arm 2, with 140 mm Hg the threshold for high blood pressure classification. This indicates that multiple regression analysis of initial blood pressure values and serum total protein values can be used to predict weight loss attributable to Bofutsushosan. Decreases in total cholesterol values at eight weeks compared to values before administration in arm 1 demonstrated a significant difference ($P<0.05$) in the high cholesterol group only. No differences in weight loss by the presence or absence of SNP were found.

8. Conclusions

Bofutsushosan appears to reduce body weight in obese individuals aged 55–65.

9. From Kampo medicine perspective

The results suggest that bofutsushosan is effective for obese individuals with high blood pressure and high serum total protein. This presumably equates to excess pattern and supports the classical literature..

10. Safety assessment in the article

None.

11. Abstractor's comments

An important DB-RCT that tested the effectiveness of bofutsushosan for obese individuals. The original paper on which was based the brief paper published as Kamohara et al. (2009) and Uebaba et al. (2003). It deserves recognition for following the CONSORT recommendations. An RCT of bofutsushosan examining excess pattern holds promise, as suggested in 'From Kampo medicine perspective'.

12. Abstractor and date

Tsuruoka K, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

References

Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of choto-san and placebo in the treatment of vascular dementia. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 246–55. Ichushi Web ID: 1996055624

Shimada Y, Terasawa K, Yamamoto T, et al. Efficacy of choto-san on vascular dementia: A well, placebo-controlled study. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 370–1 (in Japanese) Ichushi Web ID: 1996075788

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) in the treatment of vascular dementia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Multicenter clinical trials involving Toyama Medical and Pharmaceutical University Hospital, Kagoshima University, and three general hospitals, Japan.

4. Participants

Sixty patients (9 males and 51 females; mean age, 78.9 years, including both inpatients and outpatients) who satisfied the DSM-III-R criteria for dementia, were diagnosed with cerebrovascular dementia, had Carlo Loeb modified ischemic scores of ≥ 5 points, were in stable general health, and participated in the study with the consent of one or more family members.

5. Intervention

Arm 1: TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. after meals for 12 weeks (6 males and 26 females).

Arm 2: TSUMURA-manufactured placebo composed of such ingredients as lactose, dextrin, maltose, and cellulose, indistinguishable in appearance (color) and taste from chotosan (釣藤散), as determined before the trial, 2.5 g t.i.d. after meals for 12 weeks (3 males and 25 females).

6. Main outcome measures

Subjective symptoms, neurological manifestations, psychiatric manifestations, severity, and improvement in impaired activities of daily living; dementia status evaluated using the Revised Hasegawa Dementia Scale (HDS-R), every 4 weeks; overall safety and usefulness, evaluated at 12 weeks after the start of treatment.

7. Main results

Of 60 patients, 57 completed treatment (31 with chotosan and 26 with placebo). The following measures were significantly improved in patients receiving chotosan: global improvement rating ($P < 0.05$, $P < 0.01$, and $P < 0.01$ at 4, 8, and 12 weeks, respectively); usefulness ($P < 0.01$ at 12 weeks); subjective symptoms ($P < 0.05$, $P < 0.01$, and $P < 0.01$ at 4, 8, and 12 weeks, respectively); psychiatric manifestations ($P < 0.05$, $P < 0.01$, and $P < 0.01$ at 4, 8, and 12 weeks, respectively); and activities of daily living ($P < 0.05$, $P < 0.05$ at 4 and 12 weeks, respectively). Improvement of neurological manifestations did not significantly differ between arms at 4, 8, and 12 weeks. Subjective symptoms (“dizziness,” “shoulder muscle stiffness,” and “palpitations”) and psychiatric manifestations (“interest in TV programs and books,” “lack of expression,” and “disorientation”) were significantly improved in the chotosan group. Chotosan significantly improved HDS-R from 15.34 ± 3.76 at baseline to 16.65 ± 4.43 at 4 weeks ($P < 0.05$), 17.94 ± 4.79 at 8 weeks ($P < 0.01$), and 19.39 ± 5.71 at 12 weeks ($P < 0.01$), although there was no significant difference between arms.

8. Conclusions

Chotosan is effective for cerebrovascular dementia.

9. From Kampo medicine perspective

Chotosan has traditionally been used to treat headache and dizziness in patients who are past middle age and relatively weak physically. These symptoms are considered to be indicators of cerebral arteriosclerosis and cerebrovascular disorder by modern medicine. The present study succeeded in objectively evaluating the clinical efficacy of chotosan for cerebrovascular dementia.

10. Safety assessment in the article

Treatment was discontinued in 1 patient receiving chotosan (3.1%) who had a history of hepatopathy and whose oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) levels increased during treatment and returned to normal after treatment discontinuation. Another patient receiving chotosan (3.1%) had a decrease in potassium that was too mild to affect treatment. There was no significant difference in overall safety between arms.

11. Abstractor’s comments

This is a well-designed RCT that generated high-quality evidence. There is much to learn from this study, which included blinding, included a placebo arm, considered dropouts, and analyzed safety and usefulness in an intent-to-treat population. A larger-scale RCT performed later to re-evaluate efficacy (Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. *Phytomedicine* 1997; 4: 15–22.) is also informative.

12. Abstractor and date

Tsuruoka K, 22 September 2008, 31 December 2013.

5. Psychiatric/behavior disorders

References

Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: A double blind, placebo-controlled study. *Phytomedicine* 1997; 4: 15-22.

Terasawa K. Chotosan in the treatment of vascular dementia. *Pharma Medica* 2007; 25: 57-9 (in Japanese). Ichushi Web ID: 2008035997 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for vascular dementia using more objective criteria.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Nine hospitals including university hospitals of Toyama Medical and Pharmaceutical University, Kagoshima University, Tohoku University, etc., Japan.

4. Participants

A total of 139 patients (50 males and 89 females with a mean age of 76.6 years) who were diagnosed with vascular dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for dementia and who fulfilled the following guidelines (Carlo Loeb modified ischemic score of ≥ 5 points; stable physical condition; informed consent obtained).

5. Intervention

Arm 1: treatment with TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. after meals for 12 consecutive weeks (n=69; 28 males and 41 females).

Arm 2: treatment with placebo consisting of lactose, dextrin, maltose, cellulose, etc., which was manufactured by Tsumura & Co. and not distinguishable from chotosan in terms of color or taste, at the same dose and frequency as in arm 1 (n=70; 22 males and 48 females).

6. Main outcome measures

The rating of severity and improvement in subjective symptoms, neurological symptoms, psychiatric symptoms, and disturbance in activities of daily living (ADL) as well as cognitive function using the Revised Hasegawa's Dementia Scale (HDS-R) assessed every 4 weeks. The overall safety rating and utility rating assessed at Week 12.

7. Main results

In the chotosan group compared with the placebo group, the scores for overall improvement ($P < 0.01$ at Week 8, $P < 0.001$ at Week 12), utility ($P < 0.001$ at Week 12), improvement in subjective symptoms ($P < 0.05$ at Week 8, $P < 0.01$ at Week 12), psychiatric symptoms ($P < 0.05$ at Week 4, $P < 0.001$ at Week 8, $P < 0.001$ at Week 12), and ADL ($P < 0.05$ at Week 12) were significantly higher. No significant between-group difference was observed in neurological symptoms. The following symptoms improved significantly in the chotosan group compared with the placebo group: spontaneity of conversation; lack of facial expression; decline in simple arithmetic ability; global intellectual ability; nocturnal delirium; sleep disturbance; hallucination or delusion. The HDS-R score tended to be higher in the chotosan group.

8. Conclusions

These results suggest that chotosan may be effective in the treatment of vascular dementia.

9. From Kampo medicine perspective

Chotosan has traditionally been used in physically weak, middle-aged or older patients with symptoms such as headache, heaviness of head, vertigo, hot flashes, sleeplessness, or tinnitus. Since these symptoms may also be associated with cerebrovascular disorder, the clinical efficacy of chotosan for vascular dementia was objectively evaluated in this study.

10. Safety assessment in the article

While adverse drug reactions occurred in 5 patients in the chotosan group (rash, diarrhea, appetite loss, heartburn, and hypertension), there was no difference in the overall safety rating between the two groups.

11. Abstractor's comments

This RCT evolved from a prior larger study that evaluated the efficacy of chotosan for vascular dementia (Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of Chotosan and placebo in the treatment of vascular dementia. *Wakan Iyakugaku Zasshi [Journal of Traditional Medicines]* 1994; 11: 246-55.). It was well designed and produced high-quality evidence. The results were generally similar to those of the previous study, with a few differences in the symptoms that showed improvement (refer to the above reference). In the future, chotosan should be compared to the gold standard treatment in modern medicine. The article by Terasawa (2007) is the Japanese digest of the paper by Terasawa et al (1997).

12. Abstractor and date

Tsuruoka K, 22 April 2008, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine “ba wei di huang wan” in the treatment of dementia. *Journal of the American Geriatrics Society* 2004; 52: 1518-21. CENTRAL ID: CN-00491098, Pubmed ID: 15341554

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸) for dementia.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Single hospital (long-term care facility), Japan.

4. Participants

Thirty-three anticholinergic-untreated dementia patients with an MMSE score of 0 – 25.

5. Intervention

Arm 1: oral administration of Uchida Hachimijiogan (八味地黄丸) 2.0g t.i.d. after meals for 8 weeks (n=16).

Arm 2: oral administration of 2.0 g of honey-mixed black rice powder as placebo t.i.d. after meals for 8 weeks (n=17).

6. Main outcome measures

Mini-Mental State Examination (MMSE) score, Barthel Index, and internal carotid artery pulsatility index at baseline, 8 weeks after start of dosing, and 8 weeks after completion of dosing.

7. Main results

After 8 weeks of dosing, in arm 1, a significant improvement over baseline was observed in MMSE score, from 13.5±8.5 to 16.3±7.7, Barthel Index, from 61.8±34.6 to 78.9±21.1, and pulsatility index, from 2.5±1.7 to 1.9±0.5, whereas no changes were noted in these variables in arm 2. At 8 weeks after completion of dosing (16 weeks after start of dosing), MMSE score and Barthel Index of arm 1 returned to control (arm 2) levels.

8. Conclusions

Hachimijiogan improves cognitive function, activities of daily living, and internal carotid arterial blood flow in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study period, no adverse drug reactions occurred in either group. After completion of dosing, a hospital change due for personal reasons, and urinary tract infections and upper respiratory tract infections occurred in 1 and 2 patients in arm 1, respectively.

11. Abstractor’s comments

This study, which investigated the efficacy of hachimijiogan for preserving or restoring cognitive function and activities of daily living in elderly dementia patients in a double-blind RCT, provides high-quality evidence. At week 16, MMSE scores of the hachimijiogan group had a large standard deviation (SD), indicating wide inter-individual variation in dementia severity. Even in the placebo group, MMSE score and Barthel Index did not worsen, though the study population included patients with Alzheimer’s disease, suggesting disease progression may have been slower in these very old patients (aged 83 to 85 years, on average). In addition, whether the hachimijiogan-induced improvement (a mean of 2.8 points) in the dementia score of the MMSE led to clinical improvement will require further investigation. It is recommended that investigation separate patients with cerebrovascular disorders from those with Alzheimer’s disease. To further elucidate the efficacy of hachimijiogan, longer-term observation of a larger sample is expected.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Suzuki T, Futami S, Igari Y, et al. A Chinese herbal medicine, choto-san, improves cognitive function and activities of daily living of patients with dementia: A double-blind, randomized, placebo-controlled study. *Journal of the American Geriatrics Society* 2005; 53: 2238-40. CENTRAL ID: CN-00554102, Pubmed ID: 16398922

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for improvement of cognitive function and activities of daily living in dementia patients.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Not mentioned (authors belong to Department of Geriatric Medicine, Nippon Medical School Hospital, and another hospital), Japan.

4. Participants

Thirty patients with mild or moderate dementia: 13, Alzheimer type dementia (MMSE¹ score 14 – 25) and 17, Alzheimer disease (MMSE score 10 – 21) or cerebrovascular disorders (MMSE score not indicated). All were included in the analysis population.

¹MMSE: Mini-Mental State Examination

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Chotosan (釣藤散) Extract Granules t.i.d. before meals for 8 weeks (n=10).

Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. before meals for 8 weeks (n=10).

Arm 3: oral administration of 2.5 g of placebo t.i.d. before meals for 8 weeks (n = 10).

6. Main outcome measures

Cognitive function evaluated by the MMSE; activities of daily living, by Barthel Index (BI); and caregiver burden, by Zarit Caregiver Burden Scale (Z score).

7. Main results

In arm 1, a significant improvement over baseline was observed in MMSE score, from 15.5±4.0 to 17.5±4.9, and BI, from 67.5±34.6 to 71.5±35.8, whereas no such improvement was seen in arm 2 or 3. There was no significant difference in Z score among the 3 arms.

8. Conclusions

Chotosan improves cognitive function and activities of daily living in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned

11. Abstractor's comments

This study, which investigated the efficacy of chotosan and goshajinkigan for cognitive function and activities of daily living in elderly patients with dementia in a double-blind RCT, provides high-quality evidence. Although the sample size was small and no statistically significant difference between the arms was found, cognitive function and activities of daily living were significantly improved over baseline in the chotosan group. However, no baseline characteristics except for age and sex are indicated, the underlying disease is not mentioned, and MMSE scores of patients with cerebrovascular disorders are not given. Patient characteristics and each score should be provided. Furthermore, MMSE score in the chotosan group was improved over baseline, but the level after 8-week dosing was almost equal to that in the placebo group (presumably because there was a significant difference in MMSE score at baseline between 2 groups). A future investigation of the efficacy of chotosan for improving cognitive function and activities of daily living is expected with a larger sample size and for a longer period.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine yi-gan san for improvement of behavioural and psychological symptoms and activities of daily living in dementia patients. *Journal of Clinical Psychiatry* 2005; 66: 248-52. CENTRAL ID: CN-00502716, Pubmed ID: 15705012

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treating behavioral disorders and improving activities of daily living in dementia patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three hospitals (long-term care facilities), Japan.

4. Participants

A total of 60 patients with dementia due to Alzheimer's disease, cerebrovascular disorder, or Lewy body disease, having a Mini-Mental State Examination (MMSE) score of <24 and a neuropsychiatric inventory (NPI) score of >6; of these, 52 patients were included for analysis.

5. Intervention

Arm 1: oral administration of 7.5 g/day of TSUMURA Yokukansan (抑肝散) Extract Granules in 3 divided doses before meals for 4 weeks (n=27).

Arm 2: untreated control group (n=25).

6. Main outcome measures

MMSE score, Barthel Index, and NPI score.

7. Main results

No changes were found in MMSE score in either group. Significant improvements (compared with baseline) were observed in Barthel Index, from 56.4±34.2 to 62.9±35.2, and NPI score, from 37.9±16.1 to 19.5±15.6, in arm 1. In NPI subscales for hallucination, anxiety/excitement, etc., significant improvements over baseline were noted in arm 1. Additional treatment with tiapride hydrochloride, a dopamine D₁ selective neuroleptic, was required in 11 patients in arm 2 but in none in arm 1.

8. Conclusions

Yokukansan is effective for improvement of behavioral disorders and activities of daily living in dementia patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dizziness and impaired postural sway were reported in 6 patients (54.5%) treated with tiapride hydrochloride. Two patients (7.4%) who continued yokukansan after the end of the observation period became oversedated but recovered with a reduced dose.

11. Abstractor's comments

This study, which investigated the efficacy of yokukansan for cognitive function and activities of daily living in elderly dementia patients in an RCT, provides high-quality evidence. However, the same nurses who rated MMSE and NPI scores, and Barthel Index may also have administered yokukansan, suggesting the possibility of a lack of blinding, which may have affected evaluations. In future, the effects of yokukansan in dementia patients are expected to be studied over a longer term.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Mizukami K, Asada T, Kinoshita T, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *The International Journal of Neuropsychopharmacology* 2009; 12: 191-9. CENTRAL ID: CN-00704589, Pubmed ID: 19079814

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioural and psychological symptoms of dementia.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

Twenty medical institutions (the first author belongs to the faculty of the Department of Clinical Neuroscience, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba), Japan.

4. Participants

One hundred and six patients aged 55–85 years and diagnosed with Alzheimer's disease, including mixed-type dementia or dementia with Lewy bodies. There were 59 outpatients (20 males and 39 females, mean age 78.7±5.4 years) and 47 inpatients (19 males and 28 females, mean age 78.5±6.7 years).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. orally for 4 weeks, followed by observation with no treatment for 4 weeks (n=54).

Arm 2: No treatment with observation for 4 weeks, followed by TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. orally for 4 weeks (n=52).

6. Main outcome measures

Behavioural and psychological symptoms of dementia (BPSD) and cognitive functions were evaluated using the Neuropsychiatric Inventory (NPI) and Mini-Mental State Examination (MMSE), respectively. Activities of daily living were evaluated using the Instrumental Activities of Daily Living (IADL) in outpatients and the Barthel Index in inpatients. Patients were evaluated at baseline, 4 weeks, and 8 weeks.

7. Main results

In both arms, total scores on the NPI significantly improved after 4 weeks of yokukansan treatment ($P<0.01$), but not during the no-treatment period. Among the NPI subscales, delusion, hallucination, agitation/aggression, and irritability/lability ($P<0.01$ for each) improved in arm 1 and agitation/aggression ($P<0.01$), depression, anxiety, and irritability/lability ($P<0.05$ for each) improved in arm 2 after the yokukansan treatment.

8. Conclusions

Oral administration of yokukansan improves behavioural and psychological symptoms associated with dementia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions were reported in 6 patients. Gastrointestinal symptoms including vomiting, diarrhea, nausea, and epigastric pain developed in 3 patients. When yokukansan treatment was discontinued, these symptoms promptly resolved. Hypokalemia was reported in 2 patients, one of whom experienced oversedation. When yokukansan treatment was discontinued, serum potassium levels returned to normal in both patients. Another patient developed lower leg edema. No serious adverse reactions, such as extrapyramidal symptoms and hallucination, were observed.

11. Abstractor's comments

This is a very meaningful clinical study that demonstrated the efficacy of yokukansan for improving BPSD in a multicentre setting. In both arms, symptoms improved during yokukansan treatment compared with the no-treatment period. The results would be more valuable if the data had been analyzed rigorously as a cross-over design. In the future, larger-scale multicentre placebo-controlled studies and clinical studies of longer-term treatment with yokukansan are needed to further demonstrate the efficacy of this agent.

12. Abstractor and date

Goto H, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Takase S. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly. *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 132-4 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Cardiovascular Surgery, Fukushima Medical University, Japan.

4. Participants

Thirty patients who underwent cardiovascular surgery since April 2009.

5. Intervention

Arm 1: administration of TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. from 5 days prior to surgery until the day of discharge except for the day of surgery (n=15).

Arm 2: no administration (n=15).

6. Main outcome measures

Each item on the 10-item Delirium Rating Scale-J (DRS-J) (orientation, hallucination, delusions, agitation, motor restraints, perceptual disturbances, physical disorders, sleep-wake cycle disturbance, lability of mood, fluctuation of symptom severity). Assessment by physicians of 10 items of the DRS-J at 5 days prior to surgery, and 3 and 10 days after surgery. Assessment by nurses of 6 items at 5 days prior to surgery and 1–5, 7, 10, 12, 14, and 16 days after surgery.

7. Main results

In the assessments by physicians, there were significant between-arm differences in orientation ($P=0.0033$), delusion ($P=0.021$), agitation ($P=0.0011$), and lability of mood ($P=0.0044$). In the assessments by nurses, there were significant between-arm differences in hallucination ($P=0.0383$), agitation ($P=0.0049$), and lability of mood ($P=0.0364$). Both physicians ($P=0.0331$) and nurses ($P=0.0245$) found that the overall score had improved significantly after treatment (Arm 1).

8. Conclusions

Yokukansan is effective for preventing delirium after cardiovascular surgery in elderly patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No hypokalemia, which often occurs after cardiovascular surgery, was observed.

11. Abstractor's comments

This is an innovative clinical trial evaluating the efficacy of yokukansan for delirium after cardiovascular surgery in the elderly. It is meaningful that they used yokukansan to solve an actual clinical problem such as post-operative delirium and demonstrated its effectiveness. However, this article is a summary of conference presentation, and regrettably fails to describe the methods and results precisely. Details of the study including the number of withdrawals, the degree of improvement for items such as "orientation" and "delusion" in comparison to the control group, and the method for calculating overall score, are awaited in a journal article, which has not yet been published. This interesting clinical study provides a helpful perspective for a future large-scale study assessing the efficacy of yokukansan for preventing post-operative delirium in the elderly.

12. Abstractor and date

Goto H, 25 December 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders

Reference

Miyaoka T, Furuya M, Yasuda H, et al. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia: An open-label study. *Clinical Pharmacology* 2009; 32: 6–9.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Psychiatry, Shimane University School of Medicine, Japan.

4. Participants

Patients diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) who met treatment-resistance criteria as follows:

- a) no satisfactory response to antipsychotic drugs from at least 2 different classes, in a dose equivalent to at least 1000 mg/d of chlorpromazine for at least 6 weeks during the course of illness;
- b) no period of good functioning within the preceding 2 years;
- c) positive and negative syndrome scale (PANSS) scores in the 70th percentile or higher, based on normative data for patients with chronic schizophrenia.

5. Intervention

The study was brief (4 weeks) and had an open-label design.

Arm 1: administration of Yokukansan (抑肝散) 6.7 ±2.5 g (range, 2.5–7.5 g)/day (n=34).

Arm 2: no administration of Yokukansan (抑肝散) (n=25).

All patients were taking conventional and/or atypical antipsychotic medications, including olanzapine, risperidone, quetiapine, aripiprazole, perospirone, haloperidol, levomepromazine, and zotepine.

6. Main outcome measures

PANSS and drug-induced extrapyramidal symptom scale (DIEPSS) were assessed at baseline, and after 2 and 4 weeks of treatment.

7. Main results

In Arm 1, treatment with Yokukansan significantly reduced the PANSS positive symptoms subscale score of 27.7±6.1 at baseline by 68.2% at 2 weeks (means score 18.9±5.0) ($P<0.001$) and 43.0% at 4 weeks (mean score, 11.9±3.7) ($P<0.001$), the PANSS negative symptom subscale score of 30.4±5.8 at baseline by 73.7% at 2 weeks (mean score, 22.4±4.3) ($P<0.001$) and 59.9% at 4 weeks (mean score, 18.2±2.2) ($P<0.001$), and the PANSS general psychopathology subscale score of 65.1±5.4 at baseline by 70.5% (mean score, 45.9±9.0) ($P<0.001$) at 2 weeks and 60.8% (means score, 39.6±6.9) ($P<0.001$) at 4 weeks. In the control group, each PANSS subscale remained unchanged. There was no significant difference in the DIEPSS scores in both groups.

8. Conclusions

In this pilot study, statistically significant improvement in clinical assessment scale was observed after yokukansan treatment, suggesting that yokukansan has efficacy for treatment-resistant schizophrenia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

DIEPSS corresponds to the safety assessment, and no serious adverse effects of yokukansan were reported. A few mild and transient adverse events included 2 cases of nausea and 1 case of tiredness.

11. Abstractor's comments

This RCT was designed to evaluate the efficacy of yokukansan for schizophrenia, as it has been shown to be effective in treating psychiatric disorders such as dementia. The idea is great and the result is clinically significant. As the authors discuss, the absence of blinding may have introduced bias into the outcome assessment. The total number of the participants of the two arms is 59. However, the Figure 1 legend states that 54 completed a 4-week trial, making unclear the number of subjects who dropped out. Because of the small sample size, the number of subjects used as denominator for analyses is a concern. More precise design for the main trial is anticipated.

12. Abstractor and date

Tsuruoka K, 2 January 2011.

5. Psychiatric/Behavioral Disorders

Reference

Ishida H, Otake T, Kurihara H, *et al.* Clinical study on augmentative effect of saiboku-to for anxiolytic and antidepressant action of diazepam. *Pain Clinic*, 1999; 20: 395-9 (in Japanese).

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) as a potentiator of the anxiolytic and antidepressant effects of diazepam.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single clinic (pain clinic), Japan.

4. Participants

Fifteen patients with chronic anxiety or depression were included for analysis.

5. Intervention

Arm 1: oral administration of 7.5 g/day of saibokuto (柴朴湯) extract granules (manufacturer, not specified; frequency, not specified) for 2 weeks followed by 6 mg/day of diazepam for 2 weeks. (n=7)

Arm 2: oral administration of 6 mg/day of diazepam for 2 weeks. (n=8)

6. Main outcome measures

Hamilton Rating Scale (HS) score, diazepam and desmethyldiazepam blood levels, motor nerve conduction velocity (MCV)

7. Main results

Mean HS scores were 11.0, 7.4, and 4.1 before and after saibokuto and after diazepam, respectively, in Arm 1, while 8.9 and 5.5, respectively, before and after diazepam in Arm 2. Significant improvement in HS score was observed after diazepam in both arms. No between-arm difference was seen in diazepam and desmethyldiazepam blood levels or MCV.

8. Conclusions

Administration of saibokuto followed by diazepam, compared with diazepam monotherapy, has at least an equal anxiolytic and antidepressant effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The study comparing diazepam monotherapy with saibokuto and subsequent diazepam for anxiolytic and antidepressant treatment in patients with anxiety neurosis in a randomized controlled trial provides a high quality of evidence. The statement concluding that administration of saibokuto was likely to be associated with clinical improvement of symptoms was in the Discussion, although not in the Results. Despite the small sample size, it is likely that the effect of diazepam was enhanced by prior saibokuto treatment, so studies with larger sample size are needed. A trend towards clinical improvement of symptoms in the saibokuto arm was presented as a conclusion in the Discussion, but the measures of clinical symptoms are not mentioned. Providing details of these measures would improve the quality of this study.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Yamagiwa M, Sakakura Y, Harada T, et al. Therapeutic response to various drugs in patients with continuous or periodic discomfort in the throat. *Jibiinkoka Rinsho (Practica Otologica)* 1990; 83: 1687–92 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) for relieving discomfort in the throat.

2. Design

Randomized controlled trial (RCT).

3. Setting

The departments of otorhinolaryngology of Mie University Hospital and of related hospitals (not identified), Japan.

4. Participants

Four-hundred and ninety-four patients seen in the above hospitals with a chief complaint of discomfort in the throat, diagnosed with and treated for laryngopharyngeal discomfort without adverse drug reactions and with available efficacy data.

5. Intervention

Arm 1: placebo (sugar-coated tablet indistinguishable from Alprazolam tablets 0.4 mg), 3 tablets/day for 2 weeks (n=73).

Arm 2: lysozyme chloride granules, 270–300 mg/day for 2 weeks (n=91).

Arm 3: tiaprofenic acid, 6 tablets/day for 2 weeks (n=99).

Arm 4: Alprazolam 0.4 mg, 3 tablets/day for 2 weeks (n=72).

Arm 5: dosulepin hydrochloride, 1–2 capsules/day for 2 weeks (n=59).

Arm 6: saibokuto (柴苓湯) extract granules (manufacturer unknown), 7.5 g/day for 2 weeks (n=100).

6. Main outcome measures

The percentage of patients whose discomfort in the throat disappeared, evaluated at weeks 0, 1, 2, and 3 after the start of treatment in patients with “constant discomfort” and patients with “frequent discomfort” in arms 1–6.

7. Main results

In arms 1, 2, and 5, “frequent discomfort” disappeared in a higher percentage of patients than did “constant discomfort,” showing that frequent discomfort is more tractable. In arms 3 and 6, there was no difference between the percentage of patients whose “frequent discomfort” disappeared and the percentage of patients whose “constant discomfort” disappeared. In arm 4, “frequent discomfort” disappeared in a higher percentage of patients than did “constant discomfort” during treatment, but “frequent discomfort” recurred in these patients at week 3.

8. Conclusions

“Constant discomfort” is not necessarily more intractable to treatment than “frequent discomfort.”

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This clinical trial is unique because it investigated the rate of response to each treatment separately in patients with “constant discomfort” and patients with “frequent discomfort,” but did not evaluate the efficacy of the investigational product over placebo. However, the number of participants varied among groups, and the method of allocation described in the paper as “randomly” allocated to treatment is not clear. Furthermore, the analysis population included only patients without adverse drug reactions and with available drug efficacy data. Indicating the method used to allocate the original medicines, reporting the number of dropouts, and evaluating the efficacy of the investigational product over placebo, would have improved this clinical trial.

12. Abstractor and date

Goto H, 17 August 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Yamagiwa M, Fujita K. Effect of treatment using lansoprazole on patients with an abnormal sensation in the throat and concomitant heart burn. *Jibi to Rinsho (Otologia Fukuoka)* 2007; 53: 109-15 (in Japanese with English abstract). Ichushi Web ID: 2007166411

1. Objectives

To evaluate the efficacy of lansoprazole in patients with pharyngolaryngeal paresthesia and acid reflux symptoms (compared with rikkunshito (六君子湯) as a control).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Two institutions including Matsusaka Chuo General Hospital, Japan.

4. Participants

Eighty-six patients with pharyngolaryngeal paresthesia and acid reflux symptoms who presented to the participating institutions between May 2003 and November 2005.

5. Intervention

Arm 1: administration of TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 2 weeks in 38 patients who started treatment on odd-numbered days.

Arm 2: administration of lansoprazole 15 mg/day for 2 weeks in 48 patients who started treatment on even-numbered days.

6. Main outcome measures

Pharyngolaryngeal discomfort and reflux symptoms.

7. Main results

Rates of excellent, moderate, mild, and no improvement in pharyngolaryngeal discomfort after 2 weeks of treatment were 29, 34, 11, and 26%, respectively, in arm 1 and 33, 27, 19, and 21%, respectively, in arm 2. The respective rates of improvement in heartburn/acid reflux symptoms were 57, 30, 3, and 10% in arm 1 and 89, 9, 0, and 2% in arm 2.

8. Conclusions

No conclusions were drawn from this data (the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper describes the efficacy of lansoprazole (compared with rikkunshito as a control) in patients with pharyngolaryngeal paresthesia and acid reflux symptoms. But, since the two treatment arms were not compared, the analysis seems to be incomplete. As the authors say they will publish a new paper describing the outcomes in detail for rikkunshito-treated patients, a follow-up report is anticipated.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

5. Psychiatric/Behavioral Disorders

Reference

Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of combination treatment of hatimi-zio-gan and Red Ginseng powder on unidentified clinical complaints - estimation of double blind comparative study in many hospitals -. *Therapeutic Research* 1989; 10:4951-65 (in Japanese). Ichushi Web ID: 1991057823 [MOL](#), [MOL-Lib](#)

1. Objectives

To clinically evaluate the symptom-relieving effects of hachimijiogan (八味地黄丸) alone, kojigin (紅参) alone, or in combination in elderly patients with underlying chronic disease.

2. Design

Double-blind randomized controlled trial using sealed envelopes for allocation (DB-RCT-envelope).

3. Setting

Eleven facilities belonging to the Matsuyama Red Ginseng Research Group, mainly including Kaneko Heart Clinic, Japan.

4. Participants

Fifty-four inpatients or outpatients at the above facilities with underlying hypertension, cerebrovascular disorder, arteriosclerosis, diabetes mellitus, hyperlipidemia, etc.

5. Intervention

Arm 1: KOTARO Hachimiganryo (八味丸料) Extract Granules 1 sachet (3.0 g) t.i.d. (after meals) (8 males, 9 females).

Arm 2: CHEONG-KWAN-JANG Kojigin (正官庄紅参) Powder 1 sachet (1.0 g) t.i.d. (after meals) (4 males, 15 females).

Arm 3: combination (mixture of 6.0 g of KOTARO Hachimiganryo (八味丸料) and 3.0 g of CHEONG-KWAN-JANG Kojigin Powder), 3 g t.i.d (after meals) (4 males, 14 females).

Two weeks of observation followed by 12 weeks of treatment.

6. Main outcome measures

Improvement in clinical symptoms: evaluation on a seven-point scale using a check sheet at baseline and 4, 8, and 12 weeks of treatment.

Relationship between clinical symptom improvement rating and *kyojitsu* (虚実, excess or deficiency) *sho* (証, pattern): comparison of therapeutic improvement rating with *kyojitsu* rating evaluated using an original *sho* scoring table.

Laboratory tests: hematology (red blood cell [RBC] count, hemoglobin, hematocrit value, etc.), serum biochemistry (glutamate oxaloacetate transaminase [GOT], glutamate pyruvate transaminase [GPT], lactate dehydrogenase [LDH], blood urea nitrogen [BUN], etc.) evaluated at baseline, and 4, 8, and 12 weeks of treatment.

7. Main results

Symptoms improved significantly or tended to improve in arm 2 and arm 3. Particularly, the combination therapy had the earliest and greatest therapeutic effect. Only the combination therapy had a significant therapeutic effect on cold limbs, numbness, and lightheadedness. In association with *kyojitsu sho*, *sho* tending towards *jitsusho* (実証, excess pattern) was associated with significantly higher subjective symptom improvement in the combination group ($r=0.61$, $P<0.05$). There were no changes in laboratory values or adverse drug reactions.

8. Conclusions

Both hachimijiogan and kojigin, particularly their combination, are useful for improving unidentified complaints in elderly patients with various chronic diseases. Furthermore, *sho* tending towards *jitsusho* is associated with the greater effect of the combination.

9. From Kampo medicine perspective

The larger effect of hachimijiogan and kojigin, which are intended for *kyosho* (虚証, deficiency pattern) and *jitsusho*, suggests that the empirically/traditionally defined rule does not apply in some cases.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

Underlying chronic diseases in the 54 patients enrolled in this study vary but all impair quality of life. This paper demonstrates that hachimijiogan/kojigin combination therapy can improve unidentified complaints in these patients. In this study, analysis was appropriately performed through symptom evaluation on a 7-point scale using a detailed health check list and data collection using a *sho* determination table reflecting the theory of Kampo medicine, and thus made the conclusion highly credible. Further valuable clinical studies on how to use *hojin* (補腎, kidney-tonifying) medicinals in the elderly are expected.

12. Abstractor and date

Ushiroyama T, 6 August 2008, 1 June 2010, 31 December 2013.

5. Psychiatric/Behavioral Disorders**Reference**

Sato Y, Horita H, Adachi N, et al. Effect of oral administration of prostaglandin E1 on erectile dysfunction. *British Journal of Urology* 1997; 80: 772-5.

1. Objectives

To compare the efficacy and safety of limaprost, an oral prostaglandin E1 derivative, with those of goshajinkigan (牛車腎気丸) in the treatment of erectile dysfunction.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to Department of Urology, Sapporo Medical University and Sanjukai Hospital), Japan.

4. Participants

Fifty patients with mild erectile dysfunction.

5. Intervention

Arm 1: treatment with goshajinkigan (牛車腎気丸; manufacturer, not specified) 2.5 g t.i.d. for 8 weeks (n=25; of these 24 were included for analysis).

Arm 2: treatment with limaprost 10 µg t.i.d. for 8 weeks (n=25; of these 24 were included for analysis).

6. Main outcome measures

Achievement of two consecutive vaginal penetrations, nocturnal penile tumescence measurements, and self-reported penile rigidity (0-5 points) and maintenance of erection (0-5 points).

7. Main results

Four of 24 analyzable patients in arm 1 and 11 of 24 in arm 2 achieved at least two consecutive vaginal penetrations; the rate of response was significantly higher in arm 2 than in arm 1 ($P<0.05$). However, not all patients who achieved vaginal penetrations experienced full erection. The mean increase of penile circumference was 6.0 ± 6.6 mm for 23 patients who had measurements in arm 2 and only 2.3 ± 5.8 mm for 21 patients in arm 1. The increase of penile circumference was significantly greater in arm 2 than in arm 1. There were no significant between-arm differences in the penile rigidity and maintenance of erection.

8. Conclusions

Limaprost, an oral prostaglandin E1 derivative, is more effective than goshajinkigan in the treatment of mild erectile dysfunction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One limaprost-treated patient developed facial flush.

11. Abstractor's comments

This study demonstrated that limaprost, an oral prostaglandin E1 analogue, was more effective than goshajinkigan in the treatment of mild erectile dysfunction. All patients in this study had achieved full erection after local injection of prostaglandin E. Limaprost resulted in a response in 45.1% of patients, but not in full erection. In this study, treatment assignment was in the order of patient presentation, but a randomized assignment is preferred.

12. Abstractor and date

Okabe T, 19 August 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Satoh T, Takahashi T, Iwasaki K, et al. Traditional Chinese Medicine on four patients with Huntington's disease. *Movement Disorders* 2009; 24 453-5.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in patients with Huntington's disease.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

Not mentioned (the first author belongs to the faculty of Yonezawa National Hospital), Japan.

4. Participants

Four female patients with Huntington's disease (aged 48, 51, 52, and 68 years).

5. Intervention

Arm 1: TSUMURA Yokukansan (抑肝散; dose, not specified) Extract Granules for 8 weeks, followed by 4 weeks of wash-out, then TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯; dose, not specified) Extract Granules for 8 weeks (n=2).

Arm 2: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯; dose, not specified) Extract Granules for 8 weeks, followed by 4 weeks of wash-out, then TSUMURA Yokukansan (抑肝散; dose, not specified) Extract Granules for 8 weeks (n=2).

6. Main outcome measures

Motor functions, cognitive functions, and activities of daily living were evaluated using the Unified Huntington's Disease Rating Scale - motor assessment (UHDRS-m), Mini-Mental State Examination (MMSE), and Barthel Index, respectively, at the start and end of yokukansan and saikokaryukotsuboreito treatments in both arms.

7. Main results

The UHDRS-m was decreased significantly during yokukansan treatment in all 4 patients (from 106.3±4.7 to 89.6±5.8; $P=0.0004$), but not significantly during saikokaryukotsuboreito treatment in 3 out of 4 patients (from 105.5±3.8 to 101±2.9). There were no changes in MMSE and Barthel Index after either treatment.

8. Conclusions

Yokukansan may improve motor function (UHDRS-m score) in patients with Huntington's disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no abnormal findings in hematology and blood biochemistry after the yokukansan or saikokaryukotsuboreito treatment.

11. Abstractor's comments

In this clinical study, the effects of yokukansan on Huntington's disease, an intractable disease, were objectively evaluated using the UHDRS-m. Videos are also available on this Journal website, thus the article may have a powerful impact on readers. Notably, the authors attempted to evaluate the effects of yokukansan in a cross-over design, despite the difficulties in collecting cases of this rare disease. However, in one of the four participants, improvement was greater during the saikokaryukotsuboreito treatment than during the yokukansan treatment. The results would be more valuable if the data had been analyzed rigorously as a cross-over design. Because there is no established treatment, it might be difficult to have a control group. Yet the use of non-Kampo medicine as a control should be considered. As the authors noted, in the future, a controlled trial with a larger number of patients should be conducted. Still, this study is meaningful in that it provided findings that suggest, albeit hypothetically, the efficacy of yokukansan for this rare disease with no remedy at present.

12. Abstractor and date

Goto H, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**References**

Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2009; 33: 308-11. 33: 308-11. Pubmed ID: 19138715

Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer's disease — Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. *No 21 (Brain 21)* 2009; 12: 446-51 (in Japanese). Ichushi Web ID: 2010037668, [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease

2. Design

Randomized controlled trial (RCT)

3. Setting

Kyushu University and its affiliated hospitals (number of institutions, not specified), Japan

4. Participants

Fifteen patients (2 males and 13 females, mean age 80.2±4.0 years) who were diagnosed with dementia and Alzheimer's disease based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and National Institute of Neurological and Communicative Disorders and Stroke / the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, respectively, and had a Mini-Mental State Examination (MMSE) score of 6 to 23 and a Neuropsychiatric Inventory (NPI) score of 6 or higher after 2 weeks of pre-study treatment with sulpiride 50 mg/day

5. Intervention

Arm 1: Continuation of oral sulpiride 50 mg/day plus treatment with oral yokukansan (抑肝散; manufacturer, not specified) 2.5 g (containing 1.5 g of extracts) t.i.d. for 12 weeks (n=10)

Arm 2: Continuation of oral sulpiride 50 mg/day alone (n=5).

During the evaluations performed every 4 weeks, the dose of sulpiride was increased when any NPI subscore was 8 or higher and decreased when all NPI subscores were below 4.

6. Main outcome measures

BPSD and cognitive functions were evaluated using the NPI and MMSE, respectively. The Barthel Index was used for the evaluation of activities of daily living. Patients were evaluated at baseline, 4, 8, and 12 weeks.

7. Main results

One patient in arm 2 was excluded due to severe edema. NPI was significantly improved at 8 and 12 weeks compared with the baseline in arm 1 ($P<0.001$), whereas no change was observed in arm 2. The dose of sulpiride at 12 weeks was less, but not significantly less, in arm 1 than in arm 2. There were no changes in MMSE and Barthel Index from the baseline in both arms.

8. Conclusions

Yokukansan improves BPSD in elderly patients with Alzheimer's disease and can reduce the dose of antipsychotics.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Hypokalemia was reported in 2 patients in arm 1. In addition, extrapyramidal symptoms developed and the dose of sulpiride was decreased from 150 mg/day to 100 mg/day in one patient in arm 1.

11. Abstractor's comments

This is a valuable clinical study that evaluated the efficacy of yokukansan in elderly patients with Alzheimer's disease over 12 weeks from various aspects, including behavioral and psychological symptoms, cognitive functions, and activities of daily living. Because patients in both arms were prescribed sulpiride at baseline and yokukansan was evaluated in an add-on design, there is a possibility that the efficacy of yokukansan alone was not adequately evaluated. The differences in NPI and MMSE score from those in arm 2 were not significant owing to the small number of patients. However, the trend in these scores over time suggests that significant improvements over baseline might be found if more patients were included. Even in a small population, it is suggested that yokukansan may improve NPI and reduce the dose of antipsychotics. In the future, the efficacy of yokukansan in the field of psychiatry could be more convincingly demonstrated by increasing the number of patients and selecting the appropriate control agent.

12. Abstractor and date

Goto H, 1 June 2010, 1 February 2011, 31 December 2013

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Okahara K, Ishida Y, Hayashi Y, et al. Effects of yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2010; 34: 532–6. CENTRAL ID: CN- 00752183, Pubmed ID: 20170698

1. Objectives

To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Hospitals and Clinics in Miyazaki and Kagoshima prefecture, 12 institutions, Japan.

4. Participants

Sixty-three outpatients were registered from July 2006 to December 2008 and met the following inclusion criteria: 1) have dementia and a diagnosis of Alzheimer's disease (including mixed-type dementia), 2) show at least one symptom score ≥ 4 in the Neuropsychiatric Inventory (NPI) subscales, 3) aged ≤ 85 years, 4) taking donepezil hydrochloride for at least 4 weeks.

5. Intervention

Arm 1: administration of TSUMURA Yokukansan (抑肝散) Extract Granules, 2.5 g t.i.d. for 4 weeks (n=30).

Arm 2: no administration (n=33).

6. Main outcome measures

Evaluations of BPSD using the NPI subscales (delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity), cognitive function by the Mini-Mental State Examination (MMSE), activities of daily living (ADL) by the Disability Assessment of Dementia (DAD), burden of caregivers by the Zarit Burden Interview, caregiver's depression by the Self-rating Depression Scale (SDS) at the start and at 4 weeks of the study.

7. Main results

One patient in arm 1 and one patient in arm 2 withdrew, and the efficacy analysis set included 29 patients in arm 1 and 32 patients in arm 2. Inter-group comparison revealed significantly more improvement in arm 1 compared with arm 2 in the total NPI score after 4 weeks of treatment ($P < 0.05$). On analysis of individual NPI subscale scores, significant improvement was observed for agitation and irritability in arm 1 compared to arm 2 ($P < 0.05$). Intra-group comparison of values at the start and at 4 weeks of treatment identified a significant improvement in the NPI total score in arm 1 ($P < 0.05$). Analysis of each NPI subscale scores at baseline and after 4 weeks of treatment demonstrated significant improvement in delusions, agitation, dysphoria, anxiety, apathy, or irritability in arm 1 ($P < 0.05$), and in apathy in arm 2 ($P < 0.05$). Inter-group and intra-group comparisons found no changes in MMSE, DAD, Zarit Burden Interviews, or SDS.

8. Conclusions

Yokukansan significantly accelerates improvement in BPSD in patients with Alzheimer's disease treated with donepezil.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None of the patients had any adverse reactions to yokukansan such as decreased serum potassium or edema.

11. Abstractor's comments

This is a clinical trial to determine the efficacy of yokukansan for dementia in patients with Alzheimer's disease treated with donepezil by evaluating its effect on behavioral and psychological symptoms. The result of the clinical trial can be applied immediately to daily practice. Despite improvement in NPI scores, scores reflecting the burden of caregivers were not improved. To assess this effect, further studies with larger sample size and longer study period would be necessary. However, as no drugs effective for peripheral symptoms of dementia are presently available, demonstration of the efficacy of yokukansan is a great achievement.

12. Abstractor and date

Goto H, 27 December 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Furuhashi Y. Comparative efficacy of risperidone versus yokukansan (抑肝散) on behavioral and psychological symptoms of dementia in patients with Alzheimer's disease. *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 120–1 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD)

2. Design

Randomized controlled trial (RCT).

3. Setting

Asahi Hospital, units of psychiatry, psychosomatic internal medicine, and geriatric psychiatry, Japan.

4. Participants

Twenty patients admitted to the hospital between January 2008 and January 2009 who met Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) or International Classification of Diseases (ICD) criteria for Alzheimer's disease.

5. Intervention

Arm 1: yokukansan (抑肝散) (manufacturer not specified) 7.5 g/day for 4 weeks (n=10)

Arm 2: risperidone 0.5 mg/day for 4 weeks (n=10)

6. Main outcome measures

Neuropsychiatric Inventory (NPI; for psychological symptoms) and the Cohen-Mansfield Agitation Inventory (CMAI; for behavioral symptoms) were used for evaluation.

7. Main results

Significant improvements in NPI scores and CMAI scores were observed in both the risperidone arm and yokukansan arm ($P<0.01$).

8. Conclusions

Both yokukansan and risperidone have a similar effect on BPSD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Sedation, malaise, drowsiness, and constipation were reported in arm 2, but no adverse events were reported in arm 1.

11. Abstractor's comments

This paper discusses the effect of yokukansan on the peripheral symptoms of Alzheimer's disease. More and more patients with dementia are being treated with yokukansan, and this paper reflects this recent trend. From the viewpoint of Kampo medicine, yokukansan is expected to reduce anger. Most anticipated is the efficacy of yokukansan on peripheral symptoms, especially on agitation, which should alleviate the burden on caregivers. Though no data were shown, this paper stated that yokukansan significantly improved CMAI scores for aggressive behaviors such as beating, kicking, grabbing, scratching, and breaking, and unaggressive behaviors such as repeating the same action over and over and asking questions continuously. These seem to be the exact effects of yokukansan. A precise report with details is awaited.

12. Abstractor and date

Nakata H, 12 January 2011, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Higashi K, Rakugi H, Yu H, et al. Effect of kihito extract granules on cognitive function in patients with Alzheimer's-type dementia. *Geriatrics & Gerontology International* 2007; 7: 245-51. Ichushi Web ID: 2008113647

1. Objectives

To evaluate the efficacy and safety of kihito (帰脾湯) for Alzheimer-type dementia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Hanwa Daini Senboku Hospital, Japan.

4. Participants

Seventy-five elderly patients diagnosed with Alzheimer's disease according to DSM-IV criteria, with Hachinski ischemic score of ≤ 4 points and Mini-Mental State Examination (MMSE) score of 10–26 points. Patients with marked hypertension, diabetes, hypercholesterolemia, heart disease, renal failure, or depression, or MRI findings of marked cerebral infarction were excluded.

5. Intervention

Arm 1: no treatment, n=20.

Arm 2: oral administration of 2.5 g of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules t.i.d. after meals for 3 months, n=24.

Arm 3: Oral administration of 2.5 g of TSUMURA Kihito (帰脾湯) Extract Granules t.i.d. after meals for 3 months, n=20.

6. Main outcome measures

MMSE score, activities of daily living (ADL) evaluated in all patients at baseline and 3 months. Brain blood flow measured by single photon emission computed tomography (SPECT) in 6 patients in arm 2 and 4 patients in arm 3 at baseline and 3 months (selection criteria for performing SPECT not indicated).

7. Main results

Of 75 participants, 64 were included in the analysis population. MMSE score in arm 3 was significantly improved from baseline at 3 months and was also significantly improved compared with arm 1 and arm 2. In particular, disorientation and attentiveness were markedly improved. There were no among-arm differences in ADL and between baseline and 3 months. SPECT revealed no obvious changes in brain blood flow.

8. Conclusions

Kihito is an effective treatment for Alzheimer-type dementia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in arm 2 experienced diarrhea and 1 patient in arm 3 increased blood pressure, leading to discontinuation of treatment.

11. Abstractor's comments

This excellent clinical study investigated and demonstrated the efficacy of kihito for Alzheimer's dementia using a non-Kampo-treatment and goshajinkigan as controls. The authors selected goshajinkigan as a control because of its *onji*-free composition and the lack of reports showing an effect on cognitive function. However, since the efficacy of hachimijiogan, containing goshajinkigan ingredients other than gohitsu and shazenshi, for elderly dementia has already been reported (Iwasaki K, Kanbayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "Ba wei di huang wan" in the treatment of dementia. *Journal of the American Geriatrics Society* 2004; 52: 1518-21.), goshajinkigan was considered inappropriate for a control, although the results showed significantly improved MMSE score only with kihito. Furthermore, although they attribute, in the discussion, the absence of a difference in brain blood flow to the small sample size, information on selection criteria for performing SPECT would be necessary. The number of dropouts in arm 1 should be indicated. Although these details were omitted, this clinical research demonstrated the efficacy of kihito for treatment of dementia, and investigation of the mechanism of action and long-term effect using a larger sample size is expected.

12. Abstractor and date

Goto H, 28 November 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Maruyama T. Goshuyuto versus lomerizine hydrochloride in the prophylactic treatment of migraine headaches: an open crossover trial.. *Itami to Kampo (Pain and Kampo Medicine)* 2006; 16: 30-9 (in Japanese with English abstract). Ichushi Web ID: 2006303125

1. Objectives

To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for treatment of migraine.

2. Design

A crossover randomized controlled trial (RCT-crossover).

3. Setting

No description of the setting is available; the authors belong to the Department of General Medicine, Iida Municipal Hospital, Japan.

4. Participants

Fourteen patients with at least a 1-year history of migraine and suffering a mean of 3 or more migraine attack events monthly.

5. Intervention

Arm 1: Oral administration of lomerizine hydrochloride 5 mg 5 mg b.i.d. for 28 days, followed by a wash-out period of two weeks, and then oral administration of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g t.i.d. for 28 days (n=7).

Arm 2: Oral administration of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g t.i.d. for 28 days, followed by a wash-out period of two weeks, and then oral administration of lomerizine hydrochloride 5 mg b.i.d. for 28 days (n=7).

Oral triptans to treat migraine attacks were allowed.

6. Main outcome measures

Frequency of migraine attacks, visual analogue scale (VAS) score, number of triptan oral tablets used, response to a triptan (time to relieve attacks), evaluated in the pretreatment period (28 days), course 1 (28 days), withdrawal period (14 days), course 2 (28 days), and final period (28 days).

7. Main results

Differences in measures of drug efficacy (i.e., frequency of migraine attacks, VAS peak value, and number of triptan oral tablets used) were greater in goshuyuto group than in lomerizine hydrochloride group.

8. Conclusions

Goshuyuto is more effective for migraine attacks than lomerizine hydrochloride.

9. From Kampo medicine perspective

As indications of goshuyuto, the following *shoes* were identified: *genchimyaku* (弦遲脈, string-like, slow pulse), *katsuhakutai* (滑白苔, slippery white tongue coating), *shinsuion* (振水音, splashing sounds in the stomach), *shinkahikou* (心下痞鞭, stiffness and rigidity below the heart), *shishikanrei* (四肢厥冷, reversal cold of the limbs) in 71.4, 57.1, 64.3, 85.7, and 100% of patients.

10. Safety assessment in the article

While 2 patients receiving lomerizine hydrochloride experienced sleepiness, none receiving goshuyuto experienced any adverse drug reactions.

11. Abstractor's comments

This excellent clinical study investigated the effect of goshuyuto on migraine using lomerizine hydrochloride as the control and demonstrated that it prevented migraine attacks. However, the author stated in the discussion of his paper that lomerizine hydrochloride used as the control was weaker than reported in previous clinical research. Therefore, it would be necessary to determine whether migraine was correctly diagnosed in participants and whether response to previous oral treatment with lomerizine hydrochloride was poor. Furthermore, in arm 2, goshuyuto was received in course 1, and the frequency and severity of migraine attack had not returned to baseline levels by the start of lomerizine in course 2, suggesting that the pace of withdrawal was too rapid. This may explain the stronger effect of goshuyuto in arm 1 (patients who received goshuyuto in course 2). Moreover, compliance with goshuyuto treatment (74%) was significantly lower than compliance with lomerizine hydrochloride treatment (93%), warranting improvement in future compliance. Nevertheless, this research demonstrated that goshuyuto prevented migraine, and further investigation of its efficacy is expected with various prescriptions.

12. Abstractor and date

Goto H, 17 November 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Matsushita M, Saito M, Katayama S, et al. Clinical evaluation of DS-4773 on sedative effect: a cross-over trial. *Yakuri to Chiryō (Japanese Pharmacology & Therapeutics)* 1994; 22: 2371–82 (in Japanese). Ichushi Web ID: 1995083169

1. Objectives

To evaluate the efficacy and safety of DS-4773 for sedation versus sansoninto (酸棗仁湯) used as control.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

The Department of Neurology and Psychiatry, University of Tokyo Hospital, departments of psychiatry of 5 hospitals, and 2 clinics, Japan.

4. Participants

Seventy-nine male and female patients (≥ 15 years old) with medical histories taken by specialists in the fields of internal medicine, psychosomatic medicine, or psychiatry and any of the following five complaints: insomnia, daytime irritability, daytime bad mood, daytime hypobulia, and lack of refreshing sleep.

5. Intervention

Arm 1: oral administration of DS-4773 (containing 0.5 g dried extract of sansonin [酸棗仁], 0.1 g dried extract of bukuryo [茯苓], and 0.2 g of sanshishi [山梔子]) granules 1 sachet (1 g) b.i.d. before breakfast and before bedtime for 2 weeks (n=79).

Arm 2: oral administration of sansoninto (酸棗仁湯) extract granules for medical use (manufacturer unknown) 1 sachet (3.75 g) b.i.d. before breakfast and before bedtime for 2 weeks (n=79).

6. Main outcome measures

Ease of falling asleep, depth of sleep, mood on awakening, daytime mood, daytime physical condition, daytime motivation, anorexia, constipation and diarrhea, rated on a 4-point scale.

7. Main results

After exclusions and withdrawals, 59 patients were included in the analysis population. Slight or more improvement was reported in 63.5%/51.9% of patients (arm 1/arm 2) for ease of falling asleep, 63.6%/45.5% for depth of sleep, 64.9%/50.9% for mood on awakening, 50.0%/37.5% for daytime mood, 47.4%/38.6% for daytime physical condition, 35.8%/26.4% for daytime motivation, 27.8%/23.2% for anorexia, 41.2%/35.3% for constipation, and 100%/75.0% for diarrhea. Group comparison revealed a significant improvement in the ease of falling asleep, depth of sleep, mood on awakening, daytime physical condition, and daytime motivation in arm 1 compared with arm 2.

8. Conclusions

DS-4773 is more efficacious than sansoninto extract granules for sedation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Safety was evaluated in 68 patients. No adverse reactions were noted in 64 patients receiving DS-4773 (94.1%) and 61 patients receiving sansoninto (89.7%). Adverse reactions requiring treatment discontinuation were palpitations, dizziness, and anxiety, each occurring in 1 patient.

11. Abstractor's comments

This is a well-designed clinical study with a cross-over design. It investigated the efficacy of DS-4773 using sansoninto extract granules as control. However, lack of a washout period between treatments may have resulted in carry-over effects of the first drug. Furthermore, 7 patients receiving DS-4773 and 1 patient receiving the control drug were noncompliant at the time of either inclusion or exclusion after 2 weeks of treatment, suggesting that more participants received DS-4773 first and this may have contributed to the greater efficacy of DS-4773. In the section on concomitant drugs, combinations with hypnotics were used to treat persistent sleep disorder, suggesting that the hypnotic may have improved the efficacy of the investigational product. The contribution of concomitant drugs to the efficacy of DS-4773 should be evaluated to better determine the actual efficacy of this Kampo medicine.

12. Abstractor and date

Goto H, 18 August 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**References**

Zhuang H.Y., Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation of normal young adults. *Shinkei Seishin Yakuri (Japanese Journal of Neuropsychopharmacology)* 1992; 14: 319–25 (in Japanese with English abstract). Ichushi Web ID: 1994094031

Hagino H, Kim Y, Kurachi M, et al. Effect of kakkon-to on sleepiness after sleep deprivation with quantitative EEG method. *Noha to Kindenzu (Japanese Journal of Electroencephalography and Electromyography)* 1995; 23: 361–7 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of kakkonto (葛根湯) on sleepiness after sleep deprivation.

2. Design

Double blinded randomized cross-over controlled trial (DB-RCT-cross over).

3. Setting

Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital, Japan.

4. Participants

Seven healthy female students (aged 20 or 21 years).

5. Intervention

Arm 1: oral administration of Kanebo Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals on day 2 of the experiment. After one month of washout, oral administration of placebo (lactose) 2.5 g t.i.d. before meals on the second day of the experiment (n=3).

Arm 2: oral administration of placebo (lactose) 2.5 g t.i.d. before meals on day 2 of the experiment After one month of washout, oral administration of Kanebo Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals on day 2 of the experiment (n=4).

6. Main outcome measures

Subjective sleepiness (Sleepiness Scale), Critical Flicker Frequency (CFF), Multiple Sleep Latency Test (MSLT), blood pressure, heart rate, body temperature, and electroencephalogram (EEG).

7. Main results

An hourly comparison revealed significantly less subjective sleepiness in arm 1 than in arm 2 at 10:00 a.m. on day 2 of the experiment ($P<0.05$). No between-arm differences were found in the mean values for CFF, MSLT, subjective sleepiness, blood pressure, heart rate, and body temperature. The mean latency in the MSLT value was significantly longer in kakkonto group than in placebo group ($P<0.05$). The calculated relative power contribution ratio at each frequency band was reported significantly lower δ at 16:00 and 18:00 and significantly higher α at 16:00 in the kakkonto group than in the placebo group.

8. Conclusions

Kakkonto is effective for relieving sleepiness after sleep deprivation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an excellent clinical study report by Zhuang et al (1992) investigating the effect of kakkonto on sleepiness after sleep deprivation using a cross-over design and subjective sleepiness and objective measures, e.g., EEG, for evaluation. However, as discussed by the authors, kakkonto was deemed effective on the basis of different measures at different hours, making sleepiness difficult to evaluate. In addition, the attempts to blind the participants to treatment allocation, including administration with a soft drink, were inadequate. Ideally, encapsulation should have been used. Significant differences in some measures have been shown in a larger sample size. Nevertheless, this is an interesting report elucidating the efficacy of a Kampo medicine. The original article by Hagino et al (1995) included an analysis of EEG results..

12. Abstractor and date

Goto H, 19 August 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's disease)**Reference**

Yamada K, Kanba S, Ohnishi K, et al. Clinical effectiveness of oren-gedoku-to for sleep disorder associated with acute schizophrenia and other psychotic disorders. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1997; 47: 827-31 (in Japanese with English abstract). [CiNii](#)

1. Objectives

To evaluate the efficacy of orengekuto (黄連解毒湯) for sleep disorder associated with acute psychotic disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

No study site was specified (authors belonged to the Kampo Clinic, School of Medicine, Keio University and/or Department of Neuropsychiatry, School of Medicine, Keio University), Japan.

4. Participants

Eighteen untreated male patients who were diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or brief psychotic disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, and had sleep disorder among their chief complaints.

5. Intervention

Arm 1: standard therapy with haloperidol in combination with oral treatment with TSUMURA Orengekuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=9).

Arm 2: only standard therapy with haloperidol for 4 weeks (n=9).

6. Main outcome measures

Dose of nitrazepam used as needed for insomnia; assessment of schizophrenic symptoms by the Brief Psychiatric Rating Scale (BPRS).

7. Main results

In assessment of schizophrenic symptoms, there was no between-arm difference. In addition, there was no significant between-arm difference in the oral dose of nitrazepam.

8. Conclusions

In patients with sleep disorder associated with acute schizophrenia and other psychotic disorders, orengekuto used in combination with the antipsychotic tends to improve thought disorder and decrease the dose of nitrazepam.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This is an interesting clinical study comparing the effect of antipsychotic in combination with orengekuto for sleep disorder associated with acute schizophrenia, etc. with the effect of antipsychotic alone. While it was stated in the Methods section that "in both groups, haloperidol was the only antipsychotic used, and biperiden was the only anti-parkinson agent used", the number of patients treated with each drug was not specified. In addition, it was stated that "the attending physician initiated standard therapy with haloperidol in the presence or absence of concomitant orengekuto", failing to provide information on patients treated with each of these two drugs. Moreover, the statement "tended to improve schizophrenic thought disturbance and decrease the dose of nitrazepam" indicating that there was no significant difference between the orengekuto group and control group, was inconsistent with the statement in the Abstract that "additional treatment with orengekuto may be effective for sleep disorder". Nevertheless, this is a meaningful clinical study in determining the efficacy of Kampo medicine in this field because it suggests the possibility that the efficacy of orengekuto for sleep disorder could be demonstrated by a larger study.

12. Abstractor and date

Goto H, 11 September 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Aizawa R, Kanbayashi T, Saito Y, et al. Effects of yoku-kan-san-ka-chimpi-hange on the sleep of normal healthy adult subjects. *Psychiatry and Clinical Neurosciences* 2002; 56: 303-4 CENTRAL ID: CN-00444122, Pubmed ID: 12047606, Ichushi Web ID: 2003024669

1. Objectives

To evaluate the efficacy of yokukansankachimpihange (抑肝散加陳皮半夏) for sleep disorders.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Not mentioned (probably the Akita Red Cross Hospital), Japan.

4. Participants

Of 20 normal healthy men receiving yokukansankachimpihange before the start of the study, 7 with sleep disorders favorably affected were selected for the study.

5. Intervention

Arm 1: oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of anchusan (安中散) extract for 3 days.

Arm 2: oral administration of anchusan (安中散) extract (manufacturer, dosage, and dosing frequency unknown) for 3 days followed by 1-week withdrawal and then by oral administration of yokukansankachimpihange (抑肝散加陳皮半夏) extract product for 3 days.

(The grouping method for the 7 subjects is not indicated).

6. Main outcome measures

Sleep time, sleep latency, sleep depth, and rapid eye movement (REM) sleep time.

7. Main results

Total sleep time was significantly prolonged in arm 1 (438±13 min vs 371±19 min in arm 2).

8. Conclusions

Yokukansankachimpihange increases sleep time.

9. From Kampo medicine perspective

Seven subjects responding to yokukansankachimpihange were selected for the double-blind study.

10. Safety assessment in the article

No adverse drug reactions occurred in either group.

11. Abstractor's comments

This study, which investigated the efficacy of yokukansankachimpihange for sleep in a double-blind RCT, provides high-quality evidence. However, giving participants yokukansankachimpihange as pretreatment and using anchusan (which has a similar taste) as the control may have compromised blinding. Nevertheless, the research content is advantageous in that it involved objective evaluation of sleep using all-night polysomnography. Investigation with a larger sample size is expected.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)**References**

Kimura H, Otake T, Ishikura H. Efficacy of shakuyakukanzoto for relieving facial spasm*. *Shindan to Chiryō (Diagnosis and Treatment)* 1991; 79: 2505–8 (in Japanese).

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving facial spasm.

2. Design

Randomized controlled trial (RCT).

3. Setting

Outpatient department of anesthesia of one hospital, Japan.

4. Participants

Twenty patients visiting hospital with facial spasm (3 males and 17 females; mean age, 58.3 years), all receiving a centrally-acting muscle relaxant (afloqualone, tolperisone hydrochloride, and tizanidine hydrochloride in 15, 3 and 2 patients, respectively) and minor tranquilizer (diazepam and etizolam in 11 and 9 patients, respectively).

5. Intervention

Arm 1: administration of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 7.5 g/day in 9 patients and 5.0 g/day in 1 patient (2 males and 8 females).

Arm 2: no administration of shakuyakukanzoto (芍薬甘草湯) (1 male and 9 females).

6. Main outcome measures

Severity of spasm rated before and 4, 8, 12, and 16 weeks after the start of treatment on a 4-point scale (disappeared, rare, repetitive, persistent).

7. Main results

There was no difference in baseline severity between arms. The severity in both arms decreased with time resulting in no significant between-arm differences at 4 and 8 weeks and significantly larger decrease in severity in arm 1 at 12 and 16 weeks (12 weeks, $P<0.05$; 16 weeks, $P<0.05$).

8. Conclusions

Combination of shakuyakukanzoto with a centrally-acting muscle relaxant and minor tranquilizer significantly decreases severity of facial spasm.

9. From Kampo medicine perspective

The authors state that “shakuyakukanzoto can be used without considering *sho* (証, pattern), which should be usually taken into account in prescribing a Kampo formulation, suggesting its usefulness for facial spasma.”

10. Safety assessment in the article

No adverse drug reactions suspected to be attributable to shakuyakukanzoto occurred.

11. Abstractor's comments

First, this study is respectable for conducting an RCT of a Kampo medicine in 1991, when the term evidence-based medicine had only just emerged. From the perspective of CONSORT statement, however, this study raises some concerns; the drugs and their doses differed between arms, suggesting that the study may have been biased. It is not known whether the study was blinded. A study with a more rigorous design to re-evaluate efficacy is expected.

12. Abstractor and date

Tsuruoka K, 23 September 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)

Reference

Sekine R, Watanabe H, Mimura M, et al. The effects of gosha-jinki-gan on the low back pain and lower limb pain caused by the lumbar spine: A comparison of Gosha-jinki-gan with Benfotiamine. *Itami to Kampo (Pain and Kampo Medicine)* 2003; 13: 84-7 (in Japanese with English abstract). Ichushi Web ID: 2006247217

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for treatment of lumbar (low back) and leg pain.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One general hospital and one university hospital, Japan.

4. Participants

Twenty patients with lumbar degeneration (aged 60 years or older) with a chief complaint of low back and leg pain persisting over 6 months.

5. Intervention

Arm 1: oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks, followed by oral administration of 75 mg/day of benfotiamine for 4 weeks (n=10).

Arm 2: oral administration of 75 mg/day of benfotiamine for 4 weeks, followed by oral administration of 7.5 g/day of goshajinkigan (牛車腎気丸) extract granules for 4 weeks (n=10).

In each group, one patient experienced gastrointestinal symptoms following administration of goshajinkigan (牛車腎気丸) and was excluded from the statistical analysis.

6. Main outcome measures

Subjective symptoms (low back pain at rest, low back pain with motion, leg pain at rest, leg pain with motion, leg numbness, and leg fatigue), and clinical laboratory tests (hematology, blood biochemistry, and urinalysis).

7. Main results

Subjective symptoms – low back pain at rest, low back pain with motion, and leg numbness – were significantly improved after administration of goshajinkigan, compared with benfotiamine.

8. Conclusions

Goshajinkigan is more effective than benfotiamine, a vitamin B1 derivative, in the treatment of lumbar (low back) and leg pain.

9. From Kampo medicine perspective

In each arm, 6 patients with *jinkyō* (腎虚, kidney deficiency) were included. No difference was observed in the efficacy between patients with and without *jinkyō*.

10. Safety assessment in the article

Of 20 patients receiving goshajinkigan, 2 experienced gastrointestinal symptoms, which led to discontinuation of treatment. Hematology/biochemistry tests and urinalysis revealed no abnormalities in either arm.

11. Abstractor's comments

This study suggests the efficacy of goshajinkigan for low back and leg pain. To confirm that efficacy is not influenced by the presence of *jinkyō*, a clinical trial with a larger sample size is recommended.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 1 June 2010.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Miyabe Y, Taniguchi C, Kawashima M, et al. Effect of Kampo medicines (sokeikakketsuto, shakuyakukanzoto) for taxol-caused peripheral nerve disorder – evaluation by current perception threshold measured by Neurometer®. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2006; 23: 65-8 (in Japanese).

1. Objectives

To evaluate the potential use of sokeikakketsuto (疎経活血湯) and shakuyakukanzoto (芍薬甘草湯) in preventing peripheral nerve disorder in patients receiving taxol.

2. Design

A randomized crossover controlled trial (RCT-crossover).

3. Setting

Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, University Hospital, Japan.

4. Participants

Seven patients who received monthly paclitaxel–carboplatin (TJ) as the initial anticancer therapy (18 cycles) for gynecological malignant tumors (ovarian cancer, uterine cervical cancer, and endometrial cancer) at the above facility between April 2002 and March 2005.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: monthly TJ + oral administration of Kampo medicines (sokeikakketsuto (疎経活血湯), shakuyakukanzoto (芍薬甘草湯)) (manufacturer unknown) before meals for 14 days before and after TJ therapy.

Arm 2: monthly TJ.

6. Main outcome measures

Current perception threshold (CPT) measured by Neurometer® (2000 Hz, 250 Hz, and 5 Hz) 7 days before and 7 days after the start of TJ therapy: CPT value.

7. Main results

The value (predose CPT – postdose CPT)/predose CPT × 100 (%) decreased after TJ therapy, indicating deteriorating perception without Kampo treatment but remained unchanged with Kampo treatment.

8. Conclusions

TJ therapy when combined with Kampo medicines (sokeikakketsuto, shakuyakukanzoto), but not TJ therapy alone, reduces the severity of peripheral nerve disorder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Administration of medicines caused no adverse drug reactions.

11. Abstractor's comments

This is a valuable study verifying the efficacy of sokeikakketsuto and shakuyakukanzoto for peripheral nerve disorder, an occasional adverse reaction to anticancer drug treatment that is evaluated by current perception threshold measurement. However, considering the small sample size (7 subjects), individual characteristics may greatly affect and bias the results; thus, increased number of cases may change the results. It is also important to ensure symptoms are consistent and relief of actual symptoms is documented by measured values, warranting continued research efforts. Furthermore, logically, the effect of a Kampo medicine is not constant but depends on the physical status of the host in each cycle of anticancer therapy. Therefore, identification of the “*sho*” (証, pattern) of each individual in each cycle is recommended to investigate the correlation between pathological analysis in Kampo medicine and the objective evaluation by current perception threshold used in this study. This may lead to proper usage of Kampo medicines and establishment of highly effective regimens in cancer treatment.

12. Abstractor and date

Ushiroyama T, 19 December 2008, 1 June 2010, 31 December 2013.

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Nishioka M, Shimada M, Kurita N, et al. The Kampo medicine, goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. *International Journal of Clinical Oncology* 2011; 16: 322–7. CENTRAL ID: CN-00812737, Pubmed ID: 21258836

1. Objectives

To clarify the efficacy and adverse effects of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by oxaliplatin therapy for advanced or recurrent colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokushima Hospital, Japan.

4. Participants

Forty-five outpatients who received mFOLFOX6 (oxaliplatin + l-LV + 5FU) therapy for advanced colorectal cancer from Jan. 2007 to Dec. 2009. Each patient had performance status (PS) 0–2, and no patient had bone marrow, hepatic, renal, or cardiac function abnormalities, clinical neuropathy, diabetes, alcohol-related diseases, or brain lesions.

5. Intervention

Arm 1: TSUMURA Goshajinkigan Extract Granules (7.5 g/day, in 2 or 3 divided doses) in combination with mFOLFOX6 therapy (n=22).

Arm 2: mFOLFOX6 therapy alone (n=23).

6. Main outcome measures

Incidence of grade 3 peripheral neuropathy, percentage of patients who developed grade 2 or 3 peripheral neuropathy after each treatment period, grade 3 adverse effects other than peripheral neuropathy, and modification of the effects of mFOLFOX6 therapy. (Peripheral neuropathy was assessed according to DEB-NTC [Neurotoxicity Criteria of Debiopharm]).

7. Main results

There were no significant differences in background factors between groups (age, gender, PS, proportion of rectal/colon cancer, site of metastasis, proportion of previously treated patients, proportion of patients taking bevacizumab in combination, number of completed courses, and cumulative oxaliplatin dose). Grade 3 peripheral neuropathy incidence was significantly lower in arm 1 than arm 2 ($P < 0.01$) and percentage of patients with grade 2 and 3 peripheral neuropathy at the beginning of each course was lower in arm 1. However, goshajinkigan did not modify the incidence of other adverse effects (grade 3) or therapeutic effects of mFOLFOX6 therapy.

8. Conclusions

Goshajinkigan decreased the incidence of severe peripheral neuropathy induced by mFOLFOX6 therapy (oxaliplatin + l-LV + 5FU) in patients treated for non-resectable or recurrent colon cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects mentioned.

11. Abstractor's comments

The recent advent of oxaliplatin has been a major advance in the chemotherapy of colorectal cancer. Because peripheral neuropathy is the main dose-limiting toxicity of the therapy, its prevention is vital to improve the effectiveness of chemotherapy. Varieties of options have so far been tested in vain. The present trial suggested that goshajinkigan effectively decreased the incidence of severe peripheral neuropathy induced by mFOLFOX6. But it did not improve the prognosis of the patients, because it did not extend the treatment period of mFOLFOX6. We look forward to the investigations of the mechanisms of action of goshajinkigan for peripheral neuropathy as well as the establishment of the measures to increase the courses of mFOLFOX6 for colorectal cancer.

12. Abstractor and date

Hoshino E, 1 December 2012

6. Nervous System Diseases (including Alzheimer's Disease)**Reference**

Kaku H, Kumagai S, Onoue H, et al. Objective evaluation of the alleviating effects of goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study. *Experimental and Therapeutic Medicine* 2012; 3: 60-5. Pubmed ID: 22969845

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for peripheral neuropathy induced by chemotherapy (paclitaxel and carboplatin) for uterine and ovarian cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Obstetrics and gynecology departments at four university hospitals (Iwate Medical University, Tottori University, Kitasato University, and Keio University), Japan.

4. Participants

Twenty-nine patients (20–70 years old) with peripheral neuropathy rated grade 1 or higher under the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and treated with paclitaxel/carboplatin after uterine or ovarian cancer had been histologically diagnosed.

5. Intervention

Arm 1: oral administration of vitamin B12 (1.5 g/day) and TSUMURA Goshajinkigan (牛車腎気丸) (7.5 g/day) (n=14).

Arm 2: oral administration of vitamin B12 (1.5 g/day) (n=15).

6. Main outcome measures

Visual analogue scale (VAS) evaluation of subjective numbness symptoms at 0, 3, and 6 weeks.

Rating of peripheral neuropathy (movement and sensation) under the NCI-CTCAE at 0, 3, and 6 weeks.

Evaluation of subjective peripheral neuropathy symptoms using the Functional Assessment of Cancer Treatment (FACT)-Taxane questionnaire at 0, 3, and 6 weeks.

Measurement of the current perception threshold (CPT) range in both index fingers at 0, 3, and 6 weeks.

7. Main results

There was no significant difference between groups at 0, 3, or 6 weeks in the VAS score for numbness and FACT-Taxane score for peripheral neuropathy (movement and sensation), or peripheral neuropathy symptoms. Peripheral neuropathy (sensation) was rated grade 3 under the NCI-CTCAE at 6 weeks in 2 patients of arm 2; however, no patient in arm 1 scored grade 3 or higher at 6 weeks. There was no significant difference between groups for the CPT range.

The frequency of abnormal CPT range was significantly lower in arm 1 than arm 2.

8. Conclusions

Goshajinkigan is effective for controlling the advance of peripheral neuropathy induced by paclitaxel/carboplatin.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This multicenter RCT tested whether goshajinkigan in combination with vitamin B12 can improve peripheral neuropathy induced by paclitaxel/carboplatin for gynecologic cancer patients. The study did not find effectiveness of goshajinkigan based on subjective numbness symptoms (VAS) score, NCI-CTCAE grade, or FACT-Taxane score. However, 6 weeks after administration commenced, CTCAE grade deteriorated to 3 in two participants in the vitamin B12-only group and no participant in the vitamin B12 plus goshajinkigan group (arm 1). Additionally, the frequency of abnormal CPT range was significantly lower in arm 1. On those grounds, the authors assert that goshajinkigan is useful for controlling subjective symptoms. Nevertheless, the authors did not observe any positive effect of goshajinkigan, thereby raising the issue of whether goshajinkigan is a suitable drug for controlling subjective symptoms, and whether the 6-week period of administration is appropriate. When conducting a trial such as this, researchers should first elucidate what kinds of Kampo medications are effective and for what periods by carrying out an exploratory study whereby a physician expert in Kampo medical treatment provides appropriate Kampo treatment based on Kampo patterns, and then create study protocols.

12. Abstractor and date

Hoshino E, 31 December 2013.

7. Eye Diseases

Reference

Takama N, Fujiwara T. The Efficacy of hainou-san-kyu-to for internal hordeolum. *Ganka Rinsho Iho (Japanese Review of Clinical Ophthalmology)* 2006; 100: 9-11 (in Japanese). Ichushi Web ID: 2006117653

1. Objectives

To evaluate the efficacy of hainosankyuto (排膿散及湯) for internal hordeolum in the acute phase.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals, Japan.

4. Participants

Twenty-six patients with internal hordeolum not complicated with other ophthalmopathy or diabetes who received basic treatment with 4 doses of antibiotic eye-drops (0.3% ofloxacin) + steroid eye-drops (0.1% fluorometholone) per day.

5. Intervention

Arm 1: basic treatment +oral administration of 2.5 g of TSUMURA Hainosankyuto (排膿散及湯) Extract Granules t.i.d. before meals (n=16).

Arm 2: basic treatment alone (n=10).

6. Main outcome measures

Duration of treatment (in days) required to achieve improvement in subjective symptoms, need for adjunctive treatment.

7. Main results

Duration of treatment in days required to achieve symptom improvement was significantly shorter in arm 1 (2.2±0.9) than in arm 2 (5.5±4.1) ($P<0.001$). The number of subjects requiring adjunctive treatment was not significantly different in arm 1 (1/16; 6.3%) and arm 2 (3/10; 30%). One patient in arm 1 healed 3 days after the start of treatment but had a recurrence 4 days after treatment discontinuation.

8. Conclusions

TSUMURA Hainosankyuto Extract Granules induced proliferation and differentiation of pluripotent stem cells and activity of granulocyte colony stimulating factor, strongly suggesting its suppressive effect on neutropenia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were observed in either arm.

11. Abstractor's comments

In western medicine, antibiotics are concomitantly used with anti-inflammatory drugs. Kampo medicine, which preceded the discovery of the antibiotics used in the modern medicine, targets pathogenic microorganisms by an entirely different mechanism.

12. Abstractor and date

Hoshino E, 15 March 2009, 31 December 2013.

7. Eye Diseases

References

Nagaki Y, Hayasaka S, Hayasaka Y, et al. Effects of goshajinkigan on corneal sensitivity, superficial punctate keratopathy and tear secretion in patients with insulin-dependent diabetes mellitus. *The American Journal of Chinese Medicine* 2003; 31: 103-9. CENTRAL ID: CN-00437062, Pubmed ID: 12723759

Nagaki Y. Effects of goshajinkigan on diabetic keratopathy*. *Kampo Igaku (Kampo Medicine)* 2004; 28: 63-5 (in Japanese).

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) for corneal sensitivity, superficial keratitis, and tear secretion in patients with insulin-dependent (type 1) diabetes mellitus.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital), Department of Ophthalmology, Japan.

4. Participants

Fifty patients with insulin-dependent diabetes mellitus complicated with keratopathy. Participants met the following selection criteria: (1) 5 years or longer duration of insulin dependence; (2) simple or preproliferative diabetic retinopathy; (3) diffuse superficial keratitis revealed by fluorescein staining; (4) no history of eye disease other than diabetic retinopathy; and (5) no treatment with eye drops in the past 3 months.

5. Intervention

Arm 1: treatment with TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 25.5±6.9 years; male:female = 10:15; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group A).

Arm 2: treatment with placebo granules (lactose granules not containing extract powder) 2.0 g t.i.d. (30 minutes before meals) for 3 months in 25 patients (age 26.6±5.2 years; male:female = 13:12; 14 with simple retinopathy and 11 with proliferative retinopathy; disease duration 11.6±5.7; group B).

Arm 3: treatment with goshajinkigan (牛車腎気丸) for 3 months in 25 healthy volunteers (age 26.2±5.4 years; male:female = 11:14; group C).

6. Main outcome measures

Corneal sensitivity, fluorescein staining score, and Schirmer score were evaluated before and after the treatment.

7. Main results

Corneal sensitivity significantly improved from the pre-treatment value of 2.47±1.1 to the post-treatment value of 2.03±0.63 in group A ($P<0.05$) but not in group B (2.36±1.35 and 2.33±1.02, respectively). Schirmer score markedly improved from the pre-treatment value of 9.3±3.5 to the post-treatment value of 11.0±3.3 in group A ($P<0.01$) but not in group B (9.0±3.8 and 9.0±4.0, respectively). Fluorescein staining score markedly improved from the pre-treatment value of 1.32±0.56 to the post-treatment value of 0.64±0.49 in group A ($P<0.01$) but not in group B (1.40±0.64 and 1.36±0.68, respectively). Corneal sensitivity, Schirmer score, and fluorescein staining score all remained within their normal ranges in group C.

8. Conclusions

Goshajinkigan improves reduced corneal sensitivity, increases tear secretion, and markedly repairs damage to the corneal surface, thereby improving keratopathy without affecting the progression of diabetes mellitus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

This study was a double-blind RCT involving 50 diabetic patients (groups A and B). It is a well-designed clinical trial in which both prescribing physician and patients were blinded. If more details, such as data on withdrawals, had been described, intention-to-treat (ITT) analysis data and more reliable results could have been obtained. Further studies are expected to determine effects of goshajinkigan on ocular complications of type 2 diabetes mellitus as a lifestyle-related disease.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

7. Eye Diseases

Reference

Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. *Journal of Ocular Pharmacology and Therapeutics* 2001; 17: 59-65. CENTRAL ID: CN-00347524, Pubmed ID: 11322638

1. Objectives

To evaluate the efficacy of Kampo medicines for aqueous flare elevation after small-incision cataract surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Toyama Medical and Pharmaceutical University Hospital (now Toyama University Hospital) and an affiliated hospital, Japan.

4. Participants

Fifty-four patients undergoing surgery for age-related cataract. Patients with complications (such as diabetes mellitus and autoimmune disease), a history of uveitis, or use of anti-inflammatory drugs were excluded.

5. Intervention

Arm 1: no medication in 20 patients (8 males and 12 females; 9 right eyes and 11 left eyes; mean age, 73.1 years [48-85 years]) as a control group.

Arm 2: treatment with TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 7.5 g/day for 3 days before surgery, on the day of surgery, and for 7 days after surgery in 14 patients (5 males and 9 females; 8 right eyes and 6 left eyes; mean age, 74.5 years [56-90 years]).

Arm 3: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules 7.5 g/day on the same schedule as arm 2 in 10 patients (3 males and 7 females; 6 right eyes and 4 left eyes; mean age, 75.5 years [68-83 years]).

Arm 4: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 9.0 g/day on the same schedule as arm 2 in 10 patients (5 males and 5 females; 4 right eyes and 6 left eyes; mean age, 73.8 years [61-84 years]).

Cataract surgery in all patients was performed by a single surgeon according to a standard small-incision procedure.

6. Main outcome measures

Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. Main results

Preoperatively, no differences were observed in aqueous flare intensity among the groups. Aqueous flare intensity on postoperative days 1, 3, and 5 was significantly lower in the orengedokuto group ($P<0.05$) and kakkonto group ($P<0.01$) than in the control group. There was no difference between the saireito and control groups.

8. Conclusions

Orengedokuto and kakkonto reduce aqueous flare elevation after small-incision cataract surgery.

9. From Kampo medicine perspective

Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

Aqueous flare intensity was used in this RCT as a measure of intraocular inflammation after cataract surgery. Since aqueous flare is a surrogate outcome, results from clinical trials examining other outcomes such as reduction of treatment duration and dosage of commonly used postoperative medication are anticipated. See the article "Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of Kakkon-to and Sairei-to on aqueous flare elevation after complicated cataract surgery. *The American Journal of Chinese Medicine* 2002; 30: 347-53", as a follow-up of the present study.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

7. Eye Diseases

Reference

Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of kakkon-to and sairei-to on aqueous flare elevation after complicated cataract surgery. *The American Journal of Chinese Medicine* 2002; 30: 347-53. CENTRAL ID: CN-00434525, Pubmed ID: 12230023

1. Objectives

To evaluate the efficacy of Kampo medicines for aqueous flare elevation after complicated cataract surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one department of ophthalmology), Japan.

4. Participants

Twenty-seven patients with bilateral cataracts (54 eyes were eligible) associated with idiopathic or sarcoid uveitis. Of these patients, 5 were excluded from analysis.

5. Intervention

No Kampo formulation was administered in right eye surgeries. In left eye surgeries, one of the following Kampo formulations was administered for 3 days before surgery, on the day of surgery, and for 7 days after surgery.

Arm 1: treatment with TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. in 12 patients (mean age, 64.2 years [48-75 years]; 6 males and 6 females; 9 with idiopathic uveitis and 3 with sarcoid uveitis).

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. in 10 patients (mean age, 73.8 years [61-84 years]; 7 males and 8 females; 12 with idiopathic uveitis and 3 with sarcoid uveitis).

Cataract surgery in all patients was performed by a single surgeon following a standard procedure.

6. Main outcome measures

Aqueous flare intensity (in photon counts/msec) was measured preoperatively and on postoperative days 1, 3, 5, and 7.

7. Main results

Preoperatively, aqueous flare intensity was not different between the two groups. For right eyes, flare intensity was 99.1 in the kakkonto group and 89.6 in the saireito group on postoperative day 1, and then gradually decreased in both groups. For left eyes, compared with the untreated right eyes, aqueous flare intensity was significantly decreased in the kakkonto group on postoperative days 1, 3, and 5 ($P < 0.001$ for each). In contrast, there was no difference between left and right eyes in the saireito group.

8. Conclusions

Kakkonto inhibits the elevation in aqueous flare intensity after complicated cataract surgery.

9. From Kampo medicine perspective

Evaluation of *sho* and selection of Kampo formulations for each patient were conducted at the Kampo medicine clinic (now Department of Japanese Oriental Medicine) in the above-mentioned university hospital.

10. Safety assessment in the article

No adverse drug reactions were observed.

11. Abstractor's comments

This study was conducted as a follow-up to the preceding study "Ikeda N, Hayasaka S, Nagaki Y, et al. Effects of traditional Sino-Japanese herbal medicines on aqueous flare elevation after small-incision cataract surgery. *Journal of Ocular Pharmacology and Therapeutics* 2001; 17: 59-65". Participants in the present study were different from those in the preceding study, and patients with both cataracts and uveitis were examined. Also, kakkonto, which had been more effective than orangedokuto in the preceding study, was used as a test Kampo drug. These studies were conducted by the same investigators and the blinding was not described in either article; suggesting that these might have been single-blind studies.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Inoue H. Rapid effect of combination therapy with shoseiryuto and eppikajutsuto for acute otitis media with effusion in adults*. *Jibi to Rinsho (Otologia Fukuoka)* 2001; 47: 361-6 (in Japanese). Ichushi Web ID: 2002064379

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) combined with eppikajutsuto (越婢加朮湯) for otitis media with effusion (OME) in adults.

2. Design

A quasi-randomized controlled trial (quasi-RCT).

3. Setting

A clinic (otorhinolaryngology), Japan.

4. Participants

Thirty-four patients aged 16 years or older with acute OME.

Diagnostic criteria: eligible patients were those who complained chiefly of aural fullness, hearing loss, and autophony in the preceding three weeks at interview, and who had tympanic effusion evident under a binocular microscope.

5. Intervention

Arm 1: treatment with shoseiryuto (小青竜湯) extract 1 pack t.i.d. and eppikajutsuto (越婢加朮湯) 1 pack t.i.d. (after meals).

(a total of 28 ears of 20 patients; 11 males and 9 females; aged 38.1±16.9 years).

Arm 2: treatment with carbocisteine 500 mg t.i.d. and clarithromycin 200 mg b.i.d. (after meals).

(a total of 18 ears of 14 patients; 10 males and 4 females; aged 37.9±11.5 years).

Patients in both arms were treated for 7 days. If excellent or good response was obtained and subjective symptoms disappeared at 4 days, treatment was stopped at 4 days.

6. Main outcome measures

Main variables were symptoms (assessed on interview) and eardrum findings (under a microscope) at 4 and 7 days after the first visit. Symptoms were evaluated on a 4-point scale as follows: 'excellent response,' 'good response,' 'minimal response,' and 'no response.' Eardrums were checked primarily for tympanic effusion. Tympanogram was recorded at the first visit and 7 days later (or at 4 days in patients who showed improvement at that point).

7. Main results

'Excellent or good response' with normalization or improvement of the tympanogram and with disappearance of tympanic effusion was achieved in 38.9% of the control group (arm 2) vs 75.0% of the Kampo group (arm 1); the outcome was significantly better in the Kampo group ($P=0.02$, Wilcoxon rank sum test). In patients with abnormal tympanogram at the first visit, therapeutic response tended to be more pronounced in the Kampo group. Time to the onset of improvement of subjective ear symptoms was significantly shorter in arm 2 than arm 1 ($P=0.05$).

8. Conclusions

In acute OME in adults, combination therapy with shoseiryuto extract and eppikajutsuto extract results in rapid disappearance of the effusion and improvement of ear symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Nausea was observed in one patient in arm 2, while no adverse drug reactions occurred in arm 1.

11. Abstractor's comments

This report is clinically relevant. Since patients were randomly assigned to each arm, based on odd- or even chart number, this study was strictly a randomized clinical controlled trial (CCT), not an RCT, and is classified as a quasi-randomized trial. Results from larger rigorously-designed trials are awaited.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Machii K, Ikezono T, Utasato S, et al. Comparative study of the efficacy of saireito monotherapy versus antiallergic agent plus carbocysteine combination therapy for otitis media with effusion*. *Kampo Igaku (Kampo Medicine)* 1992; 16: 200-3 (in Japanese).

1. Objectives

To compare the efficacy of saireito (柴苓湯) monotherapy versus antiallergic agent plus S-carboxymethyl-L-cysteine (S-CMC; carbocysteine) combination therapy for otitis media with effusion.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (outpatient clinic in the department of otorhinolaryngology), Japan.

4. Participants

Twenty patients with otitis media with effusion who had conductive hearing loss defined as air-bone gap (A-B GAP) of 15 dB or more (at 3 frequency average hearing levels). Otitis media with effusion was diagnosed based on eardrum findings, audiometry, and tympanogram.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 9 g/day for patients weighing ≥ 40 kg, 6 g/day for patients weighing 20–40 kg, and 3 g/day for patients weighing < 20 kg for 4 weeks (n=10 [5 males and 5 females]; age, 7–64 years).

Arm 2: Ketotifen 1.2–2.0 mg/day or oxatamide 1 mg/kg/day for children and 60 mg/day for adults plus S-CMC 30 mg/kg/day for children and 1500 mg/day for adults for 4 weeks (n=10 [5 males and 5 females]; age, 4–60 years).

6. Main outcome measures

“Good response” was defined as hearing improvement of 10 dB or greater (at 3 frequencies) as measured by pure-tone audiometry, and improvements in tympanogram and eardrum findings; “minimal response” as 1–10 dB improvement (at 3 frequency average hearing levels) and improvements in tympanogram and eardrum findings; “no response” as no change by pure-tone audiometry; “worsening” as loss of hearing by pure-tone audiometry.

7. Main results

In arm 1 and arm 2, respectively, about 50% and 60% of patients achieved moderate or mild improvement, with the response to treatment characterized as “moderate improvement” in 2 and 3, “mild improvement” in 3 and 3, “no change” in 2 and 2, and “worsening” in 3 and 2 patients, respectively. There was no statistically significant between-group difference in the percent and number of responders and in pure-tone audiogram, tympanogram, and eardrum findings.

8. Conclusions

Saireito is effective for the treatment of otitis media with effusion as standard combination therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Notable adverse reactions were not observed.

11. Abstractor’s comments

This is a valuable RCT of the efficacy of saireito for otitis media with effusion. Comparing a monotherapy with combination therapy may make blinding of patients difficult because the number of drug(s) used is obviously different. In addition, since age range of patients was wide, the treatment regimen varied accordingly. Readers might have been confused by the change of terms for assessment from “response” as defined in the outcome measures section, to “improvement” as used in the results. Reassessment using a higher-quality study design is desirable.

12. Abstractor and date

Tsuruoka K, 27 September 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Sato H, Nakamura H, Honjo I, et al. Clinical evaluation of Tsumura-Saireito in children with otitis media with effusion - A comparative randomized controlled study of cepharanthine -. *Jibiinkoka Rinsho (Practica otologica)* 1988; 81: 1383-7 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) compared with cepharanthine for otitis media with effusion.

2. Design

Randomized controlled trial (RCT)

3. Setting

Outpatient clinic at the Department of Otolaryngology, Kyoto University Hospital, Japan.

4. Participants

Sixty-four ears of 42 children diagnosed with otitis media with effusion as evidenced by type B tympanogram who had mean hearing level of 20 dB or more (at 3 frequency average levels: 500, 1000, and 2000 Hz).

5. Intervention

Arm 1: Thirty-two ears of 21 children aged 4-7 years (mean 5.2) were treated with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. for 4 weeks.

Arm 2: Thirty-two ears of 21 children aged 4-7 years (mean 5.0) were treated with cepharanthine 5.0-7.5 mg b.i.d. for 4 weeks.

6. Main outcome measures

Pure-tone audiogram and tympanogram were obtained before and after the treatment. In pure-tone audiometry, "improved" hearing after tympanoplasty was defined as an increase of 15 dB or more in mean hearing level, and "not changed" as an increase of less than a 15 dB. The otitis media with effusion was judged to be "improved" when the tympanogram changed to type A or C1, and "not changed" when it was type C2 or B. Patients were considered "responders" if either test indicated improvement and "non-responders" if neither test indicated improvement.

7. Main results

After treatment, mean hearing level increased 7.2 dB (the percentage of ears with improvement: 28.1%) in arm 1 and 3.8 dB (15.6%) in arm 2; the between-arm difference was not significant. The tympanogram was improved in 18.8% of ears in arm 1 and 3.1% of ears in arm 2; the between-arm difference was also not significant. In all, 43.8% of the saireito-treated and 18.8% of the cepharanthine-treated ears were classified as responders; the response rate was significantly higher in arm 1 (χ^2 test, $P < 0.05$).

8. Conclusions

Saireito is an effective conservative treatment for otitis media with effusion in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No notable adverse reactions were observed.

11. Abstractor's comments

This is an RCT of the efficacy of saireito for otitis media with effusion in children. Although it was published in 1988, which was before the term "EBM (evidence-based medicine)" became popular, this clinical study is well-designed. The inclusion and exclusion criteria and the outcome variables were clearly defined, and the results took into account participants who used other drugs as well. The authors also discussed the difficulty of blinding subjects to the intervention when the drugs could be identified by their respective odors. It may have been the best possible study design under the circumstances at that time.

12. Abstractor and date

Tsuruoka K, 28 September 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Kaneko T. Comparison of saireito and isosorbide in efficacy against low-frequency sensorineural hearing loss. *Kampo to Saishin Chiryō (Kampo and the Newest Therapy)* 2010; 19: 233–9 (in Japanese with English abstract). Ichushi Web ID: 2010304850

1. Objectives

To compare the effectiveness of saireito (柴苓湯) and isosorbide for low-frequency sensorineural hearing loss.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

An otorhinolaryngology clinic (Tochigi prefecture), Japan

4. Participants

One hundred and fifty-five patients with low-frequency sensorineural hearing loss who presented with ear blockage sensation as chief complaint between June 2008 and October 2009.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. (n= 76).

Arm 2: isosorbide (Kowa Pharmaceutical Co., Ltd., Isobide) 30 mL t.i.d. (n=75).

6. Main outcome measures

Two measures: pure tone audiometry and subjective symptoms. Assessment by pure tone audiometry was divided into four stages: recovered (hearing threshold levels for three low frequencies [125, 250, and 500 Hz] all found within 20 dB, or no left/right difference detected), improvement (restored to 10 dB or more, but not full recovery), no change (less than 10 dB), and worsening. Four-stage subjective assessment: improved, somewhat improved, no change, worsened.

7. Main results

The number of tested patients was 51 in arm 1 (10 males and 41 females; ages 19–76; mean age 47.8 years) and 53 in arm 2 (16 males and 37 females; ages 11–78; mean age 47.1 years). Arm 1 showed a slightly stronger tendency for improvement in the hearing test compared to arm 2, but no statistically significant difference was observed. The subjective measures “no change” and “worsened” tended to be more common in arm 2, but no significant difference was observed. Comparison of initial occurrences with recurrences showed that improvement tended to be more difficult after recurrence in both groups, but no significant difference was observed. Recovery tended to be poor in subjects with dizziness symptoms in both groups, but no significant difference was observed.

8. Conclusions

Saireito and isosorbide are similarly effective for low-frequency sensorineural hearing loss.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

Low-frequency sensorineural hearing loss is frequently encountered in daily practice, nevertheless, its causes remain unknown. A finding of the study that is significant in clinical and pathological terms is that Saireito and isosorbide have equal effectiveness. Unfortunately, the trial amounted to a quasi-RCT because allocation of participants to receive one of the treatments was in the order of diagnosis. The reliability of the results could have been improved if patients who did not return to the clinic for determination of the effects of treatment could have been followed up. Participants might not have returned because their symptoms improved or because they visited another clinic. This greatly affected the results. Hopefully the researcher will properly randomize the trial and improve the follow-up rate in the next stage of his research. In this study a doctor at the frontline of community health care has attempted an RCT to verify a medical practice that has concerned him in the clinic. It is praiseworthy for its contribution to the development of Kampo medicine.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

8. Ear Diseases

Reference

Tanaka H. Efficacy of a Kampo preparation combined with tranquilizers in patients with tinnitus. *Jibiinkoka Rinsho (Practica otologica)* 1996; suppl 89: 8 (in Japanese).

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) combined with tranquilizers for tinnitus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single institution (Department of Otorhinolaryngology, Koseiren Nagaoka Chuo General Hospital), Japan.

4. Participants

Two hundred and twelve tinnitus patients with symptoms of Eustachian tube dysfunction. (The paper mentions 212 participants, however, there are 222 in arms 1 and 2 combined.)

Inclusion criteria were: tinnitus that is 1) worsened by the common cold, nasal allergy, or sinusitis; 2) relieved by Eustachian tube insufflation; 3) still present after myringotomy for otitis media with effusion; 4) complicated by chronic otitis media and relieved by the patch test; or 5) associated with sequelae of otitis media.

5. Intervention

Arm 1: treatment with tranquilizer alone for more than 4 weeks, then combined with Kanebo Saireito (柴苓湯) Extract Fine Granules (n=104).

Arm 2: treatment with Kanebo Saireito (柴苓湯) Extract Fine Granules + tranquilizer combination for 2 weeks, then tranquilizer alone (n=118).

6. Main outcome measures

Changes in the symptoms (measured using a 3-point scale corresponding to improvement, no change, and worsening).

7. Main results

Efficacy was observed in around 60% of patients treated with the combination (69/104 in arm 1 and 58/118 in arm 2) and in 62.6% and 57.1% of patients treated with 8.1 g and 5.4 g of saireito, respectively. Even the lower-dose administration was effective.

8. Conclusions

Saireito combined with tranquilizers was effective for treating tinnitus. Current Kampo extract preparations contain large amounts of ingredients. Considering the possibility of poor drug compliance, the treatment with 5.4 g of saireito was suggested to be useful.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study was referred to as a RCT-cross over study, based on the mention of "cross-over trial" in the paper. But it was a short paper and information was scarce. Basic information, including age and sex of participants, names of tranquilizers used, and when, how, and by whom the outcomes were measured, is absent and therefore assessment of this study is difficult. The development of future studies on this topic is expected.

12. Abstractor and date

Tsuruoka K, 22 April 2008, 1 June 2010, 31 December 2013.

8. Ear Diseases

Reference

Suzuki T. *Clinical efficacy of chotosan for tinnitus. Pathology and treatment of tinnitus and dizziness**. The 28th Chiba Symposium of Japanese Traditional Medicine Tokyo: Kudansha; 2001:8-20 (in Japanese). Ichushi Web ID: 2003129990

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) for tinnitus.

2. Design

A crossover randomized controlled trial (RCT-crossover).

3. Setting

A community hospital (department of otorhinolaryngology), Japan.

4. Participants

Fifty-eight patients with tinnitus.

5. Intervention

Arm 1: oral administration of TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks, followed by mecobalamin 0.5 mg, t.i.d. for 4 weeks (n=29).

Arm 2: oral administration of mecobalamin 0.5 mg, t.i.d. for 4 weeks, followed by TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g, t.i.d. for 4 weeks (n=29).

6. Main outcome measures

The intensity (loudness level) and duration of tinnitus, and tinnitus-associated annoyance was evaluated on a 6-point scale (from 0 = disappearance to 5 = maximum) according to the diagnosis criteria established by a study group of the Japan Audiological Society. Scores of these three measures were summed before and after each treatment, and the degree of improvement was measured by reduction in the summed score from the pre-treatment value. 'Disappearance' was defined as reduction to zero, 'marked improvement' as reduction of 8 or more points, 'moderate improvement' as reduction of 4 to 7 points, 'mild improvement' as reduction of 1 to 3 points, 'no improvement' as no change in score, and 'worsening' as increase in score.

7. Main results

In the chotosan-first group (arm 1), scores were significantly reduced after 4 weeks of chotosan treatment, but significantly increased after the switch to mecobalamin treatment. In mecobalamin-first group (arm 2), scores did not change at 4 weeks, and significantly increased after the switch to chotosan treatment. The degree of improvement in tinnitus was significantly different between groups at 4 weeks, then similar at 8 weeks. Improvements were significant, as compared with the pre-treatment baseline values, in both groups. Tinnitus had disappeared in 5 ears, was markedly improved in 8 ears, and was moderately improved in 14 ears. Moderate-to-marked improvement was seen in 39.8% of ears and mild-to-marked improvement in 80.9%. There was no case of 'worsening' tinnitus. Regarding background factors, there were no between-group differences in sex, age, diagnosis, disease duration, side of diseased ear, and medical history. Chotosan showed significant efficacy for tinnitus with heaviness of head/ headache or shoulder stiffness, compared with other accompanying symptoms.

8. Conclusions

Chotosan is more effective than mecobalamin in improving tinnitus.

9. From Kampo medicine perspective

Although specific results were not provided, the author concluded that the treatment would be more effective when they took into account on the patient's condition.

10. Safety assessment in the article

Serious adverse drug reactions were not reported in either group.

11. Abstractor's comments

This study provided high-quality evidence that chotosan is efficacious for tinnitus, which is often difficult to treat. Chotosan tended to improve, though not significantly, Meniere's disease and tinnitus without hearing loss, but not C5dip-type sensorineural hearing loss. These points are helpful when the efficacy of chotosan is determined, and also provide useful insights in its mechanism. In addition, unlike previous reports showing that patients with shorter disease duration were more likely to respond, this study described striking improvement in some cases, such as 'marked improvement' in a patient with disease for 30-40 years and complete recovery in several patients with disease for 4-5 years. The problems of this study are as follows: 1) The presentation of the results is inconsistent. For example, results are presented on a patient basis at first, and then on an affected-ear basis. 2) The report is incomplete because results from a Kampo medicine perspective are not presented. And 3) there is no description of the randomization step or the method of assignment to arm 1 and arm 2. The randomization step may have been omitted because of the crossover design. Nevertheless, an accurate description is desired. However, the article presents future challenges, and further developments are expected.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010.

8. Ear Diseases

Reference

Onishi S. Kampo treatment for tinnitus and hearing impairment*. *JOHNS* 1990; 6: 535-9 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for tinnitus.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Otolaryngology Department, Kanto Teishin Hospital, Japan.

4. Participants

Thirty-nine patients who presented with tinnitus as their chief complaint (22 males and 17 females, age ranging from the 20s to 80s).

5. Intervention

Arm 1: goshajinkigan group. TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (7.5 g/day) for 8 weeks (n=22).

Eight participants from arm 2 were included in arm 1 for a total of 30 after experiencing no effect from treatment in arm 2.

Arm 2: chotosan group. TSUMURA Chotosan (釣藤散) Extract Granules (7.5 g/day) for 8 weeks (n=24).

Six participants from arm 1 were included in arm 2 for a total of 30 after experiencing no effect from treatment in arm 1.

Participants were allocated to arm 1 or arm 2 in the order of presentation, regardless of their Kampo pattern.

6. Main outcome measures

Tinnitus severity, duration, and how it becomes concerning classified into five grades: remarkable improvement, improvement, slight improvement, no change, and deterioration.

7. Main results

Although there was no significant difference between groups, effectiveness of goshajinkigan for tinnitus tended to be greater (50% with grade 'improvement' or better) than that of chotosan (30% with grade 'improvement' or better). Three out of seven participants with tinnitus following sudden hearing loss in arm 1 and one of the five such participants in arm 2 scored 'improvement' or better. In both groups, most patients experienced an effect within two months of the start of treatment.

8. Conclusions

Goshajinkigan may be effective for tinnitus. Its efficacy is at least equivalent to chotosan.

9. From Kampo medicine perspective

While the Kampo medications were administered regardless of the patient's Kampo pattern, tinnitus is a major symptom within the goshajinkigan-pattern (by stratified analysis), and no relation between effectiveness and the existence of lower limb pain, numbness, and swelling could be identified.

10. Safety assessment in the article

Diarrhea was observed in one participant in each group, however it was not severe enough to discontinue administration.

11. Abstractor's comments

This is a clinically significant study in that it compared and analyzed the clinical effects of goshajinkigan for tinnitus to those of chotosan in a controlled clinical trial. Its clinical significance would be improved by analyzing effectiveness in patients administered goshajinkigan and chotosan in a crossover manner with a required washout period after demonstrating ineffectiveness in each group. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

9. Cardiovascular diseases

References

Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 282-3 (in Japanese).

Narumi J, Kohsaka S, Miyazawa S, et al. Evaluation of the Kampo monotreatment for hypertensive patients using ambulatory blood pressure monitoring*. *Kampo Shinryo* 1996; 15: 34-5 (in Japanese).

1. Objectives

To evaluate the efficacy of chotosan (釣藤散) and orenge dokuto (黄連解毒湯) for hypertension using ambulatory blood pressure monitoring.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Eight hypertensive patients who visited the hospital for the first time.

5. Intervention

Arm 1: Tsumura Chotosan (釣藤散) Extract Granules (TJ-47) 7.5 g/day (n=3).

Arm 2: Tsumura Orenge dokuto (黄連解毒湯) Extract Granules (TJ-15) 7.5 g/day (n=5).

The period of administration was 15–265 days.

6. Main outcome measures

Blood pressure (BP) was measured using an ambulatory blood pressure monitor (ABPM) before and after treatment, and the following BP values were determined: 1) the 24-hour average systolic BP (sBP) and diastolic BP (dBP), 2) the average daytime sBP and dBP, 3) percentage of ambulatory dBPs more than 90 mm Hg during 24 hours (diastolic pressure load), and 4) BP values analyzed by a cosinor method. Hypertensive patients with or without accessory symptoms were separately assessed.

7. Main results

1) A 24-hour antihypertensive effect on sBP was observed in 3 patients in arm 2, and a 24-hour antihypertensive effect on dBP was observed in 1 patient in arm 1. 2) Daytime sBP decreased in 1 patient in arm 1 and 3 patients in arm 2, and daytime dBP decreased in 1 patient in arm 1 and 1 patient in arm 2. 3) Reduction in diastolic pressure load was noted in 2 patients in arm 1 and 1 patient in arm 2. 4) Cosinor analysis revealed efficacy in 1 patient in arm 1 and 2 patients in arm 2.

In patients with accessory symptoms, headache and heaviness of the head improved in 1 patient in arm 1, headache and shoulder stiffness improved in 1 patient in arm 1, but no indices of hypertension for these patients was affected. Lightheadedness in 1 patient in arm 2 was accompanied by decrease in BP.

8. Conclusions

Kampo monotreatment has a satisfactory hypotensive effect in some cases.

9. From Kampo medicine perspective

It is noted that in two patients with *sho* (証, pattern) for chotosan, treatment was effective (all indices) for 1 patient but not for the other. Also in a patient with *sho* for orange dokuto, no effect was observed.

10. Safety assessment in the article

In the “result” and “discussion” sections of the related article, it is noted that the Kampo diagnosis of “*sho* (証, pattern)” may not be associated with a hypotensive effect of Kampo treatment, which may not be observed even when *sho* is compatible with the Kampo prescription.

11. Abstractor’s comments

Despite the small number of the subjects, this is an important report that evaluates (using ABPM) the hypotensive effect of Kampo drugs. The results of many multicenter trials of orenge dokuto for treatment of hypertension suggest its efficacy for accessory symptoms but not for high BP. However, I have the clinical impression that orenge dokuto is effective in some cases, and these data support that impression. Analysis found no association between the accessory symptoms and *sho*. How goals *sho* for use of Kampo drugs are set (e.g., trial and error) should be further investigated.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Sasaki J, Matsunaga A, Kusuda M, et al. Efficacy of daisaikoto and chotosan in patients with essential hypertension. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1993; 70: 1965-75 (in Japanese). Ichushi Web ID: 1994042619

1. Objectives

To evaluate the efficacy and safety of daisaikoto (大柴胡湯) and chotosan (釣藤散) in patients with essential hypertension.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Five hospitals (1 university hospital and 4 clinics), Japan.

4. Participants

A total of 94 patients who met the following 4 criteria: 1) essential hypertension with unidentified complaints, 2) inadequate control of hypertension by other antihypertensive agents, 3) mild hypertension, and 4) judged to be appropriate for the study. Of these, 83 patients were included for analysis.

5. Intervention

Jitsu-sho Arm 1: thirty patients with *jitsu-sho* (実証, excess pattern). Tsumura Daisaikoto (大柴胡湯) Extract Granules (TJ-8) 2.5 g t.i.d. for 8 weeks (n=14); *jitsu-sho* arm 2: no administration (n=15).

Kyo-sho Arm 1: Sixty-two patients with *kyo-sho* (虚証, deficiency pattern). Tsumura Chotosan (釣藤散) Extract Granules (TJ-47) 2.5 g t.i.d. for 8 weeks (n=24); *kyo-sho* arm 2: no administration (n=30).

6. Main outcome measures

Blood pressure (BP). Pulse rate. Subjective symptoms assessed in 3 grades (improved, no change, or worse); headache, heaviness of the head, dizziness, shoulder stiffness, palpitation, hot flashes, irritation, tinnitus, insomnia, anxiety/restlessness, cold or hot feelings in the limbs, numbness in the limbs, loss of appetite, constipation, diarrhea, nausea, dry mouth, eye fatigue, and lassitude. Global improvement. The results of laboratory tests.

7. Main results

Diastolic BP in *jitsu-sho* arm 1 and BP in *kyo-sho* arm 1 were significantly decreased in the treatment group when compared to the untreated group after 8 weeks. Tinnitus was significantly improved ($P<0.05$) and global improvement was better in chotosan-treated arm (*kyo-sho arm 1*). The results of laboratory tests remained within normal limits.

8. Conclusions

In *kyo-sho* patients, chotosan has a significant antihypertensive effect.

9. From Kampo medicine perspective

In this study, patients were grouped into *jitsu-sho* and *kyo-sho* using a questionnaire, and were treated with Kampo drugs appropriate for their *sho* (証, pattern).

10. Safety assessment in the article

Fifteen patients in arm 1 and 26 patients in arm 2 were assessed. In the daisaikoto treatment group, 1 patient experienced watery diarrhea and withdrew from the study. In the chotosan treatment group, 1 patient discontinued treatment because of abdominal discomfort and bloating and withdrew from the study.

11. Abstractor's comments

This is an important report on the Kampo treatment of hypertensive patients based on body constitution (*sho*). In this study, a significant antihypertensive effect of chotosan in *kyo-sho* patients was observed. On the other hand, this paper did not elucidate the hypotensive effect of daisaikoto in *jitsu-sho* patients and was therefore consistent with other papers reporting that orangedokuto (黄連解毒湯) used for *jitsu-sho* or *chukan-sho* has no direct hypotensive effect ("Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orangedokuto (TJ-15) for the treatment of accessory symptoms of hypertension". *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Study)* 2003; 80: 354-72 (in Japanese)" Ichushi Web ID: 2003184342 [MOL](#), [MOL-Lib](#)). It might be that blood pressure is more closely associated with symptoms in *kyo-sho* patients. It would be interesting to know whether the effects can still be observed when the *sho* of the patients is not considered. Efficacy of chotosan for tinnitus has been previously reported, and this study confirmed this effect in *kyo-sho* patients.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

9. Cardiovascular disease

Reference

Saku K, Hirata K, Zhang B, et al. Effects of Chinese herbal drugs on serum lipids, lipoproteins, and apolipoproteins in mild to moderate essential hypertension. *Journal of Human Hypertension* 1992; 6: 393-5. CENTRAL ID: CN-00089422, Pubmed ID: 1464897

1. Objectives

To evaluate the effects of daisaikoto (大柴胡湯) and saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) on serum lipid levels in patients with mild to moderate hypertension.

2. Design

Randomized controlled study (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Thirty patients with mild to moderate hypertension.

5. Intervention

Arm 1: daisaikoto (大柴胡湯) (manufacturer not specified) 2.5 g t.i.d. for 3 months (n=15).

Arm 2: saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) (manufacturer not specified) 2.5 g t.i.d. for 3 months (n=15).

6. Main outcome measures

Blood pressure, pulse rate, total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), HDL2-C, HDL3-C, low density lipoprotein cholesterol (LDL-C), lecithin-cholesterol-acyltransferase (LCAT), apolipoprotein (apo-AI, AII, B, CII, CIII, and E).

7. Main results

In both arms, blood pressure was unchanged, but pulse rate was significantly decreased in arm 2 after 3 months of administration. In arm 1, levels of HDL-C, LCAT, and apo-AII were significantly increased, but others were unchanged. In arm 2, the level of HDL-C was significantly increased.

8. Conclusions

Both daisaikoto and saikokaryukotsuboreito affect serum lipid levels but not blood pressure.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

By studying patients before and after administration, it was shown that both daisaikoto and saikokaryukotsuboreito increase HDL-C (also known as beneficial cholesterol), which will help patients with dyslipidemia. Further studies with larger sample size and control group are warranted.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

9. Cardiovascular Diseases

References

Arakawa K, Saruta T, Abe K, et al. Double-blind placebo-controlled trial of TSUMURA Orengedokuto (TJ-15) for the treatment of accessory symptoms of hypertension*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Study)* 2003; 80: 354-72 (in Japanese). Ichushi Web ID: 2003184342 [MOL](#), [MOL-Lib](#)

Arakawa K, Saruta T, Abe K, et al. Improvement of accessory symptoms of hypertension by TSUMURA Orengedokuto Extract, a four herbal drugs containing Kampo-Medicine Granules for ethical use: a double-blind, placebo-controlled study. *Phytomedicine* 2006; 13: 1-10. [CENTRAL ID: CN-00553637, Pubmed ID: 16360926

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in patients with hypertension symptoms.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

A total of 116 university hospitals and community hospitals, Japan.

4. Participants

A total of 265 patients with hypertension who met the inclusion and exclusion criteria; 204 included and 61 not included for analysis.

5. Intervention

Arm 1: administration of TJ-15 (containing 0.25 g of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules) capsules, 2 cap, t.i.d. (n=103).

Arm 2: administration of placebo capsules, 2 cap, t.i.d. (n=101).

Oral administration before each meal. Duration of treatment: 8 weeks.

6. Main outcome measures

Reduction in blood pressure was evaluated by comparing blood pressure measurements (systolic, diastolic, and mean) obtained after the run-in period and after the treatment period, and the antihypertensive effect was classified into 5 grades. Improvement in five major accessory symptoms – irritability (feeling irritated), anxiety, sleep disorder, hot flushes, and facial flushing – and other subjective symptoms – headache/heavy-headedness, shoulder stiffness, dizziness, and malaise – were graded from –3 to 3.

7. Main results

There was no significant difference in blood pressure decrease, or antihypertensive effect, between the TJ-15 group and placebo group. Significant efficacy against hot flushes and facial flushing was observed in the treatment group. Irritability, anxiety, and sleep disorder were also improved in the treatment group as compared with the placebo group. Scores of the other subjective symptoms improved significantly. There was no significant between-group difference in the overall safety rating.

8. Conclusions

This study demonstrates the efficacy and safety of orengedokuto for the treatment of hypertension symptoms.

9. From Kampo medicine perspective

The inclusion criteria were high blood pressure and presence of hypertension symptoms (irritability, anxiety, sleep disorder, hot flushes, and facial flushing) indicating orengedokuto “*sho* (pattern)”. Also ‘patients with “*kan-sho*” (寒証, cold/yin pattern) or “*kyo-sho* (虚証, deficiency pattern)” in Kampo medicine’ were excluded. Although “*sho*” is not fully equivalent to body-mass index (BMI), patients with thin physique were excluded from this study, resulting in the mean BMI of 24.3. Thus, the focus of this study was on the patients who were most likely to respond to and benefit from orengedokuto.

10. Safety assessment in the article

Adverse effects were observed in eight patients (6.3%) in the placebo group and 15 patients (11.5%) in the TJ-15 group. Nausea (n=2), abnormal laboratory data such as liver dysfunction (elevated liver enzymes) (n=7), and generalized rash (n=1) might be associated with orengedokuto.

11. Abstractor’s comments

Orengedokuto, a typical Kampo medicine for hypertension, was reevaluated in this original article. This study targets the symptoms related to stress or hyper-activation of sympathetic nervous system such as anger, stress, anxiety, and fear. In this multicenter double-blind clinical trial, blood pressure tended to decrease, but did not significantly decrease, in response to treatment. However, significant improvement in some accessory symptoms is a milestone. Compared with benzodiazepine anxiolytics in a study of essential hypertension, Orengedokuto seemed to show more efficacy. However, simple comparison cannot be done owing to different criteria used in selecting study participants. This study suggests that treatment based on “*sho*” may be effective. **Abstractor and date**

Namiki T, 15 June 2007, 1 April 2008, 13 March 2009, 1 June 2010, 31 December 2013.

9. Cardiovascular disease

Reference

Kaneko H, Nakanishi K, Murakami A, et al. Clinical evaluation of the effect of ohrengedoku-toh and ohrengedoku-toh-Red Ginseng mixture on chronic cardiovascular disorders in middle and aged patients. *The Ginseng Review* 1991; 12: 89-93 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of orendokuto (黄連解毒湯) plus red ginseng combination therapy for relieving symptoms associated with hypertension.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Five clinics, Japan.

4. Participants

A total of 40 out-patients with stable symptoms were recruited, 29 of whom were included for analysis (hypertension, n=14; atherosclerotic disease, n=6; ischemic heart disease, n=4; others, n=5).

5. Intervention

Arm 1: Kotaro Orendokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. between meals (n=15).

Arm 2: Kotaro Orendokuto (黄連解毒湯) Extract Granules 2.0 g t.i.d. plus CHEONG-KWAN-JANG kojimatsu powder (正官庄紅參末) 1.0 g t.i.d. between meals (n=14).

6. Main outcome measures

Subjective symptoms (insomnia, numbness of the limb, palpitation, tinnitus, vertigo, orthostatic syncope, stiff shoulder, headache/heaviness of head, and amnesia), overall improvement, and general effect were evaluated. Blood pressure, pressure rate product (PRP: blood pressure × heart rate), echocardiogram (resting coronary flow velocity [RFV] and left ventricular [LV] mass) were also determined.

7. Main results

Only numbness of the limbs was significantly improved in arm 1, whereas vertigo, stiff shoulder, headache/heaviness of head and general effect were significantly improved in arm 2. When subjects in both arms were further subgrouped according to *jitsu-sho* (実証, excess pattern) and *kyo-syo* (虚証, deficiency pattern), in arm 1, improved items were observed only in subjects with *kyo-sho*. In arm 2, improvement in shoulder stiffness and vertigo was found in *jitu-syo*-type patients, and headache improved in *kyo-syo*-type patients. Improved cardiovascular hemodynamics (decreased blood pressure, increased RFV, decreased LV mass, and lower PRP) were observed in arm 2.

8. Conclusions

When compared with single administration of orendokuto, combination therapy with kojimatsu effectively improved subjective symptoms as well as cardiovascular hemodynamics.

9. From Kampo medicine perspective

Subjects in both arms were further classified on the basis of *jitsu-sho* and *kyo-syo* for evaluation, which demonstrated more efficacy in arm 2 regardless of *sho*.

10. Safety assessment in the article

None.

11. Abstractor's comments

The result here is surprising in that even after short-term (12-week) administration, combination therapy with kojimatsu was more effective than administration of orendokuto alone. Orendokuto is generally used for subjects with intermediate- or *jitsu-sho*; however, the result here demonstrating more efficacy in *kyo-syo*-type patients than in *jitsu-sho*-type patients should serve as a useful reference. Combination of the two drugs increased the effectiveness even in patients with *jitsu-sho*, suggesting its usefulness (suitability for a wider range of patients) and efficacy (improvement in cardiovascular hemodynamics). Further studies with a larger sample size are awaited.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010.

9. Cardiovascular Diseases

Reference

Yoshikawa T, Munakata S, Okuma H. Effectiveness of goreisan for recurrence prevention in elderly cases of chronic subdural hematoma surgery— Interim report on a comparative trial*. *Noshinkei Geka to Kampo (Neurosurgery and Kampo)* 2010; 16 (in Japanese).

1. Objectives

To evaluate the effectiveness and safety of goreisan (五苓散) after chronic subdural hematoma surgery in elderly people.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Neurosurgery, Kuroishi General Hospital, Japan.

4. Participants

Forty-three elderly people over 70 years who underwent surgery (trephining) for symptomatic chronic subdural hematoma between January and August 2009.

5. Intervention

Administration continued for 1 month from the day after surgery.

Arm 1: goreisan (五苓散) (manufacturer not identified) 7.5 g/day (administration frequency not indicated) (n=22).

Arm 2: no treatment (n=21).

Steroids, glyceol, or hemostatics were not used in combination.

6. Main outcome measures

Changes in the hematoma were compared using CT scan 7, 14, and 28 days after surgery.

7. Main results

The age range was 73–89 years, and the between-group differences in gender or age were insignificant. The rate of hematoma shrinkage was greater in arm 1 than arm 2, especially between the 7th and 14th days (statistical significance not specified). Repeat surgery was required for 2 of the 22 participants in arm 1 (9%) and 5 of the 21 participants in arm 2 (24%), however, there was no significant between-group difference.

8. Conclusions

Goreisan may be effective for prevention of recurrence following chronic subdural hematoma surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No complications from goreisan were observed.

11. Abstractor's comments

This is a novel clinical study that investigated the effects of goreisan in preventing recurrence in elderly after chronic subdural hematoma surgery. The study was conducted to investigate goreisan's effects in preventing recurrence of postoperative chronic subdural hematoma, because it had been suggested that goreisan was effective for non-surgical cases of the condition. However, the study was presented as an abstract at a seminar, so unfortunately no details of the methods and results are included. In addition, it is an interim report, as the title indicates, so at the time it was written, it could report no significant difference recurrence rate between the goreisan group and the control group. The authors will hopefully continue with their research because the possibility remains that enlarging the sample groups will elucidate the effectiveness of goreisan, as the authors mention in their abstract. Goreisan has few adverse effects, so once it is established that it is effective for the prevention of recurrence after surgery in elderly cases of chronic subdural hematoma, a new therapeutic domain will have opened up for Kampo medicines in the field of neurosurgery. This is, therefore, a very important clinical study that holds much interest.

12. Abstractor and date

Goto H, 31 December 2012

9. Cardiovascular Diseases

Reference

Ito E, Takahashi A, and Kazuya F. Clinical effectiveness of TSUMURA Orengedokuto in the treatment of cerebral infarction. *Geriatric Medicine* 1991; 29: 303-13 (in Japanese).* Ichushi Web ID: 1991179676

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) in the treatment of cerebral infarction.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifteen hospitals (two departments of a university hospital and 14 hospitals), Japan.

4. Participants

A total of 109 clinically stable patients with cerebral infarction (thrombosis, embolism) (57 men and 51 women, and 1 patient who withdrew consent).

5. Intervention

Arm 1: administration of Tsumura Orengedokuto (黄連解毒湯) Extract Granules (TJ-15) 2.5 g t.i.d. orally before meals for 12 weeks (n=56).

Arm 2: no administration of Kampo medicines for 12 weeks (n=52).

6. Main outcome measures

Overall severity, subjective symptoms, neurological symptoms, improvement in activities of daily living (ADL), general improvement, safety, and usefulness were evaluated before administration and 4, 8, and 12 weeks after administration. Clinical parameters were examined (blood pressure, pulse rate, blood count, standard biochemical parameters, blood coagulation and fibrinolytic activity).

7. Main results

No significant changes were observed in overall severity and in general improvement. Patients were evaluated to be “more than slightly improved” in subjective symptoms significantly more frequently in arm 1 than arm 2 ($P<0.05$). Among subjective symptoms, improvement in dull headache, vertigo, hot flashes ($P<0.05$), and cold feeling and numbness of the limbs and stiff shoulders ($P<0.01$) occurred significantly more frequently. Significant change occurred in usefulness ($P<0.05$) but not in mental symptoms, neurological symptoms, and ADL. Significant difference in the clinical parameters was observed only in blood coagulation and fibrinolytic activity.

8. Conclusions

Orengedokuto was suggested to be effective in improving subjective symptoms (hot flashes, headaches, stiff shoulders, and cold feeling and numbness of the limbs) in patients with cerebral infarction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were observed in 3 patients in arm 1 (lightheadedness or dizziness) and 1 patient in arm 2 (loose stool and vomiting).

11. Abstractor's comments

By around 1990, at the time when this article was published, efficacy of orengedokuto for cerebral infarction had been surmised from basic research, accumulation of clinical cases, and comparison with the other medicines. This is a high-quality controlled-trial demonstrating that orengedokuto improves some of the subjective symptoms in clinically stable patients with cerebral infarction.

Reported pharmacological activities of orengedokuto include increase in local blood flow in the hippocampal region, inhibition of platelet aggregation by baicalein which is a component of ogon (黄芩) present in this Kampo medicine. And these reported activities are consistent with the present study result revealing the improvement in blood coagulation and fibrinolytic activity. They observed no effect on blood pressure, which is also the result of other large-scale trials studying its efficacy against high blood pressure. Therefore, orengedokuto seems to have little effect on decreasing blood pressure.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Otomo E, Togi H, Kogure K, et al. Clinical usefulness of TSUMURA Orengedokuto for the treatment of cerebrovascular disease: a well-controlled study comparing TSUMURA Orengedokuto versus Ca hopantenate, using sealed envelopes for allocation. *Geriatric Medicine* 1991; 29: 121–51 (in Japanese). Ichushi Web ID: 1991224400

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) for relieving psychiatric symptoms in patients with late effects of cerebrovascular disease.

2. Design

Randomized controlled trial used sealed envelopes for allocation (RCT-envelope).

3. Setting

Thirty university hospitals (including departments of neurology of Iwate Medical University, Tohoku University School of Medicine, and Gunma University Faculty of Medicine) and 20 general hospitals, Japan.

4. Participants

One hundred and forty-eight post-stroke patients with psychiatric symptoms due to cerebral infarction, cerebral hemorrhage, or stroke with unknown origin.

5. Intervention

Arm 1: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. orally after meals for 12 weeks (n=81).

Arm 2: calcium hopantenate 500 mg t.i.d. orally after meals for 12 weeks (n=67).

The treatment was discontinued at the time of disappearance of symptoms.

6. Main outcome measures

Psychiatric symptoms (apathy; problematic behaviors; emotional, intellectual, and mental disturbances), subjective symptoms (heaviness of head, headache, hot flush, etc.), neurological symptoms (aphasia, dysarthria, motor paralysis, etc.), and impairment in activities of daily living (sitting up, standing, walking, etc.) were evaluated at baseline and after 4, 8, and 12 weeks of treatment. Hasegawa's dementia scale and laboratory tests were performed at baseline and after 12 weeks of treatment.

7. Main results

Five patients in arm 1 (1 with concomitant cancer, 3 lost to follow-up after the initial treatment, and 1 who acted contrary to envelope method) were excluded from the study. The safety analysis included 76/67 patients (arm 1/arm 2) and efficacy analysis included 74/67. The percentages of patients who achieved moderate-or-greater and mild-or-greater overall improvement in psychiatric symptoms were significantly higher in arm 1 than in arm 2 at 8 and 12 weeks. There were no between-arm differences in each of the global improvement scores for subjective symptoms, neurological symptoms, and impairment in activities of daily living. The percentages of patients who achieved moderate-or-greater improvement in abulia at 4 weeks and moderate-or-greater and mild-or-greater improvements at 8 and 12 weeks were significantly higher in Arm 1 than in arm 2. Among other items of spontaneity, reduced expression of desires, decreased interest in others, decreased interest in performing activities of daily living, decreased interest in housekeeping, leisure activities, hobbies, etc., and inability to communicate with others were significantly improved at 12 weeks compare with at baseline in both arms to a similar extent.

8. Conclusions

Orengedokuto is effective for relieving psychiatric symptoms in patients with cerebrovascular disease and its efficacy is comparable to that of cerebral metabolic activator.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Three patients in arm 1 (3.9%) discontinued treatment, respectively, because of nausea and abdominal distention, chest discomfort, and headache. In arm 2, one patient (1.5%) discontinued treatment due to fever and disturbances in consciousness. Changes in laboratory data were within normal range in both arms.

11. Abstractor's comments

This clinical study revealed the effects of orengedokuto on psychiatric symptoms in patients with late effects of cerebrovascular disease in a controlled trial using sealed envelopes for allocation. As noted by the authors, the evaluation of the efficacy of orengedokuto may have been influenced by the following two factors: i) the designation of calcium hopantenate as a powerful drug around the same time as this study was performed, which biased selection of cases; and ii) lower efficacy of calcium hopantenate in the present trial than in other clinical trials. Despite the limitations on evaluation, this clinical study was excellent and demonstrated comparable efficacy of orengedokuto and a cerebral metabolic activator.

12. Abstractor and date

Goto H, 12 September 2008.

9. Cardiovascular Diseases

Reference

Shimada Y. Efficacy of tokishakuyakusan for hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder*. *Kosei Rodo Kagaku Kenkyuhoi Hojokin Chouju Kagaku Kenkyu Jigyo Koreisha no Nokekkan Shogai no Shinten Yobo wo Mokuteki to Shita Kampoyaku niyoru Tailor-made Iryo no Kaihatsu - Heisei 18 Nendo Buntan Kenkyu Hokokusho (Ministry of Health, Labour and Welfare, Science Research Grant, Comprehensive Studies on Science of Aging, Development of Personalized Medicine using Kampo Medicines to Prevent Progression of Cerebrovascular Disorders in the Elderly: Working-group Research Report Fiscal Year 2006) 2007: 22-30 (in Japanese)*

1. Objectives

To evaluate the efficacy and safety of tokishakuyakusan (当帰芍薬散) for treatment of hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder.

2. Design

Randomized controlled trial (RCT) (assigned by randomized allocation in 20 cases and chosen by the patient in 6 cases), Japan.

3. Setting

University hospital and community hospital.

4. Participants

Thirty-one patients with sequelae of cerebrovascular disorder.

5. Intervention

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules between meals (n=16) (for 12 months).

Arm 2: no administration of Kampo medicines (n=15).

6. Main outcome measures

The Stroke Impairment Assessment Set (SIAS), Functional Independence Measure (FIM), body weight and *oketsu* (瘀血, static blood), *qikyo* (気虚, qi deficiency), *qiutsu* (気鬱, qi movement stagnation) and *jinkyō* (腎虚, kidney deficiency), evaluated on a 5-point scale at baseline and every 3 months thereafter.

7. Main results

Both SIAS and FIM scores remained at baseline levels in arm 1 but decreased significantly in arm 2 at 12 months, resulting in a significant between-arm difference. In arm 2, stroke recurred at 9 or 12 months.

8. Conclusions

Tokishakuyakusan suppresses hypofunction and decreased independence in patients with sequelae of cerebrovascular disorder requiring an intermediate level of care.

9. From Kampo medicine perspective

At 12 months, *oketsu* and *jinkyō* significantly improved in arm 1, but *oketsu* remained unchanged and *jinkyō* worsened in arm 2, resulting in a significant between-arm difference. In contrast, there was no significant difference in *qikyo* and *qiutsu* between arms.

10. Safety assessment in the article

One patient in arm 1 felt numbness in hands and feet. Since the cause (tokishakuyakusan, amantadine hydrochloride, or captopril) was unclear, all these drugs were discontinued in this patient.

11. Abstractor's comments

In this valuable report about the 1-year follow-up of patients with sequelae of cerebrovascular disorder, tokishakuyakusan was shown to suppress the hypofunction and decreased independence observable in the control group at 12 months. Since the sample size is small (15 or 16 patients), a study with a larger sample size is expected in the future. Further exploration of Kampo medicines potentially able to improve this condition is also expected.

12. Abstractor and date

Namiki T, 12 March 2009, 1 June 2010.

9. Cardiovascular Diseases

References

Goto H, Satoh N, Hayashi Y, et al. A Chinese herbal medicine, tokishakuyakusan, reduces the worsening of impairments and independence after stroke: A 1-year randomized, controlled trial. *Evidence-based Complementary and Alternative Medicine* 2009: 1–6 (2011: 1-6. doi: 10.1093/ecam/nep026).

Evidence-based Complementary and Alternative Medicine 2009: 1-6. (2011: 1-6. doi: 10.1093/ecam/nep026) Pubmed ID: 19332457

1. Objectives

To evaluate the effectiveness of tokishakuyakusan (当帰芍薬散) in reducing impairment and increasing independence in post-stroke patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Tonami General Hospital and Yoshimi Hospital, Japan.

4. Participants

Thirty-one post-stroke patients hospitalized between October 2005 and January 2006 with a history of cerebral bleeding, infarction, or subarachnoid hemorrhage as well as paralysis due to cerebral lesions. (cerebral infarction, 23 cases; cerebral bleeding, 7 cases; subarachnoid hemorrhage, 1 case). The patients were in the post-acute phase of recovery.

5. Intervention

Arm 1: Tokishakuyakusan (Tsumura Tokishakuyakusan [当帰芍薬散] Extract Granules [TJ-23] 7.5 g/day for 12 months).

Arm 2: no tokishakuyakusan treatment.

6. Main outcome measures

Impairments were assessed using the Stroke Impairment Assessment Set (SIAS). Independence status was assessed using the Functional Independence Measure (FIM).

7. Main results

SIAS scores for several items such as finger-function and knee-extension decreased significantly in arm 2 ($P < 0.05$), whereas no significant change was observed in arm 1. Likewise, FIM scores indicated a worsening of functional status in arm 2 and prevention of that worsening in arm 1.

8. Conclusions

Tokishakuyakusan reduces the increase in impairment after stroke.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in the tokishakuyaku arm withdrew because of numbness in his limbs, which was not attributable to tokishakuyakusan.

11. Abstractor's comments

This protocol of post-stroke tokishakuyakusan administration was not expected (from the *Kampo* way of thinking) to prevent impairment. Suffice it to say that tokishakuyakusan administration might reduce *kan-kekkyo* (肝血虚, liver blood deficiency). The authors conducted this study on the basis of the reports suggesting the efficacy of tokishakuyakusan for the treatment of cognitive impairment due to Alzheimer's disease. As evidence-based medicine (EBM) becomes widely accepted, there will be more reports of applications that transcend classical *Kampo* theory. As societies age, the importance of preventing post-stroke impairment will increase, and therefore the result obtained in this study is meaningful.

12. Abstractor and date

Nakata H, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Akiyama Y, Ohno S, Asaoka T, et al. The combination therapy with sarpogrelate hydrochloride and Kampo medicine (oren-gedoku-to or toki-shakuyaku-san) for Raynaud's phenomenon. *Japanese Journal of Oriental Medicine* 2001; 51: 1101-8 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the effectiveness of orengekuto (黄連解毒湯) in improving peripheral circulation in Raynaud's phenomenon.

2. Design

Quasi-RCT.

3. Setting

Two departments (Department of Rheumatology and Department of Oriental Medicine) in Saitama Medical School, Japan.

4. Participants

Twenty patients with Raynaud's phenomenon who consulted at the above two departments between October and March from 1994 to 1997 (3 men and 17 women).

5. Intervention

Arm 1: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals.

Arm 2: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals, and orengekuto (黄連解毒湯) 2.5 g t.i.d. before meals.

Arm 3: oral administration of sarpogrelate hydrochloride (100 mg) in three divided doses after meals, and tokishakuyakusan (当帰芍薬散) 2.5 g t.i.d. before meals.

6. Main outcome measures

Raynaud's phenomenon – subjective symptoms (cold sensation, numbness, pain) and increase in skin temperature assessed by thermography (increase of more than 0.6°C in the mean temperature of all 10 fingertips of both hands) – were evaluated before and after 12-week treatment. The efficacy was compared among subjects with different “*sho*” (証, pattern) (*jitsu-sho* [実証, excess pattern], *chukan-sho* [中間証, intermediate pattern], and *kyo-sho* [虚証, deficiency pattern]) in Kampo medicine.

7. Main results

After 12-week treatment, the combination with orengekuto had significantly higher efficacy than sarpogrelate hydrochloride alone (90% vs. 52.5%; $P<0.02$), while the combination with tokishakuyakusan had similar efficacy to sarpogrelate hydrochloride alone. Skin temperature at the fingertips was significantly increased in arm 3 ($1.8\pm 1.9^{\circ}\text{C}$; $P<0.02$) compared with arm 1 ($0.6\pm 0.8^{\circ}\text{C}$), and also significantly elevated in arm 2 ($4.1\pm 2.1^{\circ}\text{C}$; $P<0.005$) compared with arm 3. Combination therapy with Kampo formulations was effective in patients with *jitsu-sho*, but not in patients with *kyo-sho*.

8. Conclusions

Orengekuto combined with sarpogrelate hydrochloride has higher efficacy in the treatment of Raynaud's phenomenon. However, *kyo-sho* patients did not respond to this combination therapy and had higher incidence of adverse drug reactions (ADRs), suggesting the importance of prescriptions according to the patient's “*sho*.”

9. From Kampo medicine perspective

In this study, 72.7% of the subjects were regarded as *kyo-sho* type. No subject was identified as the so-called orengekuto-*sho* type – having conditions that are expected to respond to orengekuto therapy. In *kyo-sho* subjects, the efficacy of the orengekuto combination therapy was similar to that of sarpogrelate hydrochloride monotherapy, and a higher dropout rate was observed because of ADRs from the bitherapy. Therefore we suggest that administration of sarpogrelate hydrochloride plus orengekuto should be withheld from *kyo-sho* subjects.

10. Safety assessment in the article

ADRs of the orengekuto combination occurred in *kyo-sho* patients, including nausea (n=2) and diarrhea (n=2), neither of which was serious. No serious ADRs due to the tokishakuyakusan combination were noted.

11. Abstractor's comments

Sarpogrelate hydrochloride in combination with orengekuto, which has been reported to improve peripheral circulation, improved more efficiently peripheral circulation in Raynaud's phenomenon when compared with sarpogrelate hydrochloride monotherapy as positive control in this study. It is interesting that improvement was greater with this combination than with the tokishakuyakusan combination, even when more than 70% of subjects were *kyo-sho*. Further scientific evaluation with a larger number of subjects is awaited.

12. Abstractor and date

Ushiyama T. 1 April 2008, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Uchida N. A Randomized controlled trial of the Chinese herbal medicine keisi-bukuryo-gan (gui-zhi-fu-ling-wan) in the treatment of deep vein thrombosis. *Jomyakugaku (The Japanese Journal of Phlebology)* 2009; 20: 1-6 (in Japanese with English abstract). Ichushi Web ID: 2009139345

1. Objectives

To evaluate the effect of keishibukuryogan (桂枝茯苓丸) on swelling in patients with deep vein thrombosis (DVT) of the lower limb.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery, Mito Red Cross Hospital, Japan.

4. Participants

Twelve patients diagnosed with DVT of the lower limb by ultrasonography at the above-mentioned institution between January 2003 and December 2007.

5. Intervention

Arm 1: heparin (10,000 units/day) and urokinase (240,000 units/day), followed by oral warfarin plus TSUMURA Keishibukuryogan (桂枝茯苓丸) 2.5 g t.i.d. before meals for 6 months (n=6).

Arm 2: heparin (10,000 units/day) and urokinase (240,000 units/day), followed by oral warfarin (n=6). There were no differences in age, gender, and status of the affected limbs between the two arms.

6. Main outcome measures

Difference in the lower-leg circumference between the healthy and affected limb over the 6-month period of keishibukuryogan administration.

7. Main results

The difference in the lower-leg circumference decreased significantly in both arms ($P < 0.05$), while the rate of improvement ($[\text{pre-treatment circumference difference} - \text{post-treatment circumference difference}] / \text{pre-treatment circumference difference} \times 100\%$) was significantly higher in arm 1 ($66.1 \pm 20.5\%$) than in arm 2 ($34.0 \pm 13.7\%$; $P = 0.05$).

8. Conclusions

The administration of keishibukuryogan combined with warfarin following heparin and urokinase appears to be effective for reducing swelling associated with DVT of the lower limb.

9. From Kampo medicine perspective

Keishibukuryogan is a therapeutic agent for *oketsu* (瘀血, static blood) and appears to be effective for the treatment of DVT of the lower limb stemming from pathological conditions such as changes in blood coagulability, reduced blood fluidity, and microcirculatory disturbance. Patient selection and outcome from the perspective of Kampo medicine, such as the *bensho* (弁証, Kampo diagnosis) of *qi-ketsu-sui* (気血水, qi, blood, and water) or *gozou roppu* (五臟六腑, five viscera and six bowels) (気血水、五臟六腑弁証), are not mentioned in this paper.

10. Safety assessment in the article

Adverse reactions to keishibukuryogan were not reported.

11. Abstractor's comments

This study evaluated the effects of keishibukuryogan, a *kuoketsuzai* (驅才血劑, blood stasis-expelling formula), on swelling associated with DVT of the lower limb. This swelling may be caused by venous system dysfunction, impaired circulation through lymph vessels, or inflammation. While the site of action of keishibukuryogan is unknown, the paper suggests that *oketsu* may be involved in the pathogenesis of the swelling. The findings in this paper have introduced a new treatment for refractory DVT of the lower limb that appears to be valuable for clinical practitioners. I hope that, in the future, the mechanism (or mechanisms) of action of keishibukuryogan will be elucidated by the accumulation of cases and investigational approaches from different directions.

12. Abstractor and date

Ushiroyama T, 6 January 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Kato N, Kato K, Hosoi Y. Effects of Otsuji-to in patients with hemorrhoid using ALTA and LE combined therapy. *Igaku to Yakugaku (Journal of Medicine and Pharmaceutical Science)* 2008; 60: 747-53 (in Japanese). Ichushi Web ID: 2009068979 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the clinical efficacy of otsujito (乙字湯) combined with aluminum potassium sulfate/tannic acid (ALTA) sclerotherapy, the latest treatment for hemorrhoids.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two institutions: Furudate Kato Proctology & Surgery Clinic and Hosoi Surgery Clinic, Japan.

4. Participants

Twenty patients with hemorrhoids (stage III or IV according to the Goligher classification) who underwent ALTA alone or ALTA-LE (ligation and excision) at the above-mentioned two institutions between March and September 2008.

5. Intervention

Arm 1: ALTA alone or ALTA-LE, followed by treatment with Kanebo Otsujito (乙字湯) Extract Fine Granules 3 g b.i.d. orally before meals from postoperative day 1 for 4 weeks (n=10).

Arm 2: ALTA alone or ALTA-LE (n=10).

Non-steroidal anti-inflammatory drugs (NSAIDs) were used as needed for pain relief in both arms.

6. Main outcome measures

Spontaneous pain, pain during defecation, and blood C-reactive protein (CRP) level at weeks 1, 2, and 4 of the otsujito treatment; and usage of analgesics up to postoperative week 2.

7. Main results

The effects on blood CRP level at week 1, pain during defecation at week 2, and spontaneous pain at weeks 1 and 2 were significantly greater in arm 1 than in arm 2 ($P<0.05$). The usage of analgesics tended to be reduced in arm 1 than in arm 2 (median, 2 vs. 10 tablets; $P=0.09$). Although the incidence of induration and hemorrhoid shrinkage after ALTA was similar between arms, the period of induration-persistence (time to disappearance of induration) was significantly reduced in arm 1 (11.3 weeks) than in arm 2 (15.3 weeks; $P<0.05$).

8. Conclusions

Otsujito relieves postoperative spontaneous pain, pain during defecation, and persistent induration in patients who undergo ALTA with or without LE.

9. From Kampo medicine perspective

This study revealed that otsujito (unlike common Kampo medicines) has a rapid onset of action. The prevention of constipation seemed to mainly result from the purging effect of daio (大黃) and the intestine-moistening effect of toki (當歸). Unfortunately, postoperative pain relief from the perspective of Kampo medicine was not discussed in this paper.

10. Safety assessment in the article

Adverse reactions to otsujito were not reported in this study.

11. Abstractor's comments

Hemorrhoids are highly prevalent in the general population and can sometimes cause great discomfort and social embarrassment. This study demonstrated that otsujito, a traditional treatment for hemorrhoids, combined with ALTA sclerotherapy, the latest Western medical treatment for hemorrhoids, relieves pain after surgery and reduces the period of induration persistence. This study indicates the integration of modern Western therapy with oriental therapy (i.e., otsujito, long known, by itself, to be effective treatment for hemorrhoids) can enhance efficacy. The findings of this study have important implications for the future direction of hemorrhoids treatment. Otsujito may enhance the effects of tannic acid, such as inhibition of sterile inflammation and reduction of tissue damage. Further studies are expected to elucidate the mechanism of action of otsujito.

12. Abstractor and date

Ushiyama T, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

References

Abe Y. The efficacy of goshajinkigan against lymphedema*. *Kampo Igaku (Kampo Medicine)* 2002;25:284-7 (in Japanese). Ichushi Web ID: 2002140795

Abe Y, Kosugi I, Kasashima F, et al. Lymphedema and Kampo*. *Progress in Medicine* 2003; 23: 1538-9 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of lymphedema.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (department of cardiovascular surgery), Japan.

4. Participants

A total of 80 patients with lymphedema of the upper limbs (n=40) and lower limbs (n=40).

5. Intervention

Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (TJ-107) 2.5g t.i.d for 1 month in combination with compression therapy (n=40).

Arm 2: compression therapy without administration for 1 month (n=40).

6. Main outcome measures

Percentage reduction in edema: reduction in limb circumference assessed between the first visit (baseline) and after 1-month treatment was divided by baseline limb circumference, and expressed in percentage.

7. Main results

For lymphedema of the upper limbs, there was significant percentage reduction in arm 1 (15±3.4%) compared with arm 2 (5.7±1.2%; $P<0.05$). For lymphedema of the lower limbs, the percentage reduction was also significant in arm 1 (17.5±2.8% vs 6.7±0.8% in Arm 2; $P<0.05$).

8. Conclusions

Edema is significantly reduced in both patients with lymphedema of the upper limbs and those with lymphedema of the lower limbs by TSUMURA Goshajinkigan Extract Granules (TJ-107).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The indications for goshajinkigan are chronic nephritis, nephritic syndrome, low back pain, edema in the lower extremity, and oliguria. This RCT assessed the efficacy of goshajinkigan for the treatment of lymphedema secondary to surgical procedures. Secondary lymphedema is generally intractable in many cases despite combined treatments including lymph drainage massage, compression skin care, exercise therapy under compression, and administration of anticoagulants. It is very meaningful that goshajinkigan was shown to be efficacious. The problem is that this paper is published in a business periodical without peer review, and information on patients' background and so on is therefore insufficient. Also, since the efficacy of goshajinkigan plus compression was assessed, the effect of goshajinkigan alone will need to be evaluated by comparison with placebo and positive control drugs in the future.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

9. Cardiovascular Diseases

Reference

Nakamura H, Nakamura T, Nakagawa S et al. Efficacy of goreisan in treatment of orthostatic hypotension in patients with diabetes mellitus*. *Diabetes Frontier* 2000; 11: 561-3 (in Japanese). Ichushi Web ID: 2001041016 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the safety and efficacy of goreisan (五苓散) in the treatment of orthostatic hypotension in patients with diabetes mellitus.

2. Design

Randomized controlled trial (crossover design) (RCT- crossover).

3. Setting

One internal medicine clinic, Japan.

4. Participants

Ten patients with diabetes mellitus (type 1, 2; type 2, 8) associated with orthostatic hypotension diagnosed according to McDowell's criteria.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: Kanebo Goreisan (五苓散) Extract Tablets (EKT-17) 18 tablets/day, for 1 month, n=10.

Arm 2: placebo 18 tablets/day, for 1 month, n=10.

6. Main outcome measures

Body weight, subjective symptoms, and response to orthostatic challenge (change in blood pressure, plasma adrenaline noradrenaline, and aldosterone concentrations, and plasma renin activity) were evaluated at baseline, and 1 and 2 months after the start of treatment; adverse drug reactions (ADRs) were checked during the study.

7. Main results

There was no difference in body weight between the goreisan and placebo groups. The subjective symptom of orthostatic dizziness improved in 9 of 10 patients in the goreisan group, whereas no change was reported in all 10 subjects in the placebo group. Results of orthostatic challenge: Before standing, no significant difference was found in blood pressure between at baseline and after administration of goreisan or placebo. After standing, systolic and diastolic pressures increased significantly in the goreisan group ($P<0.05$), while no significant change was observed in the placebo group. There were no changes in the concentration of adrenaline, noradrenaline, or aldosterone, nor in plasma renin activity at orthostatic challenge after administration of goreisan or placebo.

8. Conclusions

In diabetic patients with orthostatic hypotension, goreisan improves subjective symptoms and normalized the decrease in blood pressure on standing.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no observed adverse drug reactions.

11. Abstractor's comments

General indications for goreisan are edema, nausea, vomiting, dizziness in subjects with thirst and decreased urine output. Authors applied this to diabetic orthostatic hypotension, which is neuropathic and intractable/ resistant to therapies in most cases. Modern medicine can prevent the decline in blood pressure on standing; however, problems such as adverse increase in supine blood pressure remain. In contrast, goreisan causes no increase in supine blood pressure, suggesting this Kampo formulation as an ideal therapeutic agent for orthostatic hypotension in diabetic patients. It is very meaningful that this randomized controlled trial demonstrated that goreisan has efficacy.

It is thought that further investigation with increased case numbers and multicenter trials will improve the reliability of data.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Homma Y. Kampo treatment of patients with common cold syndrome associated with fever. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1995; 46: 285–91 (in Japanese with English abstract). [CiNii](#)

1. Objectives

To compare the efficacy of Kampo treatment and fenoprofen as antipyretics in patients with common cold syndrome associated with fever.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Medical Administration Center, Hokkaido University, Japan.

4. Participants

Out of 246 patients with common cold, 80 patients with a temperature of 37°C or higher (Hokkaido University students) were included.

5. Intervention

Arm 1: administration of Kampo extracts (manufacturers, not specified): kakkonto (葛根湯; n=18), maoto (麻黄湯, n=9), keimakakuhanto (桂麻各半湯, n=3), chikujountanto (竹茹温胆湯, n=2), shoseiryuto (小青竜湯, n=1), keishikashakuyakuto (桂枝加芍薬湯, n=1), or kososan (香蘇散, n=1) 2.5 or 3.0 g t.i.d. according to *sho* (証, pattern) (total n=35).

Arm 2: administration of fenoprofen 400 mg t.i.d. (n=45).

6. Main outcome measures

Duration of fever, percentage of patients with fever during the course of treatment, rebound of fever, and duration of cold symptoms.

7. Main results

The duration of fever was significantly shorter in arm 1 (1.5±1.9 days) than in arm 2 (2.6±1.7 days; $P<0.001$). The percentage of patients with fever was significantly higher and the duration of cold symptoms was longer in arm 2 than in arm 1.

8. Conclusions

Kampo treatment is more effective than fenoprofen, an antipyretic used for fever associated with common cold.

9. From Kampo medicine perspective

Kampo prescriptions were administered according to *sho* in patients with fever associated with common cold.

10. Safety assessment in the article

None.

11. Abstractor's comments

This paper describes an interesting randomized controlled clinical trial that demonstrated the higher efficacy of Kampo treatment than fenoprofen (an antipyretic used for fever associated with common cold). In this trial, 246 patients with common cold were allocated to two groups using sealed envelopes. Of these, 80 patients with fever were selected as subjects in the trial. Allocation using sealed envelopes is often associated with poor maintenance of randomization, and, furthermore, a two-step selection process was used in this trial. Future studies are expected to improve randomization and include a placebo group.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Homma Y, Takaoka K, Yozawa H, et al. Effectiveness of mao-bushi-saishin-to in treating common cold syndrome - controlled comparative study using the sealed envelope method -. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1996; 47: 245–52 (in Japanese with English abstract). Ichushi Web ID: 1997025451 [CiNii](#)

Homma Y. Treatment of common cold by a Kampo medicine - Maobushisaishin-tou-. *Pharma Medica* 2007; 25: 19–21 (in Japanese). Ichushi Web ID: 2008035988 [MOL, MOL-Lib](#)

1. Objectives

To evaluate the effectiveness of maobushisaishinto (麻黄附子細辛湯) in relation to that of a generally available cold drug in treating common cold syndrome and in shortening the duration of symptoms.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

Nineteen hospitals in Hokkaido, Japan.

4. Participants

Inpatients and outpatients aged 3 years or older who were diagnosed as having common cold syndrome (n=171).

5. Intervention

From November 1992 until March 1993.

Duration of administration was for 3 days from the onset of the symptoms or visit to the hospital, or, in cases where the symptoms persisted, until the symptoms were relieved.

Arm 1: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules, 2.5 g t.i.d. (n=83).

Arm 2: general common cold drug (contains salicylamide, acetaminophen, anhydrous caffeine, and promethazine methylenedisalicylate), 1.0 g q.i.d. (n=88).

6. Main outcome measures

Overall improvement, overall safety (adverse effects), overall usefulness, and duration (time to relief of each symptom).

7. Main results

Overall improvement

The percent of patients with moderate or greater improvement was 81.9 in arm 2 and 60.3 in arm 1.

The between-group difference by *U*-test was significant ($P<0.01$).

Average days until the relief of symptoms

	Arm 1	Arm 2	$P<(U\text{-test})$
Fever	2.8 ± 1.5 (29)	1.5 ± 0.7 (27)	0.001
Feeling feverish	2.5 ± 1.5 (36)	1.8 ± 1.4 (29)	0.021
Cough and phlegm	3.5 ± 1.7 (20)	2.5 ± 1.2 (29)	0.034

Time to relief of symptoms

Using Kaplan-Meier method, 4 symptoms (fever, pain or discomfort in the throat, coughing, and phlegm) were relieved in significantly less time in arm 2.

8. Conclusions

Maobushisaishinto has significantly better efficacy in treating common cold syndrome than a generally available cold drug.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood urea nitrogen was mildly elevated in 1 patient in arm 1.

11. Abstractor's comments

Few RCTs have evaluated treatment for the common cold, even though it is a familiar and frequently occurring condition. This RCT appropriately uses average number of days until alleviation of fever, heat sensation, cough, and sputum secretion as the endpoints. In the early 1990s, researchers did not generally distinguish between primary and secondary endpoints. Hopefully future research will include comparative analysis of other Kampo prescriptions for the common cold, and include the Kampo pattern concept.

12. Abstractor and date

Fujisawa M, 9 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kaji M, Kashiwagi S, Yamakido M, et al. A double-blind, placebo-controlled study of TSUMURA Shosaikoto (TJ-9) for common cold*. *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Study)* 2001; 78: 2252-68 (in Japanese). Ichushi Web ID: 2002145787 [MOL](#), [MOL-Lib](#)

1. Objectives

To assess the efficacy and safety of shosaikoto (小柴胡湯) in patients with common cold.

2. Design

Double-blind randomized controlled trial (DB-RCT)

3. Setting

From September 1995 until March 1999.

Ten university hospitals, 42 community and other hospitals, and 2 clinics, Japan.

4. Participants

Patients with persistent symptoms for more than 5 days after the onset of common cold, age from 25 to 75 years, and complaints of at least one of the following symptoms: oral discomfort (bitter taste, sticky sensation, dysgeusia), anorexia, or malaise.

5. Intervention

The placebo had similar appearance and properties. Concomitant drug use was basically prohibited, except for dimemorfan phosphate (Astomin tablets) after day 3.

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules (TJ-9) 2.5g t.i.d., n=131.

Arm 2: placebo 2.5 g t.i.d., n=119.

Duration of administration: 1 week or less

6. Main outcome measures

Global improvement rating (comprehensive evaluation based on improvement rating of each symptom and patient's impression), improvement rating of each symptom], and safety evaluation.

7. Main results

At baseline, the patients allotted to arm 1 were not matched to those allotted to arm 2 in the severity of headache, and the amount and viscosity of sputum. General improvement was significantly better in arm 1 than in arm 2, with the percentage of patients rated 4 (improved) or 5 (markedly improved) on a 5-point scale being 64.1% and 43.7% in arm 1 and arm 2, respectively. Individual symptoms (throat pain and malaise at day 3-4, clearance of sputum, appetite, joint pain and muscular pain at the end of study) all were significantly better in arm 1.

8. Conclusions

For patients with persistent common cold associated with oral discomfort (bitter taste, sticky sensation, dysgeusia), decreased appetite, and/or malaise, shosaikoto is effective and useful.

9. From Kampo medicine perspective

Subject selection was made on the basis of persistent symptoms and discomfort in the mouth, which indicate "shosaikoto-*sho*"

10. Safety assessment in the article

Ten (7.4%) of 136 subjects in arm 1 and 15 (11.4%) of 132 subjects in arm 2) experienced adverse effects. However, there were no serious adverse drug reactions.

11. Abstractor's comments

This study is a large-scale DB-RCT on Kampo therapy fitted to "*sho*" in Kampo medicine.

12. Abstractor and date

Fujisawa M, 15 June2007, 1 April 2008.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Fujimori K, Suzuki E, Simojo F. Comparison between bakumondoto (mai men dong tang) and dextromethorphan hydrobromide in terms of effect on postinfectious cough: a pilot study. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 2001; 51: 725-32. Ichushi Web ID: 2001145417
[CiNii](#)

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for postinfectious cough.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Medicine, Niigata University Medical and Dental Hospital., and a general hospital (internal medicine department), Japan.

4. Participants

Non-smoking patients with postinfectious cough for whom other causes for cough were ruled out, n=25.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9g/day for 7 days, n=13.

Arm 2: administration of dextromethorphan hydrobromide 60mg/day for 7 days, n=12.

6. Main outcome measures

Cough scores (cough frequency and intensity) were self-assessed everyday on a scale ranging from 0 to 9.

7. Main results

Arm 1: the cough score of 5.4 ± 1.7 at baseline decreased significantly to 1.5 ± 1.3 on day 7.

Arm 2: the cough score of 4.1 ± 2.0 at baseline decreased significantly to 1.8 ± 1.3 on day 7.

The antitussive effect developed more rapidly in arm 1 than in arm 2.

8. Conclusions

Bakumondoto is effective for postinfectious cough in non-smoking patients, and the antitussive effect is prompt.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No serious adverse drug reactions were observed in either group.

11. Abstractor's comments

The cough in all patients resolved within 4 weeks. Dextromethorphan hydrobromide suppresses cough; however, it may adversely lead to delay in the healing process. Therefore, whether bakumondoto is effective for postinfectious cough in non-smoking patients should be studied by comparing arm 1 with an untreated/placebo control group (postinfectious cough in a natural course). As cough score is a subjective measure, assessment with objective measures is also necessary. In terms of Kampo medicine, postinfectious cough can be caused in a variety of pathologies (In: *Shanghanlun* [傷寒論, *Treatise on Cold Damage Diseases*]). There are different formulae for different pathologies. For some of these, bakumondoto is not effective.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nagano F, Yamada M, et al. A randomized comparison of cough-improvement effects between mao-bushi-saishin-to and western drugs for cold in common patients with allergic cold syndrome. *Kampo to Meneki Arerugi (Kampo and Immuno-Allergy)* 2005; 18: 56-67 (in Japanese with English abstract).

1. Objectives

To compare the cough-improvement effect of maobushisaishinto (麻黄附子細辛湯) and western drugs in patients with the common cold.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals and four clinics, Japan.

4. Participants

Patients with the common cold.

5. Intervention

The study duration was 15 years.

Arm 1: Tsumura Maobushisaishinto (麻黄附子細辛湯) Extract Granules (TJ-127), n=879.

Arm 2: Western drugs for the common cold, n=879.

6. Main outcome measures

Various subjective symptoms (i.e. fever, headache, chill etc.).

7. Main results

In various assessments, maobushisaishinto was more effective than western drugs.

8. Conclusions

Administration of maobushisaishinto is efficacious for the common cold syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

The methodology and the subjects in this randomized controlled trial were not described. "Cough-improvement effect" is mentioned only in the title, but not in the text. Considering the short time course of the common cold syndrome, it is unclear why the randomized controlled study has been conducted for the past 15 years and continues even now.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine)* 1993; 10: 19–23 (in Japanese).

1. Objectives

To compare the efficacy of treatment (Kampo medicine vs. Western medicine) for upper airway inflammation in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

Four hundred and nineteen children who presented with summer-time cold at the same clinic between 1 and 31 July 1991 were allocated to two groups in the order of presentation. High frequency rates of Coxsackie A2 and Coxsackie A4 were detected in the region at the time.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified; n=212): including those treated with keimakakuhanto (桂麻各半湯) (n=76), maoto (麻黄湯) (n=63), keishinimaoitto (桂枝二麻黄一湯) (n=14), keishinieppiitto (桂枝二越婢一湯) (n=9), ginglyosan (銀翹散) (n=8), saikokeishito (柴胡桂枝湯) (n=5), shoseiryuto (小青竜湯) (n=4), and shoseiryutogohangekobokuto (小青竜湯合半夏厚朴湯) (n=4).

Arm 2: Western medicine group (n=207). The drugs administered were not mentioned.

6. Main outcome measures

Number of consultations, and outcome assessed by the quantity of antibiotics used (oral and drip infusion), and incidence of asthmatic bronchitis, acute bronchitis, and pneumonia.

7. Main results

The numbers of consultations were one (159 patients), two (37), three (12), four (3), and five (1) in arm 1 and one (132 patients), two (44), three (14), four (7), five (6), six (2), seven (1), and eight (1) in arm 2. There were fewer consultations in arm 1. Eleven patients in arm 2 and 179 patients in arm 2 used oral antibiotics. No patients in arm 1 and 12 patients in arm 2 used intravenous drip antibiotics. Nine patients in arm 1 and eight in arm 2 suffered asthmatic bronchitis. One patient in arm 1 and 10 in arm 2 suffered acute bronchitis. No cases of pneumonia were observed in either group.

8. Conclusions

There were fewer consultations for upper airway inflammation in arm 1, which suggests that Kampo medicine accelerates recovery. There was less antibiotics use and fewer cases of acute bronchitis in arm 2.

9. From Kampo medicine perspective

The author discusses Kampo *sho* (証, pattern) in hypothetical terms, but appears to make no mention of the criteria used in this study for the selection of Kampo medicines for each patient.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Allocating participants by order of consultation made this a quasi-randomized controlled trial. This clinical trial was conducted before evidence-based medicine became widespread in Japan and before the introduction of the Consolidated Standards of Reporting Trials Statement. It is difficult to interpret the results because participants' ages or genders, details of the Western medicine interventions, or the criteria for administration of the Kampo medicines are not clearly specified. For its time, it was an advanced undertaking and may be considered a valuable report.

12. Abstractor and date

Tsuruoka K, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi (Journal of the Japan Pediatric Society for Oriental Medicine)* 2003; 19: 46–52 (in Japanese).

1. Objectives

To compare the efficacy of two different treatments, Western medicine and byakkokaninjinto (白虎加人参湯), on summertime cold.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

One hundred and sixty-four children who presented with fever of at least 38.5°C between 18 June and 17 August 2001 were allocated to two groups in order of presentation. Coxsackie A2, A4, A6, and A8, as well as adenovirus were detected in the region at the time.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified). Among 75 patients received byakkokaninjinto (白虎加人参湯), 37 patients returned their fever logs. Dosage and administration frequency are not mentioned (n=37).

Arm 2: Western medicine group. Among 89 patients received antibiotic PL granules for children (Cefzon®), 43 patients returned their fever logs. Dosage and administration frequency are not mentioned (n=43).

6. Main outcome measures

Fever duration defined as time from presentation (at least 38.5°C) to decline in body temperature to 37.5°C or less.

7. Main results

In arm 1 and arm 2, mean fever duration was 27.0 and 33.8 hours, respectively, and standard deviation was 18.3 and 28.0 hours. Fever lasted for 40 hours or more in three patients in arm 1 and 12 patients in arm 2. The longest fever duration was 106 hours in arm 1 and 144 hours in arm 2. No statistically significant differences were observed between the groups for any measure; however, fever duration, number of patients with fever duration of 40 hours or more, and longest fever duration were all less in arm 1 compared to arm 2.

8. Conclusions

Results suggest that byakkokaninjinto tends to shorten fever duration in comparison to Western medicine.

9. From Kampo medicine perspective

The characteristic symptoms of summer-time colds such as herpangina, fever, and sore throat are suggestive of the warm diseases (温病) of Kampo medicine. In Chinese traditional medicine, ginglyosan (銀翹散) is the first choice for warm diseases, while byakkokaninjinto is the first choice under the cold damage approach. Since ginglyosan is not covered by health insurance, byakkokaninjinto was used in this study because it is covered.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This trial is similar to the trial published by the author in 1993 (Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku [Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine]* 1993; 10: 19–23 [in Japanese]). This is a quasi-randomized controlled trial (i.e., participants were allocated in the order of consultation). Limiting the intervention drug to byakkokaninjinto gives the study design lucidity and facilitates interpretation of the results. Differences in the fever duration results may depend on how the time of fever onset was determined, so development of further research is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Kubo T. The effect of maoto for treatment of influenza infection in children. (from Presentation C-41 of the Japan Society for Oriental Medicine, 56th Annual Meeting) *Medicament News* 2005 Sep 5; 1846: 15 (in Japanese)

Kubo T, Nishimura H. Antipyretic effect of mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. *Phytomedicine* 2007; 14: 96-101. CENTRAL ID: CN-00577142, Pubmed ID: 17141491

1. Objectives

To evaluate the effect of maoto (麻黄湯) in combination with oseltamivir on the duration of fever.

2. Design

Randomized controlled trial (RCT) (partly).

3. Setting

A hospital screening patients from January to May 2004, Japan.

4. Participants

Children (aged 0–13 years; n=60) suffering from influenza-like illness with fever of $\geq 38^{\circ}\text{C}$.

5. Intervention

Oseltamivir 2 mg/kg b.i.d., TSUMURA Maoto (麻黄湯) Extract Granules 0.06 g/kg t.i.d

Influenza infection was screened with a rapid diagnosis test, and diagnosis was confirmed by isolation of the virus or viral detection using RT-PCR

Arm 1: oseltamivir and maoto (麻黄湯); influenza A; n=14..

Arm 2: oseltamivir; influenza A; n=18

Arm 3: maoto (麻黄湯); influenza A; n=17.

(Influenza-positive patients [by the rapid test] were randomly assigned to arm 1 and arm 2. Arm 3 included influenza-positive patients under the age of 1 year, who did not meet the criteria for oseltamivir treatment, and influenza-negative patients aged 1 year or older. Patients [n=11] without confirmed influenza virus infections were excluded.)

6. Main outcome measures

Time to becoming afebrile after initiation of the treatment.

7. Main results

Body temperature was recorded every 6 hours in patients not treated with acetaminophen. The median period from commencement of treatment to alleviation of fever was 18 h, 24 h, and 15 h in arms 1, 2, and 3, respectively. Using the Wilcoxon rank sum test, significant differences were observed in arm 1 ($P<0.05$) and 3 ($P<0.01$) when compared with arm 2.

8. Conclusions

Maoto effectively reduces the duration of fever in children with influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse events in any group.

11. Abstractor's comments

This RCT consisted of 3 arms: arms 1 and 2 (patients randomly allocated) but not arm 3 (patients not randomly allocated) were compared. Hopefully the authors will conduct an RCT with all three arms, and if possible, use a placebo in a fourth arm. Given that maoto (麻黄湯) has adverse effects, future research would preferably include cohort studies and an RCT with a design that takes into account the predicted frequency of such adverse effects, as mentioned by the authors.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 22 February 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kimoto H, Kuroki H. Efficacy of combined administration of oseltamivir phosphate and maoto in treating influenza. *Kampo Igaku (Kampo Medicine)* 2005; 29: 166-9 (in Japanese). Ichushi Web ID: 2005292428

1. Objectives

To evaluate the efficacy of maoto (麻黄湯) in combination with oseltamivir phosphate in treating pediatric influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

An internal medicine clinic screening patients from January to March 2004, Japan.

4. Participants

Adult patients (n=37) positive for influenza (rapid diagnostic test), and having fever ($\geq 38^{\circ}\text{C}$) within 48 hours of onset.

5. Intervention

Nineteen out of 37 subjects were included in the sample. Eighteen subjects were excluded because of body temperature not more than 38°C (n=5), being on a drip (n=1), preference for Kampo formulae only (n=5), preference for Western drugs only (n=2), cognitive impairment (n=1), refusal to give consent to participate in the study (n=1), and regular use of Kampo formulae (n=3).

Oseltamivir phosphate (75 mg b.i.d. for 5 days), TSUMURA Maoto (麻黄湯) Extract Granules 2.5 g t.i.d. for 3 days), and Western medicines (an antihistamine [cycloheptadine hydrochloride] with either a bronchodilator [clenbuterol hydrochloride] or expectorant [carbocysteine]) were administered for 3 days.

Treatment assignment was chronological according to examination date.

Arm 1: oseltamivir phosphate and maoto (麻黄湯), n=10.

Arm 2: oseltamivir phosphate and Western medicines, n=9.

6. Main outcome measures

Body temperature.

The magnitude and time course of symptoms such as appetite, fatigue, and dizziness/light-headedness.

7. Main results

All subjects studied were infected with influenza A. Patients in arm 1 tended to become afebrile 12 hours earlier than patients in arm 2. There were no significant between-group differences in anorexia, fatigue, and dizziness/light-headedness, though patients in arm 1 tended to improve more rapidly than patients in arm 2.

8. Conclusions

Compared with oseltamivir plus Western formulations, oseltamivir plus Kampo formulation (maoto) tended to shorten the duration of fever and allowed patients to maintain normal activity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse events in any group.

11. Abstractor's comments

The graph shows that 12 hours after administration, fever dropped below 38°C in the maoto (麻黄湯) group, and temperature was a little above 38.5°C in the Oseltamivir phosphate-only group, which was a significant difference. After 24 hours, body temperature was about 37.5°C in both groups. However, no other clear differences in symptoms were observed between the two groups. Most of the adult participants commented that they felt more comfortable on the day after taking Oseltamivir phosphate, but adults are commonly prescribed acetaminophen in single doses as an antipyretic analgesic, and significantly, the study found that patients experienced fever as part of the natural course after administration. Exceptional cases may be excluded from the total number of cases.

12. Abstractor and date

Fujisawa M. 15 June 2007, 1 April 2008, 9 March, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and maoto for influenza – 3rd report-. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy) 2006; 19: 17-25 (in Japanese with English abstract).*

1. Objectives

To evaluate the efficacy of combined oseltamivir phosphate and maoto (麻黄湯) for the treatment of influenza in paediatric patients.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

February to March 2005.
One hospital and one clinic, Japan.

4. Participants

One hundred and seven children who presented within 48 hours of symptom onset, were febrile (body temperature, 38°C or higher), and were positive for influenza by the rapid diagnostic test.

5. Intervention

Treatment assignment was chronological according to examination date.

Oseltamivir phosphate was administered at a dose of 4mg/kg/day in two divided doses or 75 mg, b.i.d. for 5 days. TSUMURA Maoto (麻黄湯) Extract Granules were administered at a dose of 0.1-0.2kg/day in three divided doses or 2.5 g, t.i.d. for 3 days.

Arm 1: treatment with oseltamivir phosphate + maoto (麻黄湯) (n=57).

Arm 2: treatment with oseltamivir phosphate alone (n=55).

6. Main outcome measures

Clinical symptoms (appetite loss, myalgia, throat soreness, insomnia, cough, nasal discharge, vomiting), physical activity (kindergarten/school attendance, play), urination characteristics/frequency, fluid intake (quantity/frequency), body temperature (measured morning, noon, and night), and spasms.

7. Main results

Time to fever alleviation tended to be longer in arm 2 than arm 1.

Although there was no significant between-arm difference in appetite loss, fatigue, or dizziness, all outcome measures were slightly better in arm 1 than in arm 2.

8. Conclusions

Maoto can be administered safely and its combination with western medicine seems to improve symptoms further. Maoto seems to be a viable treatment for influenza in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

The study compared an Oseltamivir plus maoto (麻黄湯) group with an Oseltamivir-only group and found that the former had slightly shorter fever duration and slightly improved clinical symptoms. The sample size is larger and the combined use of Oseltamivir and maoto appears to have provided slightly greater efficacy. It is hoped that in a future paper, the authors will explain more clearly the analysis of their results, clarify their sampling methods, and present the evidence in terms of RCTs, not just for conference presentation purposes. Furthermore, the 2004 study (91 participants), which was carried out under the same conditions as this paper, was unclear on several points, including group allocation, and was not treated as an RCT.

12. Abstractor and date

Fujisawa M, 8 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Iwasaki K, Taguchi M, Cyong JC, et al. Effect of mao-bushi-saishin-to on influenza vaccination in elderly subjects: a randomized controlled study. *Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)* 2004; 17: 97-103 (in Japanese with English abstract).

Iwasaki K. Influenza and Kampo in the elderly*. *TSUMURA Mail Magazine* 2008; Suppl: 22-3 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) as an adjuvant for influenza vaccination in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Not documented, Japan.

4. Participants

Eighteen patients with antibody titers of <1:10 to two types of influenza A antigens (H1N1, H3N2) as measured using an hemagglutination inhibition (HI) assay.

5. Intervention

Arm 1: oral administration of TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules ([TJ-127]), 7.5 g/day, from 7 days before influenza vaccination until 14 days after vaccination; n=10.

Arm 2: no administration of TJ-127; influenza vaccination only; n=8.

6. Main outcome measures

Rise in antibody titer from baseline was measured at 4 weeks after vaccination and the rate of rise was compared between arms.

7. Main results

There was no significant between-arm difference in anti-H1N1 antibody titer. Anti-H3N2 antibody titer increased on average 4.9-fold in arm 2 (when compared with baseline) and 57.3-fold in arm 1 which was significant ($P<0.04$) when compared with arm 2. During the observation period, 2 patients in arm 2 but none in arm 1 became infected with influenza A virus.

8. Conclusions

The rise in anti-H3N2 antibody titer (but not anti-H1N1 antibody titer) was significantly greater in arm 1 than arm 2, suggesting that maobushisaishinto enhances the anti-H3N2 antibody titer induced by influenza vaccination and enhances specific immunity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Influenza infection complicated with infections such as pneumonia contributes substantially to mortality in the elderly. Therefore, boosting the production of anti-influenza virus antibody would have an important preventive effect and reduce the cost of influenza treatment. From these points of view, this study investigated whether administration of maobushisaishinto can increase antibody level, with the expectation that maobushisaishinto acts as an adjuvant of the humoral immune response in the elderly with low influenza-antibody level. This report focuses on strategies for the prevention of influenza in the elderly with low response to influenza vaccine. Further studies are needed to determine why only anti-H3N2 antibody titer is significantly increased compared with control group whereas no significant difference was observed in anti-H1N1 antibody, and whether maobushisaishinto can promote production of specific antibodies.

The small number of patients was a problem in this study. Further analyses with an increased number of cases are necessary. Also studies on other Kampo medicines with adjuvant effects in subjects with low antibody production against influenza virus, and on methods of administration, are awaited.

Iwasaki (2008) reported that the number of the participants is higher, i.e., 18 in arm 1 (the maobushisaishinto group) and 15 in arm 2 (the control group). The results were almost the same, revealing elevated anti-H3N2 antibody titer in arm 1.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 12 March 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. *Nihon Hoka Daijiryō Gakkaishi (Japanese Journal of Complementary and Alternative Medicine)*. 2010; 7: 59–62 (in English with Japanese summary). [J-STAGE](#)

1. Objectives

To evaluate the efficacy of coadministration of maoto (麻黄湯) and shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single clinic, Japan.

4. Participants

Fourteen outpatients (18 years or older) who presented within 48 hours after onset of fever (body temperature above 37.5°C) with influenza-like symptoms (upper respiratory tract symptoms or systemic symptoms) and tested positive for influenza A antigen from December 2007 to March 2008.

5. Intervention

Arm 1: administration of TSUMURA Maoto (麻黄湯) Extract Granules 2.5 g t.i.d. + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for 3 days (n=6).

Arm 2: administration of oseltamivir 75 mg b.i.d. for 5 days (n=8).

6. Main outcome measures

Duration of fever, highest body temperature, and number of doses of antipyretics and cough medicines.

7. Main results

There was no significant between-arm difference in duration of fever after onset (2.8±0.8 [mean±SD] days in arm 1 and 2.9±0.7 days in arm 2), duration of fever after treatment (2.9±0.7 days in arm 1 and 2.0±0.6 days in arm 2), the highest body temperature (39.0±0.7°C in arm 1 and 38.8±0.5°C in arm 2), and the number of doses of antipyretics and cough medicines administered.

8. Conclusions

The efficacy of maoto plus shosaikoto for treating influenza A in adults was comparable to that of oseltamivir.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed in both arms.

11. Abstractor's comments

This paper reports a randomized controlled trial of maoto plus shosaikoto for treatment of influenza A. The effect of maoto combined with shosaikoto was comparable to that of oseltamivir. To strengthen the evidence, the efficacy needs to be confirmed in a study with a larger sample size. However, coadministration of maoto and shosaikoto is not logical from the viewpoint of Kampo medicine. Patients who did not respond to maoto should be treated with daiseiryuto (大青竜湯), keishinieppiichito (桂枝二越婢一湯), saikatsugekito (柴葛解肌湯), or saikokeishito (柴胡桂枝湯) according their excess or deficiency (虚実) pattern, and not with maoto plus shosaikoto.

12. Abstractor and date

Okabe T, 24 December 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Saita M, Naito T, Boku S, et al. The efficacy of ma-huang-tang (maoto) against influenza. *Kampo to Meneki Arerugi (Kampo and Immuno-allergy)*. 2010; 23: 17–26 (in Japanese with English abstract).

Saita M, Naito T, Boku S, et al. The efficacy of *ma-huang-tang* (maoto) against influenza. *Health* 2011; 3: 300-3.

1. Objectives

To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital outpatient department, Japan.

4. Participants

Forty-five patients (20 years or older) visiting the hospital between November 2008 and March 2009 and testing positive for type A influenza antibody using a rapid diagnosis kit.

5. Intervention

Subjects were randomized to either of two arms, using Microsoft Excel.

Arm 1: TSUMURA Maoto (麻黄湯) Extract Granules (n=22).

Arm 2: no administration of maoto (n=23).

6. Main outcome measures

Symptoms (pyrexia [period from administration of drugs to afebrility], arthralgia, myalgia, headache, cough, and malaise) scored on a 5-point scale. Scores recorded daily for 5 days and sent by mail by each participant.

7. Main results

Records of symptoms including fever, etc., were obtained by mail. After excluding 8 patients whose data were not available, patients who provided complete data for analysis (18 patients in arm 1, of whom 9 patients taking oseltamivir concomitantly, and 19 patients in arm 2, of whom 13 taking oseltamivir and 6 taking zanamivir) were included for analysis. Of these 37 patients, 7 patients in arm 1 and 11 patients in arm 2 had received influenza vaccination. At the time of the allocation, there were no significant differences in age (arm 1, 31.1 ± 9.77 years; arm 2, 33.6 ± 13.1 years), the presence or absence of fever at the first visit, and duration of fever. During the period from administration of drugs to afebrility, there was no between-arm difference in duration of fever. Although the time to improvement of myalgia tended to be faster in arm 1, the time to disappearance of other symptoms was similar in both arms.

8. Conclusions

Maoto and anti-influenza agents have the same antipyretic effects in patients with influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a conference presentation by Saita et al. This structured abstract is based on the paper. It is interesting that the authors found no significant differences in the effects of maoto and other agents on the clinical course of influenza infection. However, there is a source of bias in the use of anti-influenza agents, and the finding of no significant differences should be interpreted with caution. Their conclusion is based on a comparison of the efficacy of maoto and anti-influenza drugs, but the two groups cannot be compared using this study design. Saita et al. (2011) and Saita et al. (2010) are the same clinical controlled trial. The analysis groups are divided into four groups: a maoto-only group, a combined maoto and oseltamivir group, an oseltamivir-only group, and a zanamivir-only group. There was no significant between-group difference in fever duration, which points to maoto being a useful anti-influenza drug. While the study was a retrospective statistical analysis, its significance is clear.

12. Abstractor and date

Fujisawa M, 14 January 2011, 19 April 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. *Journal of Infection and Chemotherapy* 2012; 18: 534-43. Pubmed ID: 22350323

1. Objectives

To compare the efficacy of oseltamivir, zanamivir, and maoto (麻黄湯) in adult influenza patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Outpatient Department, Fukuoka University Hospital, Japan.

4. Participants

Thirty-three outpatients examined between January and April 2009 who were rapid diagnostic test positive within 48 hours after onset of influenza symptoms (age range: 20–64 years).

5. Intervention

Participants were divided into three groups by computer randomization.

The only concomitant drug allowed was acetaminophen (400 mg), for high fever and headache.

Arm 1: TSUMURA Maoto (麻黄湯) Extract Granules group: 2.5 g t.i.d. for 5 days taken orally (n=11).

Arm 2: Oseltamivir group (2 type B patients): 75 g b.i.d. for 5 days taken orally (n=10).

Arm 3: Zanamivir group (2 type B patients): 20 mg b.i.d. for 5 days by inhalation (n=12).

6. Main outcome measures

The main endpoints were fever after commencement of treatment and period of symptom improvement.

Other endpoints were viral persistence, safety, and serum levels of cytokines (IFN- α , IL-6, IL-8, IL-10, and TNF- α).

7. Main results

The data from 10 participants in arm 1, 8 in arm 2, and 10 in arm 3 were analyzed because there were dropouts. Participants recorded body temperature three times a day and symptoms for 5 days, then mailed the records to the hospital. The fever threshold was defined as 37.5°C. Fever duration was the time from drug administration till body temperature fell to 37.5°C or less. The period from onset to drug administration was 17 hours in arm 1, 22 hours in arm 2, and 26 hours in arm 3. Median fever duration was 29 hours in arm 1, 46 hours in arm 2, and 27 hours in arm 3, demonstrating a significant difference between arm 1 and arm 2 ($P<0.05$). There was no significant difference in persistence of symptoms among the three arms.

Viral tests and cytokine measurements were done on days 1 (the day of the examination), 3, and 5. The virus was a 2009 seasonal virus, its persistence in the body on days 1, 3, and 5, respectively, were 7/7, 3/7, and 1/7 in the maoto group, 6/6, 2/6, and 1/6 in the oseltamivir group, and 5/5, 3/5, and 1/5 in the zanamivir group. The surviving viruses were type A in the maoto group, and type B in the oseltamivir and zanamivir groups. There was no significant difference in cytokine levels among the three groups.

8. Conclusions

Maoto and neuraminidase inhibitors have similar effects on seasonal influenza viruses in healthy adults.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant in the maoto group and one in the oseltamivir group had slightly raised levels of liver function enzyme, which normalized in two weeks.

11. Abstractor's comments

The paper clearly presents the design and results of the study and is thoroughly convincing in demonstrating no significant difference in fever and symptom duration between the maoto-only group and neuraminidase inhibitor groups. The paper is also interesting for its investigation of virus survival and cytokine levels, as well as its proposition of an antiviral action unrelated to cytokines.

12. Abstractor and date

Fujisawa M, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku (Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine)* 1993; 10: 19–23 (in Japanese).

1. Objectives

To compare the efficacy of two different treatments (a Kampo medicine treatment and a Western medicine treatment) on influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

Seven hundred and eighty-three children who presented with influenza at the same clinic between 1 and 28 February 1992 were allocated to two groups in the order of presentation. Hong Kong A strain was prevalent in the region at the time and Russian A strain was also present in small numbers.

5. Intervention

Arm 1: Kampo medicine group (manufacturer not specified; n=386): including those treated with maoto (麻黄湯) (n=200), keimakakuhanto (桂麻各半湯) (n=143), makyokansekitto (麻杏甘石湯) (n=15), kakkonto (葛根湯) (n=8), keishinieppiitto (桂枝二越婢一湯) (n=8), keishinimaoitto (桂枝二麻黄一湯) (n=4), saikokeishito (柴胡桂枝湯) (n=4), shoseiryuto (小青竜湯) (n=3), etc.

Arm 2: Western medicine group (n=397). Details of the drugs administered are not mentioned.

6. Main outcome measures

Number of consultations, and outcome assessed by the quantity of antibiotics used (oral and drip infusion) and incidence of asthmatic bronchitis, acute bronchitis, and pneumonia.

7. Main results

The numbers of consultations were one (156 patients), two (130), three (51), four (32), five (11), six (4), seven (1), eight and nine (0), and ten (1) in arm 1 and one (190 patients), two (123), three (49), four (17), five (10), six (4), seven (3), eight (1), and nine ten (0) in the Western medicine group. There was no significant between-group difference in the number of clinic visits. Fifty-nine patients in arm 1 and 382 patients in arm 2 used oral antibiotics. Nine patients in arm 1 and 12 patients in arm 2 used intravenous antibiotics. Similar numbers of patients (9 in arm 1 and 12 in arm 2) suffered asthmatic bronchitis. The number of patients who suffered acute bronchitis was significantly lower in arm 1 than arm 2 (i.e., 12 vs 23, respectively, $P=0.05$). Two cases of pneumonia were diagnosed in arm 2 and none in arm 1.

8. Conclusions

There was no significant between-group difference in the numbers of consultations for influenza. The frequency of antibiotic use was lower in arm 1 while the severity and incidence of acute bronchitis was significantly higher in arm 2.

9. From Kampo medicine perspective

The author discusses Kampo *sho* (証, pattern) in hypothetical terms, but appears to make no mention of the criteria used to select Kampo medicines for each patient.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

As in the summer-time cold trial, participants were allocated in the order of consultation (i.e., this was a quasi-randomized controlled trial). This trial was conducted before evidence-based medicine became widespread in Japan and before the introduction of the Consolidated Standards of Reporting Trials Statement. It is difficult to interpret the results because participants' ages or genders, details of the Western medicine interventions, the criteria for administration of the Kampo medicines, or the statistical test details are not clearly specified. For its time, it was an advanced undertaking and may be considered a valuable report.

12. Abstractor and date

Tsuruoka K, 31 December 2013

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Abe K. Effects of treatment with Kampo medicine compared to Western medicine for cold symptoms (summer-time cold, influenza) — byakkokaninjinto and maoto*. *Nihon Shoni Toyo Igakkaishi (Journal of the Japan Pediatric Society for Oriental Medicine)* 2003; 19: 46–52 (in Japanese).

1. Objectives

To compare the efficacy on influenza of treatment with byakkokaninjinto (白虎加人参湯), maoto (麻黄湯), antibiotics, and amantadine.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A pediatric and internal medicine clinic in Shimane prefecture, Japan.

4. Participants

Children who presented with fever of at least 38.5°C between 1 February and 20 March 2002 were allocated in the order of presentation to four groups (antibiotics, amantadine, byakkokaninjinto, and maoto).

5. Intervention

Arm 1: antibiotic group: Cefzon®. Mean age 3.2 years (n=21).

Arm 2: amantadine group: Symmetrel®. Mean age 5.0 years (n=23).

Arm 3: maoto (麻黄湯) group (manufacturer not specified): Mean age 4.8 years (n=23).

Arm 4: byakkokaninjinto (白虎加人参湯) group (manufacturer not specified): Mean age 4.2 years (n=18).

Dosage and frequency are not mentioned for any of the drugs.

6. Main outcome measures

Fever duration (defined as time from presentation [at least 38.5°C] to decline in body temperature to 37.5°C or less), and outcome (bronchitis or pneumonia onset)

7. Main results

Mean fever duration (in hours) in groups treated with antibiotics, amantadine, maoto, and byakkokaninjinto was 52.7, 46.5, 47.0, and 69.3, respectively, which indicates the duration was the same for amantadine treatment and maoto treatment. Bronchitis occurred in four antibiotic patients, two amantadine patients, one maoto patient, and three byakkokaninjinto patients. Pneumonia occurred in two antibiotic patients, one amantadine patient, two maoto patients, and one byakkokaninjinto patient.

8. Conclusions

Results suggest that maoto and amantadine have similar effects on influenza.

9. From Kampo medicine perspective

Physicians should alter their prescriptions for influenza in response to the changing course of symptoms. The author discusses the need to change the prescriptions in this trial after maoto use. The changes were made in accordance with Kampo medical principles. The paper describes the clinical course of influenza in all 23 maoto patients.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This trial is similar to the trial published by the author in 1993 (Abe K. Outcomes of treatment for upper airway inflammation in children with Kampo medicine and Western medicine*. *Dai 10-kai Nihon Shoni Toyo Igaku Kenkyukai Koen Kiroku Nihon Shoni Toyo Igakkaishi [Proceedings of the 10th meeting of the Japan Pediatric Society for Oriental Medicine]* 1993; 10: 19–23 [in Japanese]). Although not mentioned in the paper, the diagrams imply that participants contracted influenza A. Unlike the previous trial, the present trial simplifies the study design by limiting the number of intervention drugs to four. However, diversification of prescription patterns after maoto use complicates interpretation of the results. The frequency of amantadine administration also decreased, so further development of this research is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2013

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kawamura K. No difference between two brands of maoto and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients*. *Nihon Shonika Rinsho (Japanese Journal of Pediatrics)* 2009; 62: 1855-61 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of two brands of maoto (麻黄湯) and oseltamivir in the time required to clear influenza virus from the pharynx in type A influenza patients.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One medical clinic, Japan.

4. Participants

One hundred and seventy-two influenza patients who tested positive for type A (quick diagnostic test kit) and whose throat swabs confirmed viral clearance from the pharynx.

5. Intervention

Arm 1: TEIKOKU (麻黄湯) Maoto Extract Granules (0.13–0.20 g/kg in three divided doses) for 1–6 days (n=64).

Arm 2: TSUMURA Maoto (麻黄湯) Extract Granules (0.11–0.21 g/kg in three divided doses) for 1–6 days (n=61).

Arm 3: Oseltamivir (2.1–4.4 mg/kg in two divided doses) for 1.5–5 days (n=47).

6. Main outcome measures

Defervescence period, general symptoms.

7. Main results

The mean defervescence period (hours) after taking medication (arm 3 [30.36 ± 20.96] vs arm 1 [45.73 ± 35.51] and arm 2 [53.90 ± 39.42]; $P < 0.01$), the mean fever period (hours) (arm 3 [45.79 ± 21.05] vs arm 1 [67.27 ± 37.88] and arm 2 [69.57 ± 39.76]; $P < 0.01$), and the period until disappearance of symptoms (hours) (arm 3 [48.47 ± 26.90] vs arm 1 [70.47 ± 41.99] and arm 2 [73.95 ± 43.01]; $P < 0.01$) were significantly shorter in arm 3. The period from onset to influenza virus clearance (hours) was similar in arm 1 (98.00 ± 31.83), arm 2 (101.72 ± 34.39) and arm 3 (95.91 ± 30.80) ($P > 0.05$). The period from defervescence to influenza virus clearance (hours) was significantly shorter in arm 1 (31.73 ± 44.26) and arm 2 (32.15 ± 36.61) than in arm 3 (50.13 ± 32.84; $P < 0.01$).

8. Conclusions

Oseltamivir clears fever and improves symptoms faster than maoto. TEIKOKU Maoto, TSUMURA Maoto, and oseltamivir have the same efficacy in clearing type A influenza virus from the pharynx. TEIKOKU Maoto and TSUMURA Maoto have the same efficacy in terms of defervescence period, symptomatic period, and period until clearance of type A influenza virus from the pharynx.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is a controlled clinical trial of the effectiveness of two brands of maoto and oseltamivir and measured the time required to clear influenza virus from the pharynx of patients with type A influenza virus. It is a quasi-randomized controlled trial in which drug treatments were allocated in the order of consultation. Oseltamivir reduced fever and improved symptoms faster than maoto. On the other hand, it is very interesting that oseltamivir and maoto had similar effectiveness in clearing influenza virus. The fact that there was no difference between the two brands of maoto verifies the homogeneity of Japanese Kampo preparations.

12. Abstractor and date

Okabe T, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kuroki H, Kimoto H. Successful treatment of combination therapy with oseltamivir and mao-to for influenza. *Kampo to Meneki-Arerugi (Kampo and Immunoallergy)* 2005; 18: 47-55 (in Japanese with English abstract).

1. Objectives

To compare the effect the combination of oseltamivir phosphate and Western medications with that of oseltamivir phosphate and maoto (麻黄湯) for pediatric influenza.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: Hospital pediatric outpatient department, Japan.

4. Participants

Ninety-one pediatric patients (1–16 years) who were examined between January and March 2004, showed flu-like symptoms within 48 hours of onset, and rapid diagnostic test positive for influenza.

5. Intervention

Treatment assignment in the order of consultation.

Oseltamivir phosphate (4 mg/kg or 150 mg in two divided doses) for 5 days, TSUMURA Maoto (麻黄湯) Extract Granules (0.1–0.2 g/kg in three divided doses) for 3 days. The Western medications were bronchial dilator, anti-histamine, and expectorant.

Arm 1: Oseltamivir phosphate plus Maoto (n=48).

Arm 2: Oseltamivir phosphate plus Western medications (n=43).

6. Main outcome measures

Clinical symptom score using the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) to assess loss of appetite, muscle ache, sore throat, insomnia, cough, nasal discharge, vomiting, activity level, and return to school/kindergarten and play; urine condition and urination frequency; fluid intake frequency and volume; body temperature (measured every eight hours: morning, noon, and evening); presence/absence of cramps; and medication as recorded by parent/guardian.

Adverse events were collected by query of visiting outpatients or by phone at weeks 2, 4, and 8.

7. Main results

Mean duration of fever (38°C, in hours) was similar between groups: 27.6 ± 3.6 (SE) in arm 1 and 36.2 ± 4.3 in arm 2, showing no significant difference, although duration tended to be shorter in arm 1. There was no significant between-group difference in the CARIFS score over the five-day follow-up period.

8. Conclusions

Maoto can be administered safely and has almost the same effectiveness when combined with Western medications. It appears that maoto combined with oseltamivir may be used effectively for pediatric influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were observed in the two groups.

11. Abstractor's comments

This report is from the proceedings of a symposium. The number of participants is sufficient for analysis, and the effects and safety outcomes appear to suggest that maoto may be used in place of Western medications for relief of symptoms. The authors neglected to mention (in the results) the outcomes that were indicated in the methods; however, hopefully they will formally address this in a further paper. Notably, the Western medications did not include any anti-pyretic analgesics.

12. Abstractor and date

Fujisawa M, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Watanabe N, Miyazawa T. Comparative investigation of the antitussive effects of bakumondoto and tipepidine hibenzate in cases of mycoplasma bronchitis. *Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)* 2007; 21: 31-6 (in Japanese with English abstract).

Watanabe N, Nakagawa T, Miyazawa T. Examination of effective antitussive against cough caused by mycoplasma bronchitis. *Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)* 2008; 22: 63-8 (in Japanese with English abstract).

1. Objectives

To compare the efficacy of bakumondoto (麦門冬湯) with that of tipepidine hibenzate for suppressing cough in patients with mycoplasma bronchitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

An internal medicine department in a hospital (the authors belong to the faculty of the Division of Respiratory and Infectious Diseases, Department of Internal Medicine, St. Marianna University School of Medicine), Japan.

4. Participants

Twenty patients with mycoplasma bronchitis who exhibited no signs of pneumonia on chest radiographs.

5. Intervention

Arm 1: azithromycin 500 mg for 3 days and TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 2 weeks (n=6).

Arm 2: azithromycin 500 mg for 3 days and tipepidine hibenzate 60 mg for 2 weeks (n=8).

Arm 3: azithromycin 500 mg for 3 days, tipepidine hibenzate 60 mg for 2 weeks, and TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 2 weeks (n=6).

6. Main outcome measures

Cough score, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) level.

7. Main results

In arms 1 and 3, cough score was significantly decreased on day 5 compared with day 1 after the first visit ($P<0.05$). In arm 2, cough score was significantly decreased on day 7 ($P<0.05$). The rate of cough score decline was significant on day 5 in arms 1 and 3 ($P<0.05$) and on day 11 in arm 2 ($P<0.05$). The cumulative decline in cough score from day 1 to day 14 was highest in arm 3. There were no significant differences in white blood cell count, erythrocyte sedimentation rate, and CRP level.

8. Conclusions

Combination therapy with azithromycin and bakumondoto or tipepidine hibenzate appears to be effective in the treatment of cough in patients with mycoplasma bronchitis. In addition, triple therapy with azithromycin, bakumondoto, and tipepidine hibenzate may be similarly effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Persistent cough in mycoplasma bronchitis is often difficult to treat. This interesting study evaluates the efficacy of azithromycin combined with bakumondoto and/or tipepidine hibenzate in treating cough in mycoplasma bronchitis in a randomized controlled trial. However, it uses allocation by the envelope method (which likely leads to difficulty in preserving randomization) and lacks a placebo-group as control. Furthermore, to determine the differences in efficacy among the three arms, post-administration cough scores must be compared among the three arms. In addition, some participants have persistent cough even after 2 weeks in all three arms. In future studies, Kampo "sho" (証, pattern) should be considered for bakumondoto.

12. Abstractor and date

Okabe T, 8 December 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Ohya Y. Kampo treatment for allergic diseases -from the viewpoint of a general hospital-. *Progress in Medicine* 1988; 8: 604–12 (in Japanese).

Ohya Y. Efficacy of preseasonal administration of shoseiryuto for cedar pollen allergy*. Kampo Shinryo 1991; 10: 42–8 (in Japanese).

1. Objectives

To evaluate the preventive effect and safety of preseasonal administration of syoseiryuto (小青竜湯) against cedar pollen allergy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (a department of otolaryngology), Japan.

4. Participants

Patients with cedar pollen allergy of mild or less severity (n=43).

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3 mg t.i.d. for 57 days (n=23).

Arm 2: ketotifen 1 g b.i.d. for 57 days (n=20).

Treatment period was from 7 February to 4 April 1987.

6. Main outcome measures

Change in subjective nasal symptoms was graded on a scale of 1–4 before and during the pollen dispersal period.

7. Main results

The data of 29 patients who completed nasal allergy diaries (15 in arm 1 and 14 in arm 2) were analyzed. There were no significant between-arm differences in moderate or better improvement effects on the following symptoms: sneezing (66.7% in arm 1, 64.3% in arm 2), nasal discharge (60% in arm 1, 57.1% in arm 2), nasal obstruction (86.7% in arm 1, 85.7% in arm 2), and overall nasal symptoms (66.7% in arm 1, 64.3% in arm 2).

8. Conclusions

Preventive effects of shoseiryuto and ketotifen on cedar pollen allergy are equivalent.

9. From Kampo medicine perspective

Among the 15 patients in the shoseiryuto arm, 1 patient had *jitsu-sho* (実証, excess pattern) and 14 patients had *chukan-sho* (中間証, intermediate pattern).

10. Safety assessment in the article

Mild diarrhea was observed in 1 patient in arm 1.

11. Abstractor's comments

This randomized controlled trial demonstrated that the clinical effectiveness of shoseiryuto for preventing mild cedar pollen allergy was equivalent to that of the oral anti-allergy drug ketotifen. The flaw in this study is that the endpoint is not objective. Change in the subjective nasal symptoms is judged from patients' nasal allergy diaries. Also the patients enrolled in this study have mild or less severity disease and therefore the results of this study should be evaluated with caution. Shoseiryuto is expected to prevent cedar pollen allergy in patients with the appropriate *sho*. However, further clinical trials considering this point are awaited.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Mori H. Comparative study of Kampo preparations sho-seiryu-to and ryokankyomishingenin-to for nasal allergy. *Therapeutic Research* 1996; 17: 3691-6 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effects of shoseiryuto (小青竜湯) and ryokankyomishingeninto (苓甘姜味辛夏仁湯) on spring nasal allergy (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital and two clinics, Japan.

4. Participants

Forty-one patients who were first diagnosed with pollinosis from January 25, 1996 to April 1, 1996.

5. Intervention

Arm 1: TSUMURA Ryokankyomishingeninto (苓甘姜味辛夏仁湯) Extract Granules 2.5 g t.i.d., 20 patients enrolled, 15 patients analyzed.

Arm 2: TSUMURA Shoseiryuto (小青竜湯) Extract Granules 3.0 g t.i.d., 21 patients enrolled, 15 patients analyzed.

Group assignment in the order of receipt; concomitant use of Intal Nasal Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Improvement in sneezing, runny nose, and nasal congestion.

7. Main results

There was no significant between-arm improvement in sneezing, runny nose, or nasal congestion.

Improvement was mild or better in 66.7% and 80.0% of patients in Arms 1 and 2, respectively, indicating no significant between-arm difference.

8. Conclusions

Ryokankyomishingeninto and shoseiryuto have similar efficacy for pollinosis, but shoseiryuto has more efficacy for nasal congestion.

9. From Kampo medicine perspective

Kyo-sho (虚証, deficiency pattern) patients were excluded.

10. Safety assessment in the article

One patient treated with ryokankyomishingeninto developed leg edema and gained body weight but had no abnormal hematology findings. Shoseiryuto was not associated with any problems.

11. Abstractor's comments

Dr. Mori has published several articles comparing Kampo preparations with shoseiryuto as control in the treatment of pollinosis. Clarification of the differences in the characteristics of Kampo preparations based on these data would be a great help to those who practice Kampo medicine.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations sho-seiryu-to and eppika-jutsu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1997; 18: 3093-9 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) and eppikajutsuto (越婢加朮湯) for spring allergic rhinitis (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

One hundred thirty-five patients who were first diagnosed with pollinosis from January 27, 1997 to April 5, 1997. *Kyo-sho* (虚証, deficiency pattern) patients were excluded.

5. Intervention

Arm 1: JPS Shoseiryuto (小青竜湯) Extract Granules 2.5 g t.i.d. (68 patients enrolled, 45 patients analyzed).

Arm 2: JPS Eppikajutsuto (越婢加朮湯) Extract Granules 2.5 g t.i.d. (67 patients enrolled, 49 patients analyzed).

Assignment in the order of receipt; concomitant use of Intal Nasal Drops/Eye Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Measures of improvement in sneezing, runny nose, nasal congestion, periocular itching, lacrimation, eye discharge, and eye pain.

7. Main results

No significant between-arm difference was observed in any symptom except runny nose, which was significantly improved in arm 1.

Mild or better improvement was achieved in the severity of periocular itching (55.6% and 65.3%) and lacrimation (13.3% and 16.3%), and moderate or better global improvement was achieved in the severity of nasal symptoms (53.3% and 67.3%) in arms 1 and 2, respectively. There was no significant between-arm difference in the percentage of patients with improved symptoms.

8. Conclusions

Both eppikajutsuto and shoseiryuto had effects on pollen allergy without significant difference between them.

9. From Kampo medicine perspective

Since shoseiryuto is used in *chukan-sho* (中間証, intermediate pattern) to *jitsu-sho* (実証, excess pattern) patients, and eppikajutsuto is used in physically strong patients, physically weak patients were excluded. Eppikajutsuto, which contains *Sekko* (石膏, gypsum), is intended to reduce fever-related symptoms such as periocular itching, hyperemia, or skin warmth.

10. Safety assessment in the article

Epigastric pain and nausea occurred in 1 patient treated with eppikajutsuto, and rash occurred in 1 patient treated with shoseiryuto.

11. Abstractor's comments

Dr. Mori's articles on pollinosis have focused on shoseiryuto. Refer to "Baba S, Takasaka T, Inamura N et al. Efficacy of shoseiryuto for perennial nasal allergy - double-blind controlled study - *Jibiinkoka Rinsho (Practica otologica)* 1995; 88: 389-405".

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Mori H. Comparative study of Kampo preparations sho-seiryu-to and dai-seiryu-to for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1998; 19: 3299-307 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of shoseiryuto (小青竜湯) and daiseiryuto (大青竜湯) (keishito plus makyokansekitto) (桂枝湯合麻杏甘石湯) for spring allergic rhinitis (pollinosis).

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One clinic, Japan.

4. Participants

Fifty-six patients who were first diagnosed with pollinosis from January 26, 1998 to April 9, 1998. *Kyo-sho* (虚証, deficiency pattern) patients were excluded.

5. Intervention

Arm 1: Kotaro Shoseiryuto (小青竜湯) Extract Fine Granules 2.5 g t.i.d. (28 patients enrolled, 15 patients analyzed).

Arm 2: Daiseiryuto (大青竜湯) (Kotaro Keishito [桂枝湯] Extract Fine Granules 5 g + Kotaro Makyokansekitto [麻杏甘石湯] Extract Fine Granules 9 g) 14.0 g/day in three divided doses (28 patients enrolled, 24 patients analyzed).

Group assignment in the order of receipt; concomitant use of Intal Nasal Drops/Eye Drops (sodium cromoglycate) for severe symptoms.

6. Main outcome measures

Measures of severity of sneezing, runny nose, nasal congestion, periocular itching, lacrimation, eye discharge, and eye pain.

7. Main results

There was no significant between-arm improvement in symptoms.

Overall improvement (in severity of nasal symptoms) was mild or better in 46.7% and 87.5% of patients in Arms 1 and 2, respectively, and significantly different between arms.

8. Conclusions

Shoseiryuto and daiseiryuto have similar efficacy for individual symptoms; daiseiryuto has significantly greater clinical efficacy than shoseiryuto for overall symptoms.

9. From Kampo medicine perspective

Since shoseiryuto is used in *chukan-sho* (中間証, intermediate pattern) to *jitsu-sho* (実証, excess pattern) patients, physically weak patients were excluded. Because “Mori H, Shimazaki Y, Kurata H, et al. Comparative study of Kampo preparations Sho-Seiryu-To and Eppika-Jutsu-To for nasal allergy and allergic conjunctivitis. *Therapeutic Research* 1997; 18: 3093-9 (in Japanese with English abstract)” showed that eppikajutsuto was effective for pollinosis, daiseiryuto (containing mao [麻黄, ephedra herb] and sekko [石膏, gypsum], constituent crude drugs of eppikajutsuto) was used in this controlled trial.

10. Safety assessment in the article

One patient treated with daiseiryuto experienced hand, foot, and eyelid edema and body weight gain, which were later found to be associated with pseudoaldosteronism.

11. Abstractor's comments

Dr. Mori's articles on pollinosis have focused on shoseiryuto. Refer to “Baba S, Takasaka T, Inamura N et al. Efficacy of shoseiryuto for perennial nasal allergy - double-blind controlled study - *Jibiinkoka Rinsho (Practica otologica)* 1995; 88: 389-405”.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Mori H, Kurata H, Shimazaki Y, et al. Comparative study of Kampo preparations sho-sei-ryu-to and kei-ma-kakuhan-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 1999; 20: 2941-7 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To compare the efficacy of shoseiryuto (小青竜湯), and keimakakuhanto (桂麻各半湯) in treating springtime nasal allergy and allergic conjunctivitis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

From 25 January 1999 until 10 April 1999.
One hospital and three clinics of internal medicine, Japan.

4. Participants

Eighty eight patients with springtime nasal allergy and allergic conjunctivitis. Of these patients, 65 were included for analysis.

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g, t.i.d. for 2 weeks, n=32.
Arm 2: keimakakuhanto (桂麻各半湯) 8.0 g/day in three divided doses (4.0 g of TSUMURA Keishito (桂枝湯) Extract Granules [TJ-45] + 4.0 g of TSUMURA Maoto (麻黄湯) Extract Granules [TJ-27]) for 2 weeks, n=33.

6. Main outcome measures

Improvement in each symptom and global improvement.

7. Main results

Efficacy (percent improvement in arm 1 and arm 2, respectively) was observed against sneezing (68.8% and 66.7%), rhinorrhea (56.3% and 63.6%), nasal sinus obstruction (40.6% and 30.3%), and periocular pruritus (46.9% and 54.5%); there was no significant difference in between-arm improvements. As for global improvement, 62.5% and 60.6% of patients in arm 1 and arm 2, respectively, were rated “moderately-to-markedly improved,” demonstrating no significant between-arm difference in efficacy.

8. Conclusions

Keimakakuhanto is as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the shoseiryuto arm, two subjects reported dry mouth, one reported gastric distension, and one reported stomach discomfort leading to discontinued administration; and in the keimakakuhanto arm, one reported dry mouth and one discontinued administration because of nausea.

11. Abstractor’s comments

As of 1999, no definite evidenced-based medicine (EBM) approach had been used to study the efficacy of Kampo formulations in treating springtime nasal allergy and allergic conjunctivitis. This paper presents a comparative study of the efficacies of two Kampo medicines, and further placebo-controlled analysis is awaited.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Yoshimoto T, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and maoh-bushi-saisin-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2002; 23: 2253-9 (in Japanese with English abstract). Ichushi Web ID: 2003161479 [MOL](#), [MOL-Lib](#)

1. Objectives

To compare the effects of shoseiryuto (小青竜湯) and maobushisaishinto (麻黄附子細辛湯) in treating springtime nasal allergy and allergic conjunctivitis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Five clinics of internal medicine, Japan.

4. Participants

Of the patients who visited the above-mentioned clinics for the first time with springtime nasal allergy and allergic conjunctivitis (allergic rhinitis), 66 having previously diagnosed pollen hypersensitivity/pollinosis or newly diagnosed rhinitis with increased eosinophils in nasal discharge and elevated IgE level were enrolled. Exclusion criteria were: “*kyo-sho* (虚証, deficiency pattern),” sinusitis, nose disorders such as nasal septal deviation, conjunctivitis other than allergic conjunctivitis, pregnancy, and refusal to take Kampo medicines.

5. Intervention

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-019) 3.0 g t.i.d., n=34.

Arm 2: TSUMURA Maobushisaishinto (麻黄附子細辛湯) Extract Granules (TJ-127) 2.5 g t.i.d., n=32.

Concomitant drug use was prohibited, with the exception of Intal eye drops or nasal spray for severe and intolerable symptoms.

6. Main outcome measures

Symptom improvement: Each of nose and eye symptoms after 2-week administration was rated on a 5-point scale (markedly improved, moderately improved, slightly improved, unchanged, and aggravated).

Global improvement: The severity of illness (nose and eye symptoms) after 2-week administration, compared with that before treatment, was rated on a 5-point scale (as maobushisaishinto acts rapidly, change in the symptoms was recorded beginning one week after the initiation of treatment.)

Overall safety: Adverse drug reactions after 2-week administration were evaluated on a 5-point scale.

Usefulness: The global improvement combined with overall safety was assessed on a 5-point scale (very useful, useful, slightly useful, indiscernible, and useless).

7. Main results

Slight-to-marked (or moderate-to-marked) improvement was seen in each of the following symptoms: sneezing (41.2% and 59.4% in arms 1 and 2, respectively), rhinorrhea (47.1% and 53.1%), nasal obstruction (58.8% and 37.5%), periocular pruritus (35.3% and 45.2%), lacrimation (23.5% and 19.4%), and ocular discharge (11.8% and 9.7%). The chi-square test and Mann-Whitney *U* test revealed no significant differences in improvement of any symptoms between the two arms. Also, there was no significant difference between the arms in global improvement (slight-to-marked global improvement in 67.6% and 71.9% for arms 1 and 2, respectively, and moderate-to-marked global improvement, 52.9% and 53.1%). As for usefulness, interventions were assessed to be “useful or very useful” in 50% for arm 1 and 50% for arm 2, with no significant between-arm difference.

8. Conclusions

Maobushisaishinto is suggested to be as effective as shoseiryuto in treating springtime nasal allergy and allergic conjunctivitis.

9. From Kampo medicine perspective

Maobushisaishinto is more suitable than shoseiryuto for treating subjects with “*kyo-sho*,” who are frail or elderly.

10. Safety assessment in the article

No adverse drug reactions were observed in either arm.

11. Abstractor’s comments

This study followed a RCT of shoseiryuto for nasal allergy and allergic conjunctivitis in spring (*Jibiinkoka Rinsho* [*Practica otologica*] 1995; 88: 389-405 [in Japanese]), and uses the same outcome measures. However, patients were allocated sequentially and not properly randomized, making this study a clinical controlled trial (CCT: quasi-RCT). Results with no significant differences in this study provide a new therapeutic option for springtime nasal allergy and allergic conjunctivitis, and can be regarded as clinically meaningful.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations sho-sei-ryu-to and go-ko-to for nasal allergy and allergic conjunctivitis in spring. *Therapeutic Research* 2001; 22: 2385-91 (in Japanese with English abstract). Ichushi Web ID: 2002138087 [MOL](#), [MOL-Lib](#)

1. Objectives

To compare the effects of shoseiryuto (小青竜湯) and gokoto (五虎湯) in subjects with nasal allergy and allergic conjunctivitis in spring.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital and four clinics, Japan.

4. Participants

Patients with nasal allergy and allergic conjunctivitis in spring who had increased nasal eosinophil count and high IgE level, n=116.

5. Intervention

Patients who visited the setting of this study for the first time between 31 January 2000 and 10 April 2000 were recruited. Patients with severe symptoms were treated with Intal (sodium cromoglicate) nasal drops and eye drops. Assessments were done after two weeks of administration of one of the following.

Arm 1: Tsumura Gokoto (五虎湯) Extraction Granules 2.5 g, t.i.d., n=58.

Arm 2: Tsumura Shoseiryuto (小青竜湯) Extraction Granules 3.0 g, t.i.d., n=58.

6. Main outcome measures

Nasal symptoms: sneezing, discharge, and obstruction. Ocular symptoms: eyelid itching, tearing, eye discharge, and orbital pain.

7. Main results

Ten subjects in arm 1 and 17 in arm 2 who stopped visiting hospital/clinic and 1 subject in arm 1 who discontinued drug administration because of adverse effect were excluded. Though not significantly different between arms, the efficacy rates were higher in arm 2 for all outcome measures except eye discharge and orbital pain, which were higher in arm 1.

8. Conclusions

There was no significant between-arm difference in treatment usefulness, with usefulness in 70.8% of arm 1 and 80.5% of arm 2 was characterized as moderate or more than moderate.

9. From Kampo medicine perspective

Subjects with *kyosho* (虚証, deficiency pattern) were excluded because shoseiryuto and gokoto are used to treat subjects with *jitsusho* (実証, excess pattern) or *chukansho* (中間証).

10. Safety assessment in the article

Adverse effects included dry mouth (n=5), abdominal pain (n=1), hard stool (n=1), palpitation (n=1, excluded from analysis) in arm 1, and dry mouth (n=1) and constipation (n=1) in arm 2.

11. Abstractor's comments

The authors also compare Kampo drugs for allergic rhinitis or nasal allergy and allergic conjunctivitis in spring in several previous papers, which should be read together.

12. Abstractor and date

Fujisawa M, 15 January 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Baba S, Takasaka T, Inamura N, et al. Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. *Jibiinkoka Rinsho (Practica otologica)* 1995; 88: 389–405 (in Japanese with English abstract). CENTRAL ID: CN-00192055, Ichushi Web ID: 1995184251

1. Objectives

To evaluate the efficacy and safety of shoseiryuto (小青竜湯) for perennial nasal allergy.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Twenty-six university hospitals and 35 other hospitals, Japan.

4. Participants

Patients with perennial nasal allergy who visited otolaryngologists in 61 hospitals in the 8-month period from June 1993 to January 1994 (n=220).

5. Intervention

The package and appearance of the placebo were indistinguishable from those of shoseiryuto. Duration of administration was 2 weeks. On-demand use of clemastine fumarate was permitted in case the symptoms were severe.

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules, 3.0 g t.i.d. (n=110).

Arm 2: placebo 3.0 g t.i.d. (n=110).

6. Main outcome measures

Overall general improvement, improvements in each symptom, safety, and the relationship between body-constitution and efficacy.

7. Main results

The number of subjects analyzed was 186 for overall general improvement, 217 for general safety, and 189 for usefulness. In arm 1, general improvement was high in 12.0% of the patients and moderate in 32.6%, and was significantly greater than in arm 2 (5.3% and 12.8%, respectively). Patients in arm 1 had significantly greater improvement in sneezing, nasal discharge, and nasal obstruction.

The efficacy of shoseiryuto was significantly higher in those with “average” or “muscular and strongly built” body type, “average to pale” facial color, “average” voice, “neither hot nor cold” or “sensitive to heat” cold or hot constitution, “warm” or “average” hands and feet, and “excess” or “average” sweating, as determined from questionnaire responses.

8. Conclusions

Shoseiryuto has significantly better efficacy (overall general improvement, improvements in each symptom, and usefulness).

9. From Kampo medicine perspective

The targets of shoseiryuto are watery and foamy phlegm, watery nasal discharge, and sneezing, in other words, the symptoms of allergic rhinitis.

10. Safety assessment in the article

Adverse reactions possibly related to the administered drug were observed in 6.4% of the placebo group and 6.5% of the shoseiryuto group. Patients treated with shoseiryuto had mild symptoms (digestive symptoms, headache, and facial edema), and one patient had mild elevations in GOT and GPT, neither of which led to the discontinuance of administration.

11. Abstractor’s comments

This is a full-scale, nationwide, and large RCT.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nakai Y, Ohashi Y, Esaki Y, et al. Clinical evaluation of maobushisaishinto for nasal allergy*. *Jibi-inkouka Tenbou (Oto-Rhino-Laryngology, Tokyo)* 1990; 33: 655–73 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of maobushisaishinto (麻黄附子細辛湯) extract granules prepared based on *Shanghanlun* (傷寒論, *Treatise on Cold Damage Diseases*) and conventionally-prepared maobushisaishinto extract powder in the treatment of perennial nasal allergy.

2. Design

Quasi-randomized controlled trial (quasi-RCT), Japan.

3. Setting

Departments of otorhinolaryngology of 5 university hospitals and 10 general hospitals (including Osaka City University Hospital, Teikyo University Mizonokuchi Hospital, and Nagoya City University Hospital).

4. Participants

One hundred and fifty-five patients with moderate or severe perennial nasal allergy.

5. Intervention

Arm 1: oral treatment with Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Fine Granules (content of currently-available capsule formulation) 1 g t.i.d. for 4 weeks (n=74).

Arm 2: oral treatment with Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Powder (old product: currently not available) 2 g t.i.d. for 4 weeks (n=81).

6. Main outcome measures

Nasal symptoms (paroxysmal sneezing, nasal discharge, nasal congestion, olfactory disturbance, interference with activities of daily living), rhinoscopic findings, severity, and nasal allergy tests (skin reaction, nasal provocation test, eosinophil count in nasal discharge).

7. Main results

Efficacy analyses revealed marked or moderate response in 28 out of 52 patients (53.8%) included in arm 1 and 27 out of 59 (45.8%) included in arm 2 at 2 weeks, and in 33 of 44 (76.7%) in arm 1 and 33 of 52 (63.5%) in arm 2 at 4 weeks; there was no between-arm difference at both time points.

8. Conclusions

The efficacy of maobushisaishinto extract powder prepared by the conventional method for perennial nasal allergy is comparable to that of maobushisaishinto extract fine granules prepared on the basis of *Shanghanlun*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In patients who received maobushisaishinto extract powder, 4 (6.15%) experienced adverse reactions: gastrointestinal symptoms in 3 (stomach ache, anorexia, nausea, and dysgeusia) and sleepiness in 1. In patients who received maobushisaishinto extract fine granules, 3 (5.17%) experienced adverse reactions: gastrointestinal symptoms in 2 (gastric distress, dry mouth) and headache/heaviness of the head in 1.

11. Abstractor's comments

It is noteworthy that this multicenter controlled clinical trial demonstrated equivalent efficacy of two different maobushisaishinto formulations for perennial nasal allergy. Outcomes were assessed using not only subjective symptoms but also objective measures (such as rhinoscopic findings) and the results are highly reliable. Unfortunately, the randomization in this study seems to be flawed. A randomized controlled trial including placebo and an active reference is desired.

12. Abstractor and date

Okabe T, 18 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Sakurada T, Ikeda K, Takasaka T, et al. Clinical effectiveness of Kampo medicine for chronic rhinitis and sinusitis. *Jibiinkoka Rinsho (Practica otologica)* 1992;85:1341–6 (in Japanese with English abstract).

1. Objectives

To determine the effectiveness of Kampo medicines for chronic rhinitis and sinusitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university and 5 hospitals, Japan.

4. Participants

Six patients with non-allergic chronic rhinitis and 61 with chronic sinusitis who first visited the participating institutions between November 1989 and June 1990.

5. Intervention

Arm 1: oral administration of TSUMURA Shin'iseihaito (辛夷清肺湯) Extract Granules 2.5 g t.i.d. before meals for 4-8 weeks (n=39).

Arm 2: oral treatment with TSUMURA Shigyakusan (四逆散) Extract Granules 2.5 g t.i.d. before meals for 4-8 weeks (n=28).

6. Main outcome measures

Severity of subjective symptoms: rhinorrhea, ease of nose blowing, postnasal drip, nasal obstruction, heaviness of head (headache), and olfactory disturbance.

Objective findings: redness and edema of the nasal mucosa, characteristics of nasal discharge.

Examinations: neutrophil count in nasal discharge, rhinomanometry.

7. Main results

Improvement in subjective symptoms was at least mild in 76.3% and 59.3% of patients in arms 1 and 2, respectively; the between-arm difference was not significant. Improvements in objective findings were not significantly different between arm 1 (60.5%) and arm 2 (70.4%). There were no significant between-arm differences in neutrophil count, nasal discharge, and rhinomanometric results.

8. Conclusions

The preceding paper was Ikeda K, Takasaka T, Kusakari J, et al. Outcome of treatment with Leftose (lysozyme hydrochloride) for chronic sinusitis – a comparison of clinical efficacy in adults versus children -. *Jibiinkoka Rinsho (Practica otologica)* 1984;77:1863–69. The present study revealed that Kampo medicines had efficacy comparable with that of Leftose (i.e., mild or greater improvement in 63% of patients with chronic sinusitis).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One shin'iseihaito-treated patient had chest distress, which was considered unlikely to be related to the drug.

11. Abstractor's comments

In the treatment of chronic sinusitis, long-term low-dose administration of 14-membered ring macrolide antibiotics became available around 1990 and now these antibiotics are used as standard conservative therapy. Anti-inflammatory enzymes, including Leftose, were commonly used before 1990 and otology physicians reported reasonably adequate efficacy of these drugs. Now they are combined with these antibiotics to relieve symptoms.

12. Abstractor and date

Fujisawa M, 1 June 2009, 1 June 2010.

10. Respiratory Diseases**Reference**

Suzuki S, Furukawa H, Ami H, et al. Experience with TSUMURA Saibokuto (TJ-96) in patients who underwent thyroid or parathyroid surgery. *Progress in Medicine* 1994; 14: 2254–8 (in Japanese). Ichushi Web ID: 1995247312

1. Objectives

To determine the efficacy of saibokuto (柴朴湯) for relieving complaints after thyroid or parathyroid surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution: the outpatient clinic of the Second Department of Surgery, Fukushima Medical University, Japan.

4. Participants

Seventy-seven patients who underwent excision via a collar incision for thyroid or parathyroid disease at the above institution.

5. Intervention

Arm 1: oral treatment with TSUMURA Saibokuto (柴朴湯) Extract Granules 1 pack (2.5 g) t.i.d. before meals for 90 days after the surgery (n=40).

Arm 2: no treatment with Kampo medicines (n=37).

6. Main outcome measures

Clinical examination: flap blood flow at 4 sites on the body surface and flow index (by a laser tissue blood flowmeter) were measured before and 1, 4, 7, and 90 days after surgery.

Improvement in clinical symptom scores: neck and systemic symptoms were evaluated on a 4-point scale using a health questionnaire at 1, 2, and 3 months after surgery.

7. Main results

The improvement in neck tenderness and pain on swallowing was significantly greater in arm 1 than in arm 2 at 2 months after surgery ($P<0.01$ and $P<0.05$, respectively). The improvement in the systemic symptoms (fatigue and insomnia) tended to be greater in arm 1. The between-arm differences in improvements disappeared by 3 months after surgery. For patients who underwent subtotal thyroidectomy or parathyroidectomy, flap blood flow was increased significantly at 4 and 7 days after surgery in arm 1 ($P<0.05$), and there was a trend of increase in flow index at 90 days in arm 2. For patients who underwent total thyroidectomy or parathyroidectomy, there were no significant between-arm differences in flap blood flow and flow index after surgery.

8. Conclusions

Saibokuto is effective for relieving neck symptoms after cervical surgery, possibly by increasing not only flap blood flow at the wound site but also systemic blood flow.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

After cervical surgery, symptoms considered as targets of saibokuto treatment, including neck tenderness or discomfort and difficulty swallowing, frequently develop. The aim of the present study was to evaluate the efficacy of saibokuto for relieving those symptoms. The main feature of this study is that all the enrolled patients had undergone thyroid or parathyroid surgery. The improvements in neck symptoms were obviously greater in the saibokuto-treated group at 2 months but not 3 months after surgery. From this, it is speculated that saibokuto may accelerate healing and thereby increase blood flow. Future investigations are expected to be from an oriental medicine perspective and to include i) oriental medical pathology during the period of maximum efficacy and ii) a study of the dependence of efficacy on *sho* (証, pattern).

12. Abstractor and date

Ushiyama T, 6 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases**Reference**

Saito Y, Mitsuhashi N, Takahashi I, et al. Effect of TSUMURA Saiboku-to as an agent for healing damage in treatment of radiomucositis due to irradiation of the head and neck area and mediastinum. *Biotherapy* 1992; 6: 1899–906 (in Japanese with English abstract).

1. Objectives

To evaluate the healing effect of TSUMURA Saibokuto (柴朴湯) on mucositis induced by head-and-neck and mediastinal irradiation.

2. Design

Randomized controlled trial (RCT).

3. Setting

Gunma University Hospital and 9 other hospitals (a total of 10 institutions), Japan.

4. Participants

Fifty-four cancer patients were included without regard to their age, sex, primary disease, disease stage, prior treatment, and inpatient or outpatient status. These patients developed symptoms of mucosal irritation in response to head-and-neck or mediastinal irradiation. Exclusion criteria were: serious concomitant diseases of the heart, lung, bone marrow, liver, or kidney; Eastern Cooperative Oncology Group performance status 4; and a determination of ineligibility by the treating physician.

5. Intervention

A telephone system was used for treatment allocation.

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 mg t.i.d. was administered orally (before or between meals) for 4 weeks from the onset of some mucosal irritation symptoms after the start of irradiation (12 males and 11 females). The primary diseases included malignant lymphoma, cervical lymph node metastasis, lung cancer, breast cancer, oropharyngeal cancer, and esophageal cancer (in descending order of frequency).

Arm 2: current therapy was continued but TSUMURA Saibokuto (柴朴湯) Extract Granules was not administered. The primary diseases included malignant lymphoma, lung cancer, breast cancer, and cervical lymph node metastasis (in descending order of frequency).

6. Main outcome measures

Severity of subjective symptoms (pharyngolaryngeal pain, foreign-body sensation in the pharyngolarynx, pain on swallowing, difficulty in swallowing, burning sensation, smarting pain) rated on a 4-point scale; objective findings of mucosa (redness, erosion, edema); and global utility (rated on a 3-point scale [marked, moderate, or no response] based on subjective and objective symptoms, laboratory values, and adverse drug reactions).

7. Main results

Three out of 54 enrolled patients in arm 1 were excluded and 20 in arm 1 and 31 in arm 2 were included in the analysis. The comparison of subjective symptom improvements failed to show any efficacy of TSUMURA Saibokuto. Marked and moderate increases in global utility scores were observed in 6 and 6 patients, respectively, in arm 1 and in 0 and 10 patients, respectively, in arm 2; the between-arm difference was significant ($P < 0.01$).

8. Conclusions

TSUMURA Saibokuto may heal mucositis induced by head-and-neck or mediastinal irradiation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

A mild increase in glutamic-oxaloacetic transaminase (GOT) and glutamic pyruvic trans-aminase (GPT) levels developed in 2 patients in arm 1 who required no specific treatment.

11. Abstractor's comments

Randomization is assumed because treatment allocation used a telephone system (though the details are not clear); so the study was classified as an RCT. There is concern that concurrent use of Predonine (prednisolone) might have influenced outcome in some patients. In this paper, rating criteria for global utility are not clear. More description of these criteria would have aided interpretation of the results. Further studies on this treatment are anticipated.

12. Abstractor and date

Tsuruoka K, 3 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Miyamoto T, Inoue H, Kitamura S, et al. Effect of TSUMURA Sho-seiryu-to (TJ-19) on bronchitis in a double-blind placebo-controlled study. *Rinsho Iyaku (Journal of Clinical Therapeutics & Medicine)* 2001; 17: 1189-214 (in Japanese with English abstract). Ichushi Web ID: 2002029631, [MOL](#), [MOL-Lib](#)

Miyamoto T. Clinical effectiveness of shosei-ryuto in bronchitis. *Pharma Medica* 2007; 25: 23-5 (in Japanese). Ichushi Web ID: 2008035989 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of shoseiryuto (小青竜湯) in the treatment of bronchitis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Seventeen university hospitals, forty-two hospitals, and three clinics, Japan.
From December 1994 until March 1999.

4. Participants

Patients aged 16 to <65 years with mild to moderate bronchitis, and evaluable symptoms (any of watery sputum, rales/rhonchi, and cough).

5. Intervention

The concomitant use of other drugs was prohibited with the exception of dimemorfan phosphate (Astomin) after day 4.

Arm 1: TSUMURA Shoseiryuto (小青竜湯) Extract Granules (TJ-19) 3.0 g t.i.d. for 7 days, n=101.

Arm 2: placebo 3.0 g t.i.d. for 7 days, n=91.

6. Main outcome measures

Global improvement (rate), improvement of bronchitis symptoms (such as cough and sputum), and safety.

7. Main results

At the end of treatment, there was a trend toward higher percentage of patients with moderate-to-marked global improvement in arm 1, compared with arm 2 (57.4% in arm 1 vs 42.9% in arm 2; $P=0.06$). No significant difference was observed at day 3 or 4. As for improvement of each symptom, ease of raising sputum, properties of sputum (purulent, viscous, etc.), and disturbance in activities of daily living, was significantly better in arm 1 at days 3-4. At the end of treatment, there was significant improvement in frequency of coughing, intensity of coughing, ease of raising sputum, and activities of daily living, and a tendency toward improvement in sneezing and nasal obstruction in arm 1.

8. Conclusions

Shoseiryuto is effective for bronchitis with mild symptoms.

9. From Kampo medicine perspective

Inclusion criteria of patients with watery sputum, rales/rhonchi, and/or cough were chosen to adopt the “*sho* (証, pattern)” for shoseiryuto in Kampo medicine. Further subgroup analyses in patients without physical frailty and those with cough and watery sputum showed a significantly higher rate of global improvement in arm 1 than arm 2.

10. Safety assessment in the article

The incidence of adverse effects was 6.7% (7 cases) in arm 1 and 9.9% (9 cases) in arm 2, with no significant difference. No serious adverse effects were found.

11. Abstractor's comments

This is a full-scale DB-RCT that addresses Kampo patterns. The authors carry out sub-group analyses based on patterns, in accordance with the clinical guidelines for re-evaluation of Kampo formulations, as indicated in Harumi K, et al.: 1991 Report of the Kampo extract formulation clinical evaluation methods research group, *Japanese Journal of Clinical Pharmacology and Therapeutics*, 1991; 22: 781-91 (in Japanese). The study finds that improvement was greater in the group with watery sputum and cough. These guidelines for the clinical evaluation of Kampo formulations ought to be more widely known and used.

12. Abstractor and date

Fujisawa M, 15 June 2007, 22 February 2009, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Sasaki H, Sato K, Sasaki M, et al. Usefulness of bakumondo-to in senile, chronic respiratory disease patients having difficulty in expectoration: comparison with bromhexine hydrochloride preparations. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)* 1993; 7: 139–45 (in Japanese with English abstract).

1. Objectives

To evaluate the effectiveness of bakumondoto (麦門冬湯) in loosening phlegm in comparison with a bromhexine hydrochloride preparation.

2. Design

Randomized controlled trial using sealed envelopes for allocation method (RCT-envelope).

3. Setting

One university hospital and six hospitals, Japan.

4. Participants

Patients aged 65 years or older with difficulty in expectoration who have chronic respiratory diseases such as chronic bronchitis, emphysema, pulmonary fibrosis, bronchial asthma, bronchiectasis, old tuberculosis, and pneumoconiosis (n=19).

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=10).

Arm 2: administration of bromhexine hydrochloride 4 mg t.i.d. for 4 weeks (n=9).

6. Main outcome measures

Subjective symptoms: frequency of cough, intensity of cough, stridor, volume of sputum, retention of sputum, and clearance of sputum.

7. Main results

No improvement in the frequency of cough, intensity of cough, stridor, and volume of sputum was observed in either arm. In contrast, there was significant improvement in retention of sputum after 2 weeks in arm 1, and a tendency toward improvement in arm 2. Clearance of sputum was also significantly improved after 2 and 4 weeks of treatment in arm 1, but less improved in arm 2. The percentage of patients with more than moderate general improvement was 60.0% in arm 1 and 11.1% in arm 2, but the between-arm difference was not statistically significant.

8. Conclusions

Bakumondoto can be used in the aged without adverse effects, and has significant efficacy in loosening phlegm in patients with chronic lung disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No safety issues were identified.

11. Abstractor's comments

As mentioned in the introduction of this article, “the significance of expectorants is not always recognized. For instance, there is no definite answer to the question whether we should increase or suppress the volume of sputum to improve difficulty in expectoration. In fact, expectorants are not sold in the United States.” This is what I realize at the moment. Moreover, bakumondoto is an expectorant I actually prescribe.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Kato S, Matsuda T, Nakajima T, et al. Clinical significance of the combination therapy of smoking cessation and seihaito for chronic obstructive pulmonary disease. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 2005; 14: 260-5 (in Japanese). Ichushi Web ID: 2005292823

Kato S, Oda K, Hasumi H, et al. The combined effect of smoking cessation and Seihai-to on airway clearance on COPD patients. *Kampo to Meneki-Arerugi (Kampo and Immuno-Allergy)* 2006; 19: 26-35 (in Japanese with English abstract).

1. Objectives

To assess the efficacy of smoking cessation combined with administration of seihaito (清肺湯) for chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT- envelope)

3. Setting

Two university hospitals, Japan.

4. Participants

Patients with GOLD stage 0, 1, or 2 COPD who had stopped smoking, but whose respiratory symptoms (cough, sputum, and dyspnea) were still present one month after smoking cessation, n=31.

5. Intervention

Arm 1: smoking cessation and administration of TSUMURA Seihaito (清肺湯) Extract Granules 9.0 g/day, for 24 months, n=16.

Arm 2: smoking cessation only, for 24 months, n=15.

6. Main outcome measures

Respiratory symptoms.

Chest radiography and chest CT findings (emphysema, organizing pneumonia, bronchial obstruction by sputum).

7. Main results

Respiratory symptoms were significantly improved in arm 1 compared with arm 2 for 1 to 6 months; however, no significant difference was found after 12 months. The imaging findings were significantly improved in arm 1 at 24 months. Diagnostic imaging showed significant improvement in organizing pneumonia and bronchial obstruction in arm 2 after 24 months and no improvement in emphysema in both arms.

8. Conclusions

Administration of seihaito for 6 months improves clinical symptoms, and administration for 24 months is necessary for improvement in imaging findings.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

The information from this RCT included guidance on how to stop smoking using Kampo medicine as an add-on treatment. Dyspnea is a respiratory symptom that can be evaluated objectively by respiratory function testing and measurement of blood oxygen saturation. Future use of these tests in the follow-up period is desired. Future developments in this area of research hold promise.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 22 February 2009, 31 December 2013.

10. Respiratory Diseases (including influenza and rhinitis)**References**

Shinozuka N, Tatsumi K, Nakamura A, et al. Evaluation of systemic inflammation and utility of hochuekkito administration in subjects with COPD*. *Kosei Rodosho Kagaku Kenkyu Kenkyu Hojokin: Nanchisei Shikkan Kokufuku Kenkyu Jigyo Kokyufuzen ni Kansuru Chosa Kenkyu, Heisei 18 Nendo Buntan Kenkyu Hokokusho* [Ministry of Health, Labour and Welfare, Science Research Grant, The Intractable Disease Treatment Research Project Research on Respiratory Failure, Working-group Research report fiscal year 2006] 2007;94-9 (in Japanese).

Shinozuka N, Tatsumi K, et al. A traditional herbal medicine hochuekkito improves systemic inflammation in patients with COPD. *American Journal of Respiratory and Critical Care Medicine* 2007; 175: A638 CENTRAL ID: CN-00651806

Shinozuka N, Tatsumi K, Nakamura A, et al. The traditional herbal medicine hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. *Journal of the American Geriatrics Society* 2007; 55: 313-4. CENTRAL ID: CN-00578499, Pubmed ID: 17302677

Fukuchi Y, Tatsumi K. Utility evaluation of Kampo in the treatment of chronic obstructive pulmonary disease*. *Kosei Rodosho Kagaku Kenkyu Hojokin Choju Kagaku Sogo Kenkyu Jigyo: Mansei Heisokusei Shikkan ni Taisuru Kampochiryō no Yuyosei Hyoka ni Kansuru Kenkyu, Heisei 18 Nendo Sokatsu Kenkyusho Hokokusho* (Ministry of Health, Labour and Welfare, Science Research Grant: Study on Evaluation of Usefulness of Kampo Treatment for Chronic Obstructive Pulmonary Disease, Summary Report Fiscal Year 2006) 2007: 1-31 (in Japanese).

Tatsumi K, Shinozuka N, Nakayama K, et al. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *The American Geriatrics Society* 2009; 57: 169-70

1. Objectives

To investigate the effect of hochuekkito (補中益気湯) on systemic inflammation in subjects with chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

Twelve university hospitals and thirteen hospitals, Japan.

4. Participants

Clinically stable patients who fulfilled the diagnostic criteria of the Japan Respiratory Society Guidelines for COPD, n=71.

5. Intervention

Assessments were done after 6 months of treatment.

Arm 1: conventional treatments with Tsumura Hochuekkito (補中益気湯) Extract Granules, 2.5 g, b.i.d. or t.i.d., n=34.

Arm 2: control: continued conventional treatments, n=37.

6. Main outcome measures

Subjective symptoms: SGRQ (St. George's Respiratory Questionnaire), symptoms related to *ki-kyo*, incidence of common cold (assessed using patients' diaries), and frequency of exacerbations (defined on the basis of Anthonisen's criteria and requirement for systemic administration of steroids).

Objective measurements: body mass index (BMI), change in body weight, respiratory function, blood gas analysis, markers of nutrition status (prealbumin, leptin, and adiponectin), and markers of inflammation (high sensitivity C-reactive protein [hsCRP], TNF- α , and IL-6).

7. Main results

SGRQ subjective symptom score was significantly improved in Arm 1. Also, incidence of the common cold and frequency of exacerbation were significantly less in Arm 1 than in Arm 2. There was no significant change in body weight in both arms during 6 months of observation. Prealbumin, a marker of nutritional status, increased significantly only in Arm 1. Leptin level remained unchanged after administration of hochuekkito. The markers of systemic inflammation (hsCRP, TNF- α , and IL-6) were negatively correlated with severity of COPD (represented by FEV₁% predicted). In Arm 1, hsCRP and TNF- α decreased significantly, but IL-6 remained unchanged. Concentration of adiponectin, secreted by adipocytes and suggested to be involved in the development of arteriosclerosis, was negatively correlated with BMI and significantly increased after treatment with hochuekkito.

8. Conclusions

Administration of hochuekkito improves systemic inflammation and nutritional status in subjects with COPD, and decreases COPD exacerbation and incidence of the common cold.

9. From Kampo medicine perspective

Among the symptoms related to *qikyo* (気虚, qi deficiency), physical lassitude, morale, fatigability, susceptibility to the common cold, and appetite improved.

10. Safety assessment in the article

There were no safety issues.

11. Abstractor's comments

Fukuchi et al. (2007) is an interim report of the findings of Shinozuka et al. (2007) and Shinozuka et al. *American Journal of Respiratory and Critical Care Medicine* (2007), while Shinozuka et al. *Journal of the American Geriatrics Society* (2007) presents only the objective outcomes of that interim report. Tatsumi et al. (2009) and Fukuchi et al. (2007) have the same intention. Airflow restriction is considered a prognostic factor that is independent of weight loss in COPD, and recognition of COPD as a systemic inflammatory disease is increasing. If numerous papers are to follow from the succession of RCTs, then each should include the clinical trial registration number to increase understanding of their interrelationships.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010, 12 October 2011, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. *Phytomedicine* 2011; 18: 625–9. CENTRAL ID: CN-00790726, Pubmed ID: 21177084

Hattori N, Mukaida K, Haruta Y, et al. A pilot study of the effects of Bakumondoto (TJ-29) on cough in chronic obstructive pulmonary disease (COPD)*. *Kampo to Meneki – Arerugi (Kampo and Immuno-Allergy)* 2011; 24: 38–45 (in Japanese with English abstract).

1. Objectives

To evaluate the effect of bakumondoto (麦門冬湯) on cough in patients with chronic obstructive pulmonary disease (COPD).

2. Design

Crossover randomized controlled trial (RCT –cross over).

3. Setting

Hiroshima University Hospital and two general hospitals, Japan.

4. Participants

Twenty-four COPD outpatients aged over 65 who presented between May 2007 and March 2009.

5. Intervention

Treatment with or without bakumondoto (麦門冬湯) for 8 weeks in a cross-over design.

Patients taking any Kampo medicine within the previous 2 weeks were excluded. Treatment with the usual COPD drugs was continued during the trial.

Arm 1: TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before meals for 8 weeks, then no bakumondoto (麦門冬湯) for 8 weeks (n=13).

Arm 2: No bakumondoto (麦門冬湯) for 8 weeks, then TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before meals for 8 weeks (n=11).

One subject in arm 1 was excluded from the efficacy analysis.

6. Main outcome measures

Frequency and intensity of cough assessed on a VAS (visual analogue scale) and changes in severity as recorded in a cough diary. Quality of life (QOL) using St. George's Respiratory Questionnaire (SGRQ). Lung functions.

7. Main results

Twenty-three patients were included in the efficacy analysis. VAS scores showed significant improvement in cough intensity and frequency during the first 8-week period of treatment with bakumondoto in arm 1 ($P=0.004$), but the magnitude of improvement gradually declined after treatment ceased. In arm 2, however, no significant improvement was observed for the latter 8-week period of treatment with bakumondoto. The authors do not mention whether or not there was a significant difference between the bakumondoto treatment and non-treatment groups for arms 1 and 2 combined. Neither QOL nor lung functions were affected by bakumondoto.

8. Conclusions

Bakumondoto may be effective for cough in elderly COPD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Increases in ALP were observed in one participant in each of arms 1 and 2, however, they both completed the course of bakumondoto.

11. Abstractor's comments

The report by Hattori et al. (2011) was presented at a conference, so it includes questions and answers. One person asked whether cough in COPD patients was a common complaint. The presenter replied that there were many cases of exposure to toxic gas among the cases at Hiroshima University, and that some of those who complained of cough symptoms were included in the study. However, there is no mention of patients being exposed to toxic gas in the article by Mukaida et al. (2011). The authors should include such background information in their article.

12. Abstractor and date

Fujisawa M, 31 December 2012.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Japanese herbal medicine, saiboku-to (cai-pu-tang) on brochospasms in aspirin-induced bronchial asthmatic patients. A randomized, double-blind test. *Jibi-inkoka Tenbo (Oto-Rhino-Laryngology Tokyo)* 2001; 44: 5-13 (in Japanese with English abstract). Ichushi Web ID: 2002025794

1. Objectives

Development of saibokuto (柴朴湯) inhalation therapy, and to evaluate its efficacy in preventing attacks of aspirin-induced asthma.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Two clinics, Japan.

4. Participants

Patients with aspirin-induced asthma in whom the threshold dose of L-lysine-aspirin for provoking an asthma attack was determined by inhalation, n=74.

5. Intervention

Saibokuto inhalant: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96) were dissolved in injectable saline, sonicated for 90 minutes, and filtered through a Millipore sterile 0.22-micron filter. After adjustment to a concentration of 100 µg/mL, 5 mL of the inhalant was inhaled three times a day.

Arm 1: inhalation of saibokuto (柴朴湯) inhalant for 6 months, n=35.

Arm 2: inhalation of saline for 6 months, n=39.

6. Main outcome measures

The efficacy and safety of inhaled saibokuto for reducing the frequency of asthma attacks.

7. Main results

Saibokuto inhalant was newly developed. Prolonged inhalant usage significantly reduced the frequency of asthma attacks (0.004 times/person/6 months in arm 1 vs 0.120 times/person/6 months in arm 2).

8. Conclusions

Inhalation, compared with oral administration, can increase the concentration of saibokuto in the lung to the same level as achieved in experiments *in vivo* and *in vitro*, resulting in suppression of the production and release of biologically active substances in bronchoalveolar lavage fluid, and thereby of asthma attacks.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects were observed in 7 cases (20.0%) in arm 1 and 7 cases (17.9%) in arm 2, none of which led to withdrawal from the study.

11. Abstractor's comments

The preparation of saibokuto inhalant (as described above) involved more than simply dissolving the extract granules in saline.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. *Itami to Kampo (Pain and Kampo Medicine)* 2001; 11: 14-21 (in Japanese with English abstract). Ichushi Web ID: 2002261501

1. Objectives

To evaluate the efficacy of long-term inhaled saibokuto (柴朴湯) in alleviating psychological suffering.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One hospital and three clinics, Japan.

4. Participants

Thirty-two patients with aspirin-induced asthma.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: Saibokuto (柴朴湯) inhalation group (TSUMURA Saibokuto (柴朴湯) Extract Granules 1 mg dissolved in 1 ml of distilled water for injection, then sonicated for 90 minutes before Millipore filtration. Concentration adjusted to 100 µg/ml and 5 ml inhaled b.i.d.)

Arm 2: Placebo inhalation group (distilled water for injection inhaled b.i.d.)

Inhalation treatment lasts 6 months and is followed by washout for 4 weeks and inhalation treatment using the other liquid for 4 weeks (n=32).

6. Main outcome measures

Chronic pain (CP): Overall quality of life (QOL), visual analogue scale for pain (VAS-P), face rating score, QOL scores (quality of well-being scale [QWB] score, Modified Health Assessment Questionnaire [MHAQ], face scale)

7. Main results

In the trial of long-term inhalation, significant improvements were observed in each QOL domain and also in global QOL scores (this global QOL assessment method was developed by the authors using a visual analog scale [VAS] to assess physical [QOL-P], mental/psychological [QOL-M], social activity [QOL-S], medical economics [QOL-E], therapeutic drug [QOL-D], and individual QOL [QOL-I] incorporated items measuring the perspectives of individuals [including his/her perspectives on philosophy, thoughts, ethics, generation, policy, religion, and so on], as well as face scale and modified health assessment questionnaires)..

8. Conclusions

Inhaled saibokuto therapy improves QOL and respiratory function.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dysguesia (or altered sensation of taste) was observed in 5 cases (15.6%) in arm 1 and in 2 cases (6.3%) in arm 2. Cacosmia (or imagining of unpleasant odors) was observed in 7 cases (21.9%) in arm 1 and in 4 cases (12.5%) in arm 2. None of these adverse effects caused withdrawal from the study.

11. Abstractor's comments

The paper also mentions a comparative study of TJ-96 immediately after inhalation; however, it did not clearly describe the sample population, method of allocation, and results. Thus, the study was not reported as an RCT. Furthermore, saibokuto (柴朴湯) inhalation liquid is not simply extract granules dissolved in distilled water for injection: it is a special medicine with an altered formulation, made using an original process.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Urata Y, Yoshida S, Irie Y, et al. Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial. *Respiratory Medicine* 2002; 96: 469-74. CENTRAL ID: CN-00390241, Pubmed ID: 12117049

1. Objectives

To investigate the clinical effect of saibokuto (柴朴湯) for the treatment of atopic asthma.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

One university hospital and one hospital, Japan.

4. Participants

Adult patients with atopic asthma, n=33.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Cross-over design (administration of saibokuto (柴朴湯) or placebo [2.5 g, t.i.d.] for 4 weeks, and then, after a washout period of at least 4 weeks, patients crossed over to receive the alternative treatment), n=33.

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules (TJ-96).

Arm 2: placebo.

6. Main outcome measures

Clinical symptoms, respiratory function test, methacholine provocation testing, eosinophil counts in blood and sputum, and eosinophilic cationic protein (ECP) in blood and sputum.

7. Main results

Symptom score (which employed similar severity classification according to Guidelines for Asthma Prevention and Management 2004 [JGL 2004]) before treatment was 1.65 ± 0.38 in arm 1 and 1.66 ± 0.43 in arm 2. After treatment, it was significantly decreased in arm 1 (0.73 ± 0.25 in arm 1 and 1.63 ± 0.39 in arm 2, $P=0.001$). Forced expiratory volume in 1 second ($FEV_{1.0}$) improved slightly but not significantly in arm 1. Response to provocation challenge with methacholine was significantly better in arm 1. Significant decreases in eosinophil counts and ECP in blood and sputum but not neutrophil counts were observed in arm 1.

8. Conclusions

Saibokuto improves clinical symptoms in patients with atopic asthma. Although $FEV_{1.0}$ and FVC were unaffected, saibokuto was able to attenuate eosinophilic inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This is a high-quality trial, a double-blind RCT with a placebo control group for evaluation of saibokuto (柴朴湯) extract granules as treatment for asthma. Although there was no between-group difference in pulmonary function ($FEV_{1.0}$ and FVC), there was a significant between-group difference in subjective symptoms. The respiratory function data obtained in this study should be useful for sample selection in future RCTs.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-intolerant bronchial asthmatic patients – a randomized, group-paralleled comparative trial –. *Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)* 2003; 46: 3-14 (in Japanese). CENTRAL ID: CN-00451669, Ichushi Web ID: 2004041278

1. Objectives

To assess the efficacy and safety of inhaled shimpito (神秘湯) for the control of aspirin-induced asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and others, Osaka prefecture, Japan.

4. Participants

Patients with histories of aspirin-induced asthma, whose threshold levels of inhaled lysine-aspirin are determined, n=114.

5. Intervention

Arm 1: inhalation of TSUMURA Shimpito (神秘湯) Extract Granules, 500 µg in four divided doses, n=53.
Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=61.
Duration of the study was 1 year.

6. Main outcome measures

The effect was evaluated by assessing 1) leukotrienes levels in bronchoalveolar lavage (BAL) fluid, 2) forced expiratory volume in 1 second (FEV_{1.0}) after lysine-aspirin inhalation, and 3) frequency of asthma attacks (or exacerbations).

7. Main results

The decrease in FEV_{1.0} after lysine-aspirin inhalation was significantly greater in arm 1 than arm 2. Also, the frequency of asthma attacks and leukotriene levels in BAL fluid were decreased in arm 1 relative to arm 2.

8. Conclusions

Inhaled shimpito is more efficacious than inhaled cromoglycate for the management of aspirin-induced asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The frequency of both abnormal laboratory findings and adverse reactions were higher in arm 2 than in arm 1 (number of cases are unclear because the results were omitted in this paper).

11. Abstractor's comments

Despite the term “multicenter, randomized” in the title, the method of randomization is not described, and the facilities where this clinical trial was actually performed (not the research institute) are unspecified. This paper does not state the number of withdrawals and analyzed cases during the 1-year follow-up of 114 subjects. Might it mean no withdrawals during the 1-year treatment period? Aspirin-induced asthma comprises 4-10% of all asthma cases. Inhaled corticosteroids are the most commonly used asthma medications. This study implies the greater efficacy of inhaled shimpito therapy in the management of asthma when compared with that of inhaled cromoglycate therapy. Further studies are awaited to assess whether oral administration of shimpito also provides similar efficacy when used by subjects with the appropriate “*sho*.”

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Goto GH, et al. A randomized, group-parallel comparative trial of the suppressive effect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium cromoglycate inhalation in improving subjective and objective symptoms in bronchial asthmatics. *Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)* 2004; 47: 20-7 (in Japanese with English abstract).
CENTRAL ID: CN-00496741, Ichushi Web ID: 2005016956

1. Objectives

To assess the efficacy and safety of inhaled shimpito (神秘湯) therapy for improving asthma symptoms in patients with aspirin-induced asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and other health care facilities, Osaka prefecture, Japan.

4. Participants

Patients with aspirin-induced asthma, whose thresholds for induction of asthma (attacks) have been determined, n=161.

5. Intervention

Arm 1: inhalation of shimpito (神秘湯), 500 µg in four divided doses, n=81.

Arm 2: inhalation of cromoglycate, 5 mg q.i.d., n=80.

Duration of the study was 3 years.

6. Main outcome measures

1) Frequency of asthma attacks (or exacerbations), 2) improvement in health-related QOL, 3) improvement in chronic pain, 4) leukotriene level in bronchoalveolar lavage (BAL) fluid

7. Main results

In arm 1, frequency of asthma attacks and leukotriene level in BAL fluid were significantly reduced, and QOL and chronic pain were significantly improved when compared with arm 2.

8. Conclusions

Inhaled shimpito therapy suppresses production of leukotrienes, prevents exacerbation of aspirin-induced asthma, alleviated chronic pain, and improved QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Fewer cases and subjects had abnormal laboratory findings and adverse reactions in arm 1 than in arm 2.

11. Abstractor's comments

The authors do not specify the medical facilities where this clinical trial (described as multicenter trial) actually took place. In this prospective, randomized study, the number of withdrawals and cases analyzed during the 3-year period of observation for 161 enrolled subjects is not stated. It is unclear whether there were any withdrawals during this period. Aspirin-induced asthma comprises 4-10% of all cases of asthma. Inhaled corticosteroids are the most common medications used for asthma therapy. This study implies that inhaled shimpito therapy is more efficacious in the management of asthma than inhaled cromoglycate therapy. In patients with aspirin-induced asthma, health-related QOL is generally not good because of limitation on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and inflammation. However, shimpito can improve these symptoms. Further studies are awaited to assess whether oral administration of shimpito also has similar efficacy when used in subjects with the appropriate "sho."

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Goto HG et al. Chronic pain in intractable and chronic internal diseases*. *Mansei Totsu (The Journal of the Japanese Society for the Study of Chronic Pain)*, 2002; 21: 67-77 (in Japanese with English abstract). Ichushi Web ID: 2003126703 [MOL](#), [MOL-Lib](#)

1. Objectives

To investigate the effect of saibokuto (柴朴湯) inhalation therapy in improving quality of life (QOL) in patients with aspirin-intolerant asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital and two clinics, Japan.

4. Participants

Patients with aspirin-intolerant asthma, n=214.

5. Intervention

The study duration was 3 years. For saibokuto (柴朴湯) inhalation, 500 µg of saibokuto was packed into capsules comparable to those used for sodium cromoglycate (DSCG) inhalation.

Arm 1: saibokuto (柴朴湯) (the manufacturer not identified), 500 µg q.i.d. inhalation, n=105.

Arm 2: DSCG 20 mg q.i.d. inhalation, n=109.

6. Main outcome measures

Subjective symptoms, various tests, chronic pain, and QOL were assessed using a visual analog “total disease-related symptoms” scale developed by the authors, and face rating scores.

7. Main results

Saibokuto inhalation improved various endpoints.

8. Conclusions

Symptom-related QOL of patients with exacerbated aspirin-intolerant asthma is improved.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The incidence of adverse effects was higher in arm 1, however, there was no significant difference in the number of cases. These results were omitted from the original article.

11. Abstractor’s comments

This RCT resembles two other RCTs of saibokuto inhalation therapy, “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Brochospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test. *Jibi-inkoka Tenbo (Oto-Rhino-Laryngology Tokyo)* 2001; 44: 5-13 (in Japanese with English abstract)” and “Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on brochospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain. *Itami to Kampo (Pain and Kampo Medicine)* 2001; 11: 14-21 (in Japanese with English abstract)”. The only difference between these studies is the method of administering the inhalant: inhalation of saibokuto dissolved in distilled water or saline, or as a powder using a sp inhaler as mentioned in this paper. Inhalation of powder should further improve QOL because powder increases accessibility. Common to these three papers is their complicated format, poorly-described rationale, and omission of results, which makes understanding the contents more difficult.

12. Abstractor and date

Fujisawa M, 22 February 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Egashira Y, Nagano H, et al. Results of a comparative clinical study of the effect of "TSUMURA Saiboku-to" (TJ-96) against steroid dependent bronchial asthma in 2 groups, a Saiboku-to administration group and a non-administration group, divided by the envelope method. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)* 1990; 4: 128-44 (in Japanese with English abstract).

Egashira Y, Nagano H. A multicenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthma. A comparison of groups allocated by the envelope method. *Annals of the New York Academy of Science* 1993; 685: 580-3. CENTRAL ID: CN-00095466, Pubmed ID: 8363267

1. Objectives

To evaluate the effectiveness, safety, and usefulness of saibokuto (柴朴湯) against steroid-dependent bronchial asthma.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Twenty university hospitals and 31 hospitals, Japan.

4. Participants

Patients with bronchial asthma treated with steroids (n=112).

5. Intervention

Arm 1: administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. for 12 weeks (n=64).

(The patients receiving more than 5 mg/day of prednisolone (-equivalent dose of steroids) [n=37]; patients with asthma for more than 5 years [n=48])

Arm 2: no administration (n=48).

(The patients receiving more than 5 mg/day of prednisolone (-equivalent dose of steroids) [n=25]; patients with asthma for more than 5 years [n=41])

6. Main outcome measures

Asthma score = attack score (severity) + treatment score (level of the concomitant drugs). Scores and the number of subjects who succeeded in decreasing steroid doses.

7. Main results

A larger percentage of patients in arm 2 had moderate or greater improvement (32.8% vs. 10.4% in arm 1) and slight or greater improvement (60.9% vs. 18.8% in arm 1; $P < 0.001$). A larger percentage of patients in arm 2 had reduction in steroid dose of 50% or more (17.2% vs. 6.3% in arm 1; $P < 0.01$), which showed the significant steroid sparing effect of saibokuto.

8. Conclusions

Saibokuto improves the clinical symptoms of asthma and leads to a reduction in the dosage of concomitantly administered steroids.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Stomach pain and stomach discomfort were observed in 1% of the saibokuto group.

11. Abstractor's comments

The article by Egashira et al (1993) was based on the original article by Egashira et al (1990), and it includes detailed analysis of individual cases. The RCT report published in *Ann. N.Y. Acad. Sci.* was also cited in "Huntley A, Ernst E. Herbal medicines for asthma: a systematic review, *Thorax*, 2000; 55:925-929." Future promise lies in an RCT incorporating Kampo patterns, after clinical trial registration.

12. Abstractor and date

Fujisawa M, 31 March 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Ito S, Mikawa H. Effect of "TSUMURA Saiboku-to" (TJ-96) on bronchial asthma in children. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)* 1990; 4: 115–25 (in Japanese with English abstract).

Ito S, Mikawa H. Clinical evaluation of saibokuto in the treatment of children with bronchial asthma. *Kiso to Rinsho (The Clinical Report)* 1992; 26: 3993–8 (in Japanese). Ichushi Web ID: 1993226668 MOL, MOL-Lib

1. Objectives

To evaluate the efficacy and safety of saibokuto (柴朴湯) for the treatment cedar pollen allergy in children with bronchial asthma.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Two university hospitals (Department of Pediatrics, Faculty of Medicine, Kyoto University, and Kansai Medical University Rakusai Newtown Hospital) and six other hospitals, Japan.

4. Participants

Children with mild or moderate (symptoms of) bronchial asthma (n=43).

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 1.25 mg b.i.d. (for children less than 7 years old) or 2.5 g b.i.d. (for children 7 years or older) for 8–12 weeks (n=22).

Arm 2: tranilast 5 mg/kg/day in two or three divided doses for 4–12 weeks (n=21).

6. Main outcome measures

Frequency of asthma attacks (very frequent, moderately frequent, infrequent) in a week, and the severity score of the attack (severe=6, moderate=4, mild=1).

7. Main results

No severe attacks were observed in either arm after 5 weeks of treatment. Frequencies of moderate attacks were not significantly different between the two arms throughout the study period. Mild attack was less frequent in arm 2 than in arm 1. The frequency and severity scores were significantly decreased in arm 2 compared to arm 1 at 4–6 weeks of treatment ($P<0.05$), and significantly decreased in arm 1 compared to arm 2 at 11–12 weeks of treatment ($P<0.05$).

8. Conclusions

Saibokuto and tranilast have equivalent efficacy in children with mild to moderate bronchial asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

Patient allocation by the envelope method makes the randomization process tenuous in this study. However, the value of this study is that it confirms the equivalent efficacy of saibokuto and tranilast as treatment for bronchial asthma in children. There is no placebo arm in this study. Use of a placebo arm may pose an ethical problem. Therefore, further randomized controlled clinical trials with cross-over design are indicated.

12. Abstractor and date

Okabe T, 19 August 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Tubaki T, Ebisawa M, Akimoto K, et al. Effects of shinpi-to (*shenbi-tang*) on bronchial asthma. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)* 1994; 8: 65–71 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of shinpito (神秘湯) on exercise-induced asthma and changes in clinical symptoms in patients with moderate to severe bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Patients aged 7–15 years with moderate asthma (n=5) or severe asthma (n=7) who were treated concomitantly with theophylline, disodium cromoglycate, inhaled beclomethasone, and beta2-agonists. Patients were excluded who received oral steroids, had a predicted FEV1 of less than 80%, or had wheezing before exercise tests.

5. Intervention

The observation period was 2 weeks, and the administration period was 12 weeks.

The administered dose was one sachet b.i.d. to patients aged less than 13 years and one sachet t.i.d. to patients aged 13 or older.

Arm 1: administration of TSUMURA Shinpito (神秘湯) Extract Granules (n=7) (dose not described).

Arm 2: EBIOS 1 g b.i.d. or t.i.d. (n=5).

6. Main outcome measures

Asthma symptom diary.

Respiratory function changes observed on ergometer exercise tests during the 2-week observation period and at the conclusion of shinpito administration.

7. Main results

In both arms, exercise lowered FEV_{1,0} below standard values after 5 minutes, and FEV_{1,0} gradually recovered. However, in arm 2 after administration of shinpito, the rate of this reduction was significantly inhibited immediately after and 5 minutes after exercise, and some inhibition was still observable 15, 30, and 60 minutes after exercise. In addition, a significant reduction in numbers of attacks was observed in arm 2, whereas no significant improvement was observed in arm 1.

8. Conclusions

Shinpito effectively improves the symptoms of bronchial asthma and reduces the number of exercise-induced asthma attacks.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The result that shinpito is effective for exercise-induced asthma attacks is interesting. However, random grouping in this study seems unbalanced even after taking the severity into consideration: 5/7 subjects in arm 2 and 2/5 in arm 1 were treated with inhaled beclomethasone, while 3/7 subjects in arm 2 and 0/5 in arm 1 were treated with beta2-agonists. Further studies with more patients are expected.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Nagano F, et al. Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropionate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation. *Jibi-inkoka Tenbo (Oto-rhino-laryngology Tokyo)* 2002; 45: 8-15 (in Japanese with English abstract).
CENTRAL ID: CN-00403706, Ichushi Web ID: 2003036732

1. Objectives

To assess the efficacy and safety of inhaled saibokuto (柴朴湯) while reducing the amount of inhaled beclomethasone during the course of treatment for bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Several clinics and others, Osaka prefecture, Japan.

4. Participants

Patients with stable bronchial asthma whose peak expiratory flow rate was maintained at more than 70% of normal for 6 months by the use of inhaled beclomethasone (800 µg/day), n=94.

5. Intervention

Amount of inhaled beclomethasone was reduced from 800 µg/day to 400 µg/day at 4 weeks before the intervention.

Arm 1: inhaled saibokuto (柴朴湯), 500 µg q.i.d., n=49.

Arm 2: inhaled cromoglycate, 20 mg q.i.d., n=45.

Duration of the study was 12 months.

6. Main outcome measures

1) Intensity of subjective symptoms (visual analogue scale), 2) peak expiratory flow (respiratory function test), 3) frequency of the use of β_2 -agonist, 4) cytokine levels in bronchial lavage fluid, 5) nitric oxide (NO) concentrations in expired air, and so on.

7. Main results

In arm 1, subjective symptoms and respiratory function were significantly improved, and compared to arm 2, patients in arm 1 had significantly reduced frequency of β_2 -agonist use, NO concentration in expired air, and cytokine levels in bronchial lavage fluid. Less than 10% decrease in the peak expiratory flow rate occurred in 67.3% of arm 1 and 13.3% of arm 2.

8. Conclusions

Inhaled saibokuto therapy is suggested to maintain the efficacy of inhaled beclomethasone as treatment for bronchial asthma despite dosage reduction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects occurred in 11 cases (22.4%) in arm 1, and in 8 cases (17.8%) in arm 2.

11. Abstractor's comments

Although they mention a multicenter study, the authors cite only one research institute, and do not specify the facilities where the clinical trials were actually conducted. The number of withdrawals during the 1-year follow-up and the percentage of the 94 enrolled patients who were actually included for analysis were not stated. Perhaps no one withdrew during the 1 year of treatment. Inhaled saibokuto therapy is assumed to be efficient compared to inhaled cromoglycate. All participants in this study should be considered adult patients with mild asthma. In terms of Kampo medicine, bronchial asthma presents a variety of “*sho* (証, pattern).” Previous studies demonstrated that oral administration of saibokuto shows only limited clinical efficiency for those who do not have “*sho*” for saibokuto.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-qing-long tang (Japanese name: shoseiryu-to) in asthmatics with anxiety and depression due to asthmatic attacks. *Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)* 2003; 18: 11-7 (in Japanese with English abstract). Ichushi Web ID: 2006192016

1. Objectives

To compare the efficacy of the anxiolytic-like agent saibokuto (柴朴湯) with that of shoseiryuto (小青竜湯) in patients with bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics and are specialists in allergy and respiratory medicine, Japan.

4. Participants

Patients with bronchial asthma who fulfilled one of the following criteria were included (n=139): comprehensive asthma inventory score ≥ 20 , both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40 .

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=71.

Arm 2: TSUMURA Shoseiryuto (小青竜湯) Extract Granules 5.0 g/day in three divided doses (in capsule form) administered between meals for 24 weeks, n=68.

6. Main outcome measures

Scores on various types of mental and psychological tests, subjective symptoms, bronchoalveolar lavage (BAL) fluid levels of hormones of the hypothalamo-pituitary-adrenal system, the assessment of suffering from chronic and intractable medical diseases, improvement in global symptoms (rated on a scale from 1 [markedly improved] to 5 [worsened], taking into account disease-related symptoms and the development of adverse reactions).

7. Main results

Various types of psychological tests, subjective symptoms, BAL fluid findings, levels of hormones of the hypothalamo-pituitary-adrenal system, chronic and intractable medical diseases, and global symptom scores showed significantly greater improvement in arm 1 than arm 2. The conditions of 66.2% of subjects in arm 1 and 7.3% in arm 2 were improved or better at the end of the study.

8. Conclusions

Saibokuto is more effective than shoseiryuto in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although the authors do not offer a detailed description, adverse effects were observed in 2 cases (2.8%) and 5 cases (7.4%) in arm 1 and 2, respectively. Abnormal laboratory findings were noted in 2 cases (2.8%) in arm 1 and 6 cases (8.8%) in arm 2.

11. Abstractor's comments

Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto and shoseiryuto are effective for asthma in patients with anxiety symptoms. As the authors refer to development of adverse reactions, the number of withdrawals and the reasons for withdrawal should have been included to make this report even better. Accumulation of the detailed comparative information about these two Kampo drugs will clarify understanding of how both drugs work.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clonazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial. *Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)* 2002; 17: 20-7 (in Japanese with English abstract). Ichushi Web ID: 2006192005

1. Objectives

To assess the efficacy of the anxiolytic-like agent, saibokuto (柴朴湯), in treating bronchial asthma.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine, Japan.

4. Participants

Patients with bronchial asthma who fulfill one of the following criteria were included (n=107): comprehensive asthma inventory score ≥ 20 , both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40 .

5. Intervention

Arm 1: administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. before meals for 3 years, n=51.

Arm 2: administration of clonazepam 15-30 mg/day (mean 23.9 mg/day) t.i.d. before meals for 3 years, n=56.

6. Main outcome measures

Clinical effects, scores various types of mental and psychological tests, airway hyperreactivity, bronchoalveolar lavage (BAL) fluid, improvement in global symptoms (as assessed by a combination of the preceding measures and the development of adverse reactions indicating worsening).

7. Main results

Scores on various types of psychological tests, airway hyperreactivity, BAL fluid findings, and global symptoms showed significantly greater improvement in subjects in arm 1 than those in arm 2. The conditions of 68.6% of subjects in arm 1 and 21.3% of subjects in arm 2 were improved or better.

8. Conclusions

Saibokuto is significantly more effective than clonazepam in reducing the severity of asthma symptoms in asthma patients with anxiety symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In arm 1, there were no adverse reactions or abnormal laboratory findings. In arm 2, there were 13 cases (23.2%) including cases of drowsiness and poor concentration.

11. Abstractor's comments

Using a double-blind randomized controlled design, this study provides high-quality evidence that saibokuto is effective for asthma in patients with anxiety symptoms. Withdrawal from the study is not documented in this paper, nor has it been stated whether bronchoscopy was performed in all cases. In the Results section, the authors often use the phrase "results omitted" and do not show the data. Because the results here indicate the efficacy of saibokuto for asthma patients with anxiety symptoms, these data should have been disclosed to further validate its efficacy. However this remains a well-designed study investigating the psychological and organic pathology of asthma and evaluating the long-term efficacy of a Kampo medicine. Further studies including other Kampo formulae are desired.

12. Abstractor and date

Goto H, 1 May 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Clinical effect of chai-to-tang (Japanese name: saiboku-to), a Chinese traditional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: A multicenter, randomized, double-blind, placebo-controlled study. *Nihon Toyo Shinshin Igaku Kenkyu (Journal of Japanese Association of Oriental Psychosomatic Medicine)* 2004; 19: 37-41 (in Japanese with English abstract). Ichushi Web ID: 2006203751

1. Objectives

To evaluate the efficacy and safety of saibokuto (柴朴湯) in patients with asthma exacerbations based on anticipatory anxiety.

2. Design

Randomized controlled trial (RCT).

3. Setting

The setting of this study is unstated; the authors of this paper work in clinics, and are specialists in allergic and respiratory medicine, Japan.

4. Participants Shimazaki Y, Mori H, Kurata H, et al. Comparative study of Kampo preparations

Patients with bronchial asthma who fulfill one of the following criteria were included (among 174 subjects participated, data from 172 subjects were analyzed): comprehensive asthma inventory score ≥ 20 , both state trait anxiety inventory (STAI) I and II scores ≥ 41 in men and ≥ 42 in women, or self-rating depression scale (SDS) ≥ 40 .

5. Intervention

Arm 1: Administration of TSUMURA Saibokuto (柴朴湯) Extract Granules 5.0 g/day three times a day before meals for 6 months, n=87.

Arm 2: Administration of lactose 5.0 g/day three times a day before meals for 6 months, n=85.

Each drug was given in indistinguishable capsule.

6. Main outcome measures

Assessment of improvement in objective and subjective symptoms concerning bronchial asthma, various types of mental and psychological tests, assessment of autonomic dysfunction, bronchoalveolar lavage (BAL) fluid, numbers of inflammatory cells in bronchial mucosa biopsy, frequency of asthma exacerbations, levels of hypothalamic, pituitary, and adrenal cortex hormones, assessment of chronic pain, and others.

7. Main results

Autonomic dysfunction, clinical symptoms, and BAL fluid analysis were significantly improved in arm 1 compared to arm 2. In arm 1, the number of subjects with asthma exacerbations decreased from 87 to 14 and the mean duration of asthma exacerbation decreased from 31.5 to 3.1 days, while both indices were increased in arm 2 (descriptions of the results in the text were imprecise).

8. Conclusions

Saibokuto is effective in improving asthma symptoms and psychiatric symptoms in patients with autonomic dysfunction due to asthma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no differences between the two arms in the incidences of adverse effects and abnormal laboratory data (no precise description in the paper).

11. Abstractor's comments

As the authors' notes in the Discussion section, this is the first clinical trial in the world to evaluate the effect of saibokuto in patients with bronchial asthma in a randomized, double-blind, controlled design. Following up a number of subjects in detail in multicenter analysis should have required substantial efforts. Declaration of the missing details such as 1) the number of withdrawals during 6 months of observation, 2) the number of subjects who underwent bronchoscopy, and 3) precise data omitted in the Result section, would be effective in making the efficacy of saibokuto widely accepted. Accumulation of such detailed studies may lead to elucidation of the action mechanisms and the efficacy of Kampo medicine, and more similar studies are awaited.

12. Abstractor and date

Goto H, 1 May 2009, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Iwasaki K, Cyong JC, Kitada S, et al. A traditional Chinese herbal medicine, banxia houp tang, improves cough reflex of patients with aspiration pneumonia. *Journal of American Geriatrics Society* 2002; 50: 1751-2. CENTRAL ID: CN-00434022, Pubmed ID: 12366640

1. Objectives

To investigate whether hangekobokuto (半夏厚朴湯; banxia houp tang) improves cough reflex in elderly patients likely to have aspiration pneumonia.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Tokyo and Tohoku University, and their related facilities, Japan.

4. Participants

Elderly patients (mean age, 78) with cerebral atrophy and lacunar infarcts, who had at least one episode of aspiration pneumonia, n=16.

5. Intervention

Arm 1: hangekobokuto (半夏厚朴湯) extract (granules) 1.5 g t.i.d. orally for 4 weeks (n=7).
Arm 2: placebo (lactose) 1.5 g t.i.d. orally for 4 weeks (n=9)

6. Main outcome measures

Subjects inhaled nebulized citric acid solution (0.3-360 mg/mL) delivered by an ultrasonic nebulizer, and the cough threshold was defined as the concentration of citric acid at which subjects coughed at least five times.

7. Main results

In arm 1, the cough threshold decreased from 59.5 to 15.7. In arm 2, the values were 47.5 and remained unchanged.

8. Conclusions

The result suggests that hangekobokuto improves the (impaired) cough reflex in the elderly with an increased risk for aspiration pneumonia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

It has been reported that angiotensin-converting enzyme inhibitor (ACE-I) improves silent aspiration, and that capsaicin improves cough reflex. This study suggests that hangekobokuto also affects the attenuated cough reflex in older patients with cerebral atrophy and lacunar infarcts. Larger RCTs to confirm its efficacy are awaited.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

10. Respiratory Diseases (including Influenza and Rhinitis)**References**

Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in older adults with dementia. *Journal of the American Geriatrics Society* 2007; 55: 2035-40. CENTRAL ID: CN-00699802, Pubmed ID: 17944889

Iwasaki K, Kato S, Monma Y, et al. A pilot study of banxia houpu tang, a traditional Chinese medicine, for reducing pneumonia risk in brain-damaged elderly. *International Journal of Stroke* 2010; 5 suppl 2: 38-9. CENTRAL ID: CN-00782273

1. Objectives

To evaluate whether hangekobokuto (半夏厚朴湯) prevents aspiration pneumonia and pneumonia-related mortality in elderly people with dementia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals (the authors belong to Tohoku University, Dokkyo University, and two hospitals), Japan.

4. Participants

One hundred and four elderly people with cerebrovascular disease, Alzheimer's disease, or Parkinson's disease (31 males, 73 females, mean age 83.5±7.8 years).

5. Intervention

Ninety-five participants were randomly allocated to two groups for treatment.

Arm 1: Tsumura Hangekobokuto (半夏厚朴湯) Extract Granules 2.5 g t.i.d. (body weight ≥50 kg) or 2.5 g b.i.d. (body weight <50 kg) for 12 months, n=47.

Arm 2: placebo (lactose) 1.0 g t.i.d. (body weight ≥50 kg) or 1.0 g b.i.d. (body weight <50 kg) for 12 months, n=48.

6. Main outcome measures

The occurrence of pneumonia, mortality due to pneumonia, and amount of oral food intake.

7. Main results

Data from 92 of the 95 subjects were analyzed. One of four patients who developed pneumonia in arm 1 died as a result, whereas 6 of 14 patients who developed pneumonia in arm 2 died as a result. There was a significant decrease in pneumonia onset in arm 1 compared to arm 2 ($P=0.008$). Mortality related to pneumonia tended to be less in arm 1 than in arm 2 ($P=0.05$). Hangekobokuto (半夏厚朴湯) reduced the relative risk of pneumonia to 0.51 (95% CI: 0.27–0.84) and death by pneumonia to 0.41 (95% CI: 0.10–1.03). Amount of oral food intake was significantly greater in arm 1 than arm 2 ($P=0.06$).

8. Conclusions

Treatment with hangekobokuto (半夏厚朴湯) reduces the risk of pneumonia in elderly people with cerebral disorder. The results also suggest that hangekobokuto (半夏厚朴湯) administration is effective in sustaining food intake.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

The findings of this well-designed randomized controlled study suggest the efficacy of hangekobokuto in preventing aspiration pneumonia in elderly people with dementia. In addition, hangekobokuto administration tended to improve activities of daily living such as self-feeding and to reduce the number of febrile days. Further studies to assess these points are expected. In Kampo medicine, hangekobokuto is a therapeutic prescription indicated for nonfebrile patients with *tan'in* (痰飲, fluid retention) pattern. However, many elderly people present with *sosho* (燥証, dryness pattern). Hopefully, the researchers will analyze the data from this study from the perspective of patterns, once the patterns of the 95 elderly participants in this study become available.

12. Abstractor and date

Okabe T, 25 November 2008, 1 June 2010, 31 December 2012.

10. Respiratory Diseases (including Influenza and Rhinitis)**Reference**

Mikamo H, Tamaya T. Usefulness of Kampo medicine for the treatment of infections from the perspective of medical economics*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2007; 24: 105-8 (in Japanese). Ichushi Web ID: 2008050180

1. Objectives

To evaluate the efficacy, impact on recurrence rate, and medical cost efficiency of antibiotics plus Kampo combination therapy for bacterial respiratory infections.

2. Design

Randomized controlled trial (RCT).

3. Setting

Obstetrics and Gynecology, Gifu University Hospital, Japan.

4. Participants

One hundred and sixteen patients diagnosed with acute bacterial respiratory infection.

5. Intervention

Arm 1: antibiotics alone group: treatment with levofloxacin for 5–10 days, n=51.

Arm 2: antibiotics + Kampo group A: treatment with levofloxacin for 5–10 days + jumentaihoto (十全大補湯) or hochuekkito (補中益氣湯) for 5–10 days, n=37.

Arm 3: antibiotics + Kampo group B: treatment with levofloxacin for 5–10 days + kakkonto (葛根湯) or keishito (桂枝湯) or kososan (香蘇散) or 1–2 days + jumentaihoto (十全大補湯) or hochuekkito (補中益氣湯) for 3–6 days, n=28.

None of the manufacturers of Kampo medicines used were specified.

6. Main outcome measures

Response rate, rate of recurrence within 7 days, and total medical cost.

7. Main results

The response rates were 96.1% in arm 1, 97.3% in arm 2, and 96.4% in arm 3; no statistically significant differences were observed. The recurrence rates were 3.9% in arm 1, 2.7% in arm 2, and 0% in arm 3; there were no significant between-group differences, although the rates were lower in arms 2 and 3. High recurrence rates were observed in cases of atypical pneumonia, caused by atypical pneumonia-related organisms. Total medical costs were significantly higher in arms 2 and 3, whereas for patients with recurrence, total costs tended to be reduced in these two arms.

8. Conclusions

Antibiotics plus Kampo combination therapy reduces the recurrence of bacterial respiratory infections. In patients infected with atypical pneumonia and prone to frequent recurrence, Kampo-combined therapy might reduce the total medical cost.

9. From Kampo medicine perspective

The drugs used in the intervention groups were selected on the basis of common applications: ephedra formulations such as kakkonto, are used to help generate body heat and sweat during the acute phase; shosaikoto is used for immune enhancement during the subacute phase; and *hozai* (補劑, formulations with tonic effects) such as hochuekkito and jumentaihoto are used during the recovery phase.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a very interesting RCT evaluating total medical cost as an outcome. We guess from the setting that all the participants were women. Inclusion of background factors (such as gender, age, and underlying disease) as well as standard criteria with which to evaluate outcomes (such as response and recurrence rates) would have helped readers understand the results. Also, using more uniform regimens in the intervention groups would have increased the value of the results. Further studies are anticipated to provide more data.

12. Abstractor and date

Tsuruoka K, 6 February 2009, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Miyazaki Y, Yamada A, Saitou M. Effect of ninjin-yoei-tou on xerostomia induced by oxybutynin hydrochloride. *Shinyaku to Rinsho (Journal of New Remedies and Clinics)* 1994; 43: 2613-7 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of ninjin'yoeito (人參養榮湯) for improvement of xerostomia induced by oxybutynin hydrochloride.

2. Design

Randomized controlled trial (RCT).

3. Setting

The department of urology of a hospital (although not mentioned, it was probably an outpatient clinic), Japan.

4. Participants

Sixteen patients who complained of dry mouth out of 20 patients who were diagnosed with psychogenic frequency or unstable bladder (chronic cystitis, neurogenic bladder) and received oxybutynin hydrochloride (6 mg/day) for 2 weeks (all females; mean age, 52.3 years; range, 31–72 years) were examined.

5. Intervention

Arm 1: oxybutynin hydrochloride alone for 2 weeks followed by oxybutynin hydrochloride combined with ninjin'yoeito (人參養榮湯; manufacturer, not specified) (8.1 g/day) for 2 weeks (a total of 4 weeks) (n=8).

Arm 2: oxybutynin hydrochloride alone for 4 weeks (n=8).

6. Main outcome measures

Severity of dry mouth (on a 5-point scale), chewing gum test, frequency of urination evaluated by interview at baseline, 2 weeks, and 4 weeks.

7. Main results

After 2-week treatment with oxybutynin hydrochloride, 16 out of 20 patients (80%) developed xerostomia symptoms (mild in 12 and severe in 4 patients). In arm 1, dry mouth worsened in 5 patients and remained unchanged in 3. In arm 2, dry mouth worsened in no patients, remained unchanged in 2, and improved slightly in 4, and moderately in 2. Dry mouth failed to disappear in any patient in either arm. Response, defined as mild or moderate improvement, was observed in 6 out of 8 patients, yielding a response rate of 75%. The chewing gum test was performed in 3 patients in arm 1 and 4 in arm 2. The total amount of saliva in arm 1 and arm 2 was, respectively, 8.00 mL and 7.30 mL at baseline, 1.27 mL and 1.30 mL at 2 weeks, and 1.13 mL and 2.40 mL at 4 weeks, suggesting that the amount of saliva had increased at 4 weeks. The frequency of urination was 11.875 ± 2.125 times/day at baseline, 8.5 ± 1.125 times/day at 2 weeks, and 8.375 ± 1.0 times/day at 4 weeks in arm 1, and 11.75 ± 2.75 times/day, 8.75 ± 1.625 times/day, and 8.5 ± 1.5 times/day, respectively, in arm 2; there was no between-arm difference.

8. Conclusions

Ninjin'yoeito improves the subjective symptoms of xerostomia induced by oxybutynin hydrochloride but not urinary frequency and therefore is considered to be effective for treating xerostomia induced by oxybutynin hydrochloride.

9. From Kampo medicine perspective

For drug-induced xerostomia, treatment with byakkokaninjinto (白虎加人參湯) or bakumondoto (麥門冬湯) has been frequently reported. Byakkokaninjinto is indicated for patients with *jitsu-sho* (実証, excess pattern) and *netsu-sho* (熱証, heat pattern). Since most patients with nonobstructive dysuria associated with frequency and incontinence are female with *kyo-sho* (虚証, deficiency pattern), ninjin'yoeito may be more effective for dry mouth induced by oxybutynin hydrochloride.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The authors said: "the study was triggered by the encounter with cases in which polydipsia had developed due to dry mouth induced by this drug (oxybutynin hydrochloride), and urinary frequency was not improved because of the increase in urine output." Clinical practice questions were transformed into research questions, and this RCT was conducted to answer them. Such a study is called a "practice-based study" and provides results that can easily be applied in clinical practice. Although there are some concerns about study design, including the small number of patients and lack of objective assessment of the oral cavity, the authors deserve praise for implementing a practice-based study. Further studies of this treatment are expected.

12. Abstractor and date

Tsuruoka K, 31 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Umemoto M, Nin T, Miuchi S, et al. Treatment of human dry mouth using various medicines. *Jibiinkoka Rinsho (Practica otologica)* 2007; 100: 145-52 (in Japanese with English abstract). Ichushi Web ID: 2007135958

1. Objectives

To compare the efficacy of bakumondoto (麦門冬湯) versus cevimeline hydrochloride hydrate (Evovac) or nizatidine (Acinon) for treating dry mouth.

2. Design

Randomized controlled trial (RCT).

3. Setting

Gustatory Outpatient Clinic, Department of Otolaryngology, Hyogo College of Medicine, Japan.

4. Participants

One hundred patients with dry mouth (13 males and 87 females; mean age, 69.0 years). Patients with a basal salivary secretion rate of 3 mL/10 min or lower and a chewing-gum-stimulated salivary secretion rate of 10 mL/10 min or lower were included in the study. Exclusion criteria were Sjögren syndrome, diabetes mellitus, use of oral antihistamine or antipsychotic, asthma, ischemic heart disease, epilepsy, prostatic hyperplasia, and glaucoma.

5. Intervention

Arm 1: treatment with bakumondoto (麦門冬湯) (manufacturer, not specified) 3.0 g t.i.d. for 90 days in 24 patients (4 males and 20 females; mean age, 67.4 years), as the bakumondoto (麦門冬湯) group.

Arm 2: treatment with cevimeline hydrochloride hydrate 30 mg t.i.d. for 90 days in 42 patients (3 males and 39 females; mean age, 72.0 years), as the cevimeline group.

Arm 3: treatment with nizatidine 150 mg b.i.d. for 90 days in 34 patients (6 males and 29 females; mean age, 66.0 years), as the nizatidine group.

6. Main outcome measures

The basal rate and chewing-gum-stimulated salivary secretion rate after 90 days of treatment. Subjective symptoms were assessed using a questionnaire on a 4-point scale (“improvement”, “mild improvement”, “no change”, or “worsening”).

7. Main results

The rate of basal salivary secretion increased from 1.0±0.2 mL/10 min to 1.3±0.2 mL/10 min after treatment with bakumondoto, from 1.1±0.1 mL/10 min to 1.6±0.2 mL/10 min after treatment with cevimeline, and from 1.1±0.2 mL/10 min to 2.4±0.3 mL/10 min after treatment with nizatidine. The rate increases in the cevimeline and nizatidine groups were significant ($P<0.001$). The change in the rate of chewing-gum-stimulated salivary secretion after treatment with cevimeline and nizatidine were similarly significant ($P<0.001$). Both the basal rate and chewing-gum-stimulated salivary secretion rate were significantly different between the bakumondoto- and the nizatidine-treated groups (both $P<0.01$) but not between the bakumondoto- and the cevimeline-treated groups. Treatment with cevimeline or nizatidine led to “improvement” in subjective symptoms in 50–57% of patients and “improvement” or “mild improvement” in 85.7% of cevimeline-treated patients and 74.2% of nizatidine-treated patients. In contrast, only 4% of bakumondoto-treated patients noted “improvement”.

8. Conclusions

Cevimeline hydrochloride hydrate and nizatidine but not bakumondoto significantly increase both basal and stimulated salivary secretions and relieve subjective symptoms in patients with dry mouth.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patients reported “worsening” of symptoms. No adverse drug reactions occurred.

11. Abstractor’s comments

This is a well-designed and well-conducted RCT. The authors speculate that saponins in ginseng, a component of bakumondoto, activate salivary cells by increasing cell membrane permeability. According to their discussion, increase in cell membrane permeability alone does not directly increase the amount of saliva. This was suggested by the fact that dry mouth in most subjects in this trial was due to age-related atrophy and impairment of salivary gland cells. Further studies are expected.

12. Abstractor and date

Tsuruoka K, 12 February 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *Journal of Traditional Medicines* 2009; 26: 122–30. Ichushi Web ID: 2010089062, [J-STAGE](#)

1. Objectives

To evaluate the effects of bakumondoto (麦門冬湯) on neuropeptide levels in human plasma and saliva.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Oita University Hospital, Japan.

4. Participants

Five non-smoking males, aged 25–30 years.

5. Intervention

Since allocation to these treatment arms is not described, the treatment arms are described in terms of treatment regimen. The washout period for each drug was four weeks.

Arm 1: a single administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 18 g.

Arm 2: placebo (lactose + maltose).

Each subject was administered these drugs with an interval of four weeks.

6. Main outcome measures

Substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and calcitonin-gene related peptide (CGRP) levels in plasma and saliva.

7. Main results

Treatment in arm 1 significantly increased saliva levels of substance P level at 40 min after administration of bakumondoto (mean±SD of 37.8±14.7 pg/mL vs 23.5±10.2 pg/mL in arm 2; $P=0.0317$) and CGRP at 90 min after administration (65.5±34.4 pg/mL vs 24.8±4.5 pg/mL in arm 2; $P=0.0079$), but not VIP, which remained unchanged. Treatment in arm 1 also significantly increased plasma levels of substance P at 90 min after administration (34.1±14.0 pg/mL vs 23.3±2.8 pg/mL in arm 2; $P=0.0127$), but not of CGRP and VIP. Saliva volume was increased by 37%, 26%, and 33% at 20, 40, and 60 min in arm 1, but not in arm 2. Saliva secretion was correlated with saliva level of substance P ($r=0.66$).

8. Conclusions

Bakumondoto increases substance P and CGRP levels in human saliva. An increase in saliva secretion by bakumondoto is partially attributable to increases in these neuropeptides.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is interesting because it evaluates the increases in substance P and CGRP secretion as a contributor to the stimulatory effect of bakumondoto on salivary secretion in a cross-over study. Considering the results of this study, which implicate neuropeptides in the mechanism of action of bakumondoto, and the reported involvement of substance P in the effect of hangekobokuto (半夏厚朴湯) on improvement of swallowing disorder, further elucidation of the pharmacological action of bakumondoto is awaited.

12. Abstractor and date

Okabe T, 27 December 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Oka S. The effects of Oren-to on stomatitis. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1995; 46: 439–45 (in Japanese with English abstract). [CiNii](#)

1. Objectives

To evaluate the efficacy and safety of orento (黄連湯) in the treatment of stomatitis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Thirty patients with stomatitis.

5. Intervention

Arm 1: TAIKODO Orento (黄連湯) Extract at a dose of 4.5 g t.i.d. for acute aphthous stomatitis (n=18).

Arm 2: oral steroid ointment 2–3 applications/day for acute aphthous stomatitis (n=5).

Arm 3: no treatment for acute aphthous stomatitis (n=5).

Arm 4: TAIKODO Orento (黄連湯) Extract at a dose of 4.5 g t.i.d. for chronic stomatitis (n=2).

6. Main outcome measures

Number of days to resolution of pain and cure of stomatitis.

7. Main results

The mean number of days to resolution of pain was 2.1, 7.0, and 17.0 in arms 1, 2, and 3, respectively, showing a significant decrease in arm 1 compared even with arm 2. The mean number of days to a cure of stomatitis was 5.5, 12.0, and 17.0 in arms 1, 2, and 3, respectively, showing that time to cure was also significantly decreased in arm 1 compared even with arm 2. In arm 4, pain recurred after resolution.

8. Conclusions

Orento is effective for acute aphthous stomatitis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

No adverse reactions were reported.

11. Abstractor's comments

This was a valuable controlled clinical trial showing that orento is effective for acute aphthous stomatitis. Despite an imbalance in the number of patients among the groups, the results definitely showed the efficacy of orento. These results suggested that acute aphthous stomatitis may be a symptom of *jitsu-sho* (実証, excess pattern). Chronic stomatitis may require treatment based on *sho*. A future randomized controlled trial should include a description of the randomization method, statistical analysis of the results, and a larger control group.

12. Abstractor and date

Okabe T, 19 August, 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Bessho K, Okubo Y, Hori S, et al. Effectiveness of Kampo medicine (sai-boku-to) in treatment of patients with glossodynia. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 1998; 86: 682-6. CENTRAL ID: CN-00158400, Pubmed ID: 9868725

Yamada T, Bessho K, Murakami K, et al. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Shika Yakubutsu Ryoho (Oral Therapeutics and Pharmacology)* 1998; 17: 18-22 (in Japanese with English abstract) [MOL](#), [MOL-Lib](#)

Yamada T, Bessho K. Clinical evaluation of sai-boku-to (Kampo medicine) for glossodynia. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 1999; 8: 261-5. Ichushi Web ID: 2000085045

1. Objectives

To evaluate the efficacy of saibokuto (柴朴湯) compared with tranquilizer plus vitamin B complex combination therapy for patients with glossodynia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Oral and Maxillofacial Surgery Kyoto University Hospital, Japan.

4. Participants

Two hundred patients with glossodynia.

5. Intervention

Arm 1: treatment with TSUMURA Saibokuto (柴朴湯) Extract Granules, 2.5g, t.i.d. for 3 months. (n=100)
Arm 2: treatment with diazepam, 2mg, t.i.d. plus vitamin B complex formulation, 1 tablets, t.i.d. for 3 months. (n=100)

6. Main outcome measures

Each of the subjective symptoms (pain, burning sensation, and unpleasant feeling) was evaluated on a 10-point scale. 'Excellent response' was defined as disappearance of all symptoms, 'good response' as improvement of pain, and 'no response' as no improvement of pain.

7. Main results

In arm 1, the percentage of excellent and good responses was 70% at 1 month, 85% at 2 months, and 92% at 3 months after the start of treatment. These values in arm 2 were 74%, 71%, and 69%, respectively ($P<0.05$). Pain relief was experienced in a significantly higher percentage in arm 1 than in arm 2 at 3 months ($P<0.01$).

8. Conclusions

It is suggested that saibokuto (in particular, the three-month treatment) is more effective against glossodynia than the diazepam plus vitamin B complex formulation.

9. From Kampo medicine perspective

The discussion contains some speculations.

10. Safety assessment in the article

Mild anorexia and diarrhea were reported, respectively, in 3 and 1 patient receiving saibokuto, and severe sleepiness was reported in 33 patients receiving diazepam.

11. Abstractor's comments

This study suggests that saibokuto monotherapy (for 3 months) is more effective against glossodynia than the combination therapy (tranquilizer plus vitamin B complex). Also, saibokuto treatment is safe, as indicated by the low frequency of adverse effects and the possibility of long-term treatment. Although the sample size of the study described in the two papers by Yamada et al (1998, 1999) was about half that in the present study, the results were very similar.

12. Abstractor and date

Okabe T, 17 September 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Mizuno S, Yamagiwa K, Iwata M, et al. Effect of early treatment with TSUMURA Rikkunshito on gastrointestinal symptoms after resection of gastric cancer – focusing on reflux esophagitis - . *Progress in Medicine* 2001; 21: 1366-7 (in Japanese). Ichushi Web ID: 2001269379 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the preventive effect of rikkunshito (六君子湯) on postoperative reflux esophagitis.

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the authors belong to the First Department of Surgery, Mie University School of Medicine, Japan.

4. Participants

Forty-six patients who underwent resection of stage I to II gastric cancer.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules, 7.5 g/day, every day from the start of postoperative oral intake in 25 patients.

Arm 2: no treatment in 21 patients.

6. Main outcome measures

1) Gastrointestinal symptoms including heartburn, dysphagia, nausea/vomiting, dyspepsia, and anorexia; 2) endoscopic findings based on the Los Angeles classification; and 3) mean length of postoperative hospital stay.

7. Main results

At postoperative week 2, gastrointestinal symptoms were observed in 7 untreated patients (33%) and 4 rikkunshito-treated patients (16%). All the symptoms occurred less commonly in the treated patients than in the untreated patients. At postoperative week 4, reflux symptoms and heavy stomach were each seen in only 1 (4%) patient in arm1, whereas reflux symptoms, heartburn, dyspepsia, and anorexia developed in 3 (14%), 1 (5%), 1 (5%), and 2 (10%), respectively, in arm 2. As for endoscopic findings at postoperative week 3, there were grade A in 2 patients (10%) and grade B in 1 (5%) in arm 2, but grade A in only 1 (5%) in arm 1. At postoperative week 6, grade A esophagitis was observed in 1 patient (5%) in arm 2, and none in arm 1. Mean length of postoperative hospital stay was not significantly different between the two arms (47 ± 13 days [arm 2] vs 39 ± 13 days [arm 1]), but a reduction of hospital days was noted.

8. Conclusions

Rikkunshito is highly effective not only for the treatment of reflux esophagitis after gastric cancer surgery, but also for the prevention of this disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Studies 1 and 2 are described in the article. Study 1 was conducted to examine the therapeutic effect of rikkunshito on postoperative reflux esophagitis. Rikkunshito at a daily dose of 7.5 g was administered between meals every day from the onset of symptoms in 7 patients with stage I-II gastric cancer. The authors reported that symptoms disappeared in most patients at week 4. But since Study 1 had no control group and provided no details such as evaluation criteria, it was excluded from this structured abstract. Only part of Study 2 was included. In Study 2, 'randomization into two groups' was reported, but the details were not clear. Also, other details, such as statistical procedures and methods of assessing subjective symptoms, were not provided. This study is clinically valuable, but most of the article, which is published in a conference record, lacks adequate descriptions. Thus, submission as an original article is desired.

12. Abstractor and date

Arai M, 1 April 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Koide A. Effect and role of TJ-43: Rikkun-shi-to from the aspects of endoscopic findings and QOL improvement in GERD patients. *Medical Tribune Online (Digestive Disease Week: DDW)* 2005: 6-7 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) combined with a proton pump inhibitor (PPI) for treating gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Fifty-six patients with gastroesophageal reflux disease.

5. Intervention

Arm 1: oral administration of omeprazole (20 mg) plus TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group.

Arm 2: oral administration of omeprazole (20 mg), as the PPI alone group.

6. Main outcome measures

Endoscopic healing rates of reflux esophagitis and Gastrointestinal Symptom Rating Scale (GSRS) scores. The follow-up was scheduled at 8 weeks.

7. Main results

The endoscopic healing rates of reflux esophagitis at 8 weeks were not significantly different between the two groups. The PPI + rikkunshito group achieved significantly better scores on the following three GSRS domains: overall gastrointestinal symptoms, reflux, and abdominal pain.

8. Conclusions

Rikkunshito combined with PPI improves the quality of life (QOL) in GERD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Rikkunshito-combined therapy resulted in further improvement of QOL in GERD patients, especially in those with endoscopy-negative GERD (non-erosive reflux disease: NERD). On this basis, the authors concluded that PPI + rikkunshito is effective for "the improvement of QOL, particularly in NERD patients who are unlikely to respond to PPI."

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Kato S, Nakajima T, Matsuda T, et al. The effectiveness of the traditional Kampo medicine, “banxia houpu tang (hangekobokuto)” to respiratory disturbance by esophageal reflux disease. *Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)* 2005; 14: 333-8 (in Japanese). Ichushi Web ID: 2006091322

1. Objectives

To evaluate the efficacy of hangekobokuto (半夏厚朴湯)-combined treatment in patients with respiratory symptoms associated with refractory gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

No description of the setting is available; the authors belong to the Department of Cardiology and Pneumology, Dokkyo Medical University, Japan.

4. Participants

Nineteen GERD patients whose digestive symptoms but not respiratory symptoms (including cough, sputum, throat discomfort, and mild dyspnea) were relieved by conventional western medical treatments. All patients had no history of smoking or respiratory disease.

5. Intervention

Arm 1: treatment with TSUMURA Hangekobokuto (半夏厚朴湯) Extract Granules (7.5 g/day) in 10 patients.

Arm 2: no treatment in 9 patients.

In arm 1, hangekobokuto (半夏厚朴湯) was administered in addition to the usual western medical treatment for 6 months, and then hangekobokuto (半夏厚朴湯) was discontinued. The course of respiratory symptoms was examined for a total of 12 months in both the hangekobokuto (半夏厚朴湯)-combined and no-treatment arms.

6. Main outcome measures

Cough, sputum, throat discomfort, and mild dyspnea.

7. Main results

The degree of improvement was evaluated on a 5-point scale. Respiratory symptoms were significantly improved after a month of treatment in arm 1, compared with arm 2 ($P < 0.01$). This effect persisted up to 6 months after start of combined treatment ($P < 0.01$) and 6 months after discontinuation of hangekobokuto ($P < 0.01$).

8. Conclusions

Hangekobokuto relieves respiratory symptoms, including cough, sputum, throat discomfort, and mild dyspnea, that are unresponsive to western medical treatments in GERD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Respiratory or ear-nose-throat symptoms are reported to occur in 30–50% of GERD patients, depending on the literature. Western medical treatments combine proton pump inhibitors, H₂ blockers, or stomachics, with theophylline formulations, expectorants, antitussives, erythromycin antibiotics, or inhaled steroids. In some patients, however, these treatments fail to improve these symptoms. This study can be praised for examining these clinically difficult-to-treat patients. The study method has several problems including failure to measure inter-subject variability of GERD scores evaluated according to the Los Angeles classification, small sample size, and lack of a safety and adverse drug reactions assessment.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Koide A. Establishment of new treatment strategy for non-erosive reflux disease (endoscopy-negative gastroesophageal reflux disease) – potential of rikkunshito*. *MedicalQ* 2006; 187 (in Japanese).

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for treatment of non-erosive reflux disease (NERD) unresponsive to proton pump inhibitors (PPIs).

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available; the author belongs to a clinic, Japan.

4. Participants

One hundred and eighteen patients with PPI-unresponsive NERD.

5. Intervention

Arm 1: treatment with omeprazole (200 mg), as the PPI alone group, n=37.

Arm 2: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the rikkunshito alone group, n=39.

Arm 3: treatment with omeprazole (200 mg) and TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g), as the PPI + rikkunshito (六君子湯) group, n=42.

The duration of treatment was 4 weeks in all arms.

6. Main outcome measures

Gastrointestinal Symptom Rating Scale (GSRS) score (which includes ratings of overall gastrointestinal symptoms, reflux, abdominal pain, and dyspepsia).

7. Main results

Scores of overall gastrointestinal symptoms and reflux were significantly more improved in arm 3 than in arms 1 and 2; the scores in arms 1 and 2 were similar. The abdominal pain score was similarly improved in all three arms. Dyspepsia score was significantly more improved in arms 2 and 3 than in arm 1, but the scores in arms 2 and 3 were similar.

8. Conclusions

TSUMURA Rikkunshito Extract Granules is effective for relieving clinical symptoms of NERD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study deserves praise for conducting a RCT using TSUMURA Rikkunshito Extract Granules as a study drug in patients with treatment-unresponsive NERD. Unfortunately, the mechanism was not discussed, and endoscopic findings and other features were not mentioned. Publication of the latter is expected in the future.

12. Abstractor and date

Kogure T, 26 January 2009.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Tominaga K, Fujiwara Y, Shimoyama Y, et al. Rikkunshito improves PPI-refractory NERD: a prospective randomized multi-center trial in Japan. *Gastroenterology* 2010; 138: S655–6.

Tominaga K, Fujiwara Y, Arakawa T, et al. GERD — rikkunshito*. *Shindan to Chiryō (Diagnosis and Treatment)* 2011; 99: 771–6 (in Japanese). [MOL](#), [MOL-Lib](#)

Tominaga K, Fujiwara Y, Fujimoto K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multi-center trial in Japan. *Journal of Gastroenterology* 2012; 47: 284-92. Pubmed ID: 22081052

1. Objectives

To evaluate the effectiveness of rikkunshito (六君子湯) for patients with proton pump inhibitor (PPI)-resistant gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Gastroenterology, Osaka City University Hospital, and four other research institutes (research groups), Japan.

4. Participants

One hundred and four PPI-resistant GERD patients who showed no improvement despite taking rabeprazole (RPZ 10 mg/day) for more than four weeks.

5. Intervention

Arm 1: combination group: Participants continued taking 10 mg/day of RPZ and also took TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for four weeks (n=53).

Arm 2: double-dose group: Participants doubled their RPZ dose to 20 mg/day for four weeks (n=51).

6. Main outcome measures

Frequency Scale for Symptoms of GERD (FSSG) score and improvement rate.

7. Main results

After allocation, three participants were excluded before administration commenced, making 50 participants in arm 1 and 51 in arm 2. There were no significant differences between participants in both groups before administration in age, gender, body mass index, or endoscopic findings after PPI monotherapy, however, FSSG scores were significantly higher in arm 1 before the trial commenced. The data for 45 participants in arm 1 and 50 in arm 2 were included for analysis after the four-week administration period concluded. FSSG total scores (arm 1, $P<0.001$; arm 2, $P<0.01$) as well as reflux and indigestion subscores improved significantly in both groups after 4 weeks of treatment compared to before administration, while the before/after improvement rates were similar in both groups. Sub-group analysis of male patients with non-erosive reflux disease (NERD) showed significant improvement in arm 1 compared to arm 2, and significant improvement in FSSG scores. Remarkably, the ectomorphic group showed similar trends for BMI.

8. Conclusions

Rikkunshito is effective for patients with PPI-resistant GERD (and especially NERD). The effects of combined treatment with RPZ and Rikkunshito are similar to treatment with double the RPZ dosage.

9. From Kampo medicine perspective

The researchers did not analyze participants' *sho* (証, patterns), but remarkable and significant effects were observed in ectomorphic males.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

There is still no clear definition of PPI-resistant GERD and no treatments have yet been established. Against that background, this RCT holds great clinical significance because it compared combined rikkunshito and RPZ with double-dosage RPZ in GERD patients who did not respond to 10 mg/day of RPZ. Participants showed similar rates of improvement; however, the exacerbation rate was lower in the rikkunshito and RPZ group, which indicates the effectiveness of rikkunshito in combination.

12. Abstractor and date

Kogure T, 31 December 2012, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical (Supplement)* 2010; 8: 27 (in Japanese).

Morita T, Furuta K, Adachi K, et al. Effects of Rikkunshito (TJ-43) on esophageal motor function and gastroesophageal reflux. *Journal of Neurogastroenterology and Motility* 2012; 18: 181-6. Pubmed ID: 22523727

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.

2. Design

Randomized controlled crossover trial (RCT - cross over).

3. Setting

Shimane University Hospital, Japan.

4. Participants

Ten healthy people.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days, no administration for one week, then placebo for 7 days (number of participants not specified).

Arm 2: placebo for 7 days, no administration for one week, then TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days (number of participants not specified).

6. Main outcome measures

Lower esophageal sphincter (LES) resting pressure, esophageal peristaltic contraction pressure after drinking water, postprandial gastroesophageal reflux frequency.

7. Main results

LES resting pressure was significantly higher in supine position with rikkunshito administration compared to placebo administration ($P=0.047$), but there was no significant difference when in sitting position. No significant between-group difference attributable to rikkunshito administration was observed for esophageal peristaltic contraction pressure after drinking water or postprandial gastroesophageal reflux frequency.

8. Conclusions

Rikkunshito raised LES resting pressure in healthy subjects in supine position, but not in sitting position, and had no effect on esophageal peristaltic contraction pressure after drinking water or postprandial gastroesophageal reflux frequency.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Gastroesophageal reflux has been increasing in recent years, especially among the elderly, prompting hope that rikkunshito would be effective for patients in whom it could not be satisfactorily controlled with proton pump inhibitors. This study in healthy subjects is the first step toward generating that evidence base. Rikkunshito raised LES resting pressure in supine position, but there was no significant difference in sitting position, and no significant difference in any of the other outcomes: it was a study of healthy young people (mean age: 22.8 years), so the results should be accepted for what they are. However, there was no mention of the numbers of participants being allocated by a randomized process. Based on these outcomes, the authors will hopefully repeat this investigation not with healthy subjects, but with actual gastroesophageal reflux patients, as the authors themselves mention in the paper.

12. Abstractor and date

Motoo Y, 31 December 2012, 31 December 2013..

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Morita T. Effects of Rikkunshito (TJ-43) on gastroesophageal reflux, esophageal motor functions and salivary secretion: placebo-controlled double-blind study. *Nikkei Medical (Supplement)* 2010; 8: 27 (in Japanese).

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on esophageal motor function and gastroesophageal reflux.

2. Design

Randomized controlled crossover trial (RCT - cross-over).

3. Setting

No description (the author is from the Second Department of Internal Medicine, Shimane University), Japan.

4. Participants

Twenty healthy volunteers.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days, then placebo for 7 days (number of participants not specified).

Arm 2: placebo for 7 days then TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 7 days (number of participants not specified).

6. Main outcome measures

Saliva amount, salivary epidermal growth factor (EGF), salivary bicarbonate concentration.

7. Main results

Rikkunshito caused no significant change in saliva amount, salivary EGF, or salivary bicarbonate concentration.

8. Conclusions

Rikkunshito increases lower esophageal sphincter (LES) resting internal pressure in healthy people, but does not affect saliva excretion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Saliva dilutes refluxed acid and neutralizes bicarbonate, while EGF appears to aid repair of esophageal mucous cells. Decreased saliva excretion in conditions including gastroesophageal reflux, Sjogren's syndrome, diabetes, old age, and stress facilitate the onset of reflux esophagitis. This trial was conducted on the assumption that increases in saliva excretion, and therefore in EGF and bicarbonate, by rikkunshito will improve gastroesophageal reflux disease (GERD). But the study found no significant effect on these factors, which at this point suggests that rikkunshito's main mechanism of action is the increase in LES pressure. The subjects in this study were healthy volunteers, so a further study might verify that the improvement of GERD by rikkunshito is due to increased saliva excretion. To confirm the mechanism, participants with reduced saliva excretion (e.g., elderly people, diabetics, or Sjögren's syndrome sufferers) should be compared to participants with normal saliva excretion to find the differences among them.

12. Abstractor and date

Motoo Y, , 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Nakahara A, Kashimura H, Fukutomi H. Gastric ulcer - saikokeishito or shigyakusan monotherapy - . *Nikkei Medical* (separate-volume supplement) 1988; 17: 20-1 (in Japanese).

Fukutomi H, Nakahara A. Traditional oriental therapy of the gastric ulcer. *Shokakika (Gastroenterology)* 1990; 12: 159-65 (in Japanese)

1. Objectives

To compare the efficacy of saikokeishito (柴胡桂枝湯), H₂ receptor antagonist, or their combination for preventing recurrence of gastric ulcer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifty-one institutions (names are not specified; the authors belong to the Institute of Clinical Medicine, University of Tsukuba), Japan.

4. Participants

One hundred and eighty-nine patients whose gastric ulcer was healed by treatment with the combination of TSUMURA Saikokeishito Extract Granules and H₂ receptor antagonist.

5. Intervention

Arm 1: treatment with TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 5.0 g/day (TJ-10 group; n=40).

Arm 2: treatment with H₂ receptor antagonist 400 mg/day (H₂-blocker group; n=32).

Arm 3: treatment with TSUMURA Saikokeishito Extract Granules plus H₂ receptor antagonist (combined group; n=54)

The dose was halved after month 4.

6. Main outcome measures

Recurrence of gastric ulcer.

7. Main results

The cumulative recurrence rate (calculated monthly) was around 24% at 6 months and similar for all three groups. In patients aged under 50 years, the recurrence rate was lowest after treatment with the combination, whereas in patients aged 50 years or older, the rate was around 20% and not different among the three groups.

8. Conclusions

For patients aged 50 or older, saikokeishito monotherapy is the preferred maintenance therapy for gastric ulcer because (unlike receptor antagonist) it is less associated with age-related reduction of drug metabolizing capacity and adverse reactions.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinically valuable report showed that the effectiveness of saikokeishito is comparable to that of H₂ receptor antagonist as a maintenance therapy for gastric ulcer. Because the cumulative rates of recurrence for the three groups were similar and the Kampo medication caused fewer adverse reactions, the authors concluded that Kampo therapy is a treatment of choice for patients aged 50 or older. However, the paper contains no results or discussion regarding adverse drug reactions. So the submission as an original article is desired, and descriptions of adverse drug reactions should be included.

12. Abstractor and date

Arai M, 18 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Watanabe H. A study of peptic ulcer maintenance therapy combined with Kampo medicines*. *Kampo Igaku (Kampo Medicine)* 1995; 19: 18-21 (in Japanese).

1. Objectives

To evaluate the usefulness of H₂-blocker (cimetidine) combined with Kampo medicine (shigyakusan [四逆散], saikokeishito [柴胡桂枝湯]) as a maintenance therapy for peptic ulcer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Department of Gastroenterology, Matsudo City Hospital), Japan.

4. Participants

Thirteen patients who were confirmed to have peptic ulcer (8 with gastric ulcer, 5 with duodenal ulcer) by upper gastrointestinal endoscopy, and received two-month initial therapy (H₂-blocker + protective factor-enhancing agent combination) and one-year maintenance therapy.

5. Intervention

Arm 1: treatment with cimetidine 400 mg s.i.d. (before bedtime) + Kampo medicine twice daily (morning and evening) (n=7; TSUMURA Shigyakusan Extract Granules (四逆散) 2.5 g b.i.d. [n=4], TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 2.5 g b.i.d. [n=3]).

Arm 2: treatment with cimetidine 400 mg s.i.d. (before bedtime) + sucralfate 1.0 g b.i.d. (morning and evening) (n=6).

6. Main outcome measures

Recurrence of ulcer, change in ulcer scar stage, and improvement of redness of the gastric antral mucosa.

7. Main results

The effects were evaluated by upper gastrointestinal endoscopy after a year of treatment. No recurrence was observed in either arm. In 4 of 6 patients (66.7%) in the sucralfate group and 5 of 7 (71.4%) in the Kampo group, scars had improved from stage S₁ at the start of maintenance therapy to stage S₂ at 1 year. In cases with marked redness of gastric antral mucosa, mild improvement was observed in 2 (33%), no change in 3 (50%), and worsening in 1 (17%) of 6 sucralfate-treated patients; moderate improvement was observed in 1 (25%) and mild improvement in 3 (75%) of 4 shigyakusan-treated patients.

8. Conclusions

Kampo medicine (TSUMURA Shigyakusan Extract Granules, TSUMURA Saikokeishito Extract Granules) plus H₂-blocker (cimetidine) combination therapy is likely to have remarkable efficacy for preventing recurrence of ulcer.

9. From Kampo medicine perspective

Based on the endoscopic findings, patients with marked redness and irregularity of gastric antral mucosa, which is regarded as *jitsu-sho* (実証, excess pattern), were assigned to the shigyakusan treatment, and patients with less evident findings, which is regarded as *kyo-sho* (虚証, deficiency pattern), to the saikokeishito treatment.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

With the recent advent of *Helicobacter pylori* eradication therapy for peptic ulcer, recurrence of ulcer and incidence of gastric cancer have remarkably decreased. However, some patients are reported to fail or be ineligible for the eradication therapy. This study may be, even now, very meaningful for those cases. Some points need further clarification, including incomplete statistical evaluation of the efficacy owing to the small sample size, the possibility that the patient population was atypical in that no one developed recurrence of ulcer, and the need for a description of adverse drug reactions. In addition, patients were assigned to the shigyakusan or saikokeishito treatment based on the author's empirical rule; this point also needs reconsideration. The study will be more meaningful when these points are considered and a larger number of patients are enrolled.

12. Abstractor and date

Arai M, 18 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ohta Y, Nishioka M, Yamamoto Y, et al. Multicenter clinical evaluation of Kampo preparations for medical use in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - comparison with gefarnate as a control - . *Shindan to Chiryō (Diagnosis and Treatment)* 1990; 78: 2935-46 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of rikkunshito (六君子湯) and hangeshashinto (半夏瀉心湯) for treating acute gastritis and acute exacerbation of chronic gastritis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four university medical schools, including Ehime University School of Medicine (Third Department of Internal Medicine), Kagawa Medical School (Third Department of Internal Medicine), and Kochi Medical School (First Department of Internal Medicine), plus 13 hospitals (17 institutions in total), Japan.

4. Participants

Sixty-four patients who (i) visited one of the participating institutions between October 1986 and May 1987; (ii) had subjective symptoms such as abdominal pain and abdominal bloating; and (iii) were endoscopically confirmed to have gastritis lesion, diagnosed with gastritis (acute gastritis or acute exacerbation of chronic gastritis), and had indications for medical therapy. Patients with the following conditions were excluded: (i) peptic ulcer (except for scarring) or gastric cancer; (ii) so-called verrucous erosion with marginal elevations, or serious complications, particularly gastrointestinal disease (such as hepatobiliary disease); or (iii) known or suspected pregnancy.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito Extract Granules (六君子湯) 2.5 g t.i.d. (n=20).

Arm 2: treatment with TSUMURA Hangeshashinto Extract Granules (半夏瀉心湯) 2.5 g t.i.d. (n=14).

Arm 3: treatment with gefarnate 100 mg t.i.d. (n=16).

Treatment duration was 4 weeks in principle; treatment was discontinued when symptoms disappeared during this period.

6. Main outcome measures

Subjective symptoms (nausea, anorexia, epigastric pain, abdominal bloating, abdominal discomfort, heartburn, belching, and fatigue), endoscopic findings (redness, erosion, edema, and hemorrhage), and laboratory findings (routine blood test, serum biochemistry, and urinalysis).

7. Main results

No statistically significant among-arm differences in subjective symptom improvement (5-point scale) and in endoscopic improvement (5-point scale) were found. The scores for both total endoscopic improvement and overall improvement (evaluated on the basis of subjective symptoms and endoscopic findings) tended to be slightly higher in arms 1 and 2 ($P<0.1$), but showed no statistically significant differences between each two arms. Overall usefulness (5-point scale) was assessed as “useful” or better in 80.0%, 85.7%, and 56.3% of patients, respectively, in arms 1, 2, and 3. The among-arm distribution of usefulness was significantly different ($P<0.05$). Multiple comparisons between two arms showed significantly higher usefulness score in arm 2 than in arm 3 ($P<0.05$).

8. Conclusions

Both TSUMURA Rikkunshito Extract Granules and TSUMURA Hangeshashinto Extract Granules result in improvements equivalent to or better than those obtained with gefarnate in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis); thus they are clinically effective and safe agents.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions or laboratory abnormalities were not reported in any of the arms.

11. Abstractor's comments

This report is clinically relevant in that the authors conducted a multicenter study comparing two types of Kampo preparations with an existing mucosal protectant and defining in detail the outcome measures. Recently, in western medicine, the idea of functional dyspepsia has been introduced and classification based on clinical symptoms prevails. In the future, the efficacy of Kampo formulas might be clarified using a symptoms-based method, in which subjective symptoms that respond specifically to each Kampo formula are identified by comparing responders and non-responders, and then selecting participants based on the specific symptoms. Future studies are expected.

12. Abstractor and date

Arai M, 20 October 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control -*. *Shindan to Chiryō (Diagnosis and Treatment)* 1991; 79: 789-810 (in Japanese).

1. Objectives

To determine the efficacy and safety of rikkunshito (六君子湯) for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Forty-five institutions including Shizuoka General Hospital, Japan.

4. Participants

Two hundred and thirty-six patients with gastritis (acute gastritis or acute exacerbation of chronic gastritis) in whom 3 or more indefinite complaints of epigastric distress, were observed and peptic ulcer and gastric cancer were excluded by endoscopy or radiography. Of 236 participants, 207 were included in the analysis population.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 4 weeks (n=109).

Arm 2: treatment with Marzulene-S Granules 2 g/day in three divided doses for 4 weeks (n=98).

6. Main outcome measures

Subjective symptoms and endoscopic findings.

7. Main results

The improvement in symptom ratings for anorexia (at 1 week), epigastric pain (at 2 and 4 weeks), abdominal discomfort (at 2 weeks), and fatigability (at 1 and 4 weeks) were significantly greater in arm 1. The improvement in endoscopically assessed erosion was significantly higher in arm 1. The overall improvement in endoscopic findings at 4 weeks, and improvements in the global symptom score and global utility rating at 4 weeks were significantly greater in arm 1.

8. Conclusions

TSUMURA Rikkunshito is clinically useful for treating gastritis (acute gastritis and acute exacerbation of chronic gastritis) as it resulted in greater improvements compared with Marzulene-S.

9. From Kampo medicine perspective

Rikkunshito tended to result in greater improvements compared with the control drug in patients who had “decreased strength and fatigability”, “choking sensation in the epigastric region”, “low tension of the abdominal wall” and “splashing sounds in the gastric region”.

10. Safety assessment in the article

Only one adverse drug reaction occurred—skin rash in one patient who consequently discontinued treatment.

11. Abstractor’s comments

This paper describes a clinical evaluation of TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis). This study triggered a series of clinical trials on rikkunshito. Notably, Kampo medical findings, such as “tension of the abdominal wall” and “splashing sounds in the gastric region”, were also included in the analysis. The experimental approach of this study may have been progressive for that time.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takemoto T, Matsuda K, Tada M, et al. Clinical evaluation of the efficacy of TJ-43 Tsumura Rikkunshi-To on gastritis with abdominal symptoms - a multicenter group study in comparison with cetraxate -. *Shokakika (Gastroenterology)* 1990; 12: 223-34 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯) for treating gastritis in a comparison with cetraxate as a control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Sixteen institutions including Yamaguchi University Hospital, Japan.

4. Participants

Seventy patients who were diagnosed with atrophic, superficial, or erosive gastritis by endoscopy and had epigastric complaints such as abdominal pain or bloating.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=38).

Arm 2: treatment with cetraxate hydrochloride 200 mg q.i.d. before meals and bedtime for 4 weeks (n=32).

6. Main outcome measures

Subjective symptoms and endoscopic findings.

7. Main results

The rate of improvement in fatigue was significantly higher in arm 1 than in arm 2. The rate of improvement in endoscopically evaluated erosive disease, rate of global improvement in symptoms (both subjective and endoscopically assessed), and the utility rating tended to be higher in arm 1. The overall rate of improvement in subjective symptoms was significantly higher in arm 1.

8. Conclusions

TSUMURA Rikkunshito seems to have an excellent clinical efficacy for treating gastritis with epigastric disturbance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

In the present paper, the clinical utility of TSUMURA Rikkunshito in comparison with that of cetraxate (the control) is determined as treatment for gastritis. It was a multicenter controlled trial, similar to that described in "Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control - *. *Shindan to Chiryō (Diagnosis and Treatment)* 1991; 79: 789-810 (in Japanese)". Both studies showed similar results, but the statistical significance of differences was weaker in the present study. This discrepancy might be due to the small number of patients enrolled.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Kawamura S, Okita K, Tada M, et al. Clinical comparison of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress - mainly the antidepressive effect and the improvement of gastric emptying -*. *Progress in Medicine* 1992; 12: 1156-62 (in Japanese with Chinese abstract).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯) compared with sulpiride for treating epigastric indefinite complaints complicated by depression.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The study appears to be multicenter, but details are not available, Japan.

4. Participants

Twenty-eight patients with indefinite complaints of epigastric distress and depression.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=15).

Arm 2: treatment with sulpiride 150 mg t.i.d. after meals for 4 weeks (n=13).

6. Main outcome measures

Subjective symptoms, gastric emptying, and score on the SRQ-D (self-rating questionnaire for depression; the test for masked depression).

7. Main results

The improvement in subjective symptoms score was greater, but not significantly greater, in arm 1 than in arm 2. The improvement in gastric emptying score was significantly greater in arm 2. The improvement in SRQ-D score tended to be greater in arm 2. The utility score was high in both arms.

8. Conclusions

TSUMURA Rikkunshito presumably has an antidepressive effect comparable to that of sulpiride in the treatment of indefinite complaints of epigastric distress complicated by depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes a comparison of the clinical utility of TSUMURA Rikkunshito and sulpiride in the treatment of indefinite complaints of epigastric distress complicated by depression. The study is appreciated because, in addition to subjective symptoms, objective outcome measures (e.g., gastric emptying and SRQ-D scores) were adopted and analyzed. However, the inclusion criteria are somewhat ambiguous and the number of patients enrolled is small, making it difficult to draw a definite conclusion. Although the authors stated "rikkunshito has an antidepressive effect comparable to that of sulpiride", this conclusion may be an exaggeration.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Komatsuzaki O. Clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress - comparison with a control agent, and assessment mainly based on the endoscopic findings and the histology of gastric mucosal biopsy specimens before and after the treatment - *. *Kampo Igaku (Kampo Medicine)* 1993; 17: 120-31 (in Japanese).

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) for treating indefinite complaints of epigastric distress, based on an analysis of gastric endoscopy findings and histological findings of gastric mucosal biopsy specimens before and after the treatment.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (Tochigi National Hospital), Japan.

4. Participants

Thirty newly-presenting patients with gastritis who had 3 or more indefinite complaints of epigastric distress.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 4 weeks (n=15).

Arm 2: treatment with Marzulene-S Granules (L-glutamine plus azulene) 2 g/day in three divided doses after meals for 4 weeks (n=15).

6. Main outcome measures

Measures of subjective symptoms, endoscopy findings, and histopathology.

7. Main results

Improvement in the subjective symptom score for abdominal bloating, global improvement score, and utility rating were significantly greater in arm 1 than in arm 2. Marked improvements in endoscopic or histopathologic findings were not observed.

8. Conclusions

TSUMURA Rikkunshito has beneficial effects on gastritis with epigastric distress and is a highly useful agent.

9. From Kampo medicine perspective

Stratified analysis of global improvement ratings revealed that improvements were greater in patients aged 61 or older than in those aged 60 or younger.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

This paper describes an evaluation of the clinical effect of TSUMURA Rikkunshito on indefinite epigastric distress, using outcome measures including gastric endoscopy findings and histological findings of gastric mucosal biopsy specimens before and after the treatment. In conclusion, marked changes in endoscopic or histopathologic findings were not observed, and the efficacy of rikkunshito for symptoms and gastrointestinal function was noted. Results of other measures were very similar to those from preceding studies.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ito J, Ito Y, Asai M, et al. Efficacy of Saireito (TSUMURA) for post-infectious dyspepsia in infants: comparison with intestinal regulators*. *Shonika Shinryo (Journal of Pediatric Practice)* 1992; 55: 2089-92 (in Japanese). Ichushi Web ID: 1993113987

1. Objectives

To evaluate the efficacy of Saireito (柴苓湯; TSUMURA) compared with that of intestinal regulators for treatment of post-infectious dyspepsia in infants.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Yokkaichi Municipal Hospital), Japan.

4. Participants

Eighty-seven infants (age range, 4 months to 5 years 10 months old; range of body weight, 7 to 19 kg) who visited the outpatient department with presenting symptoms of cough, fever, or diarrhea (after exclusion of thirty-nine infants who were hospitalized during the study period).

5. Intervention

Arm 1: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. (n=32).

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 1.5 g b.i.d. + albumin tannate 0.1 g/kg/day + natural aluminum silicate 0.1 g/kg/day + resistant lactobacillus preparation 0.1 g/kg/day (n=21).

Arm 3: treatment with albumin tannate 0.1 g/kg/day + natural aluminum silicate 0.1 g/kg/day + resistant lactobacillus preparation 0.1 g/kg/day (n=22).

Arm 4: no treatment with antidiarrheal drugs or intestinal regulators (n=12).

6. Main outcome measures

Symptoms (including the number of episodes and type of diarrhea) and food intake for 7 days were scored (using the 7-day questionnaire, which was distributed to and completed by the patient's mother).

7. Main results

There were no among-arm differences in age, body weight, and symptoms. Diarrhea scores were significantly higher in arm 2 than in arm 3 at 1 day; in arms 1 and 2 than in arm 3 at 2 days; and in arm 1 than in arm 3 at 3 days. The number of patients who withdrew from the study was 1 from arm 1, 0 from arm 2, 15 from arm 3, and 23 from arm 4.

8. Conclusions

Saireito was likely to be useful for treating post-infectious dyspepsia in infants.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes a determination of the efficacy of saireito for post-infectious dyspepsia in infants. Although it was a small study, the report is valuable considering the scarcity of evidence in the field of pediatric gastrointestinal diseases. Lower percentage of saireito-treated patients required hospitalization. Thus, saireito may not only improve symptoms, but also prevent aggravation of symptoms.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Tatsuta M, Iishi H. Effect of treatment with Liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Alimentary Pharmacology and Therapeutics* 1993; 7: 459-62. CENTRAL ID: CN-00096688, Pubmed ID: 8218760

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) compared with Combizym as a control in dyspeptic patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Osaka Medical Center for Cancer and Cardiovascular Diseases), Japan.

4. Participants

Forty-two patients who had indefinite epigastric distress persisting for at least one year; had chronic gastritis confirmed by endoscopy; and gave consent to participate in the study.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 1 week (n=22).

Arm 2: treatment with Combizym 1 tablet t.i.d. after meals for 1 week (n=20).

6. Main outcome measures

Subjective symptom scores and amount of gastric emptying (measured by acetaminophen absorption method).

7. Main results

In contrast to its absence in arm 2, significant improvement in abdominal bloating, heartburn, belching, and nausea was noted in arm 1. Significant improvement in gastric emptying measured at 30, 45, and 60 minutes was observed in arm 1 but not in arm 2.

8. Conclusions

TSUMURA Rikkunshito is useful for treating dyspeptic patients by improving gastric emptying and gastrointestinal symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the clinical utility of TSUMURA Rikkunshito, compared with Combizym as a control, in dyspeptic patients. It should be mentioned that this paper may be the only original article on rikkunshito written in English at this time and that the gastric emptying test was introduced as an objective outcome measure in this study. Most Kampo medicines seem to improve "functions". Given that it will become increasingly important to demonstrate the effects of Kampo medicines using measures for evaluating "functions" and to communicate those effects to the world, this is a landmark study.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Miyoshi A, Yachi A, Masamune O, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis - a multicenter comparative study using cisapride as a control - *. *Progress in Medicine* 1991; 11: 1605-31 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of TSUMURA Rikkunshito (六君子湯), using cisapride as a control, in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fifty institutions including university hospitals, Japan.

4. Participants

Two hundred and forty-eight patients who had so-called “non-ulcer dyspepsia” (e.g., chronic atrophic gastritis) with 2 or more indefinite complaints of gastrointestinal disorders, associated with possible impairment of gastric motility. Of 248 participants, 215 were included in the analysis.

5. Intervention

Arm 1: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before meals for 4 weeks (n=111).

Arm 2: treatment with cisapride 2.5 mg t.i.d. before meals for 4 weeks (n=104).

6. Main outcome measures

Subjective and objective symptoms.

7. Main results

The improvement in certain individual subjective symptom scores (i.e., scores for anorexia [at 3 weeks], epigastric pain [at 2, 3, and 4 weeks], abdominal discomfort [at 4 weeks], cold extremities [at 2, 3, and 4 weeks], and lightheadedness [at 2 weeks]), global score, and utility rating were significantly higher in arm 1 than in arm 2. The improvement in the ratings for belching (at 1 and 2 weeks) and tenderness (at 1 week) were significantly higher in arm 2 than in arm 1.

8. Conclusions

TSUMURA Rikkunshito is more efficacious than cisapride and is clinically useful in the treatment of indefinite complaints of gastrointestinal disorders including chronic gastritis.

9. From Kampo medicine perspective

For patients aged 60 or older and those who are thin or overweight, improvement in symptom scores tended to be higher in arm 1, supporting the effectiveness of rikkunshito for *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Two patients discontinued treatment owing to leg discomfort and diarrhea, respectively. There was no significant between-arm difference in the rate of adverse drug reactions and in global safety score.

11. Abstractor’s comments

This paper describes an evaluation of the clinical utility of TJ-43 TSUMURA Rikkunshito using cisapride as a control in the treatment of gastritis. It was a large, multicenter clinical trial. It is safe to say that evidence for the efficacy of rikkunshito treatment was established by this and another paper “Miyoshi A, Kaneko E, Nakazawa S, et al. Clinical evaluation of TJ-43 TSUMURA Rikkunshito in the treatment of gastritis (acute gastritis and acute exacerbation of chronic gastritis) - a multicenter comparative study using sodium azulene sulfonate as a control - *. *Shindan to Chiryō (Diagnosis and Treatment)* 1991; 79: 789-810 (in Japanese)”. Like the the approach of the latter study, that of the present study may have been progressive for its time, since Kampo medical parameters, such as “tension of the abdominal wall” and “splashing sounds in the gastric region”, were also evaluated in the analysis.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Koide A. Adoption of rikkunshito before endoscopy in patients with upper abdominal symptoms*. *Nikkei Medical* 2002; 31: 22-3 (in Japanese).

Koide A. The improvement of QOL by rikkunshito in patients with need for endoscopy*. *Medical Tribune* 2004: 45 (in Japanese).

Yamaguchi T, Koide A. Usefulness of Rikkun-shi-to (TJ-43), a Chinese herbal medicine, for the treatment of gastro-esophageal reflux disease (GERD). *Medical Science Digest* 2007; 33: 748-52 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) as an agent to improve symptoms before endoscopy in patients with upper abdominal symptoms and need for endoscopy of the upper gastrointestinal tract.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

None; the authors are members of the Department of Medical Oncology, Graduate School of Medicine, Chiba University, Japan.

4. Participants

One hundred and twenty patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

5. Intervention

Arm 1: treatment with H₂-receptor blocker (H2RB; ranitidine 150 mg; n=39).

Arm 2: treatment with proton pump inhibitor (PPI; omeprazole 20 mg; n=40).

Arm 3: treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g (n=41).

The duration of treatment was not specified (the administration was continued until the upper gastrointestinal endoscopy was performed).

6. Main outcome measures

Acid reflux (heartburn, reflux), abdominal pains (epigastric pain, hunger, and nausea), dyspepsia (borborygmus, abdominal distention, eructation, and flatus), diarrhea (diarrhea, loose stool, and rectal urgency), and constipation (constipation, hard stool, feeling of incomplete evacuation).

7. Main results

Overall, gastrointestinal symptoms associated with impaired quality of life (QOL) were significantly improved after the treatment in all arms; the improvement was significantly greater in arm 3 than in arms 1 and 2. Also improved were acid reflux associated with impaired QOL in arm 1, acid reflux and abdominal pains associated with impaired QOL in arm 2, and acid reflux, abdominal pains, and dyspepsia associated with impaired QOL in arm 3. Significantly greater improvements were found for acid reflux in arm 3 than in arm 1; for abdominal pains in arms 2 and 3 than in arm 1; for dyspepsia in arm 3 than in arms 1 and 2. Considering only patients with reflux esophagitis, gastrointestinal symptoms were also significantly improved by treatment in all arms. Acid reflux improved in arm 1, and acid reflux, abdominal pains, and dyspepsia improved in arms 2 and 3. H2RB, PPI, and rikkunshito had similar effectiveness.

8. Conclusions

The efficacy of rikkunshito as a pre-endoscopic medication, even as monotherapy, is comparable to that of other gastric acid secretion inhibitors in patients with upper abdominal symptoms and need for upper gastrointestinal endoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The study by Yamaguchi et al (2007) is considered to be a follow-up to the two studies by Koide (2002, 2004). This clinically valuable study showed that the efficacy of rikkunshito against upper abdominal symptoms including gastroesophageal reflux disease is comparable to that of other gastric acid secretion inhibitors. The present study also deserves praise for assessing each clinical symptom objectively using the GSRS (Gastrointestinal Symptom Rating Scale). The cost-effectiveness of rikkunshito is mentioned without detail in the conclusion of this paper, but it is addressed more completely in paper 2). The present paper provides very interesting insights, but its first half is too general. Therefore, publication as an original article is desired.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 20 January 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Harasawa S, Miyoshi A, Miwa T, et al. Double-blind multicenter post-marketing clinical trial of TJ-43 TSUMURA Rikkunshito for the treatment of dysmotility-like dyspepsia. *Igaku no Ayumi (Journal of Clinical and Experimental Medicine)* 1998; 187: 207-29 (in Japanese). Ichushi Web ID: 1999085057

Harasawa S. The role of rikkunshito against NUD (non-ulcer dyspepsia) – especially its efficacy in dysmotility-like NUD*. *Progress in Medicine* 1999; 19: 843-8 (in Japanese). [MOL](#), [MOL-Lib](#)

Harasawa S. Evidence from an RCT of rikkunshito (六君子湯) for epigastric complaints*. *Kampo Igaku (Science of Kampo Medicine)* 2011; 35: 113-7 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of TJ-43 TSUMURA Rikkunshito (六君子湯) more objectively in patients with dyspepsia caused by dysfunction of the upper gastrointestinal tract.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

A total of 54 institutions obtained approval of Institutional Review Boards, Japan.

4. Participants

Two hundred and ninety-six patients (30–80 years old) with a chief complaint of persistent or intermittent (for more than 4 weeks) dysmotility-like dyspepsia, characterized by anorexia (or poor appetite), gastric distress, and heavy stomach feeling (presumably due to dysfunction of the upper gastrointestinal tract), and indicating some “*kyo-sho* (虚証, deficiency pattern)” conditions such as gastroptosis, physical weakness.

5. Intervention

Arm 1: oral administration of TSUMURA Rikkunshito (六君子湯) Extract Granules (TJ-43) 2.5 g t.i.d. before or between meals for 2 weeks (n=147).

Arm 2: oral administration of low-dose (1:40 dilution) TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. before or between meals for 2 weeks (n=149).

6. Main outcome measures

Five symptoms associated with dysmotility-like dyspepsia (anorexia, abdominal distension, stomach discomfort, heavy stomach feeling, and nausea).

Three symptoms associated with ulcer-like dyspepsia (upper abdominal/epigastric pain, heartburn or pyrosis, and eructation).

7. Main results

A total of 235 subjects (TJ-43 group, n=118; low-dose group, n=117) were included for analysis of efficacy. Dysmotility-like dyspepsia symptoms were improved in 59.3% of the TJ-43 group and 40.2% of the low-dose group; overall symptoms including ulcer-like dyspepsia symptoms were also improved in 60.2% of the TJ-43 group and 41.0% of the low-dose group (both $P=0.004$). These indicate that efficacy is significantly higher in the TJ-43 group. Furthermore, a significantly higher percentage of the TJ-43 group than the low-dose group (58.8% versus 39.3%) deemed the treatment useful ($P=0.003$).

8. Conclusions

The safety and effectiveness of TJ-43 was validated for the treatment of dysmotility-like dyspepsia in this double-blind study. We therefore conclude that TJ-43 Rikkunshito is clinically useful.

9. From Kampo medicine perspective

In this study, the inclusion criteria were “deficiency pattern” symptoms (i.e., decreased tone of abdominal wall, subjective/objective splashing sound, gastroptosis tendency, and mental/physical weakness) and the exclusion criteria were “*jitsu-sho* (実証, excess pattern)” symptoms (i.e., mental and physical strength, massive and muscular body, and reddish face).

10. Safety assessment in the article

Safety problems were detected in 2 cases in the TJ-43 group (diarrhea, elevated GOT) and 2 in the low-dose group (diarrhea, elevated GOT/GPT). Adverse effects (defined as symptoms undeniably caused by the drug) occurred in 7 of the TJ-43 group and 7 of the low dose group. None were serious.

11. Abstractor's comments

Use of low-dose TJ-43 in the control group and use of Kampo diagnostic considerations when selecting the inclusion and exclusion criteria are appreciated. Improvement in “*kyo-sho*” symptoms are described in Harasawa's report (1999, mentioned above). Another report of Harasawa (2011) is a sub-group analysis (rikkunshito group [n=40] and control group [n=35]) based on the Rome III criteria (2006). Patient backgrounds were similar in both groups, and the study demonstrated significant difference in the actions of rikkunshito. However, interpretations of the study must take heed of the fact that any bias from ‘unknown factors’, the weakness of the subgroup analysis, is not clearly identified.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2012, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Arai M. Rikkunshito significantly enhances the secretion of ghrelin in patients with functional dyspepsia*. *Kampo Igaku (Kampo Medicine)* 2009; 33: 405–6.

Matsumura T, Arai M, Suzuki T, et al. The traditional Japanese medicine rikkunshito improves upper gastrointestinal symptoms in patients with functional dyspepsia. *Gastroenterology* 2010; 138: S471. CENTRAL ID: CN-00796662

Arai M, Matsumura T, Yoshikawa M, et al. Analysis of the rikkunshito efficacy on patients with functional dyspepsia*. *Nihon Yakurigaku Zasshi (Folia Pharmacologica Japonica)* 2011; 137: 18–21. (in Japanese). J-STAGE

Arai M, Matsumura T, Tsuchiya N, et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. *Hepato-Gastroenterology* 2012; 59: 62-6. Pubmed ID: 22260823

1. Objectives

To clarify the effect of rikkunshito (六君子湯) on ghrelin secretion and symptoms and to clarify its mechanism of action in patients with functional dyspepsia (FD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the author belongs to the Department of Gastroenterology, Graduate School of Medicine, Chiba University), Japan.

4. Participants

Twenty-seven patients with FD fulfilling the Rome III criteria.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 4 weeks (n=13).

Arm 2: domperidone 30 mg/day for 4 weeks (n=14).

6. Main outcome measures

Blood acylated ghrelin (AG) levels, serum leptin levels, gastrointestinal symptoms (assessed by Gastrointestinal Symptom Rating Scale [GSRs] score), and depressive symptoms (assessed by Self-rating Depression Scale [SDS] score) before administration and 2 and 4 weeks after administration began.

7. Main results

All symptoms improved significantly in arm 1 in Week 2 of administration, while gastric acid reflux, abdominal pain, and dyspepsia improved in Week 4. Although in arm 2 these three symptoms improved significantly in Week 2, only dyspepsia had improved in Week 4. And while blood AG levels in arm 1 had improved significantly after 2 weeks compared to before administration ($P<0.05$), no significant change was observed in arm 2. The AG increase and gastrointestinal symptom improvement in arm 1 demonstrated a significant, positive correlation. There were no significant changes in serum leptin levels in either arm. Depression scores did not change significantly in arm 1, but showed a significant improvement in arm 2 in Week 4 ($P=0.04$).

8. Conclusions

Rikkunshito increases blood acylated ghrelin levels and improves gastrointestinal symptoms in FD patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The authors mention that there were no adverse effects between the start and the completion of the trial.

11. Abstractor's comments

This is a valuable clinical study that demonstrated for the first time in an RCT that rikkunshito alleviates gastrointestinal symptoms by increasing blood AG levels in FD patients. In their 2010 paper, the authors did not specify the numbers of participants in each group, and AG levels showed a rising trend only in the week-four analysis. But in their 2012 paper they did specify the numbers of participants in the groups, they excluded two participants with diabetes because insulin resistance and blood sugar levels affect AG concentrations, and analysis in week two, not week four, resulted in a significant difference. Furthermore, they found that the extent of symptomatic improvement correlates to the increase in AG concentration. On the other hand, a study of the relationship of the increase in blood AG concentration and the effects of rikkunshito to the factors relevant to rikkunshito-pattern (六君子湯の証), including presence or absence of fatigue or sensitivity to cold and whether participants exhibit *kyo-sho* or *jitsu-sho* (虚証/実証, deficiency or excess pattern), might yield even more definitive and clinically significant results.

12. Abstractor and date

Motoo Y, 1 June 2010, 1 January 2012, 1 June 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Nishida T. Effect of rikkunshito on gastrointestinal function in patients after gastrectomy*. *Progress in Medicine* 2006; 26: 3224-5 (in Japanese). [MOL](#), [MOL-Lib](#)

Takahashi T, Endo S, Nakajima K, et al. Effect of Rikkunshito, a Chinese herbal medicine, on stasis in patients after pylorus-preserving gastrectomy. *World Journal of Surgery* 2009; 33: 296-302. CENTRAL ID: CN-00686725, Pubmed ID: 19082653

1. Objectives

To evaluate the efficacy of TSUMURA Rikkunshito (六君子湯) Extract Granules for delayed excretion after pylorus-preserving gastrectomy (PPG).

2. Design

Osaka University Hospital, Japan.

3. Setting

Randomized controlled trial (cross-over) (RCT cross-over).

4. Participants

Eleven patients who underwent pylorus-preserving gastrectomy.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 4 weeks and then not treated with TSUMURA Rikkunshito (六君子湯) Extract Granules for 4 weeks (n=4).

Arm 2: not treated with TSUMURA Rikkunshito (六君子湯) Extract Granules for 4 weeks and then treated with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for 4 weeks (n=7).

6. Main outcome measures

Gastrointestinal quality of life (QOL) index (GIQLI), stasis-related symptom score, Sigstad score, gastrointestinal excretion scintigram.

7. Main results

While there was no significant between-arm difference in the GIQLI and Sigstad score (dumping syndrome), the stasis-related symptom score significantly decreased on treatment in arm 1. In the scintigram, the gastric residual rate of solids (but not liquids) excretion decreased on treatment with TSUMURA Rikkunshito (六君子湯) Extract Granules.

8. Conclusions

Treatment with TSUMURA Rikkunshito Extract Granules is effective for delayed gastric excretion of solids after PPG.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No drug-related or protocol-defined adverse event was reported.

11. Abstractor's comments

This is a clinical trial of high clinical significance in that scintigraphy was used to objectively evaluate excretion of liquids and solids separately. However, the study design, including randomization of patients and sample size, is questionable. It is desirable to conduct a high-quality RCT using an adequate sample size. In the previous version of Evidence Reports of Kampo treatment, structured abstract for this trial was developed and published based on the article by Nishida (2006), however, this trial was subsequently published as the reference above, and structured abstract was reconstructed on the basis of this new article.

12. Abstractor and date

Kogure T, 26 January 2009, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Shiratori M, Shoji T, Kanazawa M, et al. Effect of rikkunshito on gastric sensorimotor function under distention. *Neurogastroenterology & Motility* 2011; 23: 323-9, e155-6. Pubmed ID: 21175995

1. Objectives

To evaluate the effects of rikkunshito (六君子湯) on gastric contraction and expansion.

2. Design

Crossover randomized controlled trial (RCT-cross over).

3. Setting

Tohoku University Hospital, Japan.

4. Participants

Nine healthy volunteers.

5. Intervention

Participants were randomly assigned to either arm 1 or arm 2.

Arm 1: gastric pressure measured after observation for 2 weeks without administration and then after taking 7.5 g/day of TSUMURA Rikkunshito (六君子湯) Extract Granules for 2 weeks. Number of subjects: not reported.

Arm 2: gastric pressure measured after taking 7.5 g/day of TSUMURA Rikkunshito Extract (六君子湯) Granules for 2 weeks and then after observation for 2 weeks without administration. Number of subjects: not reported.

6. Main outcome measures

Gastric pressure measurements using a gastric barostat before and after imposition of stress.

7. Main results

Reduction in gastric volume due to stress was observed before or after but not during the period of rikkunshito administration. Pressure thresholds for epigastric bloating and for pain were lower during rikkunshito administration, regardless of stress imposition.

8. Conclusions

Rikkunshito may improve changes in gastric wall tone caused by stress or anxiety.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This article demonstrates the potential of rikkunshito in helping to control overeating when stress is not present, and in preventing appetite reduction when stress is present. Unfortunately, however, the authors did not report the number of subjects in each group. It is significant that the study used the objective measure of gastric pressure to assess the specific effects of rikkunshito on gastric contraction and expansion.

12. Abstractor and date

Nakata H, , 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Uehara R. An evaluation of gastrointestinal symptoms and gastric mobility after endoscopic submucosal dissection (ESD) and an investigation of the usefulness of Rikkunshito (TJ-43)*. *Dai 8 Kai Nippon Shokakan Gakkai Sokai Gakujutsu Syukai Workshop 4 PROCEEDING Jobu Shokaki Shoji to Kampo (Workshop 4 Proceedings of the 8th Annual Meeting of the Japanese Gastroenterological Association: Upper Gastrointestinal Symptoms and Kampo)* 2012: 16-7 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for gastrointestinal symptoms after endoscopic submucosal dissection (ESD) for early gastric cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital (Department of Gastroenterology and Hepatology, Nagasaki University), Japan.

4. Participants

Eleven patients with upper gastrointestinal symptoms following gastric ESD.

'Patients with upper gastrointestinal symptoms' were defined as patients with three or more symptoms rated in the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire: epigastric pain, hunger pain, nausea, borborygmus, bloating, belching, and flatulence.

5. Intervention

Arm 1: oral administration of proton pump inhibitor (PPI) and TSUMURA Rikkunshito (六君子湯) Extract Granules (7.5 g/day) (n=6).

Arm 2: oral administration of PPI (n=5).

6. Main outcome measures

Gastric emptying (¹³C breath test) at 0 and 8 weeks.

GSRS questionnaire symptoms (epigastric pain, hunger pain, nausea, borborygmus, bloating, belching, and flatulence) at 0, 4, and 8 weeks.

7. Main results

Gastric emptying (¹³C breath test) at 8 weeks after ESD showed no significant difference between arms 1 and 2, with no improvement compared to 0 weeks in both arms.

There was no improvement in any symptom at 4 or 8 weeks compared to 0 weeks in arm 2.

In arm 1, abdominal pain and overall score improved significantly at 4 and 8 weeks compared to 0 weeks (on GSRS subscales), and epigastric pain and hunger pain improved significantly at 8 weeks compared to 0 weeks.

8. Conclusions

Rikkunshito may be effective for relief of symptoms (epigastric pain and hunger pain) in patients with upper gastrointestinal symptoms following ESD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This trial evaluated the usefulness of rikkunshito plus a PPI, which is considered effective for functional dyspepsia, in patients with upper gastrointestinal symptoms following ESD. Changes in gastric discharge function and subjective symptoms (GSRS) served as the indicators. Gastric emptying (usually decreased after ESD) was not improved by administering rikkunshito in addition to a PPI. Epigastric pain and hunger pain improvement after ESD resulting from the combined use of rikkunshito, as the authors assert, may be attributable to rikkunshito's adaptive relaxation effect or mucosal protective effect. Further study of these mechanisms are needed. The researchers will, hopefully, investigate ways of reducing the incidence of secondary hemorrhage or hastening the healing of ulcerated mucous membranes, two complications of ESD.

12. Abstractor and date

Hoshino E, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takayama S, Seki T, Watanabe M, et al. The herbal medicine daikenchuto increases blood flow in the superior mesenteric artery. *The Tohoku Journal of Experimental Medicine* 2009; 219: 319–30.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) and orengedokuto (黃連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (Tohoku University Hospital), Japan.

4. Participants

Fourteen healthy adults (25–44 years old) without cardiac disease.

5. Intervention

Arm 1: distilled water (50 mL, 37°C).

Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules 5.0 g.

Arm 3: TSUMURA Orengedokuto (黃連解毒湯) Extract Granules 2.5 g.

6. Main outcome measures

Hemodynamic parameters including CO, blood pressure, heart rate, and SMA blood flow, measured by impedance cardiography (ICG) before and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min after administration of distilled water, daikenchuto, and orengedokuto.

7. Main results

Although neither daikenchuto nor orengedokuto affected CO, daikenchuto significantly increased SMA blood flow compared with distilled water or orengedokuto ($P < 0.05$). Five grams of daikenchuto significantly increased SMA blood flow between 5 min ($P < 0.01$) and 90 min after administration, with a peak reached at 20 min.

8. Conclusions

Daikenchuto increases SMA blood flow without changing CO in healthy people.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study used a physiological approach to verify the blood flow-increasing effect of daikenchuto, which is used for *kansho* (寒証, cold pattern), and the blood flow-suppressing effect of orengedokuto, which is used for *netsusho* (熱証, heat pattern). Daikenchuto is well-known for its gastrointestinal prokinetic effect and is clinically applied to subileus cases regardless of *sho* (証, pattern) with certain efficacy. This study revealed that daikenchuto increases SMA blood flow, possibly providing practicing clinicians with valuable findings. However, as this study was performed in healthy people, it not certain that the outcome of daikenchuto therapy is the same in patients in the ileus state or with *hie* (冷え, a feeling of coldness) in the pelvis. Based on the results of this study in healthy adults, future studies are expected to identify the mechanisms of action (probably more than one) of these Kampo medicines (daikenchuto in subileus cases with *kansho* [寒証, cold pattern] and orengedokuto in hypertension and insomnia cases with *netsusho* [熱証, heat pattern]) using the same study protocol.

12. Abstractor and date

Ushiroyama T, 16 January 2011, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takayama S, Seki T, Watanabe M, et al. The effect of warming of the abdomen and of herbal medicine on superior mesenteric artery blood flow – a pilot study. *Forschende Komplementär Medizin* 2010; 17: 195–201 (in English with German abstract). Pubmed ID: 20829597

1. Objectives

Comparative evaluation of the regulatory effects of thermal stimulation to the abdomen and Daikenchuto (大建中湯) on superior mesenteric artery (SMA) blood flow in healthy people.

2. Design

Randomized controlled trial (RCT).

3. Setting

Five centers, including the Center for Asian Traditional Medicine, Graduate School of Medicine, Tohoku University, Japan.

4. Participants

Forty-two healthy male volunteers with no heart disease.

5. Intervention

Arm 1: participants received 20 minutes of thermal stimulation to the paraumbilical region with a warming device (40°C), and were then observed for 50 minutes.

Arm 2: participants took TSUMURA Daikenchuto (大建中湯) Extract Granules (5.0 g) with distilled water (50 mL, 37°C) and were then observed for 50 minutes.

Arm 3: participants took distilled water (50 mL, 37°C) and were then observed for 50 minutes.

Randomization was performed only in arm 1 and arm 2 (14 subjects per arm).

6. Main outcome measures

Hemodynamic testing: SMA blood flow was measured before taking daikenchuto, before thermal stimulation with a warming device, and before taking distilled water, and then 10, 20, 30, 40, and 50 minutes after the start of each intervention.

7. Main results

SMA blood flow increased significantly between 10 and 50 minutes after daikenchuto administration ($P < 0.01$) and between 10 and 40 minutes after thermal stimulation ($P < 0.05$). There was no significant difference between these arms. SMA blood flow did not change after administration of distilled water.

8. Conclusions

Daikenchuto increases SMA blood flow in healthy people. That increase is similar to the increase generated by thermal stimulation using a warming device.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study employed a physiological evaluation method of verification in its investigation of blood flow increase stimulated by daikenchuto, which is used for *kansho* (寒証, cold pattern). It appears to be either a follow-up of a study in *The Tohoku Journal of Experimental Medicine* (2009; 219: 319–30) or concurrent research, as it compared the effects of thermal stimulation using a warming device (positive control) with administration of distilled water only (negative control). Daikenchuto is well known for its promotion of intestinal movement and is used clinically for sub-ileus conditions regardless of pattern: it is recognized for certain effects. This study found that increases in SMA blood flow induced by daikenchuto were similar to those induced by a thermal stimulation device, which suggests that it would be valuable to practicing clinicians. However, it should be pointed out that the subjects were healthy volunteers and the study did not clarify the question of whether the same phenomenon would be observed in people suffering from ileus conditions or conditions associated with coldness in the pelvic cavity. Based on this study of healthy people, researchers should be encouraged to use the study's protocols to further elucidate the action mechanisms (probably more than one) of Kampo medicines, specifically daikenchuto, in outpatients with cold-pattern sub-ileus conditions or habitual constipation.

12. Abstractor and date

Ushiroyama T, 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Mori K, Machida S, Yoshida T, et al. Usefulness of Kampo medicine (hangeshashin-to) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Proceedings of the American Society of Clinical Oncology* 1999; 18: 518a, Abstract 1996 CENTRAL ID: CN-00716751

Mori K, Hirose T, Machida S, et al. Kampo medicines for the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)* 1998; 25: 1159-63 (in Japanese with English abstract) CENTRAL ID: CN-00153138, Pubmed ID: 9679578 [MOL](#), [MOL-Lib](#)

Mori K. Hangeshashin-to (Kampo medicined) in the prevention of irinotecan-induced diarrhea in advanced non-small cell lung cancer. *Progress in Medicine* 1999; 19: 886-90 (in Japanese with English abstract) [MOL](#), [MOL-Lib](#)

Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. *Cancer Chemotherapy and Pharmacology* 2003; 51: 403-6. CENTRAL ID: CN-00437238, Pubmed ID: 12687289

1. Objectives

To evaluate the safety and efficacy of hangeshashinto (半夏瀉心湯) (TJ-14) for CPT-11-induced diarrhea during combination chemotherapy with cisplatin (CDDP) plus irinotecan hydrochloride (CPT-11) for advanced non-small-cell lung cancer (NSCLC).

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

One hospital; the authors belong to the Department of Respiratory Disease, Tochigi Cancer Center, Japan.

4. Participants

From among inpatients with NSCLC who received dual therapy with CDDP plus CPT-11 from November 1993 through December 1996, forty one patients who met the following selection criteria were enrolled: 1) treatment-naïve with unresectable NSCLC (stage III, IV); 2) performance status 0 to 2; 3) preserved major organ function; 4) 75 years or younger; and 5) informed consent. Patients with serious complications, diarrhea, severe pleural effusion, or symptomatic cerebral metastasis were excluded from the study.

5. Intervention

Arm 1: treatment with TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (TJ-14) 2.5 g t.i.d. before meals in 18 patients.

Arm 2: no treatment in 23 patients.

In the arm 1, hangeshashinto was administered every day from at least 3 days before through 21 days or more after the start of chemotherapy.

6. Main outcome measures

Stool properties and frequency of defecation, presence and severity of abdominal pain associated with defecation, presence or absence of bowel movements at night and bloody diarrhea.

7. Main results

The onset and the highest daily frequency of diarrhea were respectively recorded at 6.3 and 9.2 days after the start of chemotherapy in arm 1, and at 5.9 and 9.0 days in arm 2. During the first cycle of chemotherapy, the severity of diarrhea was significantly improved and the incidence of grade 3 or higher diarrhea was lower in arm 1 than in arm 2. The number of diarrhea episodes and the duration (in days) of diarrhea were not significantly different between the two arms.

8. Conclusions

Hangeshashinto is effective for preventing and relieving CPT-11-induced diarrhea in advanced NSCLC.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Mild constipation was reported in 2 hangeshashinto-treated patients. Other significant adverse effects were not observed.

11. Abstractor's comments

This clinical study indicated that the concomitant use of hangeshashinto is effective for diarrhea, which can occur during chemotherapy containing CPT-11. This study lacked a placebo control group and was not double-blinded. In a study using Kampo medicines as a control, it is difficult to prepare the placebo because Kampo medicines have specific textures and smells. Nonetheless, double-blind design should be considered in order to improve the quality of study. “

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. *Gan to Kagaku Ryoho (Japanese Journal of Cancer Chemotherapy)* 2009; 36: 1485–8 (in Japanese with English abstract). CENTRAL ID: CN-00728899, Pubmed ID: 19755817, Ichushi Web ID: 2009352672, [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single facility, Japan.

4. Participants

Twenty patients with inoperable advanced recurrent gastric cancer or colorectal cancer (12 males and 8 females).

5. Intervention

Patients received a course of chemotherapy consisting of 2 weeks on and 2 weeks off oral S-1 (tegafur/gimeracil/oteracil potassium) at 80–120 mg according to body surface area and intravenous irinotecan (CPT-11) at 100–125 mg once every 2 weeks.

Arm 1: Hangeshashinto (半夏瀉心湯) extract 7.5 g/day for 3 days starting on the day of administration of irinotecan (CPT-11) (n=10).

Arm 2: no administration of hangeshashinto (半夏瀉心湯) extract (n=10).

6. Main outcome measures

Anti-tumor effect (RECIST criteria), adverse events (Common Terminology Criteria for Adverse Events v3.0), and quality of life (QOL score developed by Kurihara et al.) evaluated on days 1, 15, and 29.

7. Main results

There was no significant difference in anti-tumor effect between arms. Chemotherapy-associated adverse events were more common in arm 2 than in arm 1 (significance of difference not tested). A decrease in QOL score from day 1 to day 15 was larger in more patients in arm 2 than in arm 1. Overall QOL score was decreased by 15 points or more in 1 patient in arm 1, compared with 4 patients in arm 2, with the mean±standard deviation significantly changed from 79±19 and 87±13 on day 1 to 77±21 and 75±23 on day 15 in arm 1 and arm 2, respectively ($P<0.05$). In particular, QOL in the “social” domain decreased 2 points or more in 7 of 10 patients in arm 2 and 0 of 10 patients in arm 1.

8. Conclusions

Hangeshashinto (半夏瀉心湯) is a useful supportive therapy from the viewpoint of QOL in patients treated for advanced gastric and colorectal cancer with S-1/irinotecan (CPT-11) combination therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

Post-marketing surveillance identified gastrointestinal symptoms such as nausea/vomiting (52.5%), anorexia (48.1%), and abdominal pain (12.2%) as frequent adverse drug reactions of CPT-11, besides diarrhea (43%, serious in 10.2% of cases). Hangeshashinto has well known efficacy not only for diarrhea, as reported by Kamataki et al. (1994), but also for nausea/vomiting, anorexia, and epigastric pain. This study demonstrated that hangeshashinto improves QOL. But the study had the following problems: (1) the rationale for the 3-day hangeshashinto administration period after administration of CPT-11 is not indicated. Although the authors seem to assume that the hangeshashinto-*sho* (証, pattern) induced by CPT-11 disappears in 3 days, delayed diarrhea attributable to intestinal mucosal injury by an active metabolite (SN-38) 24 hr after administration, for example, does not disappear in 3 days, warranting consideration of duration of administration in the future; (2) hangeshashinto is effective in only some cases. As QOL score was decreased by 15 points or more in 4 of 10 patients in arm 2 in this study, only these 4 patients are likely to have exhibited hangeshashinto-*sho* (証, pattern). It is recommended that patients be enrolled in the study from the second cycle onward after determining the presence or absence of hangeshashinto-*sho* (証, pattern) and the duration of the *sho* (証, pattern), based on the response to the first cycle of CPT-11.

12. Abstractor and date

Hoshino E, 15 January 2011.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Miyauchi H. A comparative study of the preventive effects of hangeshashinto and oral alkalizer for delayed diarrhea in chemotherapy for colorectal cancer (FOLFILI)*. *Progress in Medicine* 2012; 32: 628-9 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To compare the preventive effects of hangeshashinto (半夏瀉心湯) for delayed diarrhea following administration of CPT-11 for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

No mention of participating centers (the authors are from the Department of Frontier Surgery, Graduate School of Medicine, Chiba University), Japan.

4. Participants

Thirty patients (age range: 20–80 years) with advanced recurrent colorectal cancer.

5. Intervention

Arm 1: oral administration of hangeshashinto (半夏瀉心湯) (manufacturer not specified) 7.5 g/day during FOLFILI-3 treatment (n=14).

Arm 2: administration of oral alkalizers (sodium bicarbonate 1.8 g and ursodeoxycholic acid 300 g) from the first day of FOLFILI-3 treatment (n=15).

6. Main outcome measures

Grade of diarrhea, grade of adverse events other than diarrhea, drug compliance, response rate, treatment duration.

7. Main results

No significant difference between arms 1 and 2 was noted in diarrhea grade (3/14 [21.4%] participants in arm 1 and 4/15 participants [26.7%] in arm 2 scored grade III or higher), neutropenia grade (4/14 [28.5%] participants in arm 1 and 6/15 participants [40%] in arm 2 scored grade III or higher), drug compliance (81.2% in arm 1, with 87.5% for sodium bicarbonate and 96.8% for ursodeoxycholic acid in arm 2), antitumor effect (complete response [CR] in no participants and partial response [PR] in six participants in arm 1; CR in two participants and PR in eight participants in arm 2), response rate/disease control rate (response rate of 46.2% and disease control rate of 92.3% in arm 1; response rate of 71.4% and disease control rate of 100% in arm 2), and number of FOLFILI cycles (16.1 in arm 1 and 14.5 in arm 2).

8. Conclusions

Oral alkalizer and hangeshashinto have the same preventative effect on delayed diarrhea in FOLFILI.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The authors originally held the notion that oral alkalizer prevented delayed diarrhea, which is a dose-limiting toxicity (DLT) and an adverse effect in patients receiving CPT-11 for advanced recurrent colorectal cancer. This study evaluated the previously reported inhibitory effect of hangeshashinto compared with oral alkalizer (the control group) and found no difference in their inhibitory effects. However, there is no indication that intestinal alkalizers taken orally do in fact prevent delayed diarrhea from CPT-11. A trial that uses a therapy without established efficacy as a control has little significance. It is of fundamental importance to clarify the clinical effectiveness by including a hangeshashinto group and a non-hangeshashinto group in the trial.

12. Abstractor and date

Hoshino E, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Nagashima Y, Tanaka N, Furukawa K, et al. Effects of Daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer*. *Progress in Medicine* 1998; 18: 903-5 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on intestinal paralysis after surgery for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single institution (Nippon Medical School Hospital), Japan.

4. Participants

Eighteen patients who underwent low anterior resection for rectal cancer. Exclusion criteria were: age 75 or older; history of laparotomy; American Society of Anesthesiologists (ASA) class II disease with complications.

5. Intervention

Arm 1: treatment with infusion of TSUMURA Daikenchuto (大建中湯) Extract Granules (7.5 g/day) dissolved in lukewarm water (20 mL) through a gastric tube (oral administration after the removal of gastric tube) (n=8).

Arm 2: no treatment (n=10).

6. Main outcome measures

Times to passage of flatus and first bowel movement, and transit times (upper gastrointestinal, colorectal, and whole-bowel) as assessed by radiopaque markers.

7. Main results

Among the outcome measures, time to passage of flatus and upper gastrointestinal and whole-bowel transit times were shorter in arm 1 than arm 2 and the difference in upper gastrointestinal transit time was significant.

8. Conclusions

Daikenchuto is useful for relieving intestinal paralysis by reducing the intestinal transit time after colorectal cancer surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the effects of daikenchuto on intestinal paralysis after surgery for colorectal cancer. Few transit time studies using radiopaque markers in daikenchuto (Kampo medicine)-treated patients have been reported and the present study is appreciated in that regard. Future studies including a larger number of patients are anticipated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takagaki Y, Kawasaki S, Komai H, et al. The effect of Chinese herb medicine (dai-kenchu-to) on paralytic ileus after repair of abdominal aortic aneurysm. *Nihon Rinsho Geka Gakkai Zasshi (Journal of Japan Surgical Association)* 2000; 61: 325-8 (in Japanese with English abstract). [J-STAGE](#)

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for improving intestinal peristalsis in patients with intestinal paralysis after surgery for abdominal aortic aneurysm (AAA).

2. Design

Randomized controlled trial (RCT).

3. Setting

No description of the setting is available (the authors are cardiovascular surgeons at community or university hospitals), Japan.

4. Participants

Twenty-one patients who underwent elective surgery for non-ruptured infrarenal AAA during the same time period.

5. Intervention

Arm 1: treatment with infusion of daikenchuto (大建中湯) dissolved in lukewarm water (5 g/20 mL) through a gastric tube, followed by clipping of the tube for 30 minutes, three times daily from the first postoperative day, in 7 patients.

Arm 2: treatment with infusion of lukewarm water (20 mL) in the same manner as arm 1 in 7 patients, as a control group.

Arm 3: treatment with infusion of lukewarm water (20 mL) and intravenous panthenol (100 mg/day) in 7 patients.

6. Main outcome measures

Degree of abdominal distension, and presence or absence of bowel sounds, passage of flatus, and small bowel gas on the abdominal X-ray.

7. Main results

Bowel sounds were heard immediately after the infusion of the study drug in all patients of arm 1, but not in any patient of arms 2 and 3. Time to the first passage of flatus after surgery was 3.1 ± 0.8 days in arm 1, 5.1 ± 1.3 days in arm 2, and 3.7 ± 0.8 days in arm 3; significantly earlier passage of flatus was observed in arms 1 and 3 ($P < 0.05$), but there was no significant difference in time to first passage of flatus between these two arms. Small bowel gas disappeared at 3.3 ± 1.4 days after surgery in arm 1, at 6.1 ± 1.2 days in arm 2, and at 6.3 ± 2.8 days in arm 3; the gas disappeared significantly earlier in arm 1 than in arms 2 and 3 ($P < 0.05$). No patients developed symptoms of ileus due to decreased intestinal peristalsis after resumption of oral intake.

8. Conclusions

Oral daikenchuto is effective for improving decreased intestinal peristalsis after surgery for non-ruptured AAA.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions associated with daikenchuto treatment were not reported.

11. Abstractor's comments

AAA is caused by arteriosclerosis and common in the elderly, for whom elective surgery is indicated and achieves good outcome. In such cases, early ambulation and early resumption of oral intake are important for the prevention of early postoperative delirium. Administration of daikenchuto promotes significantly earlier recovery of intestinal peristalsis and is therefore clinically useful. Although three arms were compared in this study, other studies commonly compare just two arms - daikenchuto and panthenol as a standard treatment. This study was also limited by the small number of patients in each group. Thus, a review of the study design and number of subjects will be needed.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial*. *Progress in Medicine* 1995; 15: 1954-8 (in Japanese). Ichushi Web ID:1996096061

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) in patients with adhesive ileus.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single institution (Hyogo Prefectural Awaji Hospital), Japan.

4. Participants

Fifty-three patients who were admitted with adhesive ileus and received gastric intubation. Patients with strangulation ileus were excluded.

5. Intervention

Arm 1: treatment with infusion of daikenchuto (大建中湯; manufacturer, not specified) dissolved in lukewarm water (5 g/30 mL) through a gastric tube, followed by flush with lukewarm water (30 mL), three times daily (n=28).

Arm 2: treatment with infusion of lukewarm water (60 mL) through a gastric tube, three times daily (n=25).

6. Main outcome measures

Time to passage of flatus, resolution rate with conservative treatment, rate of placement of endoscopic long tubes, and rate of progression to surgery.

7. Main results

The resolution rate with conservative treatment was higher in arm 1 ($P=0.0595$). The rates of tube placement and progression to surgery tended to be lower in arm 1.

8. Conclusions

Daikenchuto is a treatment worth trying in patients with adhesive ileus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes an evaluation of the clinical efficacy of daikenchuto in patients with adhesive ileus. Although the number of patients enrolled was small and between-group differences fell slightly short of significance in this study, the clinical utility of daikenchuto seems to be demonstrated.

12. Abstractor and date

Oikawa T, 19 September 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ishii F, Iizuka B, Nagasako K, et al. Evaluations of the therapeutic efficacy of Saikokeishito (TJ-10) versus Keishikashakuyakuto (TJ-60) for irritable bowel syndrome and Saireito (TJ-114) for ulcerative colitis. *Progress in Medicine* 1993; 13: 2893-900 (in Japanese).

1. Objectives

To compare the efficacy of saikokeishito (柴胡桂枝湯) and keishikashakuyakuto (桂枝加芍藥湯) for irritable bowel syndrome (IBS).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (authors belong to the Department of Internal Medicine, Institute of Gastroenterology, Tokyo Women's Medical University), Japan.

4. Participants

Forty-six patients clinically diagnosed with IBS. Patients were excluded for the following reasons: (i) medications (e.g., anticholinergics, tranquilizers), given within the previous week, possibly influencing the evaluation; (ii) complications including organic diseases of the gastrointestinal tract and bacterial infections.

5. Intervention

Arm 1: treatment with TSUMURA Saikokeishito Extract Granules (柴胡桂枝湯) 2.5 g t.i.d. (n=23) for 2 weeks.

Arm 2: treatment with TSUMURA Keishikashakuyakuto Extract Granules (桂枝加芍藥湯) 2.5 g t.i.d. (n=23) for 2 weeks.

6. Main outcome measures

Epigastric pain, lower abdominal pain, anorexia, abdominal bloating, feeling of retension, diarrhea, constipation, alternating diarrhea and constipation, flatulence /borborygmus, and feeling of incomplete evacuation.

7. Main results

The response was evaluated on a 4-point scale (marked, moderate, mild, none) and by comparing outcome measures before and after two weeks of treatment. Marked or moderate response was observed in 9 of 23 patients (39%) in arm 1 and 17 of 23 (74%) in arm 2. Regarding the pattern of bowel movements (diarrhea, constipation, and alternating diarrhea and constipation), the rate of marked or moderate response was 50% or more for all patterns in arm 2; in particular, it was 86% in those with alternating diarrhea and constipation. In arm 2, marked or moderate response was observed in 60% of patients with saikokeishito-type symptoms (epigastric pain, lower abdominal pain, and anorexia) and in 75% of those with keishikashakuyakuto-type symptoms (diarrhea, constipation, alternating diarrhea and constipation, abdominal bloating, stasis, flatulence/borborygmus, and feeling of incomplete evacuation). In arm 1, rates of marked or moderate response were under 50% in both symptom-based groups. Regarding individual symptoms, response rates were 50% for epigastric pain and 20–30% for the other symptoms in arm 1, whereas rates were 50% or more for alternating diarrhea and constipation, lower abdominal pain, diarrhea, constipation, and abdominal bloating in arm 2.

8. Conclusions

Keishikashakuyakuto can be prescribed to provide satisfactory effects for diagnostically confirmed IBS, irrespective of *sho* (証, pattern) or types of disease. Keishikashakuyakuto seems to act similarly to the anticholinergics or anxiolytics used in the medical therapy of IBS, and is recommended especially for patients with alternating-pattern of bowel movements.

9. From Kampo medicine perspective

The original study design included random assignment to the saikokeishito or keishikashakuyakuto treatment arms. During the analysis of results, response was evaluated separately in patients with saikokeishito-type clinical symptoms and those with keishikashakuyakuto-type symptoms.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper describes two different clinical studies. The latter part, in which therapeutic efficacy of saireito for ulcerative colitis was evaluated, was excluded from this Structured Abstract because it was not a randomized controlled trial. Many papers have been published on the efficacy of keishikashakuyakuto for IBS. The authors of this paper deserve praise for comparing keishikashakuyakuto with saikokeishito, which needs clinical differentiation. Since IBS can be a psychosomatic disease, it may be better to evaluate not only gastrointestinal symptoms, but also psychological items and systemic symptoms as measures of response. Furthermore, since IBS can be refractory, it might be better to consider treatment history and more. Further investigation of this clinically useful theme is expected.

12. Abstractor and date

Arai M, 21 October 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Sasaki D, Uehara A, Hiwatashi N, et al. Clinical efficacy of keishikashakuyakuto for irritable bowel syndrome - a multicenter, randomized, parallel-group clinical trial - . *Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine)* 1998; 75: 1136-52 (in Japanese). Ichushi Web ID: 1998224171 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) for irritable bowel syndrome.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Twenty university medical schools (including Tohoku University [Third Department of Internal Medicine, Tohoku University Hospital]; Tokai University [Sixth Department of Internal Medicine, Tokai University Hospital]; Kyushu University [Department of Psychosomatic Medicine, Kyushu University Hospital]), 53 hospitals, and 3 clinics (76 institutions in total), Japan.

4. Participants

Two hundred and eighty-six patients (age, 15–75 years) who were diagnosed with irritable bowel syndrome at one of the participating institutions and gave oral or written consent to participate in the study. Exclusion criteria were as follows: lactose intolerance; complications that might influence the evaluation; serious complications of heart, liver, kidney, or blood; pregnancy (known or possible); lactation; ineligibility as determined by the investigators.

5. Intervention

Arm 1: treatment with Kanebo Keishikashakuyakuto (桂枝加芍薬湯) Extract Fine Granules 2.0 g t.i.d. (n=148).

Arm 2: treatment with placebo (granules containing a small amount of keishikashakuyakuto extract) (n=138).

6. Main outcome measures

Bowel movement abnormalities (abnormal stool properties, number of bowel movements, and feeling of incomplete evacuation), gastrointestinal symptoms (abdominal pain, abdominal bloating, flatulence, borborygmus, anorexia, nausea/vomiting, heartburn, and belching), laboratory findings (hematology, blood biochemistry, and urinalysis), and physical findings (blood pressure, body weight, and presence and degree of edema).

7. Main results

Outcomes were evaluated after 4 weeks, or 8 weeks of treatment if the response at 4 weeks was inadequate. Final global improvement ratings were not significantly different between arms 1 and 2. As for abdominal pain, rates of “moderate” or better improvement tended to be higher in arm 1 than in arm 2 ($P=0.051$). Stratified analysis of improvement of abdominal pain according to the subtypes of disease revealed that, in the diarrhea subtype, improvement rating tended to be higher ($P=0.090$) and rate of “moderate” or better improvement was significantly higher ($P=0.037$) in arm 1. There were no significant differences between arms 1 and 2 in bowel movement abnormalities or gastrointestinal symptoms. In all, 17 and 7 adverse drug reactions occurred in 13 keishikashakuyakuto-treated patients and 6 controls, respectively.

8. Conclusions

Keishikashakuyakuto is an effective and safe agent for treating abdominal pain associated with irritable bowel syndrome, especially in patients with the diarrhea subtype.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Keishikashakuyakuto was “safe” in 110 of 124 patients (88.7%) in the keishikashakuyakuto group, and 98 of 108 (90.7%) in the control group; there was no statistically significant between-group difference in safety.

11. Abstractor’s comments

This is a well-designed clinical study conducted as a multicenter randomized parallel-group trial. Since keishikashakuyakuto is an agent with a relatively early onset of action, it is clinically necessary to monitor the course of action of this agent, including the time of action onset. Also, from a Kampo medicine perspective, discussions on the relationships between the physique or diathesis and the efficacy, would make the study more valuable.

12. Abstractor and date

Arai M, 22 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ishioka T. Comparison of the efficacy of junchoto and mashiningan for atonic constipation in the elderly stratified by physical strength*. *Kampo no Rinsho (Journal of Kampo Medicine)* 1996; 43: 1431-7 (in Japanese).

1. Objectives

To compare the efficacy of junchoto (潤腸湯) and mashiningan (麻子仁丸) for atonic constipation in the elderly.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

A special nursing home, Japan.

4. Participants

Thirty-two patients (8 males and 24 females) who usually had no bowel movements and were diagnosed with atonic constipation.

5. Intervention

Arm 1: treatment with TSUMURA Junchoto Extract Granules (潤腸湯) 2.5 g t.i.d., followed by TSUMURA Mashiningan Extract Granules (麻子仁丸) 2.5 g t.i.d. (n=14).

Arm 2: treatment with TSUMURA Mashiningan Extract Granules 2.5 g t.i.d., followed by TSUMURA Junchoto Extract Granules 2.5 g t.i.d. (n=17).

Thirty-one patients, after excluding one who withdrew, were included. After 2 weeks of the first treatment, patients were switched to the second drug without a wash-out period and followed up for 2 weeks.

6. Main outcome measures

Number of defecation supports (e.g., laxatives and enemas).

7. Main results

Disappearance of the need for defecation supports was rated as “marked response”, reduction of the number of defecation supports as “moderate response”, and no change in the number as “no response”. Response (marked + moderate) rate tended to be higher in the mashiningan-treated patients (74.2%) than in the junchoto-treated patients (61.3%) ($P<0.1$). Comparing arms 1 and 2, the efficacy was not influenced by the order of administration, and was superior in the mashiningan-treated patients in both arms ($P<0.05$). Response rate was not different between the two drugs in patients with moderate physical strength, whereas it was higher in mashiningan- than in junchoto-treated patients with low physical strength ($P<0.01$). While the rate of response to junchoto was independent of physical strength, the rate of response to mashiningan was higher in patients with low than in those with moderate physical strength ($P<0.05$).

8. Conclusions

For atonic constipation in the elderly, junchoto and mashiningan are effective drugs associated with very few adverse reactions. Mashiningan is especially effective for patients with low physical strength.

9. From Kampo medicine perspective

The response was evaluated separately in patients with moderate and low physical strength.

10. Safety assessment in the article

Compared with pretreatment levels, posttreatment levels of total cholesterol (T-Cho) ($P<0.01$) and Na ($P<0.05$) were increased and posttreatment level of uric acid (UA) was decreased ($P<0.01$). The one patient who withdrew complained of too many bowel movements during the junchoto treatment and was switched to other medications. Unusual subjective or objective symptoms were not observed.

11. Abstractor's comments

Junchoto and mashiningan are clinically difficult to use differentially. This valuable paper assesses these two drugs using a cross-over design and from a Kampo medicine perspective. However, cross-over design with no wash-out period might be unsuitable for evaluation of the efficacy of individual drugs. Also, to improve the quality of this study, its methodology should be clarified, such as the criteria used for classifying physical strength based on Kampo medicine and the standardization of empirically selected defecation supports to enable objective assessment of the response. It is hoped that higher quality studies on this clinically very interesting theme will be conducted.

12. Abstractor and date

Arai M, 9 November 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-To Extract Granules for ethical use (TJ-84) on constipation using double blind design. *Shokakika (Gastroenterology)* 1994; 18: 299-312 (in Japanese with English abstract). Ichushi Web ID: 1994189708

Miyoshi A, Masamune O, Fukutomi H, et al. The clinical effect of TSUMURA Daio-Kanzo-to Extract Granules for ethical use (TJ-84) against constipation based on the new standard. *Shokakika (Gastroenterology)* 1996; 22: 314-28 (in Japanese with English abstract). Ichushi Web ID: 1996228578

Harasawa S, Miyoshi A. Reevaluation of Kampo medicine in patients with constipation - efficacy of Daio-kanzo-to -. *Shokakigan (Japanese Journal of Cancer of the Digestive Organs)* 1996; 6: 271-7 (in Japanese with English abstract). Ichushi Web ID: 1997060417

1. Objectives

A preceding double-blinded controlled trial of daiokanzoto (大黃甘草湯), compared with placebo, in the treatment of constipation found it was effective against constipation, but not useful (no details available). The objective of this study was to reexamine the effects of daiokanzoto on constipation using a newly-defined assessment standard and the same results mentioned above.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Seven university medical schools (including Tokyo Women's Medical University [Second Department of Internal Medicine, Tokyo Women's Medical University Daini Hospital]; Tokai University School of Medicine [Sixth Department of Internal Medicine]; Kyoto University [First Department of Internal Medicine, Faculty of Medicine]) and 19 hospitals (26 institutions in total), Japan.

4. Participants

One hundred and fifty-six patients who had 3 or fewer bowel movements per week and complaints of constipation; sought therapy; and consented to participate in the study. Exclusion criteria were: age 15 or younger, constipation caused by organic disease; diagnosis of hypertension and severe edema; pregnancy, lactation, or signs of pregnancy, lactose intolerance, serious complications; patients otherwise considered ineligible by the treating physician.

5. Intervention

Arm 1: treatment with usual-dose TSUMURA Daiokanzoto (大黃甘草湯) Extract Granules 2.5 g t.i.d. (containing 1.5 g/day of extract powder) (n=53).

Arm 2: treatment with low-dose TSUMURA Daiokanzoto (大黃甘草湯) Extract Granules 2.5 g t.i.d. (containing 0.5 g/day of extract powder) (n=49).

Arm 3: treatment with placebo (excipient only) 2.5 g t.i.d (n=54).

6. Main outcome measures

Improvement in bowel movement rating, improvement in subjective and objective symptoms (global rating), efficacy, safety, and utility (global rating).

7. Main results

Outcomes were assessed after 2 weeks of treatment, using the new standard that takes "excessive response to test drugs into account. After excluding 10 withdrawals, 146 patients (47 in arm 1, 49 in arm 2, and 50 in arm 3) were included in the analysis. As for final global improvement, "marked improvement" was observed in 43.2%, 31.7%, and 27.7% of patients in arm 1, arm 2, and arm 3, respectively, and "moderate improvement" in 36.8%, 24.4%, and 14.9%, respectively; the differences among three arms ($P<0.05$) and between arms 1 and 3 ($P<0.01$) were significant. Final global improvement rate was high in arm 1. In addition, ratings of efficacy ($P<0.001$) and utility ($P<0.01$) were also high in arm 1.

8. Conclusions

Compared with placebo, Daiokanzoto had significantly higher final global improvement rating, efficacy, and utility (global rating) and was confirmed to be an effective and useful drug for treating constipation. The safety of this drug was apparent over the 2-week period of treatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Test drugs were characterized as "having no safety problem" in 91.5% of patients in arm 1, 93.9% in arm 2, and 96.0% in arm 3; as "having a mild safety problem" in 8.5%, 6.1%, and 0%, respectively; and as "having a moderate safety problem" in 0%, 0%, and 4%, respectively. There were no significant among-arm differences. No abnormal changes in laboratory data occurred.

11. Abstractor's comments

Using the new diagnostic standard, Miyoshi et al (1996) reevaluated the data of the preceding paper (Miyoshi et al [1994]). This is a highly valuable paper reporting a well-designed clinical study. Discussion from Kampo medicine perspective of cases with excessive response would make the content more meaningful. Studies that produce high-quality evidence, like this one, need to be developed for other Kampo preparations.

12. Abstractor and date

Arai M, 10 November 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Nishizawa Y, Nishizawa Y, Goto HG, et al. Prospective multicenter randomized group-parallelled study: effect of Chinese traditional herb medicine, jiu-wei-bing-lang-tang (Japanese name: kumi-binro-to) on constipation in elderly patients with renal dialysis. *Kampo Kenkyu (Kampo Research)* 2004; 388: 132-8 (in Japanese). Ichushi Web ID: 2004202082

1. Objectives

To evaluate the efficacy and safety of kumibinroto (九味檳榔湯) for chronic constipation in elderly dialysis patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Clinics and other services, Osaka, Japan.

4. Participants

Three-hundred and eighteen patients who were 75 years or older and on dialysis were enrolled during 15 years.

5. Intervention

Arm 1: treatment with Kotaro Kumibinroto (九味檳榔湯) Extract Fine Granules 2g, t.i.d., n=160.

Arm 2: treatment with magnesium laxative 2.0 g/day in three divided doses, n=158.

Duration of the study was 9 months.

6. Main outcome measures

Number of urges to have bowel movements and dosage of the laxatives (Western medicines) combined with the study drug.

7. Main results

Both the number of urges to have bowel movements and the dosage of the combined laxatives were significantly more improved in arm 1 than in arm 2. Symptoms associated with bowel movements were also significantly improved.

8. Conclusions

Kumibinroto is more effective than magnesium laxative for improving the number of bowel movements and the dosage of the combined laxatives in elderly dialysis patients with chronic constipation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Fewer adverse effects were reported in arm 1 than in arm 2 (data not shown). There were no abnormal examination findings.

11. Abstractor's comments

Although the word "multicenter" was mentioned in this article, none of the actual clinics, in contradistinction to research laboratories where this clinical trial was conducted, was specified. The authors conducted a 9-month, prospective, randomized study in 318 patients over a long period (15 years). Unfortunately, neither the number of withdrawals from the study nor the number of subjects included in the analysis was reported. Kumibinroto does not have a potent laxative effect. This study suggested that kumibinroto, combined with western laxatives, is more effective and safer than magnesium laxative for chronic constipation in elderly dialysis patients. Magnesium laxative, however, needs to be carefully administered and may cause hypermagnesemia in patients with renal impairment. Therefore, this type of laxative is usually avoided in patients undergoing hemodialysis. Regarding this point, the types and dosage of the western laxatives combined with the study drug are to be reported.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Horiuchi A, Nakayama Y, Tanaka N. Effect of traditional Japanese medicine, Daikenchuto (TJ-100) in patients with chronic constipation. *Gastroenterology Research* 2010; 3: 151–5.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) in combination for chronic constipation patients taking sennoside.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty-two patients with chronic constipation presenting with abdominal pain and bloating and treated for more than 3 months by taking sennoside (24–60 mg/day). Participants' stool frequency was less than three times a week when not taking sennoside. Colonoscopy revealed no abnormality, and participants had no history of abdominal surgery.

5. Intervention

Arm 1: Sennoside 24 to 60 mg/day with TSUMURA Daikenchuto (大建中湯) Extract Granules 7.5 g/day for 6 weeks (n=14).

Arm 2: Sennoside 24 to 60 mg/day with TSUMURA Daikenchuto (大建中湯) Extract Granules 15 g/day for 6 weeks (n=8).

6. Main outcome measures

Abdominal bloating (visual analogue scale), abdominal pain (visual analogue scale), Gastrointestinal Symptoms Rating Scale (GSRS), Gas Volume Score (GVS).

7. Main results

Abdominal bloating scores decreased significantly in both arms from 55 before intervention to 20 after four weeks of intervention in arm 1 ($P=0.006$) and from 69 to 35 in arm 2 ($P=0.007$). Abdominal pain scores decreased significantly from 32 to 9 after four weeks in arm 2 ($P=0.02$). GSRS scores also decreased significantly in both arms after four weeks, from 2.6 to 2.2 in arm 1 ($P=0.002$), and from 2.8 to 2.3 in arm 2 ($P=0.008$). GVS scores decreased significantly in both arms after six weeks, from 0.049 to 0.040 in arm 1 ($P=0.02$), and from 0.042 to 0.036 ($P=0.016$) in arm 2.

8. Conclusions

Daikenchuto alleviates abdominal pain and bloating in chronic constipation patients taking a stimulant laxative.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

This study suggests that when taken in combination with sennoside, daikenchuto alleviates abdominal pain and bloating in chronic constipation patients. However, the study only makes before/after comparisons, not between-group comparisons. Daikenchuto is a prescription that warms the middle abdominal region and treats *kyosho* (虚証, deficiency patterns) (温中補虚), so it warms the gastrointestinal tract. On the other hand, the active constituent in senna leaf (番泻葉) is sennoside, which resolves heat in the stomach and intestines and promotes intestinal peristalsis. In Kampo medical terms, these drugs are used for the opposing pattern. Hopefully, researchers will conduct a trial that compares sennoside + daikenchuto to control groups including placebo and daikenchuto alone. Lastly, if each participant's *sho* (証, pattern) had been identified in this comparative study, light might have been shed on the pathological conditions for which daikenchuto is indicated.

12. Abstractor and date

Okabe T, 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ota M. A Randomized controlled trial of perioperative daikenchuto for colorectal cancer surgery*. *Progress in Medicine* 2012; 32: 618–9 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To verify inhibition of inflammatory cytokine production and post-operative enhanced reactivation of intestinal function by daikenchuto (大建中湯) in colorectal cancer patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Yokohama City University Hospital, Japan.

4. Participants

Eighteen colorectal cancer patients scheduled for surgery.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 15.0 g/day for nine days¹⁾ (n=8).

Arm 2: no administration of daikenchuto (大建中湯) (n=10).

¹⁾ Daikenchuto was started two days before surgery, then restarted on the second day after surgery and continued until the eighth day.

6. Main outcome measures

Period between initial flatus and defecation, postoperative hospital stay (days), incidence of postoperative ileus, and postoperative white blood cell (WBC) count, C-reactive protein (CRP) level, interleukin (IL)-6 level, tumor necrosis factor (TNF)- α level, and natural killer (NK) cell activity (days 1, 3, and 7)

7. Main results

The period to initial flatus lasted one to two days in most cases and there was no between-arm difference. The period to initial defecation was significantly shorter in arm 1. There was no significant difference in the occurrence of ileus (two patients in arm 1, no patients in arm 2). CRP level tended to be decreased in patients with body mass index (BMI) under 23 in arm 1 but not in patients with a BMI over 23 in both groups. Between-group difference in IL-6 level, TNF- α level, or NK activity was not significant.

8. Conclusions

Daikenchuto enhances postoperative intestinal reactivation.

9. From Kampo medicine perspective

The tendency for reduced CRP among patients with lower BMI suggests that daikenchuto may be effective for patients with *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study was an attempt to clinically prove through evidence provided by RCT that perioperative daikenchuto enhances postoperative intestinal reactivation in colorectal cancer patients. However, the trial design (which tries to avoid bias related to the surgical procedure [laparoscopic vs. open] and disease location [colon vs. rectum]) introduces potential randomization problems. In addition, the actual sample size was 18 patients rather than the target sample size of 30; the significant difference in period until initial defecation was very small; two patients in the daikenchuto group but no patient in the no administration group suffered ileus; the tendency for decreased CRP level in patients with a BMI under 23 was very slight; and generally differences in laboratory test results were not significant. This leaves the undeniable impression that the evidence for the conclusion is fairly weak. Hopefully the author will recruit a larger sample population and include types of surgery and pathological findings (colorectal cancer invasion depth, etc.) in the analysis.

12. Abstractor and date

Motoo Y, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Ikemoto T. The role of Kampo in gastrointestinal surgery and the effectiveness of daikenchuto (大建中湯) for intestinal stress - From bacterial translocation to microbiome*. *Progress in Medicine* 2011; 31: 466-7 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To verify the anti-inflammatory effects of daikenchuto (大建中湯) on intestinal distress in the aftermath of gastrointestinal surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Gastrointestinal and Transplant Department, Tokushima University Hospital, Japan.

4. Participants

Thirty-one patients who had either minimally invasive laparoscopic colon surgery or invasive hepatectomy.

5. Intervention

Arm 1: DKT group: oral administration of TSUMURA Daikenchuto (大建中湯) Extract Granules (2.5 g t.i.d.) before meals for 7 days beginning on the first day after surgery (n=15).

Arm 2: no daikenchuto (大建中湯) treatment (n=16).

6. Main outcome measures

Body temperature, number of days till flatus, and blood C-reactive protein (CRP) concentration monitored beginning on the first postoperative day.

7. Main results

Body temperature was 36.2°C in arm 1 and 36.9°C in arm 2 on the third postoperative day. The number of days till flatus was significantly shorter in arm 1 (1.7 ± 0.4) than in arm 2 (2.9 ± 0.8) ($P < 0.05$). Blood CRP concentration was significantly lower in arm 1 (5.1 ± 2.3 mg/dL vs 7.7 ± 4.7 mg/dL) ($P < 0.05$).

8. Conclusions

Daikenchuto is clearly effective in controlling the increase in body temperature after surgery, in shortening the number of days till flatus, and in controlling inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study investigated the clinical efficacy of daikenchuto for reducing inflammation. The results are valuable because they help elucidate the mechanisms underlying well-known problems that develop following intestinal surgery. The paper refers to experiments in fasted rats showing that oral administration of daikenchuto maintains diversity in the intestinal microbiome (which is the collective genome of all intestinal microorganisms) and suggesting that the microbiome is relevant to expression of daikenchuto's anti-inflammatory effects. However, further research is needed before it is known whether these animal data are relevant to the mechanism of action in humans.

The paper deserves praise for investigating daikenchuto's mechanism of action from the perspective of enteric bacterial diversity. Hopefully the researchers will conduct further study with a more adequate number of participants, and use clinically applicable protocols.

12. Abstractor and date

Ushiroyama T, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Omori K. Prospective randomized controlled study of daikenchuto for postoperative dysmotility after total gastrectomy*. *Progress in Medicine* 2012; 32: 614-5 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after gastric cancer and total gastrectomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital surgery department, Japan.

4. Participants

One-hundred patients (age range: 44–80 years) with curability A/B who underwent total gastrectomy (Roux-en Y) for gastric cancer.

5. Intervention

Arm 1: daikenchuto (manufacturer not specified) (7.5 g/day) for three months (n=51).

Arm 2: lukewarm water (20 mL) for three months (n=49).

6. Main outcome measures

Frequency of post-surgical complications (post-surgical ileus), gastrointestinal symptom quality of life (QOL, measured on the gastrointestinal symptom rating scale [GSRS]), bowel regularity, intestinal gas.

7. Main results

After 15 participants dropped out, the data for 85 participants were evaluated. There was no significant difference in the incidence of ileus, with one case in arm 1 and three in arm 2. Improvement in constipation was greater in arm 1 than arm 2 at one month and three months. Apart from that, there was no significant between-group difference in gastrointestinal symptom QOL (GSRS). Bowel regularity during hospitalization was significantly higher in arm 1 (1.1 ± 0.6) than arm 2 (0.7 ± 0.4) ($P < 0.05$). Stools were significantly softer in arm 1 than arm 2. Intestinal gas had decreased significantly in arm 1 compared to arm 2 at one week, one month, and three months after surgery.

8. Conclusions

Daikenchuto contributes to early improvement in intestinal dysmotility in patients following total gastrectomy and is effective in reducing post-operative complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events were reported.

11. Abstractor's comments

This study was a randomized clinical trial that evaluated the effectiveness and safety of daikenchuto for postoperative bowel dysmotility after gastric cancer and total gastrectomy. The authors suggest that daikenchuto is effective for early improvement of intestinal dysmotility following surgery. The study confirms a reduction in the area of intestinal gas (an objective indicator) in the daikenchuto group at one week after surgery, as well as subjective symptoms including an increase in bowel-movement frequency.

12. Abstractor and date

Okabe T, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Yaegashi M. Usefulness of daikenchuto in the laparoscopic colorectal cancer perioperative period*. *Progress in Medicine* 2012; 32: 616-7 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for postoperative bowel dysmotility after laparoscopic surgery.

2. Design

Randomized controlled trial (RCT).

3. Setting

One center: Surgery Department, Iwate Medical University Hospital, Japan.

4. Participants

Forty-eight laparoscopic colon cancer surgery patients (age range: 44–80 years).

5. Intervention

Arm 1: daikenchuto (manufacturer not specified) (7.5 g/day) two days before surgery and from one day after surgery until discharge (n=24, 40–83 years).

Arm 2: intestinal disorder medication two days before surgery and from one day after surgery until discharge (n=24, 51–86 years).

6. Main outcome measures

Stools, presence/absence of ileus, small intestine transit time (Sitzmark's test).

7. Main results

Since one participant in arm 1 and 2 participants in arm 2 dropped out, the data from 23 participants in arm 1 and 22 in arm 2 were analyzed. There was no significant difference in ingestion start time in either group on the third day after surgery. The numbers of days after surgery until stool is passed (three in arm 1 and four in arm 2) and number of post-operative hospitalization days (seven in arm 1 and eight in arm 2) were similar in both arms. Small intestine transit time was significantly shorter in arm 1 than arm 2 ($P=0.013$).

8. Conclusions

Daikenchuto improves intestinal dysmotility early following laparoscopic surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant in the daikenchuto group developed an infection at the surgery site, and in the intestinal disorder medication group, one developed pneumonia and one ileus.

11. Abstractor's comments

This study is a randomized clinical trial that investigated the efficacy of daikenchuto for postoperative bowel dysmotility after laparoscopic surgery. The study found that small intestine transit time (Sitzmark's test) was significantly shorter in the daikenchuto group, suggesting earlier recovery of motility after surgery.

12. Abstractor and date

Okabe T, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takahashi H, Maruyama K. Clinical aspects of Kampo treatment for alcoholic liver disease. *Igaku no Ayumi (Journal of Clinical and Experimental Medicine)* 1993; 167: 811-4 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) and shosaikoto + inchingoreisan (小柴胡湯合茵陳五苓散) for alcoholic liver disease.

2. Design

Randomized controlled trial (RCT)

3. Setting

One general hospital, Japan.

4. Participants

Forty-nine alcoholics receiving inpatient treatment.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=24).

Arm 2: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. and TSUMURA Inchingoreisan (茵陳五苓散) Extract Granules 2.5 g t.i.d. (n=25).

Each drug was administered for 3 months.

6. Main outcome measures

Subjective symptoms (anorexia, nausea, fatigue, etc.) and liver function test results.

7. Main results

Subjective symptoms were improved in both arms but without any between-arm difference in improvement. Liver functions were also improved in both arms. ALP decreased more in Arm 2 than in Arm 1.

8. Conclusions

Shosaikoto and shosaikoto + inchingoreisan improve subjective symptoms and liver dysfunction in patients with alcoholic liver disease.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present paper is meaningful in that an RCT using multiple Kampo medicines was conducted. The clinical significance, however, might be limited by the absence of a non-treatment of placebo control group and the possible effects of abstinence during hospitalization (as pointed out by the authors).

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of sho-saiko-to in chronic active hepatitis. *Gastroenterologia Japonica* 1989; 24: 715–9. CENTRAL ID: CN-00064736, Pubmed ID: 2691317, Ichushi Web ID: 1991224424

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. *Kan-Tan-Sui* 1990; 20: 751–9 (in Japanese). Ichushi Web ID: 1991006763

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of chronic active hepatitis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Seven university hospitals and 31 general hospitals, Japan.

4. Participants

Two hundred and twenty-two patients who were diagnosed with chronic active hepatitis based on liver biopsy within a year of the onset of symptoms.

5. Intervention

Arm 1: Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules (containing 0.9 g of shosaikoto extract/g) at a dose of 1 pack (2.0 g) t.i.d. for at least 12 weeks (n=116).

Arm 2: placebo fine granules (containing 0.09 g of shosaikoto extract/g) at a dose of 1 pack (2.0 g) t.i.d. for 12 weeks (n=106).

6. Main outcome measures

Hepatic function test and presence of HBe antigen and anti-HBe antibody.

7. Main results

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly decreased in arm 1 at Week 12, but were almost comparable between arm 1 and arm 2 at Week 24. In arm 1 and arm 2, respectively, 4 of 27 patients and 5 of 32 patients became HBe antigen-negative, and 3 of 26 patients and 2 of 33 patients became anti-HBe antibody-positive. No significant between-arm difference was observed.

8. Conclusions

Shosaikoto significantly improves abnormal hepatic function compared with placebo.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Ten and 3 patients had adverse drug reactions to shosaikoto and placebo, respectively. Adverse drug reactions to shosaikoto requiring discontinuation of treatment were reported in 4 patients (general malaise [1 patient]; nausea [1 patient]; diarrhea [1 patient]; numbness of tongue [1 patient]). However, urinalysis results or blood pressure remained unchanged during the study.

11. Abstractor's comments

It is admirable that a multicenter DB-RCT was conducted. I consider that the efficacy of shosaikoto (24-month follow-up) was objectively evaluated. It is clinically significant that shosaikoto improved abnormal hepatic function more markedly in cases of hepatitis B, and was more effective in histologically mild disease.

12. Abstractor and date

Kogure T, 8 August, 2008, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Hirayama C, Okumura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of shosaiko-to in chronic active hepatitis. Analysis of serum enzyme activities. *Kan-Tan-Sui* 1992; 25: 551–8 (in Japanese). Ichushi Web ID: 1993125235

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) in the treatment of chronic active hepatitis.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Forty-two institutions, Japan.

4. Participants

Two hundred and twenty-two patients who were diagnosed with chronic active hepatitis based on liver biopsy within a year of symptom onset: 123 patients with non-B hepatitis and 99 patients with hepatitis B.

5. Intervention

Arm 1: Kanebo Shosaikoto (小柴胡湯) Extract Fine Granules (containing 0.9 g of shosaikoto extract/g) 2.0 g t.i.d. for 12 weeks (n=116).

Arm 2: placebo (containing 0.09 g of shosaikoto extract/g) 2.0 g t.i.d. for 12 weeks (n=106).

6. Main outcome measures

Subjective symptoms and hepatic function test (absolute value, %, and improvement rated on a 7-grade scale).

7. Main results

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly lower in arm 1 than in arm 2 and significantly decreased from baseline in arm 1 at Week 12 ($P<0.05$). There was no significant between-arm difference in γ -glutamyl transpeptidase (γ -GT), which remained unchanged from baseline in arm 1. Improvement in ALT but not AST or γ -GT was significantly greater in arm 1 ($P<0.05$).

8. Conclusions

Shosaikoto decreases serum AST, ALT, and γ -GT in chronic active hepatitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Dropouts (12 patients in the shosaikoto group and 6 patients in the placebo group) were described, but no adverse drug reactions were documented.

11. Abstractor's comments

It is admirable that a multicenter, placebo-controlled DB-RCT was conducted. The clinical significance would be further enhanced by documentation of liver histology and longer-term outcome.

12. Abstractor and date

Kogure T, 8 August, 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Sasaki D, Sudoh T, Kunikane M, et al. Usefulness of Kanebo Saireito Extract Fine Granules for chronic hepatitis - a comparative study (with randomization carried out using the sealed-envelope method) - . *Progress in Medicine* 1989; 9: 2923–37 (in Japanese). Ichushi Web ID: 1991131916

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) in the treatment of chronic hepatitis.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

One university hospital and 20 general hospitals, Japan.

4. Participants

Hundred patients who were clinically diagnosed with chronic hepatitis.

5. Intervention

Arm 1: Kanebo Saireito (柴苓湯) Extract Fine Granules 2.7 g t.i.d. for 12 weeks (n=53).

Arm 2: Proheparum 2 tablets t.i.d. for 12 weeks (n=47).

6. Main outcome measures

Hepatic function test, HBsAg level, physical findings (hepatomegaly, etc.), subjective symptoms, hematology/biochemistry, and improvement in each measure rated on a 5-grade scale. Safety was considered a measure of overall usefulness.

7. Main results

Eighty-eight patients were included in the analyses. No significant between-group difference was observed in glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), γ -glutamyl transpeptidase (γ -GTP), alkaline phosphatase (ALP), cholinesterase (ChE), zinc sulfate turbidity test (ZTT), total bilirubin, total cholesterol, triglyceride (TG), total protein (TP), albumin, or hepaplastin test (HPT). . Global improvement and usefulness were significantly greater in the saireito group ($P<0.05$).

8. Conclusions

It is suggested that saireito is useful in the treatment of chronic hepatitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the saireito group, 1 patient had dizziness and fatigability, 1 patient had anemia, and 3 patients had nausea.

11. Abstractor's comments

It is admirable that a multicenter RCT was conducted. However, caution should be used in the clinical interpretation of the usefulness and global improvement results, since these measures are not frequently evaluated. The authors stated that marked improvement was achieved in patients with high GOT and/or GPT in the saireito group.

12. Abstractor and date

Kogure T, 8 August, 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Tarao K, Shibuya A, Ohkawa S, et al. Prevention of hepatocarcinogenesis by anti-inflammatory therapy: is combination anti-inflammatory therapy targeting an ALT level of under 80 units effective for hepatitis C virus-related cirrhosis (Child A)?: comparison with monotherapy*. *Kanagawa Cancer Center – Nenpo (Annual Report)* 2003; 19: 92 (in Japanese).

Tarao K. Persistent inflammation and hepatocarcinogenesis in chronic hepatitis C and hepatitis C virus-related cirrhosis*. *Kanagawa Igakkai Zasshi (The Journal of the Kanagawa Medical Association)* 2006; 33: 115-8 (in Japanese).

Tarao K. Prevention of HCC by anti-inflammatory agents in patients with chronic hepatitis C. *Rinsho Shokaki Naika (Clinical Gastroenterology)* 2007; 22: 961-9 (in Japanese).

1. Objectives

To evaluate the efficacy of liver protectors for preventing carcinogenesis in patients with chronic hepatitis C.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (the author belongs to a specialized hospital), Japan.

4. Participants

One hundred and fifty-six patients with hepatitis C virus-related cirrhosis (stage Child A).

5. Intervention

Arm 1: target alanine aminotransferase (ALT) level ≤ 80 ; monotherapy with Stronger Neo-Minophagen C (SNMC; 40–100 mL, two or three times per week), ursodeoxycholic acid (UDCA), shosaikoto (小柴胡湯), or jumentaihoto (十全大補湯) (manufacturers, not specified) was administered. When the target level was not achieved in 2–3 months, dual therapy with SNMC + UDCA, UDCA + jumentaihoto (十全大補湯), or UDCA + shosaikoto (小柴胡湯) was administered. If the target level was still not achieved, triple therapy with SNMC + UDCA + shosaikoto (小柴胡湯) or SNMC + UDCA + jumentaihoto (十全大補湯) was administered. The choice of the therapy in each patient was not described, n=78.

Arm 2: monotherapy with UDCA, SNMC, shosaikoto (小柴胡湯), or jumentaihoto (十全大補湯) was administered; the choice of the drug was based on the ALT-lowering effect. Details, including the drug used, dose, and the number of patients who received each drug, were not available, n=50.

6. Main outcome measures

Incidence of liver cancer.

7. Main results

The incidence of liver cancer was lower in arm 1 than in arm 2.

8. Conclusions

Therapy consisting of combined Kampo medicines for liver protection is effective for suppressing carcinogenesis in patients with chronic hepatitis C.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study reports an effective treatment for suppressing carcinogenesis in patients with chronic hepatitis C. But since the specific design was not described and details (such as the choice of the therapy or the number of patients who received each drug in arm 2) were unclear, we cannot decide which of the treatments resulted in response. Studies employing easy-to-understand designs are desired.

The two studies by Tarao et al (2003) and Tarao (2008) are the interim reports

12. Abstractor and date

Kogure T, 26 January 2009, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Higuchi K, Watanabe A. Study on liver cancer-preventive effect of juzentaihoto in patients with liver cirrhosis*. *Methods in Kampo Pharmacology* 2000; 5: 29-33 (in Japanese).

1. Objectives

To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]), Japan.

4. Participants

Seventy-two patients with liver cirrhosis due to hepatitis B or C virus (B, n=14; C, n=58). However, one patient who had liver cancer within half a year after entry into the study was excluded.

5. Intervention

Arm 1: juzentaihoto (十全大補湯)-treated group (B, n=8; C, n=18).
Arm 2: juzentaihoto (十全大補湯)-untreated group (B, n=6; C, n=39).

6. Main outcome measures

Cumulative survival curve by Kaplan-Meier method (log-rank test [Mantel-Cox]).

Cumulative hazard curve for hepatocellular carcinoma development by Kaplan-Meier method (log-rank test [Mantel-Cox]).

The threshold of liver cancer development was set at the time when liver cancer was first detected on imaging-based clinical diagnosis.

7. Main results

For overall liver cirrhosis, there was no significant difference in the cumulative survival curve between arms (chi-square=3.167, $P=0.0751$), but juzentaihoto-treated patients tended to have a more favorable prognosis. For overall liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed the risk was significantly lower in the juzentaihoto-treated group than in juzentaihoto-untreated group (chi-square=5.832, $P=0.0157$). Analysis limited to liver cirrhosis type C also revealed significantly lower risk in the juzentaihoto-treated group (chi-square=4.197, $P=0.0405$).

8. Conclusions

It is suggested that administration of juzentaihoto prevents hepatocellular carcinoma from developing in patients with liver cirrhosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is valuable, since hepatocellular carcinoma frequently develops as a result of underlying hepatitis virus infection. Using sealed envelopes for allocation, this study is regarded as a randomized controlled trial. Information on the method of juzentaihoto administration and blinding may have made this report clinically more meaningful.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Higuchi K, Shimizu Y, Yasumura S, et al. Preventive effect of liver carcinogenesis by juzen-taiho-to in the patients with liver cirrhosis. *Kan-Tan-Sui* 2002; 44: 341-6 (in Japanese) Ichushi Web ID: 2002240679 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the hepatocellular carcinoma-preventive effect of juzentaihoto (十全大補湯) administered for liver cirrhosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

A university hospital (Department of Internal Medicine, Toyama Medical and Pharmaceutical University [now Toyama University Hospital]), Japan.

4. Participants

Fifty-two patients with liver cirrhosis due to hepatitis B or C virus. However, patients who had liver cancer within a year after entry into the study and those who received shosaikoto or interferon were excluded.

5. Intervention

Arm 1: juzentaihoto (十全大補湯)-treated (type B, n=8; type C, n=15; type B + type C, n=1).
Arm 2: juzentaihoto (十全大補湯)-untreated (type B, n=5; type C, n=22; type B + type C, n=1).

6. Main outcome measures

Cumulative survival curves were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). Cumulative hazard curves for hepatocellular carcinoma development were drawn by the Kaplan-Meier method (with difference between curves analyzed by the log-rank test [Mantel-Cox test], Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test). The threshold of liver cancer development was set when liver cancer was first detected on imaging-based clinical diagnosis.

7. Main results

For all liver cirrhosis, the cumulative survival curve showed that vital prognosis was significantly more favorable in arm 1 than arm 2, with chi-square values of 4.066, 6.467, and 5.217 ($P=0.0438$, 0.0190, and 0.0224) by the log-rank test (Mantel-Cox test), Bleslow Gehan-Wilcoxon test, and Peto-Peto-Wilcoxon test, respectively. Analysis of the cumulative survival curve limited to patients with liver cirrhosis type C showed a tendency toward more favorable vital prognosis in arm 1, but no significant between-group difference. For all liver cirrhosis, the cumulative hazard curve for hepatocellular carcinoma development showed significantly lower incidence of hepatocellular carcinoma in arm 1 than in arm 2, with chi-square values of 5.265, 5.578, and 5.921 ($P=0.0218$, 0.0182, and 0.0150) by these tests, respectively. Analysis limited to liver cirrhosis type C revealed significantly lower incidence of hepatocellular carcinoma in arm 1 by the Bleslow Gehan-Wilcoxon test and Peto-Peto-Wilcoxon test (chi-square=4.659, 4.483, respectively; $P=0.0309$, 0.0342, respectively).

8. Conclusions

It is suggested that in liver cirrhosis, administration of juzentaihoto prevents hepatocellular carcinoma development.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is valuable since hepatocellular carcinoma frequently develops from underlying hepatitis virus infections. This study seems to be similar to the study published in *Methods in Kampo Pharmacology* (2000; 5: 29-33). There were fewer participants in the present study because stricter exclusion criteria were followed: liver cancer development within a year vs half a year in the previous study, and shosaikoto or interferon not permitted. Furthermore, use of diverse statistical tests made the results more meaningful, particularly clinically. Use of a placebo and blinding may have made the results more reliable.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Tajiri H, Kozaiwa K, Sawada A, et al. Efficacy of shosaikoto for chronic non-A, non-B hepatitis in children (non-A, non-B hepatitis in children and shosaikoto)*. *Nihon Shoni Toyo Igaku Kenkyukai Kaishi (Journal of the Japan Pediatric Society for Oriental Medicine)* 1996; 12: 12-7 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for chronic non-A, non-B hepatitis in children.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital, Japan.

4. Participants

Patients were children with liver dysfunction persisting for at least 6 months and infected with viruses known to cause liver damage (hepatitis A virus [HAV], hepatitis B virus [HBV], cytomegalovirus [CMV], and Epstein-Barr virus [EBV]) were excluded. Six patients positive for hepatitis C virus (HCV) were included.

5. Intervention

Arm 1: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 7.5 g/day (dose adjusted for age) for at least 6 months (n=5).

Arm 2: natural course monitoring group (n=5).

One patient who took shosaikoto (小柴胡湯) for more than 6 months following natural course monitoring for 6 months was enrolled in both arms 1 and 2.

6. Main outcome measures

Levels of glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), serum neopterin, soluble interleukin-2 (IL-2) receptor, and HCV-RNA.

7. Main results

GPT and GOT levels were reduced significantly at 2, and 6 months in arm 1 ($P<0.05$). Serum neopterin was increased at 1 month in the 3 patients of arm 1 who had measurements. Soluble IL-2 receptor was also increased only at 1 month. One of the patients who showed reduction in GPT level remained positive for HCV-RNA.

8. Conclusions

Shosaikoto is effective for improving liver function in chronic non-A, non-B hepatitis, including chronic hepatitis C, in children.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present paper is valuable in that it analyzed the clinical effects of Kampo medicine on chronic hepatitis in children—who are rarely the focus of clinical trials. Unfortunately, the between-arm comparison was insufficient because of the small number of patients enrolled.

12. Abstractor and date

Kogure T, 8 August 2008, 6 January 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Mizutani Y, Imai S, Watanabe H, et al. Saiko-keishi-to in patients with pulmonary tuberculosis: effect on liver dysfunction. *Donan Igakkaishi (Journal of the Medical Association of South Hokkaido)* 1994; 29: 247-9 (in Japanese).

1. Objectives

To evaluate the efficacy of saikokeishito (柴胡桂枝湯) for hepatic dysfunction associated with chemotherapy for pulmonary tuberculosis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Four hospitals, Japan.

4. Participants

Thirty-eight patients with pulmonary tuberculosis who received combination chemotherapy containing rifampicin for the first time.

5. Intervention

Arm 1: saikokeishito (柴胡桂枝湯) (unknown manufacturer) at a dose of 7.5 g t.i.d. for 8 weeks (n=21).
Arm 2: no treatment (n=17).

6. Main outcome measures

Serum glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) levels.

7. Main results

Thirty-three patients were included in the analysis. The incidence of abnormal GOT and GPT levels was 27.8% and 38.9% in arm 1, and 6.7% and 20.0% in arm 2, respectively. More patients had abnormal GOT and/or GPT in arm 1 than in arm 2, but the between-arm difference was not significant.

8. Conclusions

Saikokeishito is not effective for hepatic dysfunction associated with chemotherapy for pulmonary tuberculosis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

While randomization by the envelope method is often difficult to attain, it is interesting that this clinical trial showed that saikokeishito was ineffective for prevention of hepatic dysfunction, an adverse reaction to chemotherapy for pulmonary tuberculosis. It is desirable to conduct a randomized controlled trial with more patients using an improved randomization scheme.

12. Abstractor and date

Okabe T, 21 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Seki M, Fujioka M, Hatano T, et al. Differences between the effects of sho-saiko-to, gorei-san, and toki-shakuyaku-san on the sphincter of Oddi - An intraoperative cholangiomanometric study - . *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1993; 43: 395-402 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of shosaikoto (小柴胡湯), goreisan (五苓散), and tokishakuyakusan (当帰芍薬散) on the sphincter of Oddi.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Forty-nine patients who were admitted for gallstone disease and underwent cholecystectomy.

5. Intervention

Arm 1: treatment with TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 gt.i.d. for 6.6±4.2 days before surgery (n=8).

Arm 2: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 gt.i.d. for 7.8±6.0 days before surgery (n=12).

Arm 3: treatment with TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 gt.i.d. for 8.2±6.3 days before surgery (n=5).

Arm 4: bed rest only (n=24).

6. Main outcome measures

Biliary pressure (basal pressure, BP; perfusion pressure, PP; the time for biliary pressure to normalize, T)

7. Main results

At a perfusion rate of 0.1 mL/s, there were no among-arm differences in BP and PP. Regarding the biliary pressure curve, only shosaikoto resulted in significantly decreased $T_{1/2}$, $T_{1/4}$, and $T_{1/5}$ compared with the control ($P<0.02-0.05$). At a perfusion rate of 0.5 mL/s, PP was significantly higher in arms 1 and 2 than in arm 4. Regarding the biliary pressure curve, only shosaikoto resulted in significantly decreased $T_{1/4}$ and $T_{1/5}$ compared with the control ($P<0.01$).

8. Conclusions

Shosaikoto and goreisan both lower the threshold of biliary pressure, and shosaikoto results in a rapid relaxation of the sphincter of Oddi.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial evaluated biliary pressure as an endpoint in 4 groups. It provides valuable insights. The authors speculate that the treatment may prevent bile stasis.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Takagi S. Increase of urinary 6-keto-prostaglandin F1 α level by preoperative administration of gorei-san or toki-shakuyaku-san to the patients of gallbladder stones or polyps. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1992; 9: 32-9 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of goreisan (五苓散) and tokishakuyakusan (当归芍薬散) on urinary 6-keto-prostaglandin F1 α excretion in patients with gallbladder stones or polyps.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-nine female patients who underwent cholecystectomy for gallbladder stones or polyps.

5. Intervention

Arm 1: TSUMURA Goreisan (五苓散) Extract Granules (n=6).

Arm 2: TSUMURA Tokishakuyakusan (当归芍薬散) Extract Granules (n=6).

Arm 3: TSUMURA Shosaikoto (小柴胡湯) Extract Granules (n=6).

Each preparation was administered at 2.5 g t.i.d. before meals for 5 or 6 days before surgery.

Arm 4: no continuous drug therapy (n=11).

6. Main outcome measures

Urinary excretions of prostaglandin E1 (PGE1) and 6-keto-prostaglandin F1 α (6-keto-PGF1 α).

7. Main results

There was no significant difference in urinary PGE1 excretion throughout the treatment course between each arm of treatment and the control arm (arm 4). Urinary 6-keto-PGF1 α excretion was increased significantly on postoperative days 1 and 5–7 in arm 1 ($P<0.05$) and on postoperative days 1 and 3–7 in arm 2 ($P<0.02$ – 0.001). The urinary 6-keto-PGF1 α excretions were not significantly different between arm 3 and arm 4, as well as between arm 1 and arm 2.

8. Conclusions

Preoperative administration of goreisan or tokishakuyakusan before cholecystectomy results in increased postoperative urinary excretion of 6-keto-PGF1 α .

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The author of the study deserves praise for conducting a 4-group RCT. The determination of relationship between urinary excretion and clinical outcome would make the study more clinically meaningful.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 12 October 2011, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Okabayashi T, Tanaka N, Orita K. The effect of a Kampo medicine, inchinko-to, on rate of bilirubin reduction after biliary drainage in patients with obstructive jaundice. *Nihon Rinsho Geka Gakkaiishi (Journal of Japan Surgical Association)* 1998; 59: 2495-500 (in Japanese with English abstract). Ichushi Web ID: 1999080276, [J-STAGE](#)

1. Objectives

To evaluate the efficacy of inchinkoto (茵陈蒿汤) for improving the bilirubin reduction rate after biliary drainage in patients with obstructive jaundice.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

First Department of Surgery, Okayama University School of Medicine and 14 associated facilities, Japan.

4. Participants

Twenty-four patients with obstructive jaundice undergoing biliary drainage procedures such as percutaneous transhepatic cholangio-drainage (PTCD). The patients satisfying any of the following criteria were excluded: 1) age <15 years or ≥80 years; 2) oral intake not possible; 3) presence of serious cirrhosis or complications; and 4) ineligibility as judged by the patient's physician.

5. Intervention

Arm 1: drainage +oral administration of TSUMURA Inchinkoto (茵陈蒿汤) Extra Granules 2.5 g t.i.d., either for 4 weeks or before the surgery (n=11; of these, 10 were analyzed [the reason of study withdrawal not shown]).

Arm 2: drainage alone (n=13).

6. Main outcome measures

Total bilirubin, direct bilirubin, and daily volume of bile. Bilirubin reduction rate as determined by the formula of Shimizu et al. Changes in anorexia and general malaise rated on a 4-point scale.

7. Main results

Bilirubin reduction rate was significantly improved in arm 2 ($P<0.05$). AST, ALT, ALP, and γ -GTP were similarly improved in both arms, although more favorable results were obtained in arm 2. Anorexia was significantly improved in arm 2 early after the start of drainage (at Day 3, $P<0.1$; at Week 1, $P<0.05$). From week 2 onwards, however, subjective symptoms were also improved in arm 1, and there was no significant between-arm difference.

8. Conclusions

Inchinkoto improves the bilirubin reduction rate and subjective symptoms, suggesting its efficacy for obstructive jaundice after biliary drainage.

9. From Kampo medicine perspective

This paper mentions the choleric action of 6, 7-demethyl-esculetin and capillarisin contained in inchinko (茵陈蒿), and geniposide contained in sanshishi (山梔子), in the discussion section from a pharmacognostic perspective.

10. Safety assessment in the article

No adverse events were observed.

11. Abstractor's comments

This paper discusses the effect of inchinkoto on bilirubin reduction. Combination of inchinkoto with drainage had only a slight additional effect on reduction of bilirubin level. Notably, however, no patients were rated grade 3 (i.e., as having relatively poor bilirubin reduction) after the inchinkoto treatment. Future reports on the mechanism of its action are awaited.

12. Abstractor and date

Nakata H, 1 January 2009, 6 January 2010, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Watanabe S, Yokoyama Y, Oda K, et al. Choleretic effect of inchinkoto, an herbal medicine, on livers of patients with biliary obstruction due to bile duct carcinoma. *Hepatology Research* 2009; 39: 247–55. Ichushi Web ID: 2009201648

1. Objectives

To evaluate the drug efficacy of inchinkoto (茵陈蒿汤) as a choleretic drug on livers of patients with biliary obstruction due to bile duct carcinoma.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery, Nagoya University Graduate School of Medicine, Department of Gastroenterology and Hepatology, University of Tsukuba, and Department of Strategic Surveillance for Functional Food and Comprehensive Traditional Medicine, Wakayama Medical University, Japan.

4. Participants

From December 2006 to June 2006, a total of 31 patients with perihilar cholangiocarcinoma or gallbladder carcinoma with hilar invasion were enrolled. Of these patients, 4 were excluded because they underwent probe laparotomy due to peritoneal dissemination.

5. Intervention

Arm 1: Inchinkoto (Tsumura Inchinkoto (茵陈蒿汤) Extract Granules (TJ-135) 7.5 g/day for at least one week before surgery (average 21 days) (n=13).

Arm 2: no treatment with inchinkoto (n=14).

6. Main outcome measures

Levels of MRP2, MRP3, and MRP4 mRNAs and proteins in the liver were determined.

7. Main results

There were no significant between-arm differences in MRP2, 3, and 4 mRNA levels. MRP2 and 3 protein levels were significantly increased in the inchinkoto arm. Postoperatively, there were no between-arm differences in serum total bilirubin, direct bilirubin, and alanine aminotransferase (ALT). Bile samples were collected from some of the patients in arm 1 by percutaneous transhepatic biliary drainage (PTBD) before and after administration of inchinkoto, and increase in the concentration of bilirubin was observed after administration.

8. Conclusions

Inchinkoto may be useful for treating obstructive cholestasis due to bile duct carcinoma, and its beneficial effect may be mediated through induction of MRP2 expression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No significant adverse drug reactions were observed for inchinkoto treatment.

11. Abstractor's comments

MRP2 protein is a transporter involved in bile acid secretion. It is interesting that the authors found and increase in MRP2 protein levels but no change in MRP2 mRNA levels. They demonstrated increased bilirubin concentration in the bile samples collected by PTBD only in the subjects in the inchinkoto arm, however, they should have studied the subjects in the both arms to make the data more reliable. Some of the documentation in this article is insufficient; even though the MRPs gene expression data for the control group is shown, the background data of the control group is not. Although there are issues regarding the methodology used in this study, it is very meaningful that administration of inchinkoto is shown clinically to increase MRP2 protein levels.

12. Abstractor and date

Nakata H, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Okuno S, Hirayama K, Inoue J, et al. Effects of rikkunshito on the postoperative nausea and vomiting (PONV) after laparoscopic gynecological surgery. *Masui (Japanese Journal of Anesthesiology)* 2008; 57: 1502-9 (in Japanese with English abstract). CENTRAL ID: CN-00668598, Pubmed ID: 19108494 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effect of rikkunshito (六君子湯) on postoperative nausea and vomiting.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

One hundred and forty-two patients undergoing gynecological laparoscopic surgery.

5. Intervention

Arm 1: oral administration of TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g on the morning of surgery + rectal administration of 2 TSUMURA Rikkunshito suppositories (containing rikkunshito 1.5 g per suppository) during surgery + oral administration of TSUMURA Rikkunshito Extract Granules (六君子湯) 7.5 g/day postoperatively for 2 days (n=91).

Arm 2: no treatment (n=51).

6. Main outcome measures

The incidence of postoperative nausea and vomiting, changes in nausea and vomiting score, postoperative dietary intake, etc.

7. Main results

There was no significant between-group difference in the incidence of postoperative nausea and vomiting and in nausea and vomiting scores at each time point. However, the vomiting score in arm 1 was significantly lower on postoperative day 2 than on arrival at the ward and on postoperative days 0 and 1, and significantly lower on postoperative day 1 than on arrival at the ward. In contrast, vomiting score in arm 2 was significantly lower only on postoperative day 2 than on postoperative day 1. The postoperative dietary intake in arm 1 had recovered by the morning of postoperative day 2, while in arm 2, it was significantly lower until lunchtime on postoperative day 2. There were no significant between-arm differences in nausea and vomiting scores or postoperative dietary intake at each time point.

8. Conclusions

Perioperative administration of rikkunshito did not decrease the incidence of postoperative nausea and vomiting. However, this study suggests that rikkunshito may relieve nausea and vomiting and facilitate earlier recovery of dietary intake.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In this study, the effect of Kampo medicine on perioperative symptoms was evaluated for the first time, and suppositories were used in patients unable to take medicines orally. Although there were no significant differences, the efficacy of rikkunshito was suggested. However, randomization itself and the method of randomization should be described in the article. The authors should have followed CONSORT guidelines for the conduct and reporting of RCTs. As the authors stated, more marked differences would have been observed if rikkunshito had been administered prophylactically at least 1 week before surgery. The dose of drug delivered by suppository inevitably tends to be low. Alternatively, rikkunshito could have been administered, for example, via gastric tube. However, as the induction of vomiting during extubation was a concern, suppositories were used on the day of surgery. Since rikkunshito suppositories are not usually used and alternative methods of administration have not been studied, there is no evidence to show that the suppository is the best method of drug delivery. Further evaluation by surgeons or anesthesiologists is expected.

12. Abstractor and date

Motoo Y, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Kubo N, Uchida Y, Akiyoshi T, et al. Efficacy of daikenchuto for ileus - a multicenter study - *. *Progress in Medicine* 1995; 15: 1962-7 (in Japanese). Ichushi Web ID: 1996096062

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) for ileus in a multicenter study.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Fourteen institutions, centered around Oita Medical University Hospital, Japan.

4. Participants

Thirty patients who developed simple adhesive ileus postoperatively and were judged by the investigator to need long tube placement. (Exclusion criteria were serious disorders of the heart, lungs, liver, or bone marrow; serious complications; determination of ineligibility by the treating physician.)

5. Intervention

Arm 1: treatment with TSUMURA Daikenchuto (大建中湯) Extract Granules dissolved in lukewarm water (5 g/20 mL) and infused through a gastric tube, three times daily for at least 5 days (n=18).

Arm 2: no treatment with daikenchuto (n=12).

6. Main outcome measures

Subjective symptoms (abdominal pain, nausea and vomiting, diarrhea, general malaise, anorexia, and abdominal bloating), radiograph, time to defecation and passage of flatus, number of days to removal of the ileus tube (long tube), number of days to resumption of oral intake, and rate of progression to surgery, as well as improvements in ileus, abdominal findings, and subjective symptoms, general improvement rating, and usefulness assessed by the attending physician.

7. Main results

There were no significant between-arm differences in the time to defecation, passage of flatus, and removal of the ileus tube, radiographic changes, and the proportion of patients who required surgery. Improvements in abdominal bloating and nausea and vomiting were significantly greater in arm 1 than arm 2. The rate of ileus resolution assessed by the attending physician was 94.4% in arm 1 and 66.7% in arm 2.

8. Conclusions

Daikenchuto is a safe and useful drug for treating postoperative adhesive ileus.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred. The global safety rating was 94.4%.

11. Abstractor's comments

Similar to the preceding papers "Nagashima Y, Tanaka N, Furukawa K, et al. Effects of daikenchuto (TJ-100) on intestinal paralysis after surgery for colorectal cancer". *Progress in Medicine* 1998; 18: 903-5 (in Japanese)" and "Ohyabu H, Matsuda S, Kurisu S, et al. Evaluation of daikenchuto in patients with adhesive ileus in a randomized trial". *Progress in Medicine* 1995; 15: 1954-8 (in Japanese)", the present paper describes an evaluation of the clinical efficacy of daikenchuto in patients with adhesive ileus. Although the number of patients was small and between-group differences fell short of significance, the clinical utility of daikenchuto seems to be demonstrated. Some kind of control drug should have been administered in the non-daikenchuto-treatment arm, and daikenchuto should have been compared with the control. This would not have required much additional effort.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Itoh T, Yamakawa J, Mai M, et al. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. *The Journal of International Medical Research* 2002; 30: 428-32. CENTRAL ID: CN-00410068, Pubmed ID: 12235926

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) for the treatment of postoperative ileus and the improvement of postoperative conditions.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Cancer Research Institute of Kanazawa University), Japan.

4. Participants

Out of 154 abdominal surgery patients, 24 developed postoperative ileus were enrolled.

5. Intervention

Arm 1: treatment with daikenchuto (大建中湯) 15.0 g in 13 patients.

Arm 2: treatment with placebo (the same quantity and frequency of doses as arm 1) in 11 patients.

The study drugs were administered orally for 14 days.

6. Main outcome measures

Frequency of surgery for ileus and recurrence of ileus.

7. Main results

Surgery for postoperative ileus could be avoided significantly more frequently in the daikenchuto arm than in the placebo arm. In addition, daikenchuto tended to decrease, though not significantly, the recurrence rate of ileus.

8. Conclusions

Daikenchuto is a cost-effective and noninvasive therapeutic agent for postoperative ileus after abdominal surgery and has no adverse effects.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This RCT examined the efficacy of daikenchuto for postoperative ileus. This seems to be clinically relevant after abdominal surgery since the treatment for postoperative ileus is not established. Although mentioned in the conclusion, the safety and cost effectiveness of daikenchuto treatment were not described in the main text. It might have been better to mention those outcomes, and examine the dependence of these differences on subjects' underlying diseases or surgical procedures.

12. Abstractor and date

Arai M, 20 February 2007, 30 October 2007, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Okabayashi T, Mimura H, Orita K. Usefulness of Shosaikoto (TJ-9) in the treatment of postoperative liver dysfunction*. *Progress in Medicine* 1989; 9: 851-5 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) in the treatment of postoperative liver dysfunction.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and 14 general hospitals, Japan.

4. Participants

Forty-six patients who had no hepatic dysfunction preoperatively and underwent surgery under general anesthesia for non-hepato-biliary-pancreatic disease, but developed liver dysfunction 2–8 weeks after surgery.

5. Intervention

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. (n=20).
Arm 2: Glycyron, a glycyrrhizin preparation, 3 tablets t.i.d. (n=26).

6. Main outcome measures

Improvements in subjective symptoms and liver function, global utility rating, and safety rating.

7. Main results

Subjective symptoms, liver function, and global utility ratings were improved in both arms, but without any significant between-arm differences in these improvements. Glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactic dehydrogenase (LDH), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP), and zinc sulfate turbidity test (ZTT) decreased in both arms but the between-arm differences were not significant. GOT, GPT, ALP, and γ -GTP tended to decrease slightly more rapidly in arm 1 than in arm 2. Abnormal total bilirubin (T-Bil) or blood urea nitrogen (BUN) was not noted postoperatively.

8. Conclusions

Shosaikoto is an effective and safe drug for the treatment of postoperative hepatic dysfunction and its efficacy is comparable to that of Glycyron.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions were not observed in the shosaikoto-treated group.

11. Abstractor's comments

This paper is clinically highly significant in that the efficacy of shosaikoto for treating postoperative liver dysfunction was demonstrated in an RCT using Glycyron as a control. Safety was evaluated in a small number of patients (n=20) in this study. Further safety studies including larger number of patients are required.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Usuba A, Gao L. S., Motoki R. Effect of sho-saiko-to (xao-chai-hu-tang) on liver dysfunction after surgery - the benefits of preoperative administration and the importance of diagnosis according to traditional Chinese logic -. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1992; 43: 1–12 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for postoperative liver disorder.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Surgery 1, Fukushima Medical University, Japan.

4. Participants

Sixty-six patients who underwent respiratory or gastrointestinal surgery.

5. Intervention

Arm 1: shosaikoto (小柴胡湯) (manufacturer not specified) at a dose of 5.0 g for 7–33 days before surgery (n=16).

Arm 2: shosaikoto (小柴胡湯) (manufacturer not specified) at a dose of 5.0 g for 8–45 days before surgery and 11–45 days after surgery (n=17).

Arm 3: no treatment (n=33).

6. Main outcome measures

General malaise, anorexia, performance status (PS), and blood biochemistry.

7. Main results

Two weeks after surgery (Week 2), the level of glutamic-pyruvic transaminase (GPT—a measure of hepatic function) was significantly decreased in arms 1 ($P<0.01$) and 2 ($P<0.01$) compared with arm 3 (53.6 ± 26.40 , 35.9 ± 16.95 , and 91.3 ± 61.84 IU/L in Arms 1, 2, and 3, respectively), and this significant decrease persisted at Weeks 4 and 6. Similar results were observed for glutamic-oxaloacetic transaminase (GOT) and γ -glutamyl transpeptidase (γ -GTP) levels. At Week 2, direct bilirubin was significantly increased to 0.80 ± 0.84 mg/dL in Arm 3, but not in Arms 1 (0.36 ± 0.24 mg/dL, $P<0.01$) or 2 (0.48 ± 0.44 mg/dL, $P<0.05$). In addition, improvement in general malaise, anorexia, and PS was greater in arms 1 and 2 than in arm 3.

8. Conclusions

Shosaikoto is effective in reducing postoperative liver disorder.

9. From Kampo medicine perspective

The efficacy of shosaikoto was evaluated according to preoperative *sho* (証, pattern).

10. Safety assessment in the article

No adverse reactions were reported.

11. Abstractor's comments

In this article, shosaikoto (even prophylactic shosaikoto) was effective for postoperative liver disorder. It seems difficult to associate the efficacy of shosaikoto with *shoko* (証候, manifestation patterns) because of the variety of surgical stresses and diversity of diseases in this trial. The efficacy of shosaikoto (as indicated by change in GOT level) did not appear to be related to *shoko*. Nonetheless, it is desirable to use simpler designs in future controlled trials.

12. Abstractor and date

Okabe T, 22 August, 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**References**

Watanabe K. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 346–7 (in Japanese). [MOL](#), [MOL-Lib](#)

Fujii S. Effects of Daikenchuto on early bowel movement after colorectal cancer surgery.* *Progress in Medicine* 2011; 31: 468–9 (in Japanese).

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) soon after colorectal cancer surgery.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Center for Gastroenterological Disease, Yokohama City University, Japan.

4. Participants

Participants received surgery (cur A resection) for colon cancer or sigmoid colon cancer between September 2009 and August 2010 (n=151). They were all over 20 years old, with performance status 0 or 1, and ability to eat and drink 2 days after surgery. No participants were asked for their laparotomy history or type of abdominal surgery (laparotomy or laparoscopic surgery). Participants with a history of emergency surgery, double cancer, or colostomy were excluded.

5. Intervention

Arm 1: daikenchuto (大建中湯) group (manufacturer not identified): 5 g t.i.d. (n=57).

Arm 2: mosapride (Gasmotin[®]) group: 5 g t.i.d. (n=54).

Arm 3: control group: no treatment (n=40).

6. Main outcome measures

Recovery of intestinal movement after surgery (period until both gas and stool passed), number of days in hospital after surgery, anti-inflammatory action (leucocytes, C-reactive protein [CRP] level), intestinal obstruction incidence, adverse events.

7. Main results

The period until gas was passed was significantly shorter in arm 1 and arm 2 than in arm 3 (2.6 days in arm 1 [$P=0.001$], 2.8 days in arm 2 [$P=0.036$], and 3.4 days in arm 3). No significant difference in the period until stool was passed was evident among the groups (arm 1, 3.4 days; arm 2, 3.8 days; arm 3, 3.8 days). The incidence of intestinal obstruction was lower but not significantly lower in arm 1 (arm 1, 1.8%; arm 2, 5.8%; arm 3, 10%). No among-group difference was observed in the leucocyte count, but the decrease in CRP in arm 1 was significant from the third day ($P<0.05$), suggesting that daikenchuto had anti-inflammatory effect. The number of days spent in the hospital after surgery was 8.7 in arm 1, 10.8 in arm 2, and 10.1 in arm 3, so hospital stay was the shortest for arm 1, and significantly shorter than that of arm 2 ($P=0.045$). Comparison with arm 3 yielded a P-value of 0.061.

8. Conclusions

Patients treated with daikenchuto soon after colorectal cancer surgery recover intestinal movement more rapidly. The results suggest that daikenchuto may shorten post-surgery hospital stay and decrease the incidence of intestinal obstruction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Rash was observed in one participant in the daikenchuto group, and liver dysfunction in one participant in the mosapride group, however, the causal relation to the medications remains unclear.

11. Abstractor's comments

This abstract summarizes the article by Fujii (2011). The trial is clinically significant for suggesting the effectiveness of Daikenchuto. The two references listed above reported on the same study. Watanabe's article (2010) appears to be an interim paper. This trial is not an RCT in the strict sense of the word because treatment was assigned on an alternate month basis. The study seems to offer the possibility of subanalysis, so further work is anticipated.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Endo S, Nishida T, Nishikawa K, et al. Dai-kenchu-to, a Chinese herbal medicine, improves stasis of patients with total gastrectomy and jejunal pouch interposition. *American Journal of Surgery* 2006; 192: 9-13. CENTRAL ID: CN-00556925, Pubmed ID: 16769267

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Osaka University Hospital, Japan.

4. Participants

Seventeen patients who underwent total gastrectomy with jejunal pouch interposition reconstruction for gastric cancer (mean age, 62 years).

5. Intervention

Arm 1: treatment with TSUMURA daikenchuto (大建中湯) Extract Granules 5 g t.i.d. before meals for 2 weeks followed by no treatment for 2 weeks (n=10).

Arm 2: no treatment for 2 weeks followed by treatment with TSUMURA daikenchuto (大建中湯) Extract Granules 5 g t.i.d. before meals for 2 weeks (n=7).

6. Main outcome measures

Gastrointestinal symptoms, emptying, motility, and quality of life (QOL) (using Visick grading scale with modification).

7. Main results

Daikenchuto significantly relieved postprandial stasis-related symptoms including upper abdominal fullness, discomfort, and abdominal pain. Scintigraphy with ¹¹¹In- and ^{99m}Tc-labeled meals showed that daikenchuto significantly accelerated clearance of both the liquid ($P<0.01$) and solid ($P=0.015$) components of food from the jejunal pouch. Manometric assessment of pouch motility (contraction time in 6 patients found a significant increase from the pretreatment levels after daikenchuto treatment ($P=0.028$)).

8. Conclusions

Daikenchuto accelerates gastrointestinal emptying and motility and improves QOL after total gastrectomy followed by jejunal pouch interposition reconstruction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper reports the effects of daikenchuto on gastrointestinal emptying and motility in patients after total gastrectomy with jejunal pouch interposition reconstruction. The authors evaluated a small number of patients in a RCT crossover and obtained highly accurate results. They deserve high praise, especially for exploring not only subjective symptoms but also gastrointestinal emptying and motility measured by relatively invasive procedures.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010, 31 December 2013.

11 Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Manabe N, Camilleri M, Rao A, et al. Effect of Daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010; 298: G970–5.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Mayo Clinic, US.

4. Participants

Sixty healthy adults (18–65 years old) without gastrointestinal disorders recruited by advertisement. Those with a history of allergic reactions to egg, ginseng, ginger, and Sichuan pepper were excluded.

5. Intervention

Treatment was administered t.i.d. immediately before meals for 5 consecutive days. Participants and study personnel were blinded (double-blind) to treatment assignment.

Arm 1: daikenchuto (大建中湯) (manufacturer, not specified) 2.5 g t.i.d. (n=19).

Arm 2: daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. (n=20).

Arm 3: identical placebo (n=21).

6. Main outcome measures

Primary outcomes: gastric emptying half-time (GE $t_{1/2}$) measured by scintigraphy; colonic geometric center at 24 h (GC24); ascending colon emptying half-time (AC emptying $t_{1/2}$).

Secondary outcomes: colonic geometric center at 4 h and 48 h (GC4, GC48); colonic filling at 6 h; stool frequency and consistency (self-assessed using the Bristol Stool Form Scale).

7. Main results

There was a difference in colonic filling at 6 h between both daikenchuto groups and the placebo group ($P=0.04$). Pair-wise comparisons between Arm 1 and Arm 3 and between Arm 2 and Arm 3 showed no significant differences. Daikenchuto 7.5 g/day tended to accelerate ascending colon emptying half-time ($P=0.07$) and daikenchuto at both doses tended to raise GC24 ($P=0.63$). However, daikenchuto had no meaningful effects on gastric emptying half-time ($P=0.45$), stool frequency ($P=0.80$), or stool consistency ($P=0.33$).

8. Conclusions

Daikenchuto accelerated colonic filling at 6 h and ascending colon emptying half-time in healthy humans, suggesting that it promotes small bowel motility and hastens ascending colon transit.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject receiving daikenchuto 7.5 g/day had increased creatine phosphokinase (CPK) 1 month after receiving the study medication, which was discovered when the subject presented to the emergency department for muscle pain. With no evidence of myopathy, CPK level returned to normal at 4 months without intervention.

11. Abstractor's comments

This is a well-designed DB-RCT. Regrettably, no statistically significant difference was detected, which may be partly because the study population was healthy volunteers, considering the characteristics of Kampo medicine. The results of future RCTs being planned by the authors in patients with gastrointestinal disorders, including irritable bowel syndrome and constipation, are expected.

12. Abstractor and date

Tsuruoka K, 7 January 2011.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Hasebe K, Machida M, Yada M, et al. Clinical application of keishi-ka-syakuyaku-to for abdominal symptoms caused by the α -glucosidase inhibitor acarbose. *Kiso to Rinsho (The Clinical Report)* 1997; 31: 3179-86 (in Japanese with English abstract). Ichushi Web ID: 1998043002 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of keishikashakuyakuto (桂枝加芍薬湯) for the treatment of acarbose-induced symptoms.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single institution (Showa General Hospital), Japan.

4. Participants

Twenty patients with non-insulin-dependent diabetes mellitus (NIDDM) and poor glycemic control in spite of diet and exercise.

5. Intervention

Arm 1: treatment with acarbose (50 mg t.i.d. right before meals) plus TSUMURA Keishikashakuyakuto (桂枝加芍薬湯) Extract Granules (2.5 g t.i.d. before meals) (n=10).

Arm 2: treatment with acarbose alone (n=10).

The treatment duration was 4 weeks.

6. Main outcome measures

Subjective symptoms (abdominal distension, flatus, flatulence, abdominal pain, borborygmus, diarrhea, loose stool, and constipation) were scored on a 4-point scale at baseline, and after 2 and 4 weeks of treatment.

Fasting blood glucose and glycosylated hemoglobin (HbA1c) levels were measured at baseline and after 4 weeks.

7. Main results

Subjective symptoms worsened in both arms at 2 weeks, but diarrhea and abdominal pain disappeared at 4 weeks only in arm 1. The total subjective symptom score decreased significantly both at 2 and 4 weeks in arm 2, while it decreased at 2 weeks but returned to baseline level at 4 weeks in arm 1. No significant change in fasting blood glucose occurred in either arm, whereas HbA1c level was significantly improved after 4 weeks of the combination therapy.

8. Conclusions

Keishikashakuyakuto is effective for relieving gastrointestinal symptoms (adverse drug reactions to acarbose, an α -glucosidase inhibitor [α -GI]). The combination can reduce HbA1c level.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no significant worsening of subjective symptoms in the combination group.

11. Abstractor's comments

Abdominal symptoms frequently occur as so-called adverse drug reactions to acarbose, an α -GI used for mild diabetes mellitus, and may lead to discontinuation of the drug. The reduction or elimination of these symptoms by keishikashakuyakuto helps patients continue acarbose treatment. For mild diabetes mellitus, however, other drugs have been developed and more treatment options are available now. Therefore, it is controversial to add an oral drug, even a Kampo medicine, just for the purpose of continuing acarbose treatment. Also, blood glucose or HbA1c level was not significantly reduced by acarbose in this study, indicating that there might have been an inhomogeneity of the study population. These results suggest that acarbose plus keishikashakuyakuto improves glucose tolerance and that oral administration of keishikashakuyakuto in selected patients may provide a way to continue the acarbose treatment. Further studies on this combination therapy are anticipated.

12. Abstractor and date

Namiki T, 29 December 2008, 1 June 2010.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. *Biopsychosoc Medicine* [Internet] 2007 [cited 2008 Dec 31]; 1: 21. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2204024> DOI: 10.1186/1751-0759-1-21. Ichushi Web ID: 2008214687

1. Objectives

To evaluate the clinical effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by fluvoxamine, an antidepressant.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Occupational and Environmental Health Hospital, Japan.

4. Participants

Fifty patients with depressive disorder (mean age, 40.2 years).

5. Intervention

Arm 1: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) and TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 8 weeks, n=25.

Arm 2: treatment with fluvoxamine 150 mg/day (escalating from 50 mg/day) alone for 8 weeks, n=25.

6. Main outcome measures

Gastrointestinal symptoms (assessed by Gastrointestinal Symptom Rating Scale [GSRS] score) and depressive symptoms (by Self-rating Depression Scale [SDS] score).

7. Main results

Overall gastrointestinal symptoms due to fluvoxamine treatment were significantly relieved to a greater extent in arm 1 (GSRS total score, 1.97 ± 0.81) than in arm 2 (2.52 ± 0.99). No significant between-arm difference was observed in post-treatment SDS score.

8. Conclusions

Rikkunshito reduces fluvoxamine-induced gastrointestinal adverse reactions, especially nausea, without affecting the antidepressant effect of fluvoxamine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the treatment, adverse reactions occurred significantly less frequently in arm 1 (6 patients) than in arm 2 (13 patients). In particular, the frequency of nausea was significantly lower in arm 1 (3 patients) than in arm 2 (9 patients).

11. Abstractor's comments

This paper reports that rikkunshito reduced nausea and other gastrointestinal adverse reactions induced by selective serotonin reuptake inhibitors (SSRI), such as fluvoxamine. Although sample size was relatively small, this trial was well-designed and valuable since it showed the usefulness of Kampo medicines from the perspective of reducing the adverse reactions to western medicines.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010, 31 December 2013.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**Reference**

Oka T. Rikkunshito attenuates milnacipran-induced adverse gastrointestinal symptoms and potentiates its antidepressant effect. *Medical Tribune* 2008; 41: 82 (in Japanese).

1. Objectives

To evaluate the effect of rikkunshito (六君子湯) on gastrointestinal adverse reactions induced by milnacipran, an antidepressant.

2. Design

Randomized controlled trial (RCT).

3. Setting

University of Occupational and Environmental Health Hospital, Japan.

4. Participants

Forty-four patients with depressive disorder.

5. Intervention

Arm 1: milnacipran 100 mg/day (final dose) + TSUMURA Rikkunshito (六君子湯) Extract Granules 7.5 g/day for 8 weeks (n=22).

Arm 2: milnacipran 100 mg/day (final dose) for 8 weeks (n=22).

6. Main outcome measures

Gastrointestinal symptoms (assessed by the Gastrointestinal Symptom Rating Scale [GSRS] score) and depressive symptoms (by the Self-rating Depression Scale [SDS] score).

7. Main results

Gastrointestinal symptoms induced by milnacipran, especially nausea, were significantly reduced in arm 1 compared to arm 2. Overall gastrointestinal symptoms, reflux symptoms, abdominal pain, and dyspepsia scores were significantly reduced in arm 1 compared to before treatment, but not in arm 2 (scores unchanged). The SDS score after 8-week but not 4-week treatment was significantly lower in arm 1 than arm 2.

8. Conclusions

Rikkunshito may suppress gastrointestinal symptoms induced by milnacipran and potentiate its antidepressant effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although the safety of rikkunshito was not addressed, rikkunshito significantly reduced adverse events of milnacipran, particularly nausea.

11. Abstractor's comments

This study reports that rikkunshito reduced gastrointestinal symptoms such as nausea, which is the most common adverse event of antidepressant treatment with the serotonin norepinephrine reuptake inhibitor (SNRI) milnacipran. The authors reported a similar study of fluvoxamine (SSRI) in 2007 "Oka T, Tamagawa Y, Hayashida S, et al. Rikkunshi-to attenuates adverse gastrointestinal symptoms induced by fluvoxamine. *Biopsychosoc Medicine* [Internet] 2007 [cited 2008 Dec 31]; 1: 21. [<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2204024> DOI:10.1186/1751-0759-1-21,]".

The combination of fluvoxamine and rikkunshito did not significantly reduce the SDS score in that study, while milnacipran with rikkunshito did significantly lower the score in this study. However, outcome measures based on subjective symptoms may have been affected by the absence of placebo administration in the control group. As SNRIs are used widely, this study provides evidence that Kampo medicines can be useful in modern medicine.

12. Abstractor and date

Motoo Y, 1 June 2010.

12. Skin Diseases**Reference**

Shimoda S, Hashizume S, Morita M, et al. Efficacy of TSUMURA Shosaikoto for atopic dermatitis*. *Hifuka ni okeru Kampo Chiryō no Genkyō (The Current State of Kampo Medicine in Dermatology)* 1991; 2: 15–24 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shosaikoto (小柴胡湯) for treating atopic dermatitis and for withdrawing or tapering topical corticosteroids.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Sixty-five atopic dermatitis patients aged 12 years and older, excluding women who were pregnant, possibly pregnant, or lactating.

5. Intervention

Betamethasone valerate (0.12% Rinderon V ointment or cream) was used as a topical corticosteroid. During the 8-week observation period, corticosteroids were used as little as possible when improvement in symptoms was observed. Oral corticosteroids were not allowed.

Arm 1: topical corticosteroids + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for at least 8 weeks (n=41).

Arm 2: topical corticosteroids (n=24).

6. Main outcome measures

Subjective symptoms: pruritus.

Objective symptoms: papule, erythema, erosion, scales, infiltration, and hypertrophy.

Corticosteroids: could be withdrawn, reduced >50%, or reduced ≤50%.

7. Main results

Corticosteroids were withdrawn in two patients in arm 1 and reduced in 87.0% of patients in arm 2 and 62.5% in arm 1.

8. Conclusions

Shosaikoto is effective in tapering topical corticosteroid treatment of atopic dermatitis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients experienced nausea in arm 2.

11. Abstractor's comments

Although Kampo medicines have been said to be effective for atopic dermatitis, currently, only the remission of symptoms or withdrawal of topical corticosteroids have been quantitatively assessed. Statistical analyses can not be performed without quantification or scoring of variables such as the severity of skin lesions and objective improvement. Further effort to improve quantification is expected.

12. Abstractor and date

Fujisawa M, 13 October 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

References

Furue M, Tanaka Y, Kobayashi H, et al. Efficacy of Kanebo Hochuekkito in patients with atopic dermatitis with “*qikyo*” – a multicenter, double-blind trial*. *Arerugi (Japanese Journal of Allergology)*. 2005; 54: 1020 (in Japanese). [MOL](#), [MOL-Lib](#)

Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, *Hochu-ekki-to* in the long-term management of *Kikyo* (delicate constitution) in patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. *Evidence-based Complementary and Alternative Medicine* 2008 1-7 (2010; 7: 367-73).

1. Objectives

To evaluate the efficacy and safety of hochuekkito (補中益気湯) in patients with *qi-kyo* (気虚, *qi* deficiency) associated with atopic dermatitis (AD).

2. Design

Double-blinded, randomized controlled trial (DB-RCT).

3. Setting

Five university hospitals, 4 general hospitals, and 6 clinics, Japan.

4. Participants

Eighty-four patients with *qi-kyo* associated with atopic dermatitis.

5. Intervention

Arm 1: Kracie Hochuekkito Extract Granules 7.5 g/day in two divided doses for 24 weeks (n=40).

Arm 2: placebo granules for 24 weeks (n=44).

In both groups, treatment with topical preparations, etc., was continued according to the symptoms.

6. Main outcome measures

Skin lesion score (according to Japanese Dermatology Association criteria), dose of topical preparation (steroid/tacrolimus).

7. Main results

The analysis included 37 patients in the hochuekkito group and 40 patients in the placebo group. Seven patients (2 patients with worsening of skin symptoms and headache, and 5 patients with insufficient oral treatment) dropped out. There was a nonsignificant trend toward improvement in skin lesion score after 24 weeks, a significant decrease in the dose of topical preparation used after 24 weeks ($P<0.05$), a higher efficacy rate ($P=0.06$), and lower rate of worsening ($P<0.05$) in arm 1 than in arm 2.

8. Conclusions

Hochuekkito effectively improves skin symptoms and decreases the dose of topical preparation needed by patients with *qi-kyo* and atopic dermatitis.

9. From Kampo medicine perspective

The efficacy of hochuekkito for AD in patients with *qi-kyo* was evaluated. Changes in “*qikyo*” scores were not significantly different between the two arms.

10. Safety assessment in the article

Adverse events were reported in 32.5% and 27.3% of patients in the hochuekkito and placebo groups, respectively (no significant difference). Abnormal values were observed in glutamic-pyruvic transaminase (GPT), immunoglobulin (IgE), blood urea nitrogen (BUN), and potassium (K) in the hochuekkito group and in lactic dehydrogenase (LDH), glutamyl pyruvic transaminase (GOT), γ -glutamyl transpeptidase (GTP), and hemoglobin (Hb) in the placebo group. All symptoms including feeling queasy were mild in severity.

11. Abstractor’s comments

This is an evidence-based appraisal of a 24-week multicenter, placebo-controlled RCT conducted using objective measures as endpoints. Since the efficacy of hochuekkito was more marked after 24 weeks than after 12 weeks, the authors state that it acts slowly. This finding may have clinical application.

12. Abstractor and date

Kogure T, 1 June 2010, 31 December 2013.

12. Skin Diseases**Reference**

Choi I, Kim S, Kim Y, et al. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. *The Journal of Alternative and Complementary Medicine* 2012; 18: 576-82. Pubmed ID: 22784344

1. Objectives

To evaluate the efficacy and safety of orengedokuto (黄連解毒湯) and goreisan (五苓散) for dampness-heat pattern in atopic dermatitis (AD) patients.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Kyung Hee University Hospital, South Korea.

4. Participants

Twenty-four dampness-heat pattern patients with AD diagnosed using Hanifin and Rajka Diagnostic Criteria. (Patients were excluded who took antihistamines and steroids within the previous four weeks; had serious disease including infection; had seizure disorder; were pregnant and lactating; and had abnormal alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], or creatinine level.)

5. Intervention

Arm 1: orengedokuto + goreisan group: administration of a mixture of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules (1.25 g) and TSUMURA Goreisan (五苓散) Extract Granules (1.25 g) t.i.d. after meals for four weeks (n=12).

Arm 2: orengedokuto group: administration of TSUMURA Orengedokuto (黄連解毒湯) (2.5 g) t.i.d. after meals for four weeks (n=12).

6. Main outcome measures

Primary endpoints: SCORing Atopic Dermatitis (SCORAD) index, and Eczema Area and Severity Index (EASI). Secondary endpoints: symptom scores for nine dampness-heat pattern symptoms and six other symptoms.

7. Main results

The SCORAD index (-27.2 ± 8.9 in arm 1 and -24.9 ± 13.7 in arm 2) and EASI (-16.9 ± 12.1 in arm 1 and -10.4 ± 7.9 in arm 2) were significantly improved by combined treatment. There was no significant difference in primary endpoints between the two arms. Reductions in symptom scores were similar in both groups (-2.4 ± 1.3 in arm 1 and -2.1 ± 1.6 in arm 2). There was no significant difference in secondary endpoints between the two arms.

8. Conclusions

Orengedokuto and orengedokuto + goreisan may be similarly effective for dampness-heat pattern AD.

9. From Kampo medicine perspective

Although administration did not deliberately target specific patterns within the two groups, yang pattern (i.e., rapid advance of symptoms, strong itchiness, wet phase rash, and tachycardia) was identified in all patients and was the precondition for inclusion in the study.

10. Safety assessment in the article

Liver and kidney function was normal in both groups. However, even though liver and kidney function was described as normal in the beginning, patients who showed elevated AST, ALT, and BUN levels were excluded from the analysis, which makes evaluation more difficult.

11. Abstractor's comments

This is a clinically significant study indicating that orengedokuto and orengedokuto + goreisan are effective for AD with dampness-heat (湿熱) in a randomized and controlled manner. While the authors assess specific clinical symptoms as secondary endpoints, it might be possible to elucidate further the effectiveness of Kampo medicines by presenting a differential analysis of those symptoms. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

12. Skin Diseases

Reference

Ohkawara A, Furuya K, Kurisu Y, et al. Experience with Orengedokuto (TJ-15) and Goshajinkigan (TJ-107) for the treatment of senile pruritus*. *Nishinohon Hifuka (The Nishinohon Journal of Dermatology)* 1991; 53: 1234-41 (in Japanese). Ichushi Web ID: 1992177261

1. Objectives

To compare the efficacy and safety of orengedokuto (黄連解毒湯) and goshajinkigan (牛車腎気丸) with antihistamine for the treatment of senile pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Fourteen institutions: five universities (Hokkaido University, Kansai Medical University, University of Tokushima, Kyushu University, and Kagoshima University) and other related medical institutions, Japan.

4. Participants

Ninety-six patients (55 or more years old) who were diagnosed with pruritus. Exclusion criteria were: 1) infection or purulent skin disease; 2) serious impairment of the liver, kidney, cardiovascular system, or gastrointestinal system; 3) oral or injectable steroids within 2 weeks before the study; 4) topical steroids including very strong ones given within a week before the study; 5) others considered ineligible by participating physicians.

5. Intervention

Based on the score table for deficiency or excess pattern identification, patients were grouped as follows according to their body type, complexion, muscle strength, and abdominal muscles strength: A group: *chukan-sho* (中間証, intermediate pattern) to *jitsu-sho* (実証, excess pattern) type (10 points or more); B group: *chukan-sho* to *kyo-sho* (虚証, deficiency pattern) type (9 points or less).

Group A

Arm 1: administration of TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. before meals for 6 weeks (11 males and 5 females). The *sho* (証, pattern) score was 12.25 ± 1.98 .

Arm 2: administration of antihistamine (Tavegyl tablet) 1 mg b.i.d. after meals for 6 weeks, (10 males and 6 females). The *sho* score was 13.05 ± 2.20 .

Group B

Arm 3: administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. before meals for 6 weeks (15 males and 10 females). The *sho* score was 6.12 ± 1.50 .

Arm 4: administration of antihistamine (Tavegyl tablet) 1 mg b.i.d. after meals for 6 weeks (19 males and 10 females). The *sho* score was 6.28 ± 1.94 .

6. Main outcome measures

One subjective symptom (itching assessed on a 3-point scale), objective symptoms (degree of scaling, dry skin, scratch marks, and ichthyosiform skin evaluated on a 4-point scale), and overall improvement (assessed on a 5-point scale: marked, moderate, and mild improvement, absent, and worse) at the start of the study and at 2, 4, and 6 weeks of treatment. Safety was evaluated on a 4-point scale based on side effects and laboratory findings.

7. Main results

At least moderate overall improvement was achieved in 68.8% (arm 1) vs. 50.0% (arm 2) in Group A, as well as 72.0% (arm 3) vs. 55.2% (arm 4) in Group B. When A and B groups are combined, 53.3% of patients given Tavegyl vs. 70.0% of patients given Kampo preparations achieved overall improvement, but the between-group difference was not significant. Likewise, the between-group difference in subjective or objective symptom-specific overall improvement and safety was not significant.

8. Conclusions

Orengedokuto and goshajinkigan are as effective as Tavegyl for senile pruritus.

9. From Kampo medicine perspective

Selection of the intervention was based on the *sho* score.

10. Safety assessment in the article

Two patients in arm 1 and one in arm 3 had gastrointestinal symptoms. One patient treated with Tavegyl had decreased urine volume.

11. Abstractor's comments

This was a well-designed RCT. Notably, the selection of the intervention with Kampo preparations was based on *sho* scores. The study could have been improved by introducing blinding methods.

12. Abstractor and date

Tsuruoka K, 10 April 2008, 1 June 2010.

12. Skin Diseases

Reference

Iida T, Nishiyama C, Suzuki H. The effects of toki-inshi and a bath preparation containing licorice extract on patients with senile pruritus. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1996; 47: 35-41 (in Japanese with English abstract). [CiNii](#)

1. Objectives

To evaluate the efficacy of tokiinshi (当帰飲子) combined with a bath preparation containing kanzo (甘草, licorice) extract in patients with senile xerosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One special elderly nursing home, Japan.

4. Participants

A total of 25 nursing home residents with xerosis senilis accompanied by senile pruritus, aged from 59 to 92 years, for whom the efficacy of tokiinshi is expected (12 men and 13 women). Of these, 19 were included for analysis.

5. Intervention

Arm 1: TSUMURA Tokiinshi (当帰飲子) Extract Granules (TJ-86) 2.5 g t.i.d. before meals for 4 weeks (n=4).

Arm 2: Bath preparation (kanzo extract, jojoba oil, and sodium bicarbonate) 30 g dissolved in 200 L of hot water (39-40°C), and used every other day for 4 weeks (n=5).

Arm 3: TSUMURA Tokiinshi (当帰飲子) Extract Granules (TJ-86) 2.5 g t.i.d. before meals used in combination with bath preparation containing kanzo extract (every other day) (n=4).

Arm 4: no treatment (n=6).

6. Main outcome measures

Degree of skin dryness (water content of the epidermal horny layer) measured using a surface hygrometer (Skicon-200, IBS Company, Hamamatsu, Japan) at baseline and at 7, 14, 21, 18, and 35 days after the start of treatment.

The average values of 3 measurements were compared. Alleviation of pruritus was evaluated by comparing the pruritus score (scale 1-5) at the beginning and the end of the treatment.

7. Main results

The ability of the skin to retain moisture after 21 days of treatment was improved in arm 1 (22.09 ± 2.27), arm 2 (18.30 ± 3.01), and arm 3 (17.07 ± 3.80), but not in arm 4 (5.65 ± 1.59). In other words, after 3-4 weeks of treatment, the ability to retain moisture increased significantly by 3-5 times in arms 1-3, compared to arm 4 ($P < 0.05$ for each). At 35 days (7 days after the treatment was discontinued), the water content of the skin was maintained at high level in arm 1 (16.42 ± 2.37) and arm 3 (15.97 ± 3.06) but not in arm 2 (5.57 ± 0.47), which was almost the same level as that in arm 4 (5.77 ± 1.29). Alleviation of pruritus did not necessarily correspond to improvement in skin dryness.

8. Conclusions

In patients with xerosis senilis, an oral preparation of tokiinshi, a bath preparation containing kanzo extract, and the combination of both, all improve skin dryness. When used alone, the bath preparation soon loses its effect when the treatment is discontinued. Since improvement in skin dryness does not necessarily alleviate pruritus, involvement of factors other than skin dryness is suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One patient in arm 4 (no treatment) died during this study (not drug related).

11. Abstractor's comments

A well-designed RCT. In the original article, the study participants were "men and women for whom the efficacy of tokiinshi is expected". However, a detailed explanation of how the enrolled patients were chosen should have been provided. Further studies with larger sample sizes using blind assessment methods are expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 6 January 2010, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ishioka T, Aoi R. Comparative evaluation of hachimijiogan and ketotifen fumarate on senile pruritus*. *Shinyaku to Rinsho (Journal of New Remedies and Clinics)* 1992; 41: 2603–8 (in Japanese).

1. Objectives

To compare the efficacy of hachimijiogan (八味地黄丸) with that of antiallergic drugs for the treatment of senile pruritus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One special nursing home for the elderly, Japan.

4. Participants

Thirty-two nursing home residents diagnosed with senile pruritus, who experienced itching almost every night (9 males and 23 females; mean age, 78.0±7.9).

5. Intervention

Arm 1: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by ketotifen fumarate (Zaditen) 1 mg b.i.d. for two weeks (5 males and 11 females).

Arm 2: ketotifen fumarate 1 mg b.i.d. for two weeks followed by TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (4 males and 12 females).

6. Main outcome measures

Changes in the severity of itching were assessed after 2 and 4 weeks. The severity was evaluated on a 4-point scale: intolerable itching causing sleep disturbance (+++), intolerable itching but not causing sleep disturbance (++) , barely tolerable itching (+), and just annoying itching (±).

Global ratings of symptom severity whether before or after treatment were as follows: (1) completely disappeared: “marked response,” (2) clearly improved: “moderate response,” (3) at least slightly improved: “mild response,” (4) no improvement: “no response,” (5) symptoms worsened: “worse.”

7. Main results

Hachimijiogan resulted in a marked response in 11 patients (34%), moderate response in 14 (44%), mild response in 2 (6%), and no response in 5 (16%); 25 had at least a moderate response (78%). Ketotifen fumarate resulted in a marked response in 15 patients (47%), moderate response in 10 (31%), mild response in 4 (13%), and no response in 2 (6%), and symptoms worsened in 1 (3%); 25 had at least a moderate response (78%). There was no significant between-arm difference. The efficacy of the drug administered later seemed to be more effective. When comparing drug efficacy in 13 patients with more physical strength with that in 19 patients with less physical strength, significantly more patients in the latter group achieved at least moderate response to hachimijiogan ($P<0.05$). The efficacy of ketotifen fumarate did not correlate with physical strength.

8. Conclusions

The responses to both hachimijiogan and antiallergic drugs for the treatment of senile pruritus are similar (response rate, 78%). They are similarly effective. Hachimijiogan is effective especially in patients with less physical strength.

9. From Kampo medicine perspective

Although there is no in-depth description regarding “*sho* (証, pattern),” analyses comparing “patients with more physical strength” and “patients with less physical strength” are informative.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor’s comments

This was an RCT with a cross-over design. Since the itching (depending on its severity) could interfere with sleep, sleepiness (an adverse reaction of ketotifen fumarate) was a concern. However, the authors stated that no drug-induced sleepiness was observed. Unfortunately, this study had no washout period, so a further more expanded study is expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ishioka T. Comparative evaluation of rokumigan and hachimi-jiogan on senile pruritus. *Therapeutic Research* 1995; 16: 1497–504 (in Japanese with English abstract). [MOL](#), [MOL-Lib](#)

1. Objectives

To compare the efficacy of rokumigan (六味丸) and hachimijiogan (八味地黄丸) for the treatment of senile pruritus.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One special nursing home for the elderly, Japan.

4. Participants

Nursing home residents with a diagnosis of senile pruritus and itching almost every night (9 males and 22 females; 62–95 years old; mean age, 77.5±9.4).

5. Intervention

Arm 1: TSUMURA Rokumigan (六味丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (4 males and 11 females).

Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks followed by TSUMURA Rokumigan (六味丸) Extract Granules 2.5 g t.i.d. before or after meals for two weeks (5 males and 10 females).

6. Main outcome measures

Changes in the severity of itching were assessed after 2 and 4 weeks. The severity was evaluated on a 4-point scale: sleep disturbance due to itching (+++), intolerable itching but no sleep disturbance (++), barely tolerable itching (+), and just annoying itching (±).

Global ratings of symptom severity whether before or after treatment were as follows: (1) completely disappeared: “marked response,” (2) clearly improved: “moderate response,” (3) at least slightly improved: “mild response,” (4) no improvement: “no response,” (5) symptoms worsened: “worse.” In addition, global assessments according to patients’ physical strength were also performed.

7. Main results

Rokumigan resulted in marked response in 17 patients (56.7%), moderate response in 6 (20.0%), mild response in 1 (3.3%), and no response in 4 (13.3%), and symptoms worsened in 2 (6.7%); 23 had at least a moderate response (76.7%). Hachimijiogan resulted in marked response in 18 patients (60.0%), moderate response in 6 (20.0%), mild response in 2 (6.7%), and no response in 4 (13.3%); 24 had at least a moderate response (80%). There was no significant between-arm difference. In the 12 patients with more physical strength, the response to rokumigan was marked in 8 (66.7%), moderate in 3 (25.0%), and mild in 1 (8.3%), while the response to hachimijiogan was marked in 4 (33.3%), moderate in 5 (41.7%), and absent in 3 (25.3%); significantly more patients achieved marked responses to rokumigan ($P<0.05$). In the 18 patients with less physical strength, response to rokumigan was marked in 9 (50.0%), moderate in 3 (16.7%), and absent in 4 (22.2%), and symptoms worsened in 2 (11.1%), while the response to hachimijiogan was marked in 14 (77.8%), moderate in 1 (5.6%), mild in 2 (11.1%), and absent in 1 (5.6%). Significantly more patients had marked response to hachimijiogan ($P<0.05$).

8. Conclusions

Rokumigan and hachimijiogan have similar efficacy for the treatment of senile pruritus. More patients with greater physical strength achieved a marked response to rokumigan while more patients with less physical strength achieved a marked response to hachimijiogan.

9. From Kampo medicine perspective

The degree of general physical strength does not necessarily correlate with *jitsu-sho* (実証, excess pattern) or *kyo-sho* (虚証, deficiency pattern) in Kampo medicine. However, the authors noted that less physical strength, assessed on the basis of ability to play balloon volleyball, almost corresponds to the minimum criterion defining weak constitution in the guidelines used to select Kampo extract formulations.

10. Safety assessment in the article

One patient (in arm 1) dropped out because of nausea and was not included in the analyses.

11. Abstractor’s comments

This study expanded the previous RCT of hachimijiogan reported by same authors (Ishioka T, Aoi R. Comparative evaluation of hachimijiogan and ketotifen fumarate on senile pruritus. *Shinyaku to Rinsho [Journal of New Remedies and Clinics]* 1992; 41: 2603–8). There was no wash out period as in the prior study. Moreover, the analyses were not performed on an intent-to-treat basis and the sample size was small, so these limitations might affect the results. Further developments are expected.

12. Abstractor and date

Tsuruoka K, 12 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Kusumoto M, Fujimura Y, Yamada H, et al. Evaluation of the effectiveness of various drugs for relieving itching due to eczema carried out by personnel in inpatient pharmacy practice: assessment based on “itching” score - *. *Iyaku Journal (Medicine and Drug Journal)* 1993; 29: 973–6 (in Japanese).

1. Objectives

To compare the effect of unseiin (温清飲), antiallergic drugs, and antihistamines on itching due to eczema and other skin disorders.

2. Design

Randomized controlled trial (RCT).

3. Setting

One dermatology ward at a general hospital, Japan.

4. Participants

One hundred inpatients with eczema-induced itching and other skin disorders (60 males and 40 females): atopic dermatitis (n=42), asteatotic eczema (n=12), contact dermatitis (n=7), psoriasis (n=7), seborrheic dermatitis (n=6), and others (n=26). Age (in years) was 0–5 (n=2), 6–15 (n=23), and 16 or older (n=75).

5. Intervention

Arm 1: Kampo monotherapy: administration of TSUMURA Unseiin (温清飲) Extract Granules 7.5 g/day for 2 weeks (n=25).

Arm 2: antiallergic drug monotherapy: administration of Cellect (oxatomide) 2 tablets/day for 2 weeks (n=23).

Arm 3: Kampo medicine + antiallergic drug: administration of TSUMURA Unseiin (温清飲) Extract Granules 7.5 g/day + Cellect 2 tablets/day for 2 weeks (n=27).

Arm 4: antihistamine: administration of Tavegyl (clemastine) 2 tablets/day for 2 weeks (n=25).

6. Main outcome measures

The degree of itching was scored on a 5-point scale (0: no symptoms, 1: slight itching, 2: mild itching, 3: moderate itching, 4: intense itching). Patients themselves recorded the score every 1 hour. Daily total scores were calculated for days at the beginning, middle, and end of hospitalization.

7. Main results

The mean total scores for arms 1, 2, 3, and 4, respectively were 15.42, 15.69, 20.33, and 21.84 (first day), 14.70, 12.62, 14.88, and 17.12 (middle of hospitalization), 7.84, 8.06, 7.07, and 9.68 (last day). In all arms, significant differences were observed between the first and last days. The mean changes in scores from the first to last day were 7.58, 7.38, 13.59, and 12.16 in arms 1, 2, 3, and 4, respectively, and there were significant differences between arms 1 and 3, 1 and 4, 2 and 3, and 2 and 4 and no significant between-arm differences in sex, type of disease, and age.

8. Conclusions

All treatments significantly decrease itching. The effects in arms 1 and 2 as well as arms 3 and 4 are similar. The antipruritic effect is greater in arms 1 and 2 than in arms 3 and 4.

9. From Kampo medicine perspective

The authors noted that assessment of the efficacy of unseiin as well as other Kampo medicines for itching based on *sho* (証, pattern) is challenging.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

In this RCT, degree of itching was considered an outcome measure. Since strong itching (scored 3 or 4) is associated with other symptoms such as insomnia, an assessment of the effect of antihistamine or antiallergic drugs on sleep would be informative. A more extensive study is expected.

12. Abstractor and date

Tsuruoka K, 13 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ohkuma M. Treatment of pruritus by Chinese drugs. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1993; 10: 126–30 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of tokiinshi (当帰飲子) and orengedokuto (黄連解毒湯) for the treatment of pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Dermatology, Kinki University School of Medicine, Japan.

4. Participants

One hundred sixty-two patients with pruritus associated with winter eczema, senile crural eczema, asteatotic eczema, and xeroderma. Nineteen patients had diabetes.

5. Intervention

Arm 1: oral administration of tokiinshi (当帰飲子) (manufacturer, not specified) + TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. after meals (n=68).

Arm 2: oral administration of tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=49).

Arm 3: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g t.i.d. after meals (n=10).

Arm 4: oral administration of antihistamines (meguitazine 6 mg/day [n=13], terfenadine 120 mg/day [n=4], ketotifen fumarate 2 mg/day [n=14], or oxamide 60 mg/day [n=4]) after meals or at bedtime (n=35).

Treatment duration: at least 4 weeks.

6. Main outcome measures

Pruritus was assessed by history taking on a 3-point scale: marked response (disappeared or almost disappeared), moderate response (improved), and no response/worse (not changed or increased).

The observation period was at least 4 weeks. Patients who showed signs of improvement only after more than 4 weeks or stopped visiting within 4 weeks (except those with marked or moderate responses) were counted as dropouts.

7. Main results

In arm 1, the response was marked in 25 patients (66%), moderate in 9 (24%), absent or worse in 4 (11%), and there were 30 dropouts. The response in arm 1 was significantly better than that in arm 2 (marked in 39%, moderate in 29%, absent or worse in 32%) and arm 3 (marked in 13%, moderate in 50%, absent or worse in 38%) ($P<0.05$). The response in arm 4 (marked in 37%, moderate in 37%, absent or worse in 26%) did not differ significantly from that in arm 1; however, sleepiness occurred in 6 patients and malaise in 2 in arm 4, while these reactions were not observed in arms 1–3.

8. Conclusions

Tokiinshi combined with orengedokuto is as effective as antihistamines for pruritus.

9. From Kampo medicine perspective

Tokiinshi is used for *in-kyo* (陰虛, yin deficiency) and orengedokuto is used for *jitsu-you* (実陽, excess yang). These are not usually combined. However, the authors stated that this combination is not irrational, since unseiin (温清飲) is orengedokuto plus shimotsuto (四物湯) (used for *in-kyo*).

10. Safety assessment in the article

In arm 4, six patients had sleepiness and two had malaise. In arm 1, two patients experienced stomach fullness.

11. Abstractor's comments

This RCT demonstrated the efficacy of tokiinshi combined with orengedokuto for pruritus. In arm 1, 30 of 68 patients dropped out, but the analyses might not have been carried out on an intent-to-treat basis. Clarification of the analyses in this study is expected.

12. Abstractor and date

Tsuruoka K, 14 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Ohkuma M. Treatment of pruritus by Chinese drugs with external application and oral antihistamine. *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1994; 11: 302–3 (in Japanese).

1. Objectives

To compare the efficacy of orengedokuto (黄連解毒湯), tokiinshi (当帰飲子), oral terfenadine (antihistamine), and heparinoid ointment containing peppermint oil monotherapy or combination therapy for the treatment of pruritus.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Dermatology, Kinki University School of Medicine, Japan.

4. Participants

Two hundred fifty-one patients with pruritus.

5. Intervention

Arm 1: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals + terfenadine 60 mg b.i.d. and topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=44).

Arm 2: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals + terfenadine 60 mg b.i.d. (n=72).

Arm 3: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=68).

Arm 4: topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=45).

Arm 5: terfenadine 60 mg b.i.d. (n=14).

Arm 6: 0.3% heparinoid ointment (n=3).

Arm 7: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) + tokiinshi (当帰飲子) (manufacturer, not specified) 2.5 g t.i.d. after meals and topical administration of 0.3% heparinoid ointment + 1% peppermint oil (n=5).

Treatment duration: not mentioned in the article.

6. Main outcome measures

The response to treatment was evaluated on a 3-point scale (disappeared or almost disappeared ++, mitigated +, not changed or increased –).

7. Main results

The number of cases with responses of ++, +, –, and the number of dropouts were, respectively: 14, 9, 2, and 19 in arm 1; 23, 9, 5, and 35 in arm 2; 25, 9, 4, and 30 in arm 3; 7, 9, 9, and 20 in arm 4; 0, 3, 2, and 9 in arm 5; 0, 1, 1, and 1 in arm 6; 1, 1, 1, and 2 in arm 7. There were significant differences between arms 2 and 4 ($P<0.05$) and 3 and 5 ($P<0.01$) but not between arms 1 and 2, 1 and 3, and 2 and 3.

8. Conclusions

Oral administration of orengedokuto, tokiinshi, and terfenadine (antihistamine) and topical administration of heparinoid ointment + peppermint oil (arm 1) is effective for pruritus in the vast majority of cases. The effect of treatment in arm 1 and arm 7 (without antihistamine) is similar.

9. From Kampo medicine perspective

The authors stated that combining tokiinshi (used for *kyo-sho* [虚証, deficiency pattern]) with orengedokuto (for *yo-sho* [陽証, yang pattern]) is not irrational, given the fact that unseiin (温清飲) is a combination of orengedokuto (for *yo-sho*) and shimotsuto (四物湯) (for *kyo-sho*).

10. Safety assessment in the article

Five patients had difficulty in swallowing in arm 1; 6 had difficulty in swallowing and 1 had dermatitis in arm 2; 5 had difficulty in swallowing in arm 3; 1 had skin warmth in arm 4; none had adverse reactions in arms 5 and 6; 1 had difficulty in swallowing and 3 had bloating in arm 7.

11. Abstractor's comments

This RCT compared the efficacy of four agents including Kampo medicines alone or in combination. Basic information including background factors such as underlying disease, age, and sex of participants as well as follow-up period is not provided, making evaluation difficult. Further detailed study is expected.

12. Abstractor and date

Tsuruoka K, 17 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases

Reference

Kobayashi K, Ohkawara A. Therapeutic effect of jumihaidokuto on chronic eczema and atopic dermatitis*. *Hifuka ni okeru Kampo Chiryō no Genkyō (Current Situation of Kampo Therapy in Dermatology)* 1994; 5:25–34 (in Japanese).

1. Objectives

Efficacy and safety of jumihaidokuto (十味敗毒湯) for the treatment of chronic eczema and atopic dermatitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Dermatology, Hokkaido University Hospital and Asahikawa Medical College Hospital, and 8 hospital departments of dermatology.

4. Participants

Seventy-four patients (12 or more years old) with mild or moderate chronic eczema (except nummular eczema) and atopic dermatitis with little exudate and sporadic red rashes.

5. Intervention

Arm 1: oral administration of TSUMURA Jumihaidokuto (十味敗毒湯) Extract Granules 2.5 g t.i.d. for 8 weeks (n=35).

Arm 2: oral administration of clemastine fumarate 1 mg b.i.d. for 8 weeks (n=39).

Mild/moderate-strength topical steroids were allowed.

6. Main outcome measures

Itching and skin manifestations (erythema, papules, nodules, lichenification, desquamation, and scratch marks) were evaluated separately on a 4-point scale at baseline and at weeks 1, 2, 4, 6, and 8, and then their improvements were evaluated on a 5-point scale as compared with baseline.

7. Main results

The improvements in patients with chronic eczema were evaluated separately from those in patients with atopic dermatitis. Seventeen participants in arm 1 and 19 in arm 2 had chronic eczema, while 18 in arm 1 and 20 in arm 2 had atopic dermatitis. Similar proportions of patients with chronic eczema in arms 1 and 2 had at least moderate overall improvement (64.7% vs. 63.2%) or at least mild overall improvement (82.4% vs. 84.2%). Likewise, overall improvement in atopic dermatitis was similar in both arms (50% vs. 60% with at least moderate improvement, and 88.9% vs. 90% with at least mild improvement).

8. Conclusions

Jumihaidokuto is as effective for chronic eczema and atopic dermatitis as clemastine fumarate.

9. From Kampo medicine perspective

Since jumihaidokuto is used for patients with moderate or more physical strength, the degree of obesity and type of physique were considered. Including only patients whose degree of obesity was 0 or more and muscular patients with negative obesity scores, analysis found 68.8% had at least moderate improvement and 93.8% had at least mild improvement in arm 1, which was insignificantly lower than in arm 2.

10. Safety assessment in the article

One patient (2.9%) in arm 1 developed hypertension and stopped taking medication. Three patients (7.7%) had sleepiness, 1 (2.6%) had leucopenia, and 1 (2.6%) had constipation in arm 2.

11. Abstractor's comments

This meaningful clinical study compares the effect of jumihaidokuto with that of clemastine fumarate on chronic eczema and atopic dermatitis and examines the effect of Kampo medicines on skin diseases often seen in daily clinical practice. However, the authors do not describe the way they evaluated overall improvement using outcome measures. The results for each measure are also interesting, so further detailed description is expected. Moreover, although they noted "one patient stopped medication due to hypertension" in arm 1, the data of all 35 participants in arm 1 were included in the analysis of overall improvement. In Kampo medicine, muscularity is not clearly defined; more detailed description is expected. Despite these limitations, this may be a valuable study demonstrating similar efficacy for jumihaidokuto and antihistamines. Given the adverse effects of antihistamines such as sleepiness, jumihaidokuto is important alternative treatment for skin diseases.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010.

12. Skin Diseases

Reference

Kukita A, Harada S, Fujisawa R, et al. The clinical efficacy of the herb medicine, TJ-114 (Sairei-to), on the topical steroid therapy of psoriasis vulgaris. *Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines)* 1991; 7: 927–36 (in Japanese with English abstract). CENTRAL ID: CN-00716584, Ichushi Web ID: 1992091847 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) combined with topical steroid therapy for psoriasis.

2. Design

Randomized controlled trial using envelopes for allocation (RCT-envelope).

3. Setting

Six university hospitals (National Defense Medical College, Showa University, Jikei University School of Medicine, Tokyo Women's Medical University, Toho University, and Nihon University) and departments of dermatology of 8 hospitals, Japan.

4. Participants

One-hundred and four patients (15 or more years old) with psoriasis vulgaris. They had skin manifestations evaluable for drug efficacy, regardless of the severity, at the start of the study. Exclusion criteria were: 1) use of at least very strong topical steroids within 2 weeks before the study; 2) serious complications; 3) pregnant or nursing mother; 4) prior use of etretinate or methotrexate; 5) a determination of ineligibility by participating physicians.

5. Intervention

Arm 1: 0.12% betamethasone valerate ointment + oral administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. before meals for 12 weeks (n=49).

Arm 2: application of 0.12% betamethasone valerate ointment (Rinderon V or Betnevate) 2 or 3 times daily. Rinderon VG lotion was used on the scalp for 12 weeks (n=45).

6. Main outcome measures

(1) Severity of symptoms including itching, erythema, scale, and infiltration/hypertrophy was assessed on a 5-point scale (4, severe; 3, moderate; 2, mild; 1, slight; 0, none). Patients were followed at the start and at 4, 8, and 12 weeks of treatment.

(2) Laboratory tests: blood count, blood biochemistry, and general urinalysis at the first visit (start) and last visit (end of the study).

(3) Overall improvement: assessed at each visit, compared to baseline values at the start of the study, on a 6-point scale (cured, markedly improved, moderately improved, mildly improved, not changed, and worsened).

(4) Safety: assessed on the basis of adverse effects and laboratory abnormalities found during the study on a 4-point scale (1: no safety problems, 2: some safety problems, 3: moderate safety problems, 4: marked safety problems).

(5) Efficacy: assessed on the basis of both overall improvement and safety (see “safety assessment” section below) on a 5-point scale (1: very effective, 2: effective, 3: slightly effective, 4: not effective, 5: unfavorable).

7. Main results

Of 104 patients, 4 in arm 2 and 7 in arm 1 were excluded because they were lost to follow-up or noncompliant with treatment. Symptom-specific severity did not differ between arms at the start of the study, but erythema and scaling improved significantly in arm 1 compared to arm 2 ($P<0.05$) and itching, infiltration, and hypertrophy tended to improve ($P<0.1$) after 12 weeks. There was a trend toward overall improvement in arm 1, compared to arm 2, after 4 weeks ($P<0.1$) and significant improvement after 12 weeks ($P<0.01$). More patients achieved at least moderate overall improvement in arm 1 (73.9%) than in arm 2 (52.5%) ($P<0.1$). The efficacy was greater in arm 1 (63.8%) than in arm 2 (44.2%) ($P<0.1$).

8. Conclusions

Combined therapy with saireito and topical steroids is suggested to be more effective than topical steroids, but only for psoriasis.

9. From Kampo medicine perspective

The authors stated that selection of Kampo medicines was not based on *sho* but disease name.

10. Safety assessment in the article

In arm 2, two patients had stomach discomfort and gastrointestinal symptoms, and one had laboratory data indicating transient hepatic dysfunction.

11. Abstractor's comments

This study examined treatment for refractory psoriasis and was a well-designed, high-quality RCT. This was not a blinded study, so the comparison of topical monotherapy with combined therapy with oral medication may be biased. Further expanded study is expected.

12. Abstractor and date

Tsuruoka K, 20 April 2008, 1 June 2010, 31 December 2013.

12. Skin Diseases**Reference**

Tanaka M. Effects of oxatomide on urticaria. *Yakuri to Chiryō (Japanese Pharmacology and Therapeutics)* 1991; 19:5029–31 (in Japanese).

1. Objectives

Efficacy of kakkonto (葛根湯) as an adjuvant for reducing adverse reactions to oxatomide.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital department of dermatology, Japan.

4. Participants

Fifty-three patients with urticaria.

5. Intervention

Arm 1: oral administration of TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals for 7 days (n=10).

Arm 2: oral administration of TSUMURA Kakkonto (葛根湯) Extract Granules 2.5 g t.i.d. before meals + oxatomide 30 mg once daily at bedtime for 7 days (n=22).

Arm 3: oral administration of oxatomide 30 mg twice daily, after breakfast and dinner, for 7 days (n=21).

6. Main outcome measures

Itching and wheals were scored separately on a 3-point scale (marked, 2; mild, 1; none, 0). The rates of improvement compared with pre-treatment values were then calculated and classified as marked, moderate, or no response. These classifications were used as scores for the global assessment. The presence of sleepiness was also evaluated.

7. Main results

The rate of improvement was 31.6%, 68.2%, and 68.8% in arms 1, 2, and 3, respectively. For global assessment, the proportion of patients who had at least moderate response was significantly smaller in arm 1 (40%) than in arms 2 and 3 (82% and 76%, respectively, $P<0.05$). No patient in arms 1 and 2 and 10% of patients in arm 3 experienced sleepiness.

8. Conclusions

When oxatomide is used with kakkonto, the dose of oxatomide can be halved to prevent sleepiness.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This was a resourceful clinical trial that evaluated the efficacy of kakkonto as an adjuvant and as a reductant of adverse effects when used with oxatomide for urticaria. However, although the authors stated that the trial was randomized, there was a big between-group difference in the number of patients. In addition, the details of dropouts should be described. Regarding sleepiness, oxatomide was administered at the bedside in arm 2 but not at the bedside (after breakfast and dinner) in arm 3. Of course more marked sleepiness is noticed on awakening in patients in arm 3. For comparison, the drug should have been administered at the bedside in arm 3, too. Daily costs of medication were also compared among the groups and the kakkonto combined therapy was less expensive than oxatomide monotherapy. This clinical study is of interest to general physicians.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010.

12. Skin Diseases

References

Ohkuma M. Treatment of acne by Chinese drugs and external application. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU) 1993; 10: 131–4 (in Japanese with English abstract).*

Ohkuma M. Treatment of acne by Chinese drugs and external application - comparison with oral antibiotics -. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine) 1993;44:173–7 (in Japanese)*

1. Objectives

Efficacy of jumihaidokuto (十味敗毒湯) and orengedokuto (黄連解毒湯) for the treatment of acne vulgaris.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (author belongs to the Department of Dermatology, Kinki University School of Medicine), Japan.

4. Participants

Two hundred sixty-eight patients with acne vulgaris.

5. Intervention

Arm 1: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. and orengedokuto (黄連解毒湯) 2.5 g t.i.d. after meals + topical application of clindamycin lotion in the morning + 1% gentamicin sulfate-containing 0.12% betamethasone valerate lotion in the afternoon or evening + topical application of sulfur-camphor lotion before sleep for eruptions (n=90).

Arm 2: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. and orengedokuto (黄連解毒湯) 2.5 g t.i.d. after meals (n=91).

Arm 3: oral administration of jumihaidokuto (十味敗毒湯) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=55).

Arm 4: oral administration of orengedokuto (黄連解毒湯) (manufacturer, not specified) 2.5 g t.i.d. after meals (n=20).

Arm 5: topical application of clindamycin lotion in the morning + 1% gentamicin sulfate-containing 0.12% betamethasone valerate lotion in the afternoon or evening + topical application of sulfur-camphor lotion before sleep for eruptions (n=12).

Observation period was 4 weeks or more.

6. Main outcome measures

Improvement in skin condition,

rated on the basis of disappearance of skin eruptions (comedones, small papules, pustules, etc.), was defined as marked (if 90% disappeared), moderate (if 50–90% disappeared), mild (if 10–50% disappeared), and absent (if less than 10% disappeared).

7. Main results

The percentage of patients who had marked response was 47, 52, 51, 20, and 8 in arms 1, 2, 3, 4, and 5, respectively. There was no significant difference in efficacy between arms 1 and 2, arms 1 and 3, and arms 2 and 3. The time to cure was significantly shorter in arm 1 than in arm 2 ($P < 0.001$).

8. Conclusions

Combined therapy with oral jumihaidokuto and orengedokuto plus clindamycin lotion, steroid lotion, and sulfur-camphor lotion is effective in reducing comedones, small papules, and pustules in acne vulgaris.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical trial compared the effect of jumihaidokuto and orengedokuto on acne vulgaris with or without topical drugs. This interesting clinical study showed that although oral administration of jumihaidokuto or orengedokuto is itself effective for the treatment of acne, combination with topical agents can further shorten the duration of treatment. This paper notes that the patients were randomly assigned to each group, but the number of patients differs between groups. The reasons for dropping out should therefore be described. Although he also notes that “patients who improved only after 4 weeks or more and who had no response within the 4-week observation period were excluded from the analysis [sic],” it is questionable because the numbers of patients who participated in the study and whose outcomes are shown in the results are same. However, this study suggests the effect of combined therapy. Further clinical study that examines the placebo effect of combined topical agents is expected. The author has reported another study published in the *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine) 1993*, in which a non-randomized group treated with minocycline was compared to the groups included in this study.

12. Abstractor and date

Goto H, 12 September 2008, 1 June 2010, 31 December 2013.

12. Skin diseases**Reference**

Nagai Y, Hasegawa M, Tago O, et al. Assessment of the therapeutic effect of jumentaihoto on pressure ulcer. *Kampo to Saishin-chiryō (Kampo & The Newest Therapy)* 2009;18:143-9. Ichushi Web ID: 2009244595

1. Objectives

To evaluate the effects of jumentaihoto (十全大補湯) on pressure ulcers.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Dermatology, Gunma University Hospital and eight affiliated hospitals, Japan.

4. Participants

Twenty-eight chronic-phase patients whose pressure ulcers showed no change or worsening during a 2-week observation period (age and sex, not specified).

5. Intervention

Arm 1: TSUMURA Jumentaihoto (十全大補湯) Extract Granules 2.5 g t.i.d. orally before or after meals for 12 weeks. For patients with a body weight below 35 kg, the drug was administered b.i.d (n=16, including 12 infected with methicillin-resistant *Staphylococcus aureus* [MRSA]).

Arm 2: continuation of conventional treatment (n=12, including 5 infected with MRSA).

6. Main outcome measures

Long × short axes, size, and depth of pressure ulcers; prealbumin level, serum albumin level, lymphocyte count, prognostic nutritional index, serum hemoglobin level, and bacterial culture from the site of pressure ulcer (scoring from – to 3+) were measured at baseline, 4, 8, and 12 weeks.

7. Main results

There were no between-arm differences in the size of pressure ulcers, prealbumin level, and prognostic nutritional index. Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) declined significantly during the course of treatment in arm 1 compared with arm 2 ($P<0.05$).

8. Conclusions

Oral administration of jumentaihoto lowers the detection rate of MRSA but has no effect on the healing rate of pressure ulcers or nutritional status.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting clinical study that evaluated the effects of jumentaihoto on various aspects of outcome, including improvement rate, nutritional status, and local antibacterial activity, in chronic-phase patients. The data of 28 patients were analyzable in this study, but the number of patients initially enrolled, including withdrawals, is not reported. Moreover, data on age, sex, underlying disease, and presence of complications are not available. Although prealbumin level, prognostic nutritional index, serum albumin level, lymphocyte count, and serum hemoglobin level were measured, only prealbumin level and prognostic nutritional index are reported. Thus, a more detailed report is desired. As for prealbumin level and prognostic nutritional index, the authors reported “no differences” in the results section based on the lack of significant between-arm differences, whereas they reported “better in arm 1” in the summary section based on the higher mean values in arm 1; the lack of significant differences should have been mentioned. Yet, as the authors noted, the disease course may be better (albeit not significantly) in patients who take jumentaihoto than in those who do not. Future studies including a larger number of patients and a longer follow-up might demonstrate the efficacy of jumentaihoto in patients with chronic pressure ulcers.

12. Abstractor and date

Goto H, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Matsuura M. Efficacy of saireito in the management of chronic rheumatoid arthritis (RA)*. *Modern Physician* 1994; 14: 403–8 (in Japanese). Ichushi Web ID: 1994187959

1. Objectives

To evaluate the efficacy of saireito (柴苓湯) in the management of chronic rheumatoid arthritis in a controlled trial using lobenzarit, a western medicine with the established efficacy, as control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Six facilities including the Department for Rheumatic Diseases, Tokyo Metropolitan Fuchu General Hospital, Japan.

4. Participants

Forty-nine patients (12 males and 37 females) seen at the above facilities and diagnosed with chronic rheumatoid arthritis.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. before meals for 16 weeks (n=24).
Arm 2: lobenzarit 80 mg t.i.d. after meals for 16 weeks (n=25).

6. Main outcome measures

Clinical usefulness taking into account improvement in clinical symptoms and incidence of adverse drug reactions after 16 weeks of treatment.

7. Main results

Symptoms were improved in 7 of 18 patients (38.9%) and 3 of 20 patients (15.0%) receiving saireito and lobenzarit, respectively, although there was no significant difference between treatments. Clinical usefulness was noted in 7 of 18 patients (38.9%) and 4 of 21 patients (19.1%) receiving saireito and lobenzarit, respectively, showing that saireito was clinically useful in a significantly larger proportion of patients ($P<0.05$).

8. Conclusions

Saireito seems to be useful for the management of systemic symptoms of chronic rheumatoid arthritis, and is associated with comparable or higher global improvement and significantly fewer adverse drug reactions compared with lobenzarit, a western medicine with established efficacy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions including laboratory abnormalities occurred in 13.0% and 36.0% of patients receiving saireito and lobenzarit, respectively. Adverse reactions to saireito included renal impairment (in 2 of 3 cases), and those to lobenzarit included gastrointestinal disorders (in 4 of 9 cases).

11. Abstractor's comments

The use of a positive control in this trial helped establish the clinical usefulness of saireito for chronic rheumatoid arthritis. However, no objective measures were used. Efficacy was based on global symptom improvement (measured by interview) and on development of adverse reactions. A prospective confirmatory study incorporating changes in biomarkers, imaging findings, and laboratory data is desired.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**References**

Matsuta K, Gu XP, Ito K, et al. Evaluation of jiinkokato and steroid combination therapy for chronic rheumatoid arthritis. *Kampo Igaku (Kampo Medicine)* 1995;19:50–2 (in Japanese).

1. Objectives

To evaluate the efficacy of jiinkokato (滋陰降火湯) for reducing adverse effects of steroids in patients with chronic rheumatoid arthritis mainly by blood cell examination.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two facilities (Department of Medicine and Physical Therapy, the University of Tokyo Hospital, and Matsuta Internal Medicine Clinic), Japan.

4. Participants

Fourteen female patients with chronic rheumatoid arthritis visiting the above facilities between 1992 and 1993 and continuously receiving prednisolone (5–7.5 mg/day) for at least 1 year (mean age, 61 years; range, 38–76 years).

5. Intervention

Arm 1: prednisolone 5–7.5 mg/day + TSUMURA Jiinkokato (滋陰降火湯) Extract Granules 2.5 g t.i.d. before meals (n=6).

Arm 2: prednisolone 5–7.5 mg/day (n=8).

6. Main outcome measures

Hemoglobin; peripheral hematological parameters, including leukocyte and lymphocyte counts; and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin/globulin (A/G) ratio as indices of the activity of chronic rheumatoid arthritis, evaluated before and after treatment (treatment period varying from 6 to 28 weeks).

7. Main results

There were no changes in any measures in the control group. In contrast, the percentage of neutrophils was significantly reduced to 64.1 ± 8.2 from 75.9 ± 9.0 and the percentage of lymphocytes was significantly increased to 24.3 ± 6.8 from 17.3 ± 9.0 after treatment ($p < 0.05$) with jiinkokato. In two patients, lymphocyte count more than doubled after jiinkokato treatment from less than $1000/\mu\text{L}$ at baseline. The indices of the activity of chronic rheumatoid arthritis remained unchanged in both arms.

8. Conclusions

Jiinkokato is effective for reducing the adverse effects of steroids including increased neutrophils (%) and decreased lymphocytes (%).

9. From Kampo medicine perspective

The adverse effects of steroids are considered to represent the state of *yinkyonainetsu* (陰虛内熱, *yin* deficiency with internal heat) according to Kampo (traditional Chinese) medicine, and are an indication for jiinkokato. The hematologic abnormalities noted in steroid-treated patients were improved by jiinkokato, suggesting an immunoregulatory effect.

10. Safety assessment in the article

Jiinkokato did not increase the incidences of the following adverse effects of steroids: hypertension, obesity, peptic ulcer, purpura, osteoporosis, diabetes mellitus, and edema.

11. Abstractor's comments

Collagen disorders including chronic rheumatoid arthritis are often treated with long-term steroid therapy, which is associated with a reduction in lymphocyte count in some cases, even to $1000/\mu\text{L}$, posing a problem for outpatient management. This study showed that the jiinkokato combination decreased neutrophil count and increased lymphocyte count, suggesting that it has efficacy for reducing the adverse effects of steroids. However, possibly because of the small sample size, the measures of chronic rheumatoid arthritis activity were unchanged, and the various adverse effects of steroids were clinically unimproved. A future case series investigation of the efficacy of long-term combination therapy is awaited.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Amenomori Y, et al. A comparison of the analgesic effect of non-steroid anti-inflammatory drugs (NSAIDs alminoprofen) and those of a Chinese traditional herbal medicine, boi-ogi-to and shuchi-bushi-powder on osteoarthropathy of the knee joint in middle-aged and elderly patients with knee-joint osteoarthropathy. *Itami to Kampo (Pain and Kampo Medicine)* 1998; 8: 17-32 (in Japanese with English abstract). Ichushi Web ID: 1999041737

1. Objectives

To compare the efficacy of Kampo medicines (boiogito [防己黄耆湯] and shuchibushimatsu [修治附子末]) with NSAIDs for improving analgesia, quality of life (QOL), and exercise capacity in patients with knee osteoarthritis.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three clinics, one hospital, and the Department of Anesthesiology, Shiga University of Medical Science, Japan.

4. Participants

One hundred and fifty patients with knee osteoarthritis associated with knee pain and swelling who were candidates for surgery or required steroid treatment were included after 9 detailed exclusion criteria were applied.

5. Intervention

Arm 1: Kampo formulations only. Oral administration of Boiogito (防己黄耆湯) (manufacturer, not specified) 0.125 mg/kg/day + shuchibushimatsu (修治附子末) (manufacturer, not specified) 15 mg/kg/day on an empty stomach with 350 mL of water at 6:00, 14:00, and 22:00 for 1 year (2 males and 48 females: n=50; mean age, 65.7±7.3).

Arm 2: NSAIDs and Kampo formulations. Oral administration of NSAIDs (alminoprofen 600 mg/day) + boiogito (防己黄耆湯) (manufacturer, not specified) 0.125 mg/kg/day + shuchibushimatsu (修治附子末) (manufacturer, not specified) 15 mg/kg/day for 1 year (4 males and 46 females: n=50; mean age, 65.3±7.8).

Arm 3: NSAIDs only. Oral administration of alminoprofen 600 mg/day for 1 year (3 males and 47 females: n=50; mean age, 64.5±8.1).

6. Main outcome measures

Pain assessment using a visual analog scale for pain (VAS-P) every month and face rating score (FRS) at the start and end of the study. The physical, mental, economic, social, and pharmacological aspects of quality of life (QOL) assessed using VASs at the start and end of the study. Motor function assessed by the Japanese Orthopaedic Association (JOA) score and others.

7. Main results

Before the study began, there were no between-group differences in VAS-P and FRS. After 1 year of treatment, both measures improved in arms 1 > 2 > 3 and for each month differed significantly between arms 1 and 3 ($P<0.01$), as well as arms 2 and 3 ($P<0.05$). Total QOL improved in arm 1 ($202.9\pm28.5\%$) > 2 ($180.6\pm28.3\%$) > 3 ($125.0\pm11.4\%$), showing significant differences between arms 1 and 3 ($P<0.01$), as well as arms 1 and 2 ($P<0.01$). Exercise capacity showed similar results. For arm 1, the response was marked in 33 patients (67.3%), moderate in 15 (20.4%), mild in 2 (4.1%), absent in 2 (4.1%), worse in 2 (4.1%) with 1 dropout (due to relocation); for arm 2, the response was marked in 15 patients (31.3%), moderate in 8 (16.7%), mild in 5 (10.4%), absent in 3 (6.3%), worse in 17 (35.4%), with 2 dropouts (due to relocation); for arm 3, the response was marked in 4 patients (8.3%), moderate in 5 (10.4%), mild in 7 (14.6%), absent in 5 (10.4%), worse in 27 (56.8%), with two dropouts (due to relocation). The response rates were higher in arms 1 > 2 > 3, and differed significantly between arms 1 and 3 and between arms 2 and 3 ($P<0.01$ for both comparisons).

8. Conclusions

Kampo medicine is useful for the treatment of elderly patients with knee osteoarthritis.

9. From Kampo medicine perspective

The authors stated that arthralgia and neuralgia correspond to “wind-dampness (風湿)” and edema corresponds to “heavy body (身重)”.

10. Safety assessment in the article

The proportion of patients with adverse effects or abnormal laboratory test results were greater in arms 3 > 2 > 1; the number of cases were reported without giving details.

11. Abstractor's comments

This study was considered an RCT because the allocation was made using a random number table. Unfortunately, it was not conducted in a blind manner, but was well designed as a whole. As knee osteoarthritis is common in the elderly and NSAIDs have adverse effects, there are great expectations for Kampo medicines.

12. Abstractor and date

Tsuruoka K, 24 April 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Therapeutic effect of boiogitokashuchibushimatsu on gonarthrosis: a 10-year prospective randomized controlled trial with loxoprofen sodium. *Pharma Medica* 2007; 25: 15-21 (in Japanese). Ichushi Web ID: 2008070613 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of boiogitokashuchibushimatsu (防已黄耆湯加修治附子末) for gonarthrosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

University hospital (Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine; Pain Clinic, Department of Anesthesiology, Shiga University of Medical Science; and Graduate School of Pharmaceutical Sciences, Osaka University) and 4 other hospitals, Japan.

4. Participants

Two hundred eleven patients with gonarthrosis.

5. Intervention

Arm 1: administration of boiogitokashuchibushimatsu (防已黄耆湯加修治附子末) (manufacturer unknown) (n=110); age at completion, 81.5±3.4 years; male/female ratio, 8:102.

Arm 2: administration of loxoprofen (n=101); age at completion, 82.0±3.1 years; male/female ratio, 9:92.

Ten-year trial. Capsules were taken with 350 mL of water 30 min before meals.

No more details (e.g. dose, dose frequencies) were indicated in the original paper.

6. Main outcome measures

Exercise capacity (EC), range of motion of knee, various chronic pains (CP), health-related quality of life (Hr-QOL), adiponectin, leptin, and orexin levels, knee circumference, synovial fluid retention as assessed by ultrasound, degree of joint space narrowing as assessed by CT scan, (direct, indirect, total) medical expenses monitored over a 10-year period.

7. Main results

All EC parameters (continuous walking distance, continuous upslope walking distance, number of steps in continuous downslope walking) were larger in arm 1 than in arm 2 ($P<0.001$). All parameters used to evaluate activities of daily living (ADL) (pain in passive exercise, spontaneous pain, pain on pressure, patella ballottement/soft tissue swelling, local heat, etc.), various CP, and Hr-QOL were significantly improved in arm 1 compared with arm 2 ($P<0.001$).

8. Conclusions

The treatment significantly improves EC, ADL, CP, and Hr-QOL and lowers total medical expenses.

9. From Kampo medicine perspective

The *sho* (pattern) concept was a criterion for inclusion. Although “gonarthrosis complying with the *sho* for boiogitokabushi” was used as a criterion, the *sho* concept was not defined. The authors appear to consider that all patients with gonarthrosis in the study satisfy the *sho* for boiogitokabushi. There was no *sho* concept as an exclusion criterion and no subgroup analyses according to *sho*.

10. Safety assessment in the article

A significantly larger number of adverse events occurred in arm 2 ($P<0.001$ for all items): gastric ulcer (0 event in arm 1 vs. 24 events in arm 2), eruption/sleepiness/stomach discomfort/oedema (11 events vs. 348 events), and laboratory abnormality (3 events vs. 417 events).

11. Abstractor's comments

The filling of capsules to make the investigational products indistinguishable from each other is necessary for double-blind study of Kampo medicine. However, the dose of loxoprofen is missing from this paper (misprint?). This study assumed that “patients with gonarthrosis satisfy the *sho* for boiogitokashuchibushi.” This assumption should have been verified in a pilot study. However, it is extremely rare that a particular disease corresponds one-on-one to an effective Kampo treatment; the treatment of most diseases needs several Kampo medicines selected according to patient conditions. Furthermore, prolonged administration of drugs (including loxoprofen used as the control drug in this study) causing potentially fatal adverse reactions in the elderly such as gastric mucosal disorder is problematic. Also problematic is the therapeutic use of fixed doses for painful disease. Moreover, duration of the study was too long, given the nature of this disease and the old age of most subjects. Conclusion should be drawn in a shorter term.

12. Abstractor and date

Hoshino E, 15 March 2009, 1 June 2010, 31 December 2013.

13. Diseases of the musculoskeletal system and connective tissue**Reference**

Majima T, Inoue M, Kasahara Y, et al. Effect of the Japanese herbal medicine, boiogito, on the osteoarthritis of the knee with joint effusion. *Sports Medicine Arthroscopy Rehabilitation Therapy & Technology* 2012; 4: 1-6. Pubmed ID: 22230247

1. Objectives

To evaluate the efficacy and safety of boiogito (防已黄耆湯), a Kampo medicine for gonarthrosis with joint effusion.

2. Design

Randomized controlled trial (RCT).

3. Setting

Hokkaido University Hospital, Japan.

4. Participants

Forty-seven gonarthrosis patients with clinically confirmed joint effusion.

5. Intervention

Arm 1: Combined group: TSUMURA Boiogito (防已黄耆湯) Extract Granules (2.5 g t.i.d.) before meals and loxoprofen (60 mg t.i.d.) after meals for 12 weeks (n=24).

Arm 2: Loxoprofen group: Loxoprofen (60 mg t.i.d.) after meals for 12 weeks (n=23).

6. Main outcome measures

Knee score (Knee Society Rating System), function score (Knee Society Rating System), joint effusion volume, and evaluation of health status and joint symptoms using the 36-item short form health survey (SF-36).

7. Main results

Knee scores (Knee Society Rating System) improved significantly in both arms, while the function score (Knee Society Rating System) improved significantly in arm 1 but not in arm 2. SF-36 Physical Function scores improved significantly in both groups, but scores for the other seven domains showed no significant improvement. Joint effusion volume decreased significantly in arm 1 after four weeks, but not in arm 2.

8. Conclusions

Boiogito may be an effective conservative therapy for gonarthrosis with joint effusion.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant in the combined group showed signs of oral dryness, but it was slight and improved after discontinuation of the drugs.

11. Abstractor's comments

This is the first clinically significant paper on an RCT demonstrating the add-on effect of boiogito with loxoprofen for gonarthrosis with joint effusion. The paper looked for significant between-group differences in before-after comparisons; however, it might also have been able to objectively demonstrate the efficacy of boiogito if it had included an examination of the stochastic differences between the two groups. Further research is anticipated.

12. Abstractor and date

Kogure T, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effects of traditional Chinese herbal medicine, mai-men-dong-tang (Japanese name: bakumondo-to) compared with bromhexine, hydrochloride on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group parallel comparative trial study with bromhexine. *Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society)* 2002; 43: 62-6. Ichushi Web ID: 2005101735

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for dryness associated with primary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

One-hundred and six patients with primary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. for 1 year. (n=51)

Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year. (n=54)

6. Main outcome measures

Dryness, amount of salivation/lacrimation, and inflammatory reaction.

7. Main results

Salivation was increased in both groups but was significantly increased in the bakumondoto group. Lacrimation was significantly increased only in the bakumondoto group. Dryness was also improved only in the bakumondoto group. The inflammatory reaction remained unchanged in both groups.

8. Conclusions

Bakumondoto is more effective than bromhexine hydrochloride and safe in the treatment of dryness associated with primary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not specified).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for relieving dryness associated with primary Sjögren's syndrome.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 12 October 2011.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Long-term effect of traditional Chinese herbal medicine, mai-men-don-tang on sicca syndrome, especially, salivary secretion in patients with primary Sjögren's syndrome: a multicenter, randomized well controlled group-parallel double-blinded study. *Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society)* 2004; 45: 66-74.

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) therapy for salivary hyposalivation associated with primary Sjögren's syndrome.

2. Design

Double-blind, randomized controlled trial (RCT).

3. Setting

Two clinics, three university hospitals, and one general hospital, Japan.

4. Participants

Two-hundred and twenty-nine patients with primary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 6 months (n=115).
Arm 2: placebo 3 g t.i.d. before meals for 6 months (n=114).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom, limb skin temperature, and inflammatory reaction.

7. Main results

Salivation was increased in the bakumondoto group but decreased in the placebo group. Subjective symptoms were improved in the bakumondoto group but remained unchanged or were aggravated in the placebo group. Inflammatory reaction improved significantly only in the bakumondoto group.

8. Conclusions

Bakumondoto is effective and safe for the relief of subjective symptoms and salivary hyposalivation associated with primary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities or fewer patients with ADRs or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group. There were no serious ADRs or laboratory abnormalities leading to treatment discontinuation in either group (the number of events not specified).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto in the treatment of dryness associated with primary Sjögren's syndrome.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Goto GH, et al. The multicenter randomized comparative study of Kampo herbal medicine, mai-men-dong-tang (Japanese name bakumondo-to) compared with bromhexine on salivary secretion in secondary Sjögren's syndrome. *Itami to Kampo (Pain and Kampo Medicine)* 2004; 14: 10-7 (in Japanese with English abstract). Ichushi Web ID: 2006260917

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of secondary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Three clinics and 3 university hospitals, Japan.

4. Participants

Eight-hundred and forty-seven patients with secondary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. before meals for 1 year (n=424).

Arm 2: bromhexine hydrochloride 4 g t.i.d. before meals for 1 year (n=423).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom, limb skin temperature.

7. Main results

The amount of salivation was increased in both arms but was significantly higher in the bakumondoto group. Among bakumondoto-treated patients, those with mild disease showed significantly larger increases, whereas those with severe disease showed larger percent increases. The amount of lacrimation was significantly increased only in the bakumondoto group. Only in the bakumondoto group, the following variables were also improved: dryness, Raynaud's symptom, joint pain, cough/amount of sputum, and lowered temperature of the limb skin.

8. Conclusions

Bakumondoto is more effective and safer than bromhexine hydrochloride and therefore beneficial for treatment of mouth dryness associated with secondary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for the treatment of dryness associated with secondary Sjögren's syndrome. In the text, the dose of bromhexine hydrochloride was indicated as 120 mg, instead of the correct dose of 12 mg.

This paper seems to include data from the preliminary clinical trial published in *Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society)* 2003; 44: 65-70.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Improving effect of Chinese herb medicine mai-men-dong-tang (Japanese name: bakumondo-to) comparative with sicca syndrome in especial salivary patients with secondary Sjögren's syndrome in multicenter, well controlled, long-term comparative study. *Nihon Daekisen Gakkaishi (Journal of the Japan Salivary Gland Society)* 2003; 44: 65-70.

1. Objectives

To evaluate the efficacy and safety of bakumondoto (麦門冬湯) for treatment of dryness associated with secondary Sjögren's syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

Seven-hundred and fifty-six patients with secondary Sjögren's syndrome.

5. Intervention

Arm 1: bakumondoto (麦門冬湯) extract granules 3 g t.i.d. for 1 year (n=380).

Arm 2: bromhexine hydrochloride 4 g t.i.d. for 1 year (n=374).

6. Main outcome measures

Dryness, amounts of salivation/lacrimation, joint pain, amount of sputum, Raynaud's symptom.

7. Main results

The amount of salivation was increased in both arms, but it was significantly higher in the bakumondoto group. The amount of lacrimation was significantly increased only in the bakumondoto group. The following outcome measures were also improved only in the bakumondoto group: dryness, Raynaud's symptom, joint pain, and cough/amount of sputum. The inflammatory reaction remained unchanged in both groups.

8. Conclusions

Bakumondoto is more effective and safer than bromhexine hydrochloride and therefore useful for treating dryness associated with secondary Sjögren's syndrome.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were fewer adverse drug reactions (ADRs) or laboratory abnormalities in the bakumondoto group than in the bromhexine hydrochloride group (the number of ADRs not indicated).

11. Abstractor's comments

This study provides objective evidence for the efficacy of bakumondoto for treating dryness associated with secondary Sjögren's syndrome. The duration and dosage of bakumondoto treatment was correlated with the amount of salivation, suggesting a dose-dependent effect.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Ohno S. The effect of Kampo medicine on salivary secretion in Sjögren's syndrome. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 2006; 15: 134-40 (in Japanese). Ichushi Web ID: 2006203175

1. Objectives

To evaluate the efficacy for Sjögren's syndrome.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Outpatient Department of Rheumatology, Samitama Medical University Hospital, Japan.

4. Participants

Sixty-four patients with Sjögren's syndrome.

5. Intervention

Arm 1: 4-week administration of Kampo medicine extracts that affect salivary secretion (3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules alone [n=23]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Rokumigan (六味丸) Extract Granules [n=3]; 3 g t.i.d. of TSUMURA Bakumondoto (麦門冬湯) Extract Granules + 2.5 g t.i.d. of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules [n=4]) according to *sho* (証, pattern) (n=32; after 2 dropped out, 30 included for analysis).

Arm 2: 4-week administration of 2.5 g t.i.d. of TSUMURA Hochuekkito (補中益氣湯) Extract Granules (n=32; after 4 dropped out, 28 included for analysis).

6. Main outcome measures

Change in salivary secretion from pre- to post-administration, measured using a chewing gum test.

7. Main results

Twenty-seven out of 30 patients in arm 1 demonstrated increase in salivary secretion, with a significant increase in mean pre-treatment secretion of 8.2+1.2 mL to post-treatment average of 12.0+1.4 mL ($P<0.005$). There was no statistical significance between pre- and post-treatment secretions in arm 2. The amount of increase in salivary secretions before and after the treatment in arm 1 was significantly greater than arm 2 ($P<0.005$).

8. Conclusions

A Kampo medicine with moisturizing effect (but not a medicine without this effect) increases the amount of salivary secretion.

9. From Kampo medicine perspective

Arm 1 used "bensho (弁証)" (Kampo diagnosis) to allocate patients, specifically "jinkyo" (腎虚, kidney deficiency) which included 3 or more of the following 6 symptoms: 1) heaviness of the back; 2) heaviness in the lower legs with pain in heels and lateral surface of the lower legs; 3) tinnitus/hearing loss; 4) loss of hair and hair luster; 5) looseness or loss of teeth; and 6) sexual dysfunction (impotence, nocturnal emission). Kampo formulations for Arm 1 were selected based on the status of jinkyo: 1) bakumondoto alone for negative jinkyo; 2) bakumondoto plus rokumigan for jinkyo without chills; and 3) bakumondoto plus hachimijiogan for jinkyo with chills.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting quasi-randomized controlled trial that is plausible for its attempt in incorporating "sho" (証) diagnosis for selection of treatment. Results from the trial demonstrated that bakumondoto, moisturizing formula, with other Kampo formulations combination effectively enhanced salivary secretion in patients with Sjögren's syndrome than hochuekkito which was used as a control. A total of three pattern of combinations of Kampo formulation(s) were established for arm 1 based on various manifestations of jinkyo. 23 out of 30 patients (77%) in arm 1 received bakumondoto only. Future studies with improved RCT design and comparison with placebo or Western drug as a control appear warranted.

12. Abstractor and date

Namiki T, 17 March 2009, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)* 2004; 13: 232-6 (in Japanese). Ichushi Web ID: 2004301321

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸), goshajinkigan (牛車腎気丸), and shuchibushi (修治附子) powder for relief of residual symptoms after surgical treatment of cervical spinal stenosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Twenty-four patients with residual symptoms following surgical treatment of cervical spinal stenosis.

5. Intervention

Arm 1: 2-month administration of hachimijiogan (八味地黄丸).

Arm 2: 2-month administration of goshajinkigan (牛車腎気丸).

Arm 3: 2-month administration of goshajinkigan (牛車腎気丸) + 1.0 g of shuchibushi powder (修治附子末).

No between-arm difference was noted in operative effect. Administration started at postoperative 2 months in all arms.

No details in original paper.

6. Main outcome measures

Subjective symptoms (pain and paresthesia) evaluated on a visual analogue scale (VAS).

7. Main results

Pain was improved in 24.8%, 37.1%, and 45.5% of patients receiving hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder, respectively. The efficacy of goshajinkigan + shuchibushi powder was significantly higher than that of hachimijiogan. Paresthesia was improved in 21.4%, 24.2%, and 28.5%, respectively, showing no difference between arms.

8. Conclusions

Hachimijiogan, goshajinkigan, and goshajinkigan + shuchibushi powder are all effective for residual symptoms of surgically treated cervical spinal disease, with the highest efficacy achieved by goshajinkigan + shuchibushi powder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions (ADRs) or withdrawals occurred (the number of ADRs not indicated).

11. Abstractor's comments

This study provides evidence that Kampo formulations can be a therapeutic option for residual symptoms of surgically treated cervical spinal diseases. Given the higher efficacy at higher doses of shuchibushi, the authors infer that shuchibushi acts on opioid receptors.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Hayashi Y, Saito E, Takahashi O. Usefulness of hachimijiogan for lumbar spinal stenosis*. *Geriatric Medicine* 1994; 32: 585–91 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of hachimijiogan (八味地黄丸) for lumbar spinal stenosis.

2. Design

Quasi-Randomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to the faculty of Tokyo Metropolitan Rehabilitation Hospital), Japan.

4. Participants

Twenty-seven patients with radiographically demonstrable spinal column stenosis and symptoms arising from compression of the sciatic nerve or its branches.

5. Intervention

Arm 1: oral administration of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 7.5 g/day for 8 weeks (n=19).

Arm 2: oral administration of propionic acid (details unknown) for 8 weeks (n=8).

6. Main outcome measures

Subjective symptoms including lumbar pain on motion, lower limb tightness, and coldness; objective parameters including lower back tension, time from the start of walking to the occurrence of intermittent claudication, and fingertips-to-floor distance in patients bending forward; Kampo medicine findings including physical strength, complexion and hot flashes; hematology/urinalysis; measurements of bilateral tibial nerve F-wave latency, blood substance P concentration, and blood β -endorphin concentration.

7. Main results

All subjective symptoms were significantly improved in arm 1 compared with arm 2. Among objective variables, duration of intermittent claudication was significantly improved in arm 1 ($P=0.03$), but bilateral tibial nerve F-wave latency, blood substance P concentration, and blood β endorphin concentration were not changed significantly in either arm.

8. Conclusions

Hachimijiogan improves subjective symptoms, but not objective measures of spinal column stenosis.

9. From Kampo medicine perspective

Within arm 1, significantly more patients without “hie” (冷え, a feeling of coldness in the body) than those with moderate or severe “hie” responded ($P=0.001$).

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor’s comments

This is an epoch-making clinical study that investigated the efficacy of hachimijiogan for spinal column stenosis using not only subjective symptoms but also objective measures. However, the introduction states that patients were randomly allocated but the method section states that patients were allocated to arm 1 and arm 2 in the order of hospital arrival time. In addition, since the analysis population consisted of 19 patients in arm 1 and 8 patients in arm 2, the method of randomization should be specified. Similarly, the dosage and method of administration of propionic acid used as control were not mentioned and should be specified since the paper says that propionic acid was not effective for subjective symptoms. Nevertheless, this is an excellent attempt because not only subjective symptoms but also objective measures are used to evaluate efficacy. Increasing its sample size would improve this excellent clinical study.

12. Abstractor and date

Goto H, 13 September 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Maeshima S, Katayama Y. Spine and spinal cord diseases 1. Traditional Chinese medicines for the spinal disorders. *Kampo to Saishin-Chiryō (Kampo & the Newest Therapy)* 2004; 13: 232-6. Ichushi Web ID: 2004301321

1. Objectives

To evaluate the efficacy of goshajinkigan (牛車腎気丸) and shuchibushi powder (修治附子末) for relief of chronic low back pain associated with lumbar spinal stenosis.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Eighty-nine patients with chronic low back pain associated with lumbar spinal stenosis for which surgery is not indicated.

5. Intervention

Arm 1: 3-month administration of western medicines including non-steroidal anti-inflammatory drugs (NSAIDs), prostaglandin E2, vitamin B12, and/or H2 blockers (n=29).

Arm 2: 3-month administration of goshajinkigan (牛車腎気丸) alone (n=30).

Arm 3: 3-month administration of goshajinkigan (牛車腎気丸) + 2.0 g of shuchibushi powder (修治附子末) (n=30).

No details indicated in the original paper.

6. Main outcome measures

Low back pain and lower limb paresthesia evaluated on a visual analogue scale (VAS).

7. Main results

Lower back pain score was decreased from 6.7, 6.5, and 6.8 to 3.5, 4.5, and 3.2 in arms 1, 2, and 3, respectively. Lower limb paresthesia score was decreased from 5.6, 5.7, and 5.9 to 4.2, 3.9, and 3.2, respectively. Thus, there were no significant between-arm differences in therapeutic effects.

8. Conclusions

Both oshajinkigan and shuchibushi powder are as effective as western medicines for the relief of chronic low back pain and lower limb paresthesia associated with lumbar spinal stenosis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions (ADRs) or withdrawals occurred in either arm (the number of ADRs not indicated).

11. Abstractor's comments

This study is of clinical significance since it provides evidence that Kampo medicines can be a therapeutic option for lumbar spinal stenosis, expanding the range of therapeutic options.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Tamakawa S, Ogawa H. The effect of shakuyaku-kanzo-to and goshakusan on lumbago. *Itami to Kampo (Pain and Kampo Medicine)* 1997; 7: 83-5 (in Japanese with English abstract).

1. Objectives

To evaluate the clinical effect of shakuyakukanzoto (芍薬甘草湯) on acute lumbago (so-called strained back).

2. Design

Randomized controlled trial (RCT).

3. Setting

Asahikawa Medical College and Pain Clinic of Wakkanai City Hospital (two institutions), Japan.

4. Participants

Seventy patients who visited the above institutions and were diagnosed with acute lumbago within 1 week after onset (44 males and 26 females).

5. Intervention

Arm 1: epidural block with 0.125% bupivacaine, acupuncture, and poultices + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g t.i.d. before meals for 2 weeks (n=35).

Arm 2: epidural block with 0.125% bupivacaine, acupuncture, and poultices for 2 weeks (n=35).

6. Main outcome measures

Improvement in subjective symptoms of lumbago assessed on a 3-point scale: marked remission of lumbago (marked response), improvement in daily living but with persistent pain (moderate response), and limitations in daily living despite remission of lumbago (no response).

7. Main results

In the shakuyakukanzoto arm, 10 patients had marked response and 18 had moderate response, while in the control arm, 8 had marked response and 12 had moderate response; there was no significant between-arm difference. However, only 7 patients in the shakuyakukanzoto arm and 15 in the control arm had no response. In this study, 5 patients with chronic lumbago who complained of *jokan-genetsu* (上寒下熱, upper body heat and lower body cold) (in terms of Kampo medicine) received goshakusan, which resulted in a marked response in 3 patients and a moderate response in 2 patients.

8. Conclusions

Shakuyakukanzoto was administered for strained back to relieve myotonia without *sho* (証, pattern) diagnosis (証診断). Since shakuyakukanzoto seems to be effective, it can be used as a symptomatic treatment in clinical practice.

9. From Kampo medicine perspective

Shakuyakukanzoto, which has two flavors known as shiroshakuyaku (白芍薬) and kanzo (甘草), strongly relaxes smooth muscles.

10. Safety assessment in the article

No corticoid-like effects due to kanzo were experienced.

11. Abstractor's comments

This study took a Kampo medical approach to the treatment of strained back. Although epidural block with local anesthetics has been used for the treatment of strained back, its efficacy is inadequate in about half of patients whose symptoms are refractory. To improve efficacy, it can be combined with oral non-steroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs have GI adverse effects that may inevitably result in the drug withdrawal. To resolve these problems, authors applied the strong muscle-relaxing effects of shakuyakukanzoto. Fewer patients seemed to have no response in the shakuyakukanzoto group. This result is encouraging to clinicians because it indicates that shakuyakukanzoto (without being a treatment based on *sho*) provides some symptomatic relief. Unfortunately, patients treated with only epidural block, acupuncture, and poultices in the control group also had a marked response, and there was no between-group difference in the response rate. Consequently, this was a controlled study in which the control treatment might also be highly effective. A study of simpler design (e.g., a controlled trial with poultices) to confirm the clinical efficacy of shakuyakukanzoto is expected. In this paper, favorable treatment outcomes with goshakusan (五積散) given according to *sho* for patients with chronic lumbago were also described, so further studies on practical treatment with Kampo medicine for lumbago are expected.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 6 January 2010, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Ohta H, Makita K. Lumbago - with emphasis on nonspecific lumbago, which obstetricians and gynecologists think is the most common form in women - . *Chiryō (The Journal of Therapy)* 1995; 77: 1646-57 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To clinically evaluate the effects of keishibukuryogan (桂枝茯苓丸) and its combination with bushi (附子) on nonspecific lumbago in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (currently the first author is affiliated with Outpatient Department for Climacteric Disorders, Tokyo Women's Medical University Hospital), Japan.

4. Participants

Thirty-seven female patients with lumbago.

5. Intervention

Arm 1: keishibukuryogan (桂枝茯苓丸) (manufacturer unknown) 2.5 g t.i.d. before meals for 3 months (n=14).

Arm 2: keishibukuryogan (桂枝茯苓丸) (manufacturer unknown) 2.5 g t.i.d. + crude drug shujibushimatsu (manufacturer unknown) 0.17 g t.i.d. before meals for 3 months (n=23).

6. Main outcome measures

Lumbago symptoms (4-point scale) evaluated after 12 weeks of treatment: complete response (increase of 2 or more points) and partial response (increase of 1 point).

7. Main results

Complete response and partial response were respectively achieved in 21.4% and 14.3% of patients receiving keishibukuryogan alone and 26.1% and 34.8% of patients receiving keishibukuryogan + shujibushimatsu.

8. Conclusions

Combining keishibukuryogan with shujibushimatsu improves nonspecific lumbago in women during menopause, indicating that a *kuoketsu* (驅才血, blood stasis-expelling) Kampo medicine is clinically useful when combined with bushi, a crude drug with an analgesic/anti-inflammatory effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Nonspecific lumbago in women during menopause has various etiologies and is not unambiguously related to the presence of inflammation and impaired blood flow. To treat it, therefore, various measures should be tried. This study produced favorable results using a therapy combining bushi (a pain reliever and blood flow enhancer) with keishibukuryogan, which is used to treat *oketsu* (才血, blood stasis), the most frequent pathology in women with climacteric unidentified complaints and a useful reference for many clinicians. It would be interesting to incorporate into the study protocol the theory of Kampo medicine, including choice of *kuoketsuzai* (驅才血劑, blood stasis-expelling formula) according to the diagnosis of *oketsu* (才血, blood stasis), and combination with bushimatsu taking the presentation of a feeling of coldness into consideration. A case series investigation incorporating the measurement of biomarkers is expected.

12. Abstractor and date

Ushiroyama T, 13 August 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Nakamura T, Souza ACA, Ouchi Y, et al. Effects of goshajinkigan on lumbago*. *Dai 4 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu (Proceedings of the 4th Meeting of the Tokyo Society for Internal Kampo Medicine)* 1989; 4: 24–9 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in comparison with that of tiaramide hydrochloride for lumbago in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One facility (Department of Geriatric Medicine, University of Tokyo Hospital), Japan.

4. Participants

Twenty-five elderly patients with lumbago visiting the above facility (3 males and 22 females; 60–87 years old).

5. Intervention

Arm 1: goshajinkigan (牛車腎気丸) (manufacturer, not specified) 2.5 g t.i.d. before meals (n=11).

Arm 2: tiaramide hydrochloride 100 mg t.i.d. after meals (n=7).

Arm 3: goshajinkigan (牛車腎気丸) (manufacturer, not specified) 2.5 g t.i.d. before meals + tiaramide hydrochloride 100 mg t.i.d. after meals (n=7).

Treatment duration: 4 weeks.

6. Main outcome measures

Improvement rating of subjective symptoms including lumbago evaluated on a 4-point scale.

7. Main results

Goshajinkigan was effective for lumbar numbness and stiffness, while tiaramide hydrochloride was effective for lumbago and irradiating pain at rest (no test for significance of the difference). Goshajinkigan had an equivalent or greater effect than tiaramide hydrochloride on reducing pain while rising to a standing position from sitting, anteflexion, retroflexion, and rolling over (no test for significance of the difference). Severity of lumbago was improved in all groups, although there was no significant among-arm difference in this improvement.

8. Conclusions

In the elderly with lumbago, goshajinkigan is equally or more effective than tiaramide hydrochloride for pain during movement but not effective for pain at rest.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse reactions occurred in 2 patients receiving goshajinkigan (discomfort [n=1]; administration discontinued] and anorexia [n=1]) and 1 patient receiving tiaramide hydrochloride (anorexia). However, anorexia disappeared during continued administration.

11. Abstractor's comments

Goshajinkigan has traditionally been reported to be effective in the elderly for lumbago, which has a pathology of *jinyokyo* (腎陽虚, kidney yang deficiency). This study demonstrated that goshajinkigan and a Western medicine with established efficacy have comparable efficacy. The small sample size regrettably prevented sufficient group comparison in this study. Future case series are expected to include investigation of the influence of *sho* (証, pattern).

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Wang XD, Yoshida K, Honda K, et al. Study of the immunoregulatory activity of the combination therapy with juzentaihoto and hachimijiogan in patients with disuse syndrome*. *Kampo Igaku (Kampo Medicine)* 2006; 30: 65-7 (in Japanese). Ichushi Web ID: 2006283912

1. Objectives

To evaluate the efficacy of juzentaihoto (十全大補湯) combined with hachimijiogan (八味地黄丸) in patients with disuse syndrome.

2. Design

Randomized controlled trial (envelope method) (RCT-envelope).

3. Setting

One community hospital, Japan.

4. Participants

Patients after a prolonged period of bed rest and tube feeding.

5. Intervention

Arm 1: Tsumura Juzentaihoto (十全大補湯) Extract Granules and Tsumura Hachimijiogan (八味地黄丸) Extract Granules 2.5 g b.i.d. each for 24 weeks, n=13.
Arm 2: No administration of Kampo drugs, n=15.

6. Main outcome measures

Laboratory tests: hemograms and urine tests performed at 0, 4, 8, 12, 16, 20, and 24 weeks. CD4 count, CD8 count, CD4/CD8 ratio, neutrophil phagocytotic activity, levels of immunoglobulins (IgM, IgG, and IgA) examined at 0, 12, and 24 weeks.

7. Main results

CD4/CD8 ratio and CD4 count were significantly increased in arm 1 compared to arm 2 at 12 weeks; however, no significant difference was observed at 24 weeks. There were no significant between-arm differences in the results of other tests.

8. Conclusions

In many cases, CD4/CD8 ratio and CD4 count are elevated at 12 weeks of administration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Immunoregulatory effect of the combination two Kampo drugs was assessed using lymphocyte surface markers CD4 and CD8. The finding of significant increases in CD4/CD8 ratio and CD4 count at 12 weeks, but not at 24 weeks, demands the conduct of further studies designed to reveal whether immune status was restored or regulated.

12. Abstractor and date

Namiki T, 12 March 2009, 1 June 2010.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Ohta H, Nemoto K. Combined effect of vitamin D₃ and TSUMURA Keishibukuryogan on osteopenia following oophorectomy*. *Kampo Igaku (Science of Kampo Medicine)* 1989; 13: 173–9 (in Japanese).

1. Objectives

To evaluate the combined effect of keishibukuryogan (桂枝茯苓丸) and vitamin D3 on osteopenia in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (Department of Obstetrics and Gynecology, Tokyo Electric Power Hospital), Japan.

4. Participants

Thirty patients diagnosed with osteopenia following oophorectomy at the above facility, with a total bone mineral density (MD) score of 4 or more points.

5. Intervention

Arm 1: oral TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals + α -calcidol 0.5 μ g b.i.d. after meals (n=6).

Arm 2: oral α -calcidol 0.5 μ g b.i.d. after meals (n=6).

Arm 3: oral α -calcidol 0.5 μ g b.i.d. after meals + Premarin 0.625 mg q.d. after meals or Metharmon F tablet t.i.d. after meals (n=7).

Arm 4: follow-up without drug administration (n=11).

6. Main outcome measures

Change in MD (mean percentage change in actual values of 5 variables: bone cortex width index, bone marrow width, bone cortex and marrow integrated density index, bone cortex density index, and bone density per unit length) compared between baseline and after 10 months of treatment.

Serum concentration of bone metabolic markers (alkaline phosphatase [AL-P], calcium [Ca], and phosphate [P] compared between baseline and after 10 months of treatment).

7. Main results

Combination of keishibukuryogan and vitamin D3 significantly increased bone mineral content compared with baseline ($P<0.05$), vitamin D3 alone, and no drug administration ($P<0.05$) and significantly increased serum AL-P and Ca concentrations ($P<0.05$). The hormones increased serum Ca concentration ($P<0.05$).

8. Conclusions

Combination of keishibukuryogan and vitamin D3 decreased osteopenia in women without ovaries.

9. From Kampo medicine perspective

Keishibukuryogan controlled mental and physical disorders associated with ovarian deficiency syndrome consisting of *qi-no-josho* (気の上衝, qi counterflow pattern syndrome), *oketsu* (才血, blood stasis), and *suidoku* (水毒, water toxin), resulting in increases in appetite, and consequently Ca intake, intestinal absorption and motility, which may have indirectly increased bone mineral content.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

A representative *kuoketsuzai* (驅才血劑, blood stasis-expelling formula), keishibukuryogan improves *suidoku* and *qitai* (氣滯, qi stagnation) and is therefore frequently used for treatment of unidentified complaints in postmenopausal women. This study demonstrated that use of vitamin D3 as an adjuvant increases bone mineral content in patients following ovariectomy. Given that long-term intervention is needed to prevent and treat osteoporosis, a Kampo therapy such as keishibukuryogan can be optimal. However, the need for keishibukuryogan in therapy according to *sho* (証, pattern) of postmenopausal women with unidentified complaints, most whom have *kyosho* (虚証, deficiency pattern), should be investigated.

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Ohta H, Nemoto K. Preventive effect of 1 α -hydroxyvitamin D₃ plus Kampo medicine combination therapy on osteopenia following oophorectomy - comparison between keishibukuryogan and tokishakuyakusan -*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 1990; 7: 65–70 (in Japanese).

1. Objectives

To evaluate the combined effect of keishibukuryogan (桂枝茯苓丸) or tokishakuyakusan (当归芍薬散) and vitamin D3 on osteopenia in women during menopause.

2. Design

Randomized controlled trial (RCT).

3. Setting

One facility (Department of Obstetrics and Gynecology, Tokyo Electric Power Hospital), Japan.

4. Participants

Thirty patients diagnosed with osteopenia following oophorectomy at the above facility, with a total bone mineral density (MD) score of 4 or more points.

5. Intervention

Arm 1: oral α -calcitriol 0.5 μ g b.i.d. after meals (n=6).

Arm 2: oral α -calcitriol 0.5 μ g b.i.d. after meals + TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals (n=6).

Arm 3: oral α -calcitriol 0.5 μ g b.i.d. after meals + TSUMURA Tokishakuyakusan (当归芍薬散) Extract Granules 2.5 g t.i.d. before meals (n=6).

Arm 4: follow-up without drug administration (n=12).

6. Main outcome measures

Change in MD (mean percentage change in actual values of 5 variables: bone cortex width index, bone marrow width, bone cortex and marrow integrated density index, bone cortex density index, and bone density per unit length) compared between baseline and after 10 months of treatment.

7. Main results

Bone mineral content was significantly higher in arm 2 than in arm 1 and arm 4 ($p < 0.05$), but similar to that in arm 3. Bone cortical width index was higher, although not significantly, in arm 3 than in arms 1 and 4.

8. Conclusions

Combination of keishibukuryogan and vitamin D3 decreases osteopenia in women without ovaries and seems to improve osteopenia.

9. From Kampo medicine perspective

These Kampo medicines controlled mental and physical disorders associated with ovarian deficiency syndrome consisting of *qi-no-josho* (気の上衝, *qi* counterflow pattern syndrome), *oketsu* (才血, blood stasis), and *suidoku* (水毒, water toxin), resulting in increases in appetite, and consequently Ca intake, intestinal absorption and motility, which may have indirectly increased bone mineral content. The higher efficacy of keishibukuryogan is attributable to its keishi and botanbi components, which may improve bone metabolism via PGE₂- and cytokine-mediated immunostimulation.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study demonstrated that use of vitamin D3 as an adjuvant increases bone mineral content in patients following ovariectomy. The study results suggested that keishibukuryogan administered to those with *jitsusho* (実証, excess pattern), and tokishakuyakusan administered to those with *kyosho* (虚証, deficiency pattern), can be used for prevention and treatment of osteoporosis, greatly contributing to climacteric and geriatric medicine. Although the slightly higher efficacy of keishibukuryogan is pharmacologically discussed from the perspective of Kampo components in this study, it is desirable that future studies use a protocol that reflects the mechanism of bone metabolism and bone substance improvement from the perspective of Kampo theory.

12. Abstractor and date

Ushiroyama T, 16 August 2008, 1 June 2010, 31 December 2013.

13. Diseases of the Musculoskeletal System and Connective Tissue**Reference**

Kanai S. The effect of kami-kihi-to on the maintenance of bone mass in patients with osteoporosis. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1998; 49: 59-66 (in Japanese with English abstract). CiNii

1. Objectives

To evaluate the effects of kamikihito (加味帰脾湯) on menopause index, bone mass, and anemia in postmenopausal women with osteoporosis.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Research Institute of Oriental Medicine, Kinki University, Japan.

4. Participants

Eighty-three women (aged 59–84 years) who visited the above institution, were diagnosed with osteoporosis according to the criteria for osteoporosis by the Ministry of Health and Welfare (currently the Ministry of Health, Labour, and Welfare), and had been followed for two years since 1993.

5. Intervention

Arm 1: oral administration of alfacalcidol (1 µg) once daily after breakfast and zaltoprofen 80 mg t.i.d. after meals.

Arm 2: oral administration of kamikihito (加味帰脾湯) (manufacturer, not specified) 2.5 g t.i.d. after meals and zaltoprofen 80 mg t.i.d. after meals.

Arm 3: oral administration of zaltoprofen 80 mg t.i.d. after meals.

All treatments were administered for 2 years.

6. Main outcome measures

Bone density measured by Computed X-ray Densitometry (CXD), cytometry, and efficacy based on Simplified Menopausal Index (SMI) score before treatment and at 1 and 2 years after the start of treatment.

7. Main results

As compared with bone mass in arm 1, bone mass in arm 2 and arm 3 increased significantly after 1 year of treatment ($P<0.05$). However, after 2 years, bone mass was further increased in arm 1, but remained stable in arm 2. Red blood cell and reticulocyte counts increased significantly after 1 year in arm 2 compared with arm 3 ($P<0.05$), but their increases were stabilized after 2 years. SMI decreased significantly after 1 year in arm 2, as compared with arms 1 and 3 ($P<0.05$). A weak but significant positive correlation between changes in bone mass and SMI was observed ($P<0.05$). In patients with increased bone mass and treated with kamikihito, compared with patients with decreased bone mass, SMI decreased and anemia improved.

8. Conclusions

Treatment of osteoporosis with kamikihito in women is clinically effective in increasing bone mass, as well as in improving anemia and decreasing SMI.

9. From Kampo medicine perspective

Kampo prescription was not based on *sho* (証, pattern). Kamikihito seemed to exert its effects by improving general physical status which resulted in increased energy in individual patients, and subsequent increase in bone density.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Kamikihito has been conventionally prescribed for nonspecific climacteric symptoms or for improving anemia and its effects are also apparent in the present study. Its bone density-increasing effect appears to be about half of that of vitamin D. However, clinical application of kamikihito for osteoporosis in postmenopausal women is strongly expected. According to a number of osteoporosis-related studies, the effect of vitamin D varies greatly among individuals. It is currently understood that vitamin D preserves but does not increase bone mass. Therefore a multidrug approach with kamikihito would be more desirable for the therapy of osteoporosis. A case series study examining the combined therapy with western medicines is expected.

12. Abstractor and date

Ushiroyama T, 20 August 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Yoshikawa N, Ito H, Sakai T, et al. A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. *Nihon Jinzo Gakkaishi (The Japanese Journal of Nephrology)* 1997; 39: 503-6 (in Japanese with English abstract). CENTRAL ID: CN-00143175, Pubmed ID: 9283216

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) in childhood IgA nephropathy with focal/minimal mesangial proliferation.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Departments of Health Science of Kobe University School of Medicine, Kidney Center of Kitasato University Hospital, Department of Pediatrics of Hokkaido University, etc. (a total of 29 institutions including 16 university hospitals and 9 departments of pediatrics), Japan.

4. Participants

One hundred and one patients aged 15 or under with newly diagnosed IgA nephropathy with focal/minimal mesangial proliferation.

5. Intervention

Arm 1: administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. (body weight ≥ 40 kg), 3.0 g b.i.d. (body weight 20–40 kg), or 1.5 g b.i.d. (body weight ≤ 20 kg) for two years (n=50).
Arm 2: no treatment (n=51).

6. Main outcome measures

Daily urinary protein excretion, hematuria in morning urine, and renal function (blood urea nitrogen, serum creatinine, creatinine clearance, etc) at the start and end of treatment.

7. Main results

At the end of the trial, mean daily urinary protein excretion was significantly decreased from the initial 0.39 ± 0.31 g/day to 0.25 ± 0.21 g/day in the 46 patients included for analysis in arm 1 ($P=0.005$), while it remained unchanged in the 48 patients included for analysis in arm 2 (0.41 ± 0.48 g/day vs. 0.43 ± 0.56 g/day). Hematuria in the morning urine was also significantly attenuated after two years of the trial in arm 1 (from 2.3 ± 1.0 to 1.0 ± 1.1) ($P < 0.0001$), but was not decreased in arm 2 (from 2.1 ± 1.1 to 1.8 ± 1.2). Urinary findings became normal in 46% of arm 1 and 10% of arm 2, showing significant difference between arms ($P < 0.001$).

8. Conclusions

Saireito is effective for childhood IgA nephropathy with focal/minimal mesangial proliferation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse reaction was observed.

11. Abstractor's comments

Although in Japan randomization by the RCT-envelope method tends not to be maintained, the present study suggests the efficacy of saireito for early treatment of childhood IgA nephropathy with focal/minimal mesangial proliferation. It is interesting that urinary findings were normalized in 46% of patients.

12. Abstractor and date

Okabe T, 22 August 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Saruta T, Konishi K. Efficacy of Kampo medicines for renal diseases - with emphasis on saireito - . *21 Seiki no Iryo to Kampo (The 21st Century Medicine and Kampo)* 1994: 157–65 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for IgA nephropathy in adults.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Internal Medicine, Keio University School of Medicine and related facilities, Japan.

4. Participants

Forty-four patients with IgA nephropathy, aged ≥ 16 years.

5. Intervention

Arm 1: saireito (柴苓湯) (manufacturer not specified) 3 g t.i.d. for 24 weeks (n=22).

Arm 2: dilazep hydrochloride 100 mg t.i.d. for 24 weeks (n=22).

6. Main outcome measures

Urinary protein excretion, RBC count in urinary sediment, and creatinine clearance.

7. Main results

The mean urinary protein excretion for the analysis population of arm 1 (13 patients) was significantly decreased from 2.1 ± 0.4 g/day at baseline to 1.5 ± 0.3 g/day at 24 weeks after administration ($P < 0.01$) but not for the analysis population of arm 2 (12 patients; 2.2 ± 0.7 g/day at baseline and 1.9 ± 0.4 g/day at 24 weeks). There were no significant changes in serum albumin concentration, cholesterol level, or creatinine clearance.

8. Conclusions

Saireito decreases urinary protein excretion in adult patients with IgA nephropathy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions in either arm.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this study suggested that saireito decreases urinary protein excretion in adult patients with IgA nephropathy. A future randomized controlled trial should be performed with larger sample size and improved allocation.

12. Abstractor and date

Okabe T, 25 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Yoshikawa N, Ito H, Takekoshi Y, et al. Standard versus long-term prednisolone with sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: A prospective controlled study. *Nihon Jinzo Gakkaishi (The Japanese Journal of Nephrology)* 1998; 40: 587-90 (in Japanese with English abstract). CENTRAL ID: CN-00158912, Pubmed ID: 9893457, Ichushi Web ID: 1999105890

1. Objectives

To evaluate the efficacy of initial steroid therapy with saireito (柴苓湯) for preventing relapse in childhood steroid-responsive nephrotic syndrome.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Departments of Health Science of Kobe University School of Medicine, Department of Pediatrics of Hokkaido University, Department of Pediatrics of Keio University School of Medicine, and others (a total of 35 institutions), Japan.

4. Participants

Two hundred and twenty-one patients diagnosed with childhood-onset minimal change nephrotic syndrome based on clinical features, and not manifesting persistent hematuria, renal dysfunction, and hypertension at onset.

5. Intervention

Arm 1: prednisolone 2 mg/kg/day in three divided doses for 4 weeks followed by prednisolone 1.3 mg/kg every other day for 4 weeks (n=109).

Arm 2: prednisolone 2 mg/kg/day in three divided doses for 4 weeks followed by prednisolone 2 mg/kg every other day for 8 weeks, 1.5 mg/kg every other day for 2 weeks, 1 mg/kg every other day for 2 weeks, and 0.5 mg/kg every other day for 2 weeks (n=112).

Kanebo Saireito (柴苓湯) Extract Fine Granules were administered in doses of 2.7 g t.i.d. (in all patients weighing ≥ 40 kg), 2.7 g b.i.d. (in all patients weighing 20–40 kg), or 1.35 g b.i.d. (in all patients weighing ≤ 20 kg).

6. Main outcome measures

The rates of relapse and frequent relapse.

7. Main results

Eighty-eight of 109 patients in arm 1 and 83 of 112 in arm 2 with steroid-responsive nephrosis were followed for 2 years. There were no between-arm differences in the rate of relapse and rate of frequent relapse (70% vs. 65% and 21% vs. 24%, respectively).

8. Conclusions

The duration of the initial steroid therapy with saireito for childhood steroid-responsive nephrotic syndrome has no effect on relapse rate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects included mild liver dysfunction in 1 patient treated with steroid for 8 weeks, and allergic cystitis in 1 patient treated with steroid for 18 weeks. Both effects were reversed with drug withdrawal.

11. Abstractor's comments

Although in Japan randomization by the RCT-envelope method tends not to be maintained, in the present study, the relapse rates did not differ between 8-week and 18-week treatments with steroid and saireito. As the authors mentioned, the rate of frequent relapse is lower in their study (21% in arm 1) than in other reports examining a short-term steroid treatment similar to that used in arm 1 (35–40%). Comparison with a treatment without saireito may be needed to confirm this observation. A randomized controlled trial using other methods of random allocation is also expected.

12. Abstractor and date

Okabe T, 25 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Kinoshita H, Kanaya H, Yamamoto S, et al. Effects of Chinese herbal medicine in promoting the spontaneous discharge of upper urinary tract stones after ESWL. *Nishinohon Hinyokika (The Nishinohon Journal of Urology)* 1993; 55: 61–6 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of choreitogoshimotsuto (猪苓湯合四物湯) + shakuyakukanzoto (芍薬甘草湯) for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Sixty-one postoperative patients undergoing extracorporeal shock wave lithotripsy for upper urinary tract stones (72 stones).

5. Intervention

Arm 1: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5 g/day + TSUMURA Choreitogoshimotsuto (猪苓湯合四物湯) Extract Granules 7.5 g/day for at least 3 months, 35 stones.

Arm 2: no administration, 37 stones.

6. Main outcome measures

Cumulative stone clearance rate.

7. Main results

The cumulative stone clearance rate at 30 and 90 postoperative days was significantly higher in arm 1 (65.7% and 82.9%, respectively) than in arm 2 (47.2% and 61.1%, respectively; $P < 0.05$) and higher in the renal pelvis/calyx and uteropelvic junction of arm 1 than in the renal pelvis/calyx and uteropelvic junction of arm 2.

8. Conclusions

The choreitogoshimotsuto + shakuyakukanzoto combination promotes the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

This study suggests the efficacy of choreitogoshimotsuto + shakuyakukanzoto for promoting the spontaneous discharge of upper urinary tract stones after extracorporeal shock wave lithotripsy. RCT using the *zuisho* (随証, based on pattern) approach to Kampo medicine may verify even higher efficacy. Future studies are expected.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Kobayashi M, Naya Y, Kino M, et al. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: Efficacy in Japanese male patients with ureteral stone. *International Journal of Urology* 2008; 15: 495-8. Ichushi Web ID: 2008254384

1. Objectives

To evaluate the efficacy of low-dose tamsulosin and choreito (猪苓湯) for stone expulsion after extracorporeal shock wave lithotripsy (ESWL) in patients with ureteral stones.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two departments of urology: one in Chiba University Hospital and one in another hospital, Japan.

4. Participants

One hundred and two patients with ureteral stones measuring at least 4 mm in diameter who underwent ESWL.

5. Intervention

Arm 1: tamsulosin 0.2 mg/day from post-ESWL day 1 to stone expulsion (n=38).

Arm 2: TSUMURA Choreito (猪苓湯) 7.5 g/day from post-ESWL day 1 to stone expulsion (n=30).

Arm 3: no treatment (n=34).

6. Main outcome measures

Stone clearance was evaluated using abdominal plain radiography and ultrasonography.

7. Main results

The stone-free rate was 84.21%, 90%, and 88.24% for arms 1, 2, and 3, respectively; there were no significant differences. The time to stone expulsion was 15.55±6.14 days, 27.74±25.36 days, 35.47±53.70 days, for arms 1, 2, and 3, respectively. The time to expulsion was significantly shorter in arm 1 than in arm 2 ($P=0.0116$) or arm 3 ($P=0.0424$), while there was no significant difference between arms 2 and 3 ($P=0.4982$).

8. Conclusions

Tamsulosin treatment after ESWL appears to reduce the time to expulsion of ureteral stones.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study demonstrated the efficacy of tamsulosin, an α 1-receptor blocker, for reducing time to expulsion of ureteral stones after ESWL. Choreito, which is thought to enhance clearance of ureteral stones by increasing urine output, on the other hand, had no effect. Previous similar studies have reported a significant reduction in time to expulsion by choreito treatment. Further studies including a larger number of patients are needed to evaluate the effects of choreito.

12. Abstractor and date

Okabe T, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka H, et al. Efficacy and safety of Chinese traditional medicine, niu-che-shwn-qi-wan (Japanese name: goshajinki-gan) versus propiverine hydrochloride on health-related quality of life in patients with overactive bladder in prospective randomized comparative study. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 2007; 16: 131-42 (in Japanese). Ichushi Web ID: 2007260946

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) and propiverine hydrochloride for overactive bladder.

2. Design

A randomized controlled trial (RCT).

3. Setting

Not mentioned (authors belong to Nishizawa Clinic, Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine and Department of Anesthesiology, Shiga University of Medical Science), Japan.

4. Participants

Seven hundred and four patients with overactive bladder, aged 45 years or older, prospectively enrolled over a 10-year period (1997–2006).

5. Intervention

Arm 1: administration of goshajinkigan (牛車腎気丸) (manufacturer not specified), 4.5 g/day, for 1 year (n=352).

Arm 2: administration of propiverine hydrochloride, 60 mg/day, for 1 year (n=352).

6. Main outcome measures

Symptoms of overactive bladder (urge to urinate, daytime urinary frequency, nocturia, and urine leak).

Quality of life (pain, erection dysfunction, cold sensation, etc.).

7. Main results

Symptoms of overactive bladder were significantly more improved in arm 2 than in arm 1 during the first month after treatment initiation, but significantly more improved in arm 1 than arm 2 during the second and subsequent months. At the completion of the study, the other concomitant symptoms and quality of life (QOL) were also significantly more improved in arm 1 than in arm 2.

8. Conclusions

It is suggested that goshajinkigan is effective for overactive bladder.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Four and 375 events of adverse drug reactions occurred in arm 1 and arm 2, respectively.

11. Abstractor's comments

This 1-year prospective randomized controlled trial in 704 patients suggests the efficacy of goshajinkigan for overactive bladder. Its efficacy for concomitant symptoms and QOL was also suggested. However, there is no mention of the number patients who withdrew, the facility or facilities where this trial was actually conducted, and the method of randomization. Future studies considering these points are awaited.

12. Abstractor and date

Okabe T, 28 November 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**References**

Toba K. Role in host defense mechanisms and effect on prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation. *Taisha (Metabolism and Disease)* 1992; 29 suppl: 350–4 (in Japanese).

Toba K. Role in host defense mechanisms and effect on the prognosis of urinary tract infections in elderly subjects: A trial of a Chinese drug formulation*. *Dai 8 Kai Tokyo Naika Kampo Kenkyukai Koen Naiyo Shu (Proceedings of the 8th Meeting of the Tokyo Society for Internal Kampo Medicine)* 1993; 8: 31–42 (in Japanese).

1. Objectives

To evaluate the efficacy of shosaikoto (小柴胡湯) for improving immunity in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Department of Geriatric Medicine, Faculty of Medicine, University of Tokyo), Japan.

4. Participants

Seventeen outpatients without urinary tract infection and 14 inpatients with urinary tract infection.

5. Intervention

Arm 1: shosaikoto (小柴胡湯) (manufacturer not specified) for at least 3 months, outpatients without urinary tract infection (n=9).

Arm 2: no administration, outpatients without urinary tract infection (n=8).

Arm 3: shosaikoto (小柴胡湯) (manufacturer not specified) for at least 3 months, inpatients with urinary tract infection (n=10).

Arm 4: no administration, inpatients with urinary tract infection (n=4).

6. Main outcome measures

Neutrophil function, lymphocyte function, nutritional index, and infection index.

7. Main results

In arm 1, significant increases from baseline were noted in neutrophil superoxide generation at 1 month post-dose ($P<0.05$), complement at 3 months post-dose ($P<0.01$), [3H]-thymidine incorporation of phytohemagglutinin (PHA)-induced lymphocytes at 3 months post-dose ($P<0.01$), interleukin-2 production ($P<0.05$), serum γ -globulin, IgA ($P<0.01$), and IgG ($P<0.05$). In arm 3, none of the following variables were increased from baseline after shosaikoto administration: neutrophil superoxide generation, complement, [3H]-thymidine incorporation of PHA-induced lymphocytes, interleukin-2 production, and γ -globulin, and the urinary bacterial culture findings were similar before and after shosaikoto administration. In arm 1 and arm 2, none of the nutritional indices (serum total protein, albumin, cholinesterase, total cholesterol) were significantly increased.

8. Conclusions

Shosaikoto partially improves immunity in elderly individuals without urinary tract infection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this study concluded that shosaikoto partially improves immunity in elderly subjects without urinary tract infection but not in those with urinary tract infection. It was also suggested that shosaikoto does not improve nutritional status. As pointed out by the author, inpatients with urinary tract infection have poor nutritional status (i.e., decreased serum albumin), which is unresponsive to shosaikoto treatment. This may be an indication for *hozai* (補劑, formulations with tonic effects) using the *zuisho* (隨証, based on pattern) approach.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Ohkawa T, Ebisuno S, Watanabe T. Urological diseases and Kampo medicine*. *Dai 23 Kai Nihon Igakkai Sokai Sateraito Shinpojiumu Nihon Toyo Igakkai Rinsho Kampo Kenkyukai Koen Naiyo Shu (Proceedings of the Meeting for Clinical Kampo Medicine of the Japan Society for Oriental Medicine, the Satellite Symposium of the 23rd General Assembly of the Japan Medical Congress) 1992: 22–39 (in Japanese).*

1. Objectives

To evaluate the efficacy of choreito (猪苓湯) and choreitogoshimotsuto (猪苓湯合四物湯) for relieving nonspecific lower urinary tract complaints.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital (Department of Urology, Wakayama Medical University), Japan.

4. Participants

Three-hundred and sixty-four patients with nonspecific lower urinary tract complaints.

5. Intervention

Arm 1: choreito (猪苓湯) (manufacturer not specified) for 4 weeks (n=150).

Arm 2: choreitogoshimotsuto (猪苓湯合四物湯) (manufacturer unknown) for 4 weeks (n=152).

Arm 3: placebo for 4 weeks (n=61).

6. Main outcome measures

Incomplete emptying, voiding discomfort, nocturnal urinary frequency, and voiding pain.

7. Main results

The analysis population consisted of 137, 134, and 50 patients in arm 1, arm 2, and arm 3, respectively. Nonspecific complaints were quantified by scoring incomplete emptying and other symptoms. Relief of nonspecific lower urinary tract complaints was significantly greater in arm 1 than in arm 3 ($P<0.02$), significantly greater in arm 2 than in arm 3 ($P<0.05$), but not significantly different between arm 1 and arm 2.

8. Conclusions

Choreito and choreitogoshimotsuto appears to have efficacy for relieving nonspecific lower urinary tract complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Although using sealed envelopes for allocation is likely to have compromised randomization, this clinical trial demonstrated the efficacy of choreito and choreitogoshimotsuto for relieving nonspecific lower urinary tract complaints. Future RCT is expected to apply improved methods of randomized allocation, and statistical processing using more objective variables and a larger control group.

12. Abstractor and date

Okabe T, 28 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Fuse H, Sakamoto M, Iwasaki M, et al. Effect of chorei-to and hachimi-jio-gan on unidentified complaints on urinary tract. *Hinyoki Geka (Japanese Journal of Urological Surgery)* 1995; 8: 603–9 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of choreito (猪苓湯) and hachimijiogan (八味地黄丸) for relieving urinary frequency, voiding pain, and incomplete emptying in patients without organic urinary tract disease.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three other hospitals, Japan.

4. Participants

Twenty-three patients with unidentified urinary tract complaints other than organic urinary tract disease (chronic prostatitis included). The analysis population consisted of 20 patients including 9 with nervous urinary frequency (all in the choreito arm) and 11 (2 with chronic prostatitis and 9 with nervous urinary frequency) in the hachimijiogan arm.

5. Intervention

Efficacy evaluated 4 weeks later by patient's physician based on subjective symptoms.

Arm 1: TSUMURA Choreito (猪苓湯) Extract Granules 2.5 g t.i.d. (n=9).

Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. (n=11).

6. Main outcome measures

Subjective symptoms: daytime urinary frequency, nocturnal urinary frequency, voiding pain, incomplete emptying, and voiding discomfort.

7. Main results

Daytime and nocturnal urinary frequency was significantly decreased from baseline in both arms, but the effect occurred earlier in arm 2 than in arm 1. Also, both treatments tended to improve voiding pain, incomplete emptying, and voiding discomfort. Usefulness was achieved in 88.9% in arm 1 and 100% in arm 2, as judged by the treating physicians.

8. Conclusions

Choreito and hachimijiogan are useful for unidentified urinary tract complaints.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study compared efficacy of two Kampo medicines. Eviprostat (herbal extract product), Cernilton (cernitin pollen extract), Bladderon, Prostal, and Harnal were released in 1967, 1969, 1979, 1981, and 2005, respectively; control drugs seem to have been available as of 1995. In addition, the distribution of underlying diseases is not uniform (i.e., there are 2 cases of chronic prostatitis v.s. 18 cases of nervous urinary frequency).

12. Abstractor and date

Fujisawa M, 14 October 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Aoki Y, Ueda K, Tsutani K, et al. The influence of formula ma-huang-fu-zi-xi-xin-tang (mao-bushi-saishin-to; Mbst) on the results of urodynamic studies. *Journal of Traditional Medicine* 2001;18:203-9. Ichushi Web ID: 2002139756 [CiNii](#)

1. Objectives

To evaluate the effect of single-dose administration of maobushisaishinto (麻黄附子細辛湯) on urine flow.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Urology, Nagoya City University Medical School and associated facilities, Japan.

4. Participants

Thirteen young male volunteers (mean age: 38.0 years) and six elderly male volunteers (mean age: 64.5 years).

5. Intervention

Arm 1: administration of 2 capsules of Kotaro Maobushisaishinto (麻黄附子細辛湯) in the 1st course followed by 2 capsules of placebo in the 2nd course, with 4-week withdrawal between courses.

Arm 2: administration conducted in the reverse order of arm 1.

6. Main outcome measures

Maximum urine flow rate at 3 hr after administration, mean urine flow rate, and voiding efficiency.

7. Main results

Regardless of the order of administration, no significant differences were observed in the maximum urine flow rate at 3 hr after administration, mean urine flow rate, or voiding efficiency between maobushisaishinto - and placebo-groups. There was no significant difference in the maximum urine flow rate, mean urine flow rate, or voiding efficiency between pre- and post-dose levels when treated with maobushisaishinto in the elderly.

8. Conclusions

It is suggested that single-dose administration of maobushisaishinto has no effect on urine flow in both young and old men.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In elderly males with impaired urination due frequently to prostatic hyperplasia, ephedrine-containing formulations such as mao have been shown to aggravate the problem. This study concludes that single-dose administration of maobushisaishinto does not adversely affect urine flow in the elderly. However, since treatment with a Kampo formulation usually requires repeated administration for a certain period, the results of a clinical study with repeated administration will also need to be considered.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Sakamoto Y, Iwasaki M, Kazama T, et al. Study of effects hachimi-jio-gan and chorei-to on prostatic hypertrophy. *Dai 13 Kai Hinyokika Kampo Kenkyukai Koen Shu (Proceedings of the 13th Meeting of the Urological Society for Kampo Medicine)* 1996: 7-14 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hachimijiogan (八味地黄丸) and choreito (猪苓湯) in patients with prostatic hyperplasia.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and three hospitals, Japan.

4. Participants

Fifty-three patients with prostatic hyperplasia who were enrolled from May 1992 to April 1994.

5. Intervention

Arm 1: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules for Prescription 2.5 g t.i.d., for 8 weeks (n= 27 patients, 15 patients analyzed; 12 patients excluded from the analysis, including 2 patients with worsening symptoms).

Arm 2: TSUMURA Choreito (猪苓湯) Extract Granules for Prescription 2.5 g t.i.d., for 8 weeks (n=26 patients, 14 patients analyzed; 12 patients, most of whom failed to return to the hospital, were excluded).

No concomitant use of drugs for urinary disturbance was allowed.

6. Main outcome measures

Subjective symptoms and objective findings before and after treatment.

7. Main results

Significant subjective improvement was observed in six symptoms (delayed urination, prolonged urination, weak urinary stream, feeling of residual urine, and urination within 2 hours) after treatment with hachimijiogan and in two symptoms (prolonged urination and feeling of residual urine) after treatment with choreito. Significant objective improvement was observed in the maximum and mean urinary flow rates after treatment with hachimijiogan ($P<0.01$) and choreito ($P<0.05$).

8. Conclusions

According to the investigators, both drugs are useful in 80% of patients. Even if all of the patients excluded from the analysis were included in the analysis and were unresponsive, the utility rate would be 40%, indicating that both drugs are moderately useful in improving subjective symptoms associated with prostatic hyperplasia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Appetite loss was observed in 1 patient treated with hachimijiogan, and sleepiness and stomach discomfort were observed in 2 patients treated with choreito.

11. Abstractor's comments

According to the "Abstract" and "Discussion", this study evaluated the efficacy of individual Kampo medicines for urinary disturbance in order to determine whether combinations of these drugs with western medications for urinary disturbance (antiandrogenic agents, α -blockers, plant extracts, amino acid preparations, etc.) were useful. Good results were obtained, showing that hachimijiogan and choreito are meaningful concomitant drugs. According to the "Methodology" and "Analytical Methods" sections, patients were randomly assigned to one of two groups. The absence of significant between-group differences was not mentioned in the Abstract or Discussion. Since this was an RCT, a group of patients treated with both drugs should have been included.

12. Abstractor and date

Fujisawa M, 13 October 2008, 6 January 2010, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Horiba M, Kato S, Tanaka T, et al. Clinical validity of gosha-jinki-gan in the treatment of chronic prostatitis - open comparative study with gosha-jinki-gan vs ciprofloxacin -. *Gendai Toyo Igaku (The Journal of Traditional Sino-Japanese Medicine)* 1994; 15: 37-44 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) in the treatment of chronic prostatitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Fifty-eight patients with chronic prostatitis.

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. for 4 weeks (n=15).

Arm 2: ciprofloxacin 200 mg b.i.d. for 4 weeks (n=15).

Arm 3: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 2.5 g t.i.d. + ciprofloxacin 200 mg b.i.d. for 4 weeks (n=14).

Arm 4: serratiopeptidase 10 mg t.i.d. for 4 weeks (n=14).

6. Main outcome measures

Subjective symptoms, prostate palpation findings, and white blood cell (WBC) in expressed prostatic secretion.

7. Main results

The analysis population consisted of a total of 48 patients: 14, 13, 9, and 12 patients in arm 1, arm 2, arm 3, and arm 4, respectively. Subjective symptoms were improved in 60.0%, 54.5%, 68.1%, and 33.3% of patients in arms 1 to 4, respectively, at 2 weeks; and in 80.0%, 66.7%, and 71.4% of patients in arms 1 to 3, respectively, at 4 weeks. Prostate palpation findings were improved in 21.5%, 10.0%, 14.3%, and 20.0% of patients in arms 1 to 4, respectively, at 2 weeks; and in 28.6%, 11.1%, and 44% of patients in arms 1 to 3, respectively, at 4 weeks. Normalization of WBC count in expressed prostatic secretion was noted in 12.5%, 11.1%, 28.6%, and 12.5% of patients in arms 1 to 4, respectively, at 2 weeks; and 30%, 12.5%, and 16.7% in arms 1 to 3, respectively, at 4 weeks. The efficacy rate judged by investigators was 85.7%, 63.6%, 88.8%, and 25% in arms 1 to 4, respectively, showing significantly higher efficacy in arm 1 than in arm 4 ($P<0.05$). As well, higher efficacy was obtained in arm 3 than in arm 4 ($P<0.05$).

8. Conclusions

It was suggested that Goshajinkigan is effective for chronic prostatitis.

9. From Kampo medicine perspective

Mentioned in the discussion section of the reference.

10. Safety assessment in the article

Mild adverse drug reactions were observed in 6 and 1 patient receiving ciprofloxacin and goshajinkigan, respectively, for a total of 7. The reactions were gastrointestinal symptoms, central nervous system symptoms, and allergic symptoms occurring in 3, 3, and 1 patient, respectively. The adverse reaction to goshajinkigan was intraoral inflammation in 1 patient.

11. Abstractor's comments

Although using seal envelopes for allocation is likely to have compromised randomization, this clinical trial demonstrated the efficacy of goshajinkigan for chronic prostatitis. A future randomized controlled trial is expected to be performed and to use an improved method of randomized allocation, statistical analysis of results, more objective variables, and larger sample size.

12. Abstractor and date

Okabe T, 28 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Ishizuka O, Yamanishi T, Gotoh M, et al. LUTS: new evidence – clinical efficacy of Kampo formulations focusing on goshajinkigan - . *Urology View* 2009; 7: 81-41. Ichushi Web ID: 2009114396

1. Objectives

To evaluate the efficacy and safety of goshajinkigan (牛車腎気丸) for relieving lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH) and concomitant overactive bladder (OAB).

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Multiple institutions (urology departments in 5 university hospitals including Shinshu University), Japan.

4. Participants

Eighteen male patients aged under 80 years with BPH, concomitant OAB, and urinary frequency and urgency even after receiving 8-week treatment with tamsulosin hydrochloride.

5. Intervention

Arm 1: tamsulosin hydrochloride 0.2 mg/day + TSUMURA goshajinkigan (牛車腎気丸) Extract Granules 7.5 g/day for 4 weeks, followed by monotherapy with tamsulosin hydrochloride 0.2 mg/day for 4 weeks (n=9).

Arm 2: tamsulosin hydrochloride 0.2 mg/day for 4 weeks, followed by tamsulosin hydrochloride 0.2 mg/day + TSUMURA goshajinkigan (牛車腎気丸) Extract Granules 7.5 g/day for 4 weeks (n=9).

6. Main outcome measures

OAB symptoms (frequencies of daytime urination, nighttime urination, urgency, and incontinence), BPH symptoms (International Prostate Symptom Score [IPSS], postvoid residual urine volume), King's Health Questionnaire (KHQ), and quality of life (QOL) index.

7. Main results

Comparing the combination therapy period and the monotherapy period, there were no significant differences in frequencies of daytime urination, nighttime urination, and urgency ($P=0.225$, $P=0.882$, and $P=0.348$, respectively). The QOL index improved significantly ($P=0.008$) and the frequency of incontinence tended to improve, though not significantly, during the combination therapy period ($P=0.090$). No significant differences were found in IPSS ($P=0.563$), postvoid residual urine volume ($P=0.846$), and KHQ score.

8. Conclusions

The concomitant use of goshajinkigan improves QOL but not urinary urgency in patients who have OAB symptoms after treatment with tamsulosin hydrochloride for BPH.

9. From Kampo medicine perspective

It was mentioned in the “discussion” section.

10. Safety assessment in the article

Gastric distress and diarrhea occurred in one goshajinkigan-treated patient each.

11. Abstractor's comments

This study reports that the concomitant use of goshajinkigan did not improve frequency of urination or urinary urgency, but did improve QOL in patients with BPH who had OAB symptoms after the treatment with tamsulosin hydrochloride, an α 1-receptor blocker. In the practice of Kampo medicine, goshajinkigan is effective for nocturia. Demonstration of the efficacy of this agent requires selection of patients based on differential diagnosis using Kampo medicine-based criteria (*sho* [証, pattern]), such as *kan-netsu* (寒熱, cold and heat) and *kyo-jitsu* (虚実, excess or deficiency), as the authors mentioned in the discussion. Clinical trials with a new design are needed.

12. Abstractor and date

Okabe T, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Hiramatsu M, Maehara I, Takahashi M, et al. Treatment experience with saikokaryukotsuboreito and hochuekkito in male infertility patients*. *Kampo Igaku (Kampo Medicine)* 1993;17: 246–8 (in Japanese).

1. Objectives

To objectively evaluate the positive effect of saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) or hochuekkito (補中益氣湯) monotherapy on sperm profiles of male infertility patients.

2. Design

Randomized controlled trial (RCT).

3. Setting

Four facilities including the Department of Urology, Tohoku University Hospital, Japan.

4. Participants

Twenty-eight patients diagnosed with oligozoospermia (sperm concentration of $<20 \times 10^6/\text{mL}$) or asthenospermia (motility of $<50\%$) at the above facilities between February 1990 and March 1992.

5. Intervention

Arm 1: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蠣湯) Extract Granules 2.5 g t.i.d., before meals for 12 weeks (n=12).

Arm 2: TSUMURA Hochuekkito (補中益氣湯) Extract Granules 2.5 g t.i.d., before meals for 12 weeks (n=16).

6. Main outcome measures

Sperm parameters including sperm concentration, motility, and sperm motile efficiency index (SMEI); and luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and prolactin levels. Global improvement evaluated at baseline and at weeks 4, 8, and 12 of treatment.

7. Main results

Both saikokaryukotsuboreito and hochuekkito significantly increased sperm motility and SMEI at 8 weeks of treatment but had no effect on sperm concentration or hormone levels. However, SMEI returned to baseline level at 12 weeks of treatment with hochuekkito. Saikokaryukotsuboreito and hochuekkito markedly improved sperm concentration (in 41.7% and 18.8% of patients, respectively) and sperm motility (in 41.7% and 50.0% of patients, respectively). Furthermore, 75.0% and 37.5% of patients showed moderate or marked global improvement, respectively.

8. Conclusions

Saikokaryukotsuboreito or hochuekkito monotherapy improves sperm parameters and is effective for male infertility.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

While an effective therapy for male infertility has not yet been established, this study demonstrated the effectiveness (overall efficacy and improved sperm parameters) of Kampo medicines in clinical practice. Particularly, saikokaryukotsuboreito increased sperm concentration to $20 \times 10^6/\text{mL}$ or higher and sperm motility $\geq 30\%$ in more than 40% of patients, increasing the number of candidates for artificial insemination and expectations for spontaneous pregnancy in clinical practice. However, since therapy was not prescribed according to *sho* (証, pattern) and random assignment to an experimental or control drug was not performed, the results of this study do not necessarily reflect true drug efficacy. The mechanism of action of Kampo medicines was not considered, and therefore in a future study protocol, the drug should be prescribed on the basis of *sho* (証, pattern) (*jitsu* [実, excess] or *kyo* [虚, deficiency]), *saiko-sho* (柴胡証), and presence or absence of *jinkyō* (腎虚, kidney deficiency).

12. Abstractor and date

Ushiroyama T, 20 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Kazama T. Male infertility*. *Current Therapy* 1988; 6: 1683–6 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of hochuekkito (補中益気湯) in the treatment of male infertility in comparison with Kallikrein (kallidinogenase).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Urology, Toyama Medical and Pharmaceutical University Hospital, Japan.

4. Participants

Forty-two patients (including ten withdrawals) diagnosed with male infertility (sperm count, 10–40 × 10⁶/mL) at the above facility between January 1987 and January 1988.

5. Intervention

Arm 1: hochuekkito (補中益気湯) (manufacturer, not specified) 2.5 g t.i.d., before meals (n=16).

Arm 2: Carnaculin Capsule (kallinogenase 150 IU) t.i.d., after meals (n=16).

Treatment duration: 12 weeks (up to 36 weeks).

6. Main outcome measures

Sperm profiles including sperm concentration, motile sperm count, and percentage of motile sperm evaluated at baseline and week 12 of treatment. Treatment was considered effective if sperm concentration increased by $\geq 20 \times 10^6$ /mL and motility increased $\geq 20\%$.

7. Main results

Sperm concentration increased in 56.3% of the patients in arm 1 and 25.0% of the patients in arm 2, and motility increased in 25.0% of the patients in arm 1 and 18.8% of the patients in arm 2. In addition, the total count of motile sperm was higher in the hochuekkito group than in the kallidinogenase group, although the between-group difference was not significant.

8. Conclusions

Treatment with hochuekkito confers a favorable outcome without adverse reactions and is therefore useful and indicated for male infertility.

9. From Kampo medicine perspective

Although drug prescription was not based on *sho* (証, pattern) in this study, activities including peripheral vasodilation, lipid metabolism improvement, protein synthesis promotion, and immunostimulation are suggested.

10. Safety assessment in the article

No adverse reactions occurred in both arms.

11. Abstractor's comments

No therapeutic approach to male infertility is currently established. This controlled study comparing hochuekkito with kallidinogenase (a conventional western medicine with reported efficacy for treatment of male infertility) demonstrated that hochuekkito confers a favorable clinical outcome with no adverse reactions. This study suggests that hochuekkito is a viable pharmacotherapeutic option for treating male infertility. However, sperm motility was not necessarily improved in all patients of this study but varied between individuals, indicating the importance of *sho*. Additionally, probably because the study period (12 weeks) was too short, successful pregnancy, a general endpoint of fertility treatment, was not reported, making it impossible to know whether sperm quality was improved enough to ensure pregnancy. It would be interesting to find out the diagnosis (based on the concept of oriental medicine *sho*) of patients responding favorably to hochuekkito and the characteristics of those responding poorly to it. Future studies using a protocol focusing on *sho* are expected to investigate the relationship between improved sperm profile and pregnancy rate in hochuekkito-treated patients, as well as ascertain the true therapeutic effect of hochuekkito on male infertility.

12. Abstractor and date

Ushiroyama T, 20 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Sugimoto K, Shigehara K, Izumi K, et al. Effect of combination of saiko-ka-ryukotsu-borei-to with androgen replacement therapy for LOH syndrome. *Nihon Sei Kino Gakkai Zasshi (Japanese Journal of Sexual Medicine)* 2009; 24: 349–53 (in Japanese). Ichushi Web ID: 2010196632

1. Objectives

To evaluate the efficacy of androgen replacement therapy (ART) combined with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two facilities (Kanazawa University Hospital and Ishikawa Prefectural Central Hospital), Japan.

4. Participants

Thirteen subjects who were diagnosed with LOH syndrome at the above facilities and desired to receive treatment.

5. Intervention

Arm 1: intramuscular testosterone enanthate 250 mg/3–4 weeks + administration of saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) (manufacturer, not specified) 2.5 g t.i.d. immediately before meals for 12 weeks (n=6).

Arm 2: intramuscular testosterone enanthate 250 mg/3–4 weeks for 12 weeks (n=7).

6. Main outcome measures

1) Aging Males Symptoms (AMS) rating scale, 2) Self-rating Depression Scale (SDS), 3) self-rating Internal Index of Erectile Function-5 (IIEF-5), and 4) blood testosterone concentration, evaluated at the start of treatment and after 12 weeks of treatment.

7. Main results

Combination treatment tended to improve AMS, SDS, and IIEF-5 scores compared with ART alone. Decreases in blood total testosterone and free testosterone concentrations were greater after ART alone than after combination treatment.

8. Conclusions

Saikokaryukotsuboreito plus ART for late-onset hypogonadism (LOH) syndrome improves psychiatric and physical symptoms and alleviates ART-induced gonadal function depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood biochemistry identified no serious adverse events.

11. Abstractor's comments

This study focused on the central nervous system depressant activity of saikokaryukotsuboreito as a *saiko-zai* (柴胡劑, saiko formulation) or ryukotsu (竜骨)- and borei (牡蛎)-containing Kampo medicine, and compared the effect of its combination with androgen replacement therapy to that of androgen replacement therapy alone, using major rating scales clinically used to evaluate late-onset hypogonadism (LOH) syndrome. Its attempt to find out the favorable effects of Kampo medicine (when in combination) is worthy of appreciation. This study, however, fails to determine *sho* (証, pattern) of cases with appreciable depression and unidentified complaints, which are common in middle-aged and elderly men, and its finding that saikokaryukotsuboreito is more effective than ART alone for anxiety and depressive symptoms in cases of *ki-tai* (氣滯, qi stagnation) and *hi-ki-kyo* (脾氣虛, spleen qi deficiency) is consistent with conventional clinical wisdom and practice, and is not new. Furthermore, the sample size of 6–7 subjects per group was extremely small. It is hoped that similar studies will be performed with many more “saiko-*sho* (証, pattern)” and “ryukotsuborei- *sho* (証, pattern)” cases, which can be diagnosed by clinicians relatively early and without uncertainty to establish the guidelines for not only combination therapy with ART but also for selecting usage according to *sho* (証, pattern). Evaluation of whether a high percentage of patients with LOH syndrome is indicated for saikokaryukotsuboreito is also expected.

12. Abstractor and date

Ushiroyama T, 15 January 2011, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Inoue M. Kampo treatment for mastitis - kamishoyosan - *. *Kampo Igaku (Kampo Medicine)* 1994; 18: 238–41 (in Japanese).

1. Objectives

To evaluate the efficacy of kamishoyosan (加味逍遙散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and eighty-one patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography.

5. Intervention

Arm 1: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules 2.5 g t.i.d. for 4 weeks (n=169).

Arm 2: TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. for 4 weeks (n=39).

6. Main outcome measures

Patients were classified into *jitsusho* (実証, excess pattern), *chukansho* (中間証, intermediate pattern), or *kyosho* (虚証, deficiency pattern) based on appetite, bowel movements, sensitivity to heat or cold, presence or absence of feeling cold, menstruation, use of hormones, tongue diagnosis, abdominal examination, etc. In patients with each *sho* (証, pattern), efficacy for breast pain, mammary gland swelling, symptoms of mastopathy, was judged from patient complaints.

7. Main results

Kamishoyosan and keishibukuryogan had similar efficacies.

8. Conclusions

Since *kuoketsuzai* (駆才血劑, blood stasis-expelling formulae) such as keishibukuryogan and tokakujokito are indicated for *jitsusho* (実証, excess pattern), kamishoyosan will provide another therapeutic option.

9. From Kampo medicine perspective

Mastopathy is frequently treated with *kuoketsuzai* (駆才血劑, blood stasis-expelling formulae); however, since its symptoms overlap with those of *kanqiukketsu* (肝気鬱結, liver qi depression) including breast pain, kamishoyosan, a saiko-agent (柴胡劑), would also be important.

10. Safety assessment in the article

There were no adverse events.

11. Abstractor's comments

This paper argues that while keishibukuryogan is used for *jitsusho* (実証, excess pattern), formulae for *chukansho* (中間証, intermediate pattern) or *kyosho* (虚証, deficiency pattern) such as kamishoyosan are necessary. This trial is meaningful because it was designed from such a viewpoint. This argument is verifiable, only if patients with *kyosho* (虚証, deficiency pattern) are allocated to and do not respond to treatment with keishibukuryogan (used as control). Regrettably, however, the allocation of patients at a ratio of 3:1 to kamishoyosan and keishibukuryogan in this trial resulted in a keishibukuryogan group without patients with *kyosho* (虚証, deficiency pattern), making it impossible to justify the author's argument. A similar trial demonstrating the usefulness of kamishoyosan in patients with *kyosho* (虚証, deficiency pattern) is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Inoue M. Kampo therapy for mastitis - shigyakusan - *. *Kampo Igaku (Kampo Medicine)* 1990; 14: 132–6.

1. Objectives

To evaluate the efficacy of shigyakusan (四逆散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and twenty patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1988 and June 1989.

5. Intervention

Arm 1: shigyakusan (四逆散) group, TSUMURA Shigyakusan (四逆散) Extract Granules 2.5 g t.i.d. (n=111).

Arm 2: keishibukuryogan (桂枝茯苓丸) group, TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. (n=41).

Patients were allocated to arm 1 and arm 2 at a ratio of 3:1.

Patients with symptoms completely resolved when primary efficacy was evaluated at 4 weeks completed treatment. Patients showing a tendency for improvement were given the same prescription for additional 4 weeks. Patients showing no tendency for improvement underwent fine-needle aspiration biopsy to eliminate the possibility of malignancy, received keishibukuryogan (桂枝茯苓丸) when they were in arm 1 and shigyakusan (四逆散) when they were in arm 2, and underwent a final efficacy evaluation at 8 weeks.

6. Main outcome measures

Patients were classified into *jitsusho* (実証, excess pattern), *chukansho* (中間証, intermediate pattern), or *kyosho* (虚証, deficiency pattern) based on appetite, bowel movements, sensitivity to heat or cold, presence or absence of feeling of cold, menstruation, use of hormones, tongue diagnosis, abdominal examination, etc. In patients with each *sho* (証, pattern), efficacy for breast pain and mammary gland swelling, and symptoms of mastopathy was judged from patient complaints.

7. Main results

There were 68 dropouts. Shigyakusan and keishibukuryogan had similar efficacy.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

Mastopathy is frequently treated with *kuoketsuzai* (驅才血劑, blood stasis-expelling formula); however, since its symptoms overlap with those of *kanqiukketsu* (肝氣鬱結, liver *qi* depression) including breast pain, shigyakusan, a saiko-agent, is important.

10. Safety assessment in the article

There were no adverse events.

11. Abstractor's comments

This study investigated the efficacy of shigyakusan, a different series of Kampo medicines from those of *oketsu* (才血) (blood stasis) treatment including keishibukuryogan, tokakujokito, and tokishakuyakusan. In this trial, keishibukuryogan was used as the control; however, since its efficacy has not been established, the results are quite obscure. If the efficacy of shigyakusan is to be considered a new therapeutic option, as intended by the author, more in-depth discussion of the indications for shigyakusan and keishibukuryogan will be needed. A follow-up report is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Inoue M. Clinical study of effects of tsu-do-san on mastitis. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1993; 43: 517–21 (in Japanese).

1. Objectives

To evaluate the efficacy of tsudosan (通導散) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast Medicine, Japanese Red Cross Medical Center, Japan.

4. Participants

Two-hundred and forty-eight patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1990 and June 1991, and classified into *chukansho* (中間証, intermediate pattern) or *jitsusho* (実証, excess pattern).

5. Intervention

Arm 1: TSUMURA Tsudosan (通導散) Extract Granules 2.5 g t.i.d. for 4 weeks (n=150).

Arm 2: TSUMURA Keishibukuryogan (桂枝茯苓丸群) Extract Granules 2.5 g t.i.d. for 4 weeks (n=33).

Patients were allocated to arm 1 and arm 2 at a ratio of 4:1.

6. Main outcome measures

The measures (disappearance of subjective breast pain and percent disappearance of mammary gland swelling) are not clear, since only exceptionally large reduction in mammary gland swelling was defined as a response.

7. Main results

Sixty-five patients dropped out. There was no difference in the efficacy of tsudosan between the *chukansho* (中間証, intermediate pattern) and *jitsusho* (実証, excess pattern) groups. The statistical significance of the difference in efficacy between tsudosan and keishibukuryogan was not mentioned.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

The historical background of *oketsu* (才血, blood stasis) as an indication was discussed.

10. Safety assessment in the article

Twenty patients (14%) were withdrawn because of diarrhea/abdominal pain.

11. Abstractor's comments

The intention of this study was to investigate the efficacy of tsudosan for mastitis and thereby to provide another therapeutic option, while keishibukuryogan is used for treatment of patients with *jitsusho* (実証, excess pattern). Patients were classified into groups based on criteria (not mentioned) defining *chukansho* (中間証, intermediate pattern: medium build, well-developed breast, slightly weak or strong tone of the abdominal wall, good appetite, normal bowel movements or slight *hiketsu* [秘結, constipation], and normal menstruation), and *jitsusho* (実証, excess pattern: details not mentioned) by one physician. However, with a wide range of diagnostic criteria, the classification remains obscure. It is unclear whether the absence of difference between *chukansho* (中間証, intermediate pattern) and *jitsusho* (実証, excess pattern) groups reflects misclassification or the meaninglessness of the classification system itself. Although this paper demonstrated a response to tsudosan in some patients, it is desirable that the above problems be solved in a future report.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Inoue M. Clinical studies on effects of tokakujoki-to for fibro-cystic disease of the breast. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1992; 42: 415–8 (in Japanese).

1. Objectives

To evaluate the efficacy of tokakujokito (桃核承気湯) in the treatment of mastitis.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Outpatient Department of Breast, Japanese Red Cross Medical Center, Japan.

4. Participants

One-hundred and ninety-six patients diagnosed with mastopathy based on findings of breast imaging, ultrasonography, and mammography between July 1989 and June 1990.

5. Intervention

Arm 1: tokakujokito (桃核承気湯) group, tokakujokito (桃核承気湯) (manufacturer unknown) 2.5 g t.i.d. (n=103).

Arm 2: keishibukuryogan (桂枝茯苓丸群) group, keishibukuryogan (桂枝茯苓丸群) (manufacturer unknown) 2.5 g t.i.d. (n=22)

Patients were allocated to arm 1 and arm 2 at a ratio of 4:1.

Patients whose symptoms were resolved when efficacy was evaluated at 4 weeks were considered to be responders and treatment was ended. Patients showing a tendency for improvement were given the same prescription for an additional 4 weeks and final efficacy was evaluated at 8 weeks. Patients with no therapeutic effect at the time of the primary efficacy evaluation were considered to be non-responders and treatment was stopped.

6. Main outcome measures

The presence or absence of subjective breast pain and mammary gland swelling was used to evaluate efficacy, and therefore the criteria for efficacy are not clear.

7. Main results

There were 71 dropouts. The significance of the difference in efficacy between tokakujokito and keishibukuryogan was not indicated.

8. Conclusions

No definite conclusions were reached.

9. From Kampo medicine perspective

Aspects of the topic “crude drug” are discussed in the discussion section of the reference.

10. Safety assessment in the article

Treatment was stopped in 13 patients (11%) because of diarrhea and abdominal pain.

11. Abstractor’s comments

This paper reported the efficacy of tokakujokito for patients with mastopathy. Tokakujokito and keishibukuryogan had similar efficacy, but the former was associated with a higher incidence of diarrhea, which occurred in nearly half the patients treated. Without knowing the criteria used to select treatment with tokakujokito rather than keishibukuryogan, the intent of the article is obscure. A follow-up report with in-depth discussion on the indications for tokakujokito is awaited.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Oribe K, Nishida Y. Efficacy of hachimijiogan for discomfort after surgery for uterine prolapse. *Gekkan Kampo Ryoho (Monthly Journal of Kampo Medicine and Herbs)* 2006; 10: 282-8 (in Japanese).

1. Objectives

To evaluate the hachimijiogan (八味地黄丸)-induced improvement in postoperative discomfort associated with surgery for uterine prolapse and quality of life (QOL).

2. Design

A randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, National Hospital Organization Oita Medical Center, Japan.

4. Participants

Nineteen patients with uterine prolapse who did not respond to hochuekkito and underwent vaginal radical operation for uterine prolapse at the above facility between December 2005 and March 2006.

5. Intervention

Arm 1: oral administration of TSUMURA Hachimijiogan (八味地黄丸) Extract Granules 2.5 g t.i.d. before meals, n=12.

Arm 2: no treatment, n=7.

6. Main outcome measures

Frequency of urination per day and mean residual urine volume at the start and 1 and 2 weeks after the start of hachimijiogan.

7. Main results

There was no significant difference in urination frequency. Residual urine volume was significantly decreased after hachimijiogan treatment for 1 week (21 ± 2.3 mL vs. 13 ± 4.2 mL, $P < 0.05$) and 2 weeks (12 ± 1.7 mL vs. 8.3 ± 1.5 mL, $P < 0.05$). In addition, 2 weeks of treatment with hachimijiogan decreased residual urine volume more significantly in patients with *shofukufujin* (小腹不仁, soft, weak lower abdomen) than in those without *fukusho* (腹証, abdominal pattern) (8.3 ± 1.5 mL vs. 5.3 ± 2.5 mL, $P < 0.05$).

8. Conclusions

Hachimijiogan administered after surgery for uterine prolapse may accelerate tissue repair postoperatively, thereby improving patient QOL, particularly in patients with *shofukufujin*.

9. From Kampo medicine perspective

Traditionally, hochuekkito has been considered to be the effective treatment for uterine prolapse. However, because of a change in nutritional status, many women do not present conventional “*sho*”, leaving room for reconsideration of the appropriate agent. Hachimijiogan is highly effective for decreasing residual urine volume after surgery for uterine prolapse and aiding recovery of the bladder and surrounding tissues.

10. Safety assessment in the article

No adverse drug reactions occurred after hachimijiogan treatment.

11. Abstractor’s comments

This research raises questions about what Kampo medicine should be or how it should be utilized in an aging society. None of the existing treatments for genitourinary prolapse (including surgery, pessary insertion, and pharmacotherapy) are totally effective, raising concerns among clinicians. This research demonstrated that hachimijiogan is highly effective in decreasing postoperative residual urine volume particularly in patients with *shofukufujin*. Future research is desired to determine whether this clinical approach fusing western and oriental medicines can prevent recurrent uterine prolapse and how Kampo medicine can be used to treat uterine prolapse for *sho* of unclear *jinkyō* (腎虚, kidney deficiency).

12. Abstractor and date

Ushiroyama T. 12 December 2008, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Iwabuchi S. Effect of kyuki-kyogai-to on stopping dysfunctional uterine bleeding – comparison with occidental hemostatic drugs -. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 2000; 50: 883-903 (in Japanese with English abstract). Ichushi Web ID: 2000172969 [CiNii](#)

1. Objectives

To evaluate the efficacy and safety of kyukikyogaito (キユウ婦膠艾湯) for menometrorrhagia.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Obstetric and gynecologic practitioner, Yamagata, Japan.

4. Participants

The analysis population included 183 out of 200 randomized patients with menometrorrhagia.

5. Intervention

Arm 1: administration of 9.0 g of TSUMURA Kyukikyogaito (キユウ婦膠艾湯) Extract Granules for 7 days (n=100). Ninety-three patients were included for analysis.

Arm 2: administration of tranexamic acid (3 tablets of Transamin) and carbazochrome/VK mixture (3 tablets of Ophtharum K) for 7 days (n=100). Ninety patients were included for analysis.

6. Main outcome measures

Number of days from exploratory endometrial curettage to hemostasis.

7. Main results

The time to hemostasis was significantly shorter in arm 1 (4.29±1.54 days) than in arm 2 (5.45 ± 2.13 days). When response was determined by the criterion of ‘hemostasis by day 7’, the response rate was significantly higher (94.6%) in arm 1, compared with 72.2% in arm 2. By *sho* (証, pattern), cases of hypofunction or intermediate function required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of hyperfunction showed no difference in the days to hemostasis between arms. By the appearance of the endometrium on imaging, cases of the proliferative phase or simple hyperplasia required significantly fewer days to hemostasis when receiving kyukikyogaito, whereas cases of stationary phase, atrophic phase and mixed proliferative/secretory phase or secretory phase showed no difference in the days to hemostasis between arms.

8. Conclusions

Kyukikyogaito is more effective for hemostasis in menometrorrhagia, compared with hemostatic drugs tranexamic acid and carbazochrome/VK mixture.

9. From Kampo medicine perspective

After, but not before, dosing, differential diagnosis of *sho* was made visually and by abdominal palpation, and it was concluded that kyukikyogaito is effective regardless of *sho*.

10. Safety assessment in the article

A 32-year-old patient complained of feeling bad after receiving 1 sachet of kyukikyogaito, and of stomach discomfort and nausea after receiving 2 sachets, and then discontinued the medicine after receiving 4 sachets and was switched to another drug.

11. Abstractor’s comments

Various pathogenic mechanisms can cause menometrorrhagia in Kampo medicine, as in western medicine. Kyukikyogaito is a combination of a single medicine that acts on one of these mechanisms, called *shoninkyoson* (衝任虚損), and a hemostatic drug (In: *Jinguiyaolue* [金匱要略, *Synopsis of Prescriptions of the Golden Chamber*]). Presence of both responders and non-responders to this combination suggests that the disease has a more than one pathogenesis. Although this study is a quasi-randomized controlled trial, in which patients were alternately randomized and placed in the order of visitation, a certain efficacy of kyukikyogaito for menometrorrhagia is suggested.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Kotani N, Oyama T, Sakai I, et al. Analgesic effect of an herbal medicine for treatment of primary dysmenorrhea - a double-blind study. *The American Journal of Chinese Medicine* 1997; 25: 205-12. CENTRAL ID: CN-00143317, Pubmed ID: 9288368

1. Objectives

To evaluate the efficacy of tokishakuyakusan (当帰芍薬散) on dysmenorrhea.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Not indicated (the authors were affiliated with the Department of Anesthesiology, Hirosaki University School of Medicine), Japan.

4. Participants

Forty females suffering from dysmenorrhea for at least 1 year, with all *kikyo* (気虚, *qi deficiency*), *in* (陰, *yin*), and *oketsu* (瘀血, static blood) scores of 30 or more, without orthopedic disorders, and not receiving oral low-dose medications or prescribed anxiolytics.

5. Intervention

The study covered a total of 6 menstrual cycles (half a year): 2 cycles for baseline observation, followed by two cycles for treatment and then two cycles for follow-up observation.

Arm 1: oral administration of tokishakuyakusan (当帰芍薬散) (manufacturer unknown) 2.5 g t.i.d. (during the third to fourth menstrual cycles in the treatment period) (n=20).

Arm 2: oral administration of placebo (during the third to fourth menstrual cycles in the treatment period) (n=20).

6. Main outcome measures

Pain assessed on a visual analogue scale (VAS) and use of diclofenac sodium (Voltaren).

7. Main results

Dysmenorrhea was significantly improved in patients receiving tokishakuyakusan ($P < 0.001$).

8. Conclusions

Adding Kampo indices *kikyo*, *in*, and *oketsu* to the diagnostic criteria enables selection of patients indicated for tokishakuyakusan, who can benefit from its analgesic effect.

9. From Kampo medicine perspective

Although the usefulness of each score is mentioned, it is not discussed from a Kampo medicine perspective.

10. Safety assessment in the article

No adverse events occurred.

11. Abstractor's comments

This study can be recognized as an attempt to define the indications for tokishakuyakusan using the Kampo diagnostic system (i.e., rating *kikyo*, *in*, and *oketsu* in patients with dysmenorrhea. While it is important to reduce the use of analgesics through pain relief, continued studies are expected on, for example, whether tokishakuyakusan is also effective for patients not responding to analgesics and how patients indicated for tokishakuyakusan differ from those indicated for keishibukuryogan (桂枝茯苓丸) or shakuyakukanzoto (芍薬甘草湯).

12. Abstractor and date

Nakata H, 1 January 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Tanaka E, Saito H, Hiroi M. Kampo treatment for nonspecific complaints in climacteric women - comparison of clinical efficacy of Kampo medicine alone versus Kampo medicine combined with tofisopam - *. *Kampo Shinryo* 1997; 16: 22-4 (in Japanese).

1. Objectives

To compare the clinical effects of keishibukuryogan (桂枝茯苓丸) monotherapy with combined therapy (keishibukuryogan plus autonomic modulator).

2. Design

Randomized controlled trial (RCT).

3. Setting

The Department of Obstetrics and Gynecology, Oguni Municipal Hospital, Japan.

4. Participants

Forty-three women who visited the above institution with climacteric complaints between April 1994 and September 1995.

5. Intervention

Arm 1: oral administration of Tsumura Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals (n=21).

Arm 2: oral administration of Tsumura Keishibukuryogan (桂枝茯苓丸) Extract Granules 2.5 g t.i.d. before meals and tofisopam 50 mg t.i.d. after meals (n=22).

6. Main outcome measures

Assessment of severity based on simplified menopausal index (SMI). Clinical efficacy evaluated according to the post-treatment SMI score: marked response (25 or less), moderate response (reduction of 35 or greater compared with the pretreatment score, even if the score was over 25), and slight response (reduction of 6–34). Time to onset of the clinical effect assessed on a three-point scale: within 1 week, 2 weeks, and 4 weeks after the initiation of the treatment.

7. Main results

The percentage of patients achieving marked responses was similar between arms (33.3% of arm 1 vs. 28.6% of arm 2), and the percentage achieving moderate responses was also similar between arms (40.9% vs. 36.4%, respectively). The clinical effect was observed within 1 week after the start of treatment in 14.3% patients in arm 1 and 36.4% in arm 2, and within 2 weeks in 33.3% and 40.9%, respectively (no significance test was reported).

8. Conclusions

Addition of tofisopam to keishibukuryogan for the treatment of nonspecific climacteric symptoms accelerated the onset of the clinical effect. Clinical benefits of the combination therapy are suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Two patients in arm 2 experienced sleepiness.

11. Abstractor's comments

In climacteric patients with undefined complaints, the combined therapy accelerates the onset of the effect, as compared with keishibukuryogan monotherapy. This conclusion may lead to improvement in the treatment of climacteric women. However, *sho* (証, pattern), which is the most important aspect of the Kampo medicine, was not considered in patient selection. The data therefore give a strong impression that tofisopam itself was effective for nonspecific climacteric symptoms. That is to say, a randomized controlled trial including patients whose *sho* is appropriate for keishibukuryogan could determine the true effect of keishibukuryogan monotherapy vs. keishibukuryogan combined with autonomic agents. In this study, 60% of patients treated with keishibukuryogan experienced at least a moderate response, and about half of patients became aware of improvement in symptoms within 2 weeks, even they were diagnosed with “climacteric complaints” not based on *shisin* (四診, four examinations) nor *sho*. Moreover, the combined therapy showed enhanced clinical efficacy. These results might be of benefit to clinical practice.

12. Abstractor and date

Ushiroyama T, 27 August 2008, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**References**

Samukawa K, Ogita S. Climacteric disorders and medicinal ginseng*. *Chiryogaku (Biomedicine & Therapeutics)* 1994; 28: 57–62 (in Japanese).

1. Objectives

To evaluate the clinical effect of kojimatsu (紅参末), tokishakuyakusan (当帰薬芍散), and their combination on climacteric disorders.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One facility (the Department of Obstetrics and Gynecology, Osaka City University Hospital), Japan.

4. Participants

One-hundred and thirteen patients diagnosed with climacteric disorders and 124 postmenopausal women with unidentified complaints but not yet seen by a physician.

5. Intervention

Study 1: therapeutic effects on climacteric disorders

Arm 1: CHEONG-KWAN-JANG Kojimatsu (正官庄紅参末) 6 g/day (divided doses and time of administration not indicated) for 4 weeks (n=83).

Arm 2: KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) for 4 weeks (n=30).

Arm 3: CHEONG-KWAN-JANG Kojimatsu (正官庄紅参末) 6 g/day + KOTARO Tokishakuyakusan (当帰薬芍散) Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=61).

Study 2: preventive effects on those who are likely to visit a hospital for climacteric disorders in future.

Arm 1: CHEONG-KWAN-JANG Kojimatsu (正官庄紅参末) 3 g/day (divided doses and time of administration not indicated) (n=36).

Arm 2: CHEONG-KWAN-JANG Kojimatsu (正官庄紅参末) 6 g/day (divided doses and time of administration not indicated) (n=20).

Arm 3: KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=34).

Arm 4: CHEONG-KWAN-JANG Kojimatsu (正官庄紅参末) 3 g/day + KOTARO Tokishakuyakusan (当帰薬芍散) ryo Extract Granules 9 g/day (divided doses and time of administration not indicated) (n=34).

6. Main outcome measures

Improvement in clinical symptoms (decrease in Kupperman's index): marked improvement (80% or more decrease); moderate improvement (60–80% decrease); slight improvement (30–60% decrease); and no improvement (30% or less decrease). The evaluation in study 1 and study 2 was at 4 weeks and 8 weeks of treatment, respectively.

7. Main results

Study 1: Marked improvement occurred in a higher percentage of patients receiving kojimatsu alone (18.1%) or kojimatsu + tokishakuyakusan (19.7%) than in those receiving tokishakuyakusan alone (10.0%) ($P<0.05$). Moderate improvement occurred in a higher percentage of patients receiving the combination (47.5%) than in those receiving either tokishakuyakusan or kojimatsu alone (33.3% and 28.9%, respectively) ($P<0.01$).

Study 2: Kojimatsu alone tended to have a higher efficacy rate at 3 g/day than 6 g/day. Marked improvement occurred in considerably more subjects receiving the combination (32.4%) than in those receiving kojimatsu 6 g/day alone (5.0%), although there was no significant difference due to the small sample size.

8. Conclusions

Kojimatsu may improve the symptoms of climacteric disorders, and even more so when combined with tokishakuyakusan.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study concludes that the effect of kojimatsu on climacteric disorders in postmenopausal women is both therapeutic and preventive, widening the clinical application of Kampo formulations. However, it does not mention whether subjects with unidentified complaints had *qikyo* (氣虚, qi deficiency), which needs kojimatsu, and how much they had *oketsu* (才血, blood stasis), *kekkyo* (血虚, blood deficiency), or *suidoku* (水毒, water toxin), which needs tokishakuyakusan combination. In-depth studies taking into account Kampo concepts of pathogenesis are desired in future.

12. Abstractor and date

Ushiyama T, 27 August 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Ota H. Positioning of Kampo therapy and hormone replacement therapy in treatment of climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2001; 18: 21-9 (in Japanese). Ichushi Web ID: 2002170744

1. Objectives

To compare hormone replacement therapy (HRT) and Kampo therapy as treatment of climacteric disorders.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. The author belonged to the Department of Obstetrics and Gynecology, Tokyo Women's Medical University, Japan.

4. Participants

Ninety-six postmenopausal or ovariectomized patients with climacteric disorders.

5. Intervention

Arm 1: Kampo therapy (keishibukuryogan (桂枝茯苓丸), n=19; kamishoyosan (加味逍遙散), n=11; goshajinkigan (牛車腎氣丸), n=8; tokishakuyakusan (当帰芍薬散), n=2; tokakujokito (桃核承気湯), n=2; kihito (帰脾湯), n=2; nyoshinsan (女神散), n=2) (n=46).

Arm 2: HRT (0.625 mg of conjugated estrogen and 2.5 or 5 mg of medroxyprogesterone acetate) (n=50).

No details indicated in the original paper.

6. Main outcome measures

Score on Keio modified menopause index, measured at baseline, 1, 6, and 12 months after the start of administration. Severity was defined as mild for 0–10 points, moderate for 10–20 points, and severe for 20–30 points, and response was defined as a change from severe to moderate, moderate to mild, or a score reduction by two-thirds in mild cases.

7. Main results

HRT improved the following 6 symptoms in 1 month: vasomotor manifestations; nervousness; low back and back pain; depression; insomnia; and headache. In contrast, Kampo therapy did not improve any symptoms in 1 month but improved the following 4 symptoms in 6 months: vasomotor manifestations; malaise; low back and back pain; and nervousness. Among Kampo medicines, only goshajinkigan was effective for low back and back pain.

8. Conclusions

The therapeutic effect of HRT is superior for hot flashes, perspiration, depression, and insomnia, whereas that of Kampo therapy is superior for malaise and chill.

9. From Kampo medicine perspective

The number of patients receiving keishibukuryogan (n=19), kamishoyosan (n=11), or tokishakuyakusan (n=2) was explained by the small number of cases with *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper outlines the characteristics of Kampo medicines and HRT. It recommends that Kampo medicine be administered in more responsive cases with specific symptoms. Subsequent publication of a study of individual Kampo medicines with more sensitive design is awaited.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

References

Takamatsu K, Musha C, Okano H, et al. Study of usefulness of Kampo therapy for climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2002; 19: 111-6 (in Japanese) Ichushi Web ID: 2002193391

Takamatsu K. HRT and Kampo medicine*. *Nippon Konenki Igakukai Zasshi (The Journal of the Japan Menopause Society)* 2004; 12: 155-7 (in Japanese)

Takamatsu K, Makita K, Tanabe K, et al. HRT and Kampo medicine*. *Rinsho Kensa (The Journal of Medical Technology)* 2004; 48: 877-84 (in Japanese)

Takamatsu K, Tanabe K. Efficacy of Kampo medicine against climacteric disorders*. *Sanfujinka Chiryō (Obstetrical and Gynecological Therapy)* 2004; 89: 408-15 (in Japanese). [MOL](#), [MOL-Lib](#)

Takamatsu K. Study of the usefulness of Kampo therapy for climacteric disorders – a randomized trial of three major Kampo medicines for treatment of gynecological disease*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2006; 23: 35-42 (in Japanese). Ichushi Web ID: 2006288782

1. Objectives

To compare the efficacy of Kampo therapy with that of hormone replacement therapy (HRT) for climacteric disorders and to compare the efficacy of three non-*sho*-based (非随証) Kampo medicines for gynecological disease.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Departments of Obstetrics and Gynecology, Tokyo Women's Medical University (1) and Keio University Hospital (2), Japan.

4. Participants

(1) Seventy women receiving ambulatory treatment for climacteric disorders between November 2000 and January 2002.

(2) One hundred women receiving ambulatory treatment for climacteric disorders between January 1993 and December 2000.

5. Intervention

Comparison of clinical efficacy of HRT and Kampo medicine

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules, TSUMURA Kamishoyosan (加味逍遙散) Extract Granules or TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=70).

Arm 2: continuous coadministration of 0.625 mg t.i.d. of Premarin (conjugated equine estrogen) and 2.5 mg of Provera (medroxyprogesterone acetate) before meals for 4–8 weeks (n=110).

Evaluation of the efficacy of non-*sho*-based therapy with three major Kampo medicines for gynecological disease.

Arm 1: administration of 2.5 g t.i.d. of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules before meals for 4–8 weeks (n=23).

Arm 2: administration of 2.5 g t.i.d. of TSUMURA Kamishoyosan (加味逍遙散) Extract Granules before meals for 4–8 weeks (n=23).

Arm 3: administration of 2.5 g t.i.d. of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules before meals for 4–8 weeks (n=24).

6. Main outcome measures

Presence/absence and improvement of symptoms self-evaluated on a 4-point symptom severity scale using the Keio modified menopause index questionnaire.

7. Main results

Overall response rates for HRT and Kampo therapy were comparable (78.0% responders to HRT and 68.6% responders to Kampo therapy), although improvement was greater in patients receiving Kampo therapy (severity reduced by 2 or more points in 83.0% of patients receiving HRT and 21.4% of those receiving Kampo therapy). There was no difference in the percent who responded to the three non-*sho*-based therapies (65.2% were responders to tokishakuyakusan, 74.0% were responders to kamishoyosan, and 70.8% responders to keishibukuryogan). Kampo therapy was particularly effective for psychiatric manifestations including excitability, depression, irritation, anxiety, and brooding.

8. Conclusions

Using the same questionnaire, this study demonstrated that Kampo therapy has some effect on climacteric disorders, in particular, relieving subjective symptoms at almost the same rate as HRT and showing high efficacy against psychotic manifestations.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In this paper, the rate of symptom improvement after Kampo therapy was approx. one-quarter that after HRT and the three Kampo medicines had comparable efficacy, showing that non-*sho*-based Kampo therapy for "climacteric disorders" is limited. Thus, this study is valuable in that it supports the importance of the *zuisho* (随証, based on pattern) approach to Kampo therapy in the treatment of climacteric disorders.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 20 December 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**References**

Ogita Y, Fujimoto S, Ushiroyama T, et al. Efficacy of formulation TK-061 for various climacteric symptoms – comparison with Teikoku Keishibukuryogan Extract Granules*. *Rinsho Fujinka Sanka (Clinical Gynecology and Obstetrics)* 2002; 56: 799-810 (in Japanese). Ichushi Web ID: 2003004448

Ogita Y, Fujimoto S, Ushiroyama T, et al. Keishibukuryogan formulation TK-061 prepared with crude drug – verification of efficacy for various climacteric symptoms*. *Sanka to Fujinka (Obstetrics and Gynecology)* 2002; 69: 953-62 (in Japanese). Ichushi Web ID: 2003004359 [MOL](#), [MOL-Lib](#)

1. Objectives

To investigate the equivalence between non-extracted keishibukuryogan (桂枝茯苓丸) and keishibukuryogan (桂枝茯苓丸) extract.

2. Design

Randomized controlled trial (RCT).

3. Setting

Twenty facilities (the Department of Obstetrics and Gynecology, Osaka City University School of Medicine, the Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, the Department of Obstetrics and Gynecology, Osaka Medical College School of Medicine, et al.), Japan.

4. Participants

One-hundred and ninety-three patients who were diagnosed with climacteric disorders during a 1 year and 5 month period from November 1999 to March 2001, untreated with hormone replacement therapy within 4 weeks before the start of the study, and having body mass index (BMI) ≥ 20 and body fat $< 35\%$. (The per-protocol population included 158 out of these 193 patients).

5. Intervention

Arm 1: oral administration of 6 keishibukuryogan (桂枝茯苓丸) pills containing 5 ingredients (TK-061) t.i.d. (18 tablets/day), n=75.

Arm 2: oral administration of 2.5 g of TEIKOKU Keishibukuryogan (桂枝茯苓丸) Extract Granules (TKK-25) t.i.d. (7.5 g/day), n=83.

6. Main outcome measures

Simple Menopause Index (SMI) improvement rated on a 5-point scale; improvement in blood stasis score; changes in blood hormone concentrations; adverse events.

7. Main results

Response rate to TK-061 and TKK-25 were similar (55.8% vs 51.0%, respectively). Blood stasis score was decreased with time after the start of treatment to similarly reduced levels for both arms at week 8. Blood concentrations of estradiole (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) remained unchanged from baseline. The incidences of adverse drug reactions were similar: 22.4% with TK-061 and 23.2% with TKK-25. These adverse drug reactions disappeared naturally or were relieved by symptomatic therapy, suggesting that a causal relationship with treatment cannot be ruled out.

8. Conclusions

TK-061 is equivalent or superior to TKK-255 in increasing the SMI improvement rating, the primary endpoint. Both increase blood stasis score to a similar extent. In addition, neither affects the endocrine system.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events occurred in 22 patients receiving keishibukuryogan pills (22.4%) and 23 patients receiving keishibukuryogan extract granules (23.2%). No serious adverse events occurred. Adverse drug reactions occurred in 12 patients (12.2%) and 9 patients (9.1%), respectively. The global safety was “satisfactory” in 79 patients (80.6%) and 88 patients (88.9%), respectively.

11. Abstractor’s comments

This paper describes a clinical trial comparing keishibukuryogan pills to its extracted formulation, and demonstrates the efficacy of both for climacteric symptoms. Regrettably, however, *ganzai* (丸剂, pills), which proved more effective than the extract in the per-protocol population, is not on the NHI Drug Price list. For the moment, keishibukuryogan pill is only available as an OTC drug.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. *Clinical Neuropharmacology* 2004; 27: 157-62. CENTRAL ID: CN-00490860, Pubmed ID: 15319700

1. Objectives

To evaluate the efficacy of unkeito unkeito (温経湯) for climacteric disorders with depressive symptoms.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One university hospital and one clinic, Japan.

4. Participants

Twenty-four women with climacteric disorders with depressive symptoms and unresponsive to hormone replacement therapy (HRT).

5. Intervention

Arm 1: administration of 7.5 g/day of TSUMURA Unkeito (温経湯) Extract Granules for 6 months followed by administration of 7.5 g/day of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules for 6 months, with 1-month washout between interventions (n=12).

Arm 2: administration of 7.5 g/day of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules for 6 months followed by administration of 7.5 g/day of TSUMURA Unkeito (温経湯) Extract Granules for 6 months, with 1-month washout between interventions (n=12).

HRT was continued in both arms.

6. Main outcome measures

Zung's Self-Rating Depression Scale (ZSDS), State-Trait Anxiety Inventory (STAI-1, 2).

7. Main results

Administration of unkeito produced significant improvement in ZSDS and STAI-1, 2 at 3 months, which persisted to 6 months. The improvement in ZSDS and STAI-1, 2 was significantly greater after unkeito than tokishakuyakusan at both 3 months and 6 months.

8. Conclusions

Unkeito is effective as an adjuvant therapy for climacteric disorders with depressive symptoms in patients unresponsive to HRT, and has superior efficacy to that of tokishakuyakusan.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

This study is a randomized cross-over trial of unkeito and tokishakuyakusan. It suggests that the mechanism of efficacy is the promotion of secretion of cytokine-induced neutrophil chemoattractant (CINC).

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**References**

Higuchi T, Tarakida A, Abe K, et al. Comparing the effects of hormone replacement therapy and kamishoyosan treatment on climacteric disorders*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2009; 26: 18-23. Ichushi Web ID: 2009197632

Higuchi T, Iino K, Tarakida A, et al. A comparing the effects of kamishoyosan or HRT on climacteric disorders in postmenopausal women: results from a randomized controlled trial. *Nihon Josei Igaku Gakkai Zasshi (The Journal of Japan Society for Menopause and Women's Health)* 2012; 20: 305-12 (in Japanese).

1. Objectives

To evaluate effects of hormone replacement therapy (HRT) alone and in combination with kamishoyosan (加味逍遙散) on climacteric disorders.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Study Group for Treatment of Menopausal Unidentified Complaints, Hirosaki University Hospital and twenty other centers, Japan.

4. Participants

One hundred and three patients who were diagnosed with climacteric disorders at the above-mentioned institutions and sought treatment.

5. Intervention

Arm 1: KSS group: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules 2.5 g t.i.d. orally before meals for 8 weeks (n=35).

Arm 2: HRT group: conjugated estrogen formulations or 17β-estradiol patch for 8 weeks (in patients with uterine preservation, medroxyprogesterone acetate was concomitantly administered) (n=34).

Arm 3: Arm 1 + Arm 2 (KSS/HRT group; n=34)

6. Main outcome measures

Changes in climacteric symptom rating scale developed by the Japan Society of Obstetrics and Gynecology (JSOG), at 4 and 8 weeks of treatment from baseline.

7. Main results

Since six participants dropped out of arm 1, 10 from arm 2, and five from arm 3, the efficacy analysis set consisted of a total of 82 patients. 'Dizziness' improved significantly ($P<0.05$) at Week 4 in arm 1 compared to arm 2. The rate of improvement for 'burning sensation in the head and upper body' was significantly higher ($P<0.05$) in arm 2 than in arm 1 and the rate for 'proneness to sweating' was significantly higher ($P<0.01$) in the HRT group than the KSS and the KSS/HRT groups. The KSS/HRT group demonstrated a significantly higher rate of improvement ($P<0.05$) than the KSS and HRT groups for nocturnal waking and tightness in the chest.

8. Conclusions

As therapies for climacteric disorder, HRT and kamishoyosan demonstrate differing effects for different symptoms. Given the choices for their application and combined use, it would seem that asking patients about the details of their symptoms and carefully analyzing them would be beneficial.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study compared the effects of kamishoyosan, the widely used conventional treatment for female climacteric disorder, and HRT, the standard therapy in Western medicine, and made certain evaluations. As speculated, the study reconfirmed that the effects of these therapies differ for different symptoms. That is, HRT demonstrates greater efficacy for vasomotor nerve disturbance symptoms, as diagnosed by Western medicine. Meanwhile, Kampo medical theory can explain the effects of kamishoyosan for hot flashes, palpitations, burning sensation, sweating in the upper body, and other symptoms. If possible, the authors should make their conclusions after using this study's protocols for comparison of kamishoyosan-pattern and non-kamishoyosan-pattern (非証) participants through rigorous pattern identification. My hope is that guidelines are formulated for appropriate usage with HRT according to Oriental medical principles and on the basis of diagnosis of the absence or presence of saiko-pattern or blood stasis, which would be relatively straightforward for a clinical physician. In terms of future practice, I also hope that the researchers take on the challenge of building the evidence base for proposing the incorporation of kamishoyosan into standard therapy in Japan for climacteric disorder.

12. Abstractor and date

Ushiroyama T, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Plotnikoff GA, Watanabe K, Torkelson C, et al. The TU-025 Keishibukuryogan clinical trial for hot flash management in postmenopausal women: result and lessons for future research. *Menopause* 2011; 18: 886–92. CENTRAL ID: CN-00810843, Pubmed ID: 21738077

1. Objectives

To evaluate the clinical effects of keishibukuryogan (桂枝茯苓丸) for hot flashes in menopausal American women.

2. Design

Randomized controlled trial (RCT).

3. Setting

Allina Center for Health Care Innovation (Minneapolis, MN, USA).

4. Participants

Participants were menopausal American women between 45 and 58 years with a hot flash score of at least 28 points/week (n=178).

5. Intervention

Arm 1: oral administration of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (12.5 g/day) for 12 weeks (n=57).

Arm 2: oral administration of TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (7.5 g/day) for 12 weeks (n=62).

Arm 3: oral administration of placebo for 12 weeks (n=59).

6. Main outcome measures

The Greene Climacteric Index (GCI), Pittsburgh Sleep Quality Index (PSQI), and a hot flash scale score.

7. Main results

The hot flash scale score decreased significantly ($P<0.001$) in all groups 12 weeks after commencement of the study, however no significant difference was observed among the three groups. Similarly, no significant among-group difference was observed in the Greene Climacteric Index (GCI) or the Pittsburgh Sleep Quality Index (PSQI).

8. Conclusions

There is no difference between the effects of keishibukuryogan and placebo on overall climacteric disorder symptoms and sleep quality in American menopausal women.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The incidence of diarrhea was 1.7% in the placebo group, but approximately 20% in the keishibukuryogan groups.

11. Abstractor's comments

This study tested the effects of keishibukuryogan on climacteric disorder, a traditional therapy used in Japan, with the researchers asking menopausal American women to score their symptoms, chiefly hot flashes. keishibukuryogan has been one of the main therapeutic Kampo medicines used for climacteric disorder; it is the subject of many academic articles, and its clinical effects have been reported from a variety of perspectives. The present study found that keishibukuryogan extract preparation, compared to placebo, did not improve outcome in American women. However, keishibukuryogan is not necessarily the first choice for symptoms such as hot flashes, which frequently occur in estrogen-deficiency and climacteric disorder. This study might have demonstrated the superiority of estrogen preparations, which are chiefly Western drugs. However, the study did compare keishibukuryogan's effects on menopausal women whose hot flash score exceeded a certain number and its results do not appear to negate the use of keishibukuryogan in therapy for menopausal women, who suffer a variety of unspecified complaints (especially *oketsu* [瘀血, blood stasis] conditions). The authors say they hang their hopes on the emergence of more effective trial methods to test the effectiveness of traditional therapies such as Kampo. One hopes that the development of such research will revolve around RCTs that compare groups according to objective data based on *sho* (証, pattern).

12. Abstractor and date

Ushiroyama T, 31 December 2012.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Yasui T, Matsui S, Yamamoto S, et al. Effects of Japanese traditional medicines on circulating cytokine levels in women with hot flashes. *Menopause* 2011; 18: 85–92. CENTRAL ID: CN-00787935, Pubmed ID: 20647958

1. Objectives

To evaluate the effects of keishibukuryogan (桂枝茯苓丸) and kamishoyosan (加味逍遙散) on levels of circulating cytokines in patients with hot flashes.

2. Design

Quasi-randomized controlled trial (Quasi-RCT).

3. Setting

Outpatients Clinic, Department of Obstetrics and Gynecology, Tokushima University Hospital, Japan.

4. Participants

One hundred twenty women with vasomotor symptoms (hot flashes, night sweats, etc.) but no use of drugs affecting the immune system within the previous year, including 17 women who received bilateral ovariectomy within the previous year and 103 perimenopausal women who were menstruating regularly (n=7), menstruating irregularly within the previous 12 months (n=51), and no longer menstruating (last menses within the previous year; n=45).

5. Intervention

Participants who wanted to receive treatment were allocated to arm 2 (odd-number days) or arm 3 (even-number days). Participants who did not want treatment were allocated to arm 1.

Arm 1: follow up only, no treatment (n=40).

Arm 2: TSUMURA Keishibukuryogan Extract Granules (2.5 g t.i.d) for 6 months (n=40).

Arm 3: TSUMURA Kamishoyosan Extract Granules (2.5 g t.i.d) for 6 months (n=40).

6. Main outcome measures

Hot flash symptoms (severe, moderate, or mild according to FDA hot flash assessment criteria); circulating levels of IL-1 β , IL-5, IL-6, IL-7, IL-8, IL-10, TNF- α , MCP-1, and MIP-1 β before and 6 months after administration.

7. Main results

Improvement rates in hot flashes were significantly higher in arm 2 and arm 3 compared to arm 1 ($P<0.01$). Comparisons before and after treatment in the hot flash improvement group showed that MCP-1, IL-8, and MIP-1 β decreased significantly in arm 2 ($P<0.05$ for both), while IL-6, IL-8, and MIP-1 β decreased significantly in arm 3 ($P<0.05$ for both).

8. Conclusions

Keishibukuryogan and Kamishoyosan improve hot flashes by lowering circulating levels of IL-8 and MCP-1, which are indicators of blood vessel inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This article describes the therapeutic value and mechanism of action of keishibukuryogan and kamishoyosan in menopausal hot flashes. Animal research has shown that keishibukuryogan is effective for peripheral hot flashes mediated by calcitonin gene-related peptide, and kamishoyosan is effective for central hot flashes mediated by luteinizing hormone-releasing hormone; therefore, it may be possible to clarify the differences between keishibukuryogan and kamishoyosan by allocating participants according to their *sho* (証, pattern), using a medical questionnaire or the like. The outcomes of further research are anticipated.

12. Abstractor and date

Nakata H, 31 December 2012

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Takamatsu K, Fujii E, Mizuno H, et al. An investigation of the usefulness of nyoshinsan for climacteric disorder*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2003; 20: 95-100 (in Japanese).

1. Objectives

To verify the efficacy of nyoshinsan (女神散) for female climacteric disorder.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: Tokyo Women's Medical University Hospital, Japan.

4. Participants

Eighty-eight post-menopausal women referred to a menopausal outpatient clinic for climacteric disorder between November 2000 and January 2002.

5. Intervention

Arm 1: TJ-67 group: TSUMURA Nyoshinsan (女神散) Extract Granules (2.5 g t.i.d.) taken before meals (n=18).

Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=23).

Arm 3: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=23).

Arm 4: TSUMURA Keishibukuryogan (桂枝茯苓丸) Extract Granules (2.5 g t.i.d.) taken orally before meals (n=24).

The administration period was 4–8 weeks, depending on the patient.

6. Main outcome measures

Objective evaluation of symptom changes and their details.

(Keio menopausal index questionnaire, Self-rating Depression Scale [SDS] questionnaire).

7. Main results

There was no significant difference in the overall results for climacteric disorder between arm 1 and arms 2 to 4 collectively, and between each arm. The effect on the psychiatric symptoms of nocturnal awakening and depression appeared to be strong in arm 1. The effect on symptoms least affected by treatment was about the same in arm 1 and in arms 2 to 4. 'Palpitations', the symptom most responsive to treatment in arms 2 to 4, was significantly less responsive to treatment in arm 1, while comparison with each formulation showed a significant difference to arm 2 and to arm 3. The raw SDS scores changed significantly in response to treatment in arms 2 to 4 collectively and also to arm 4 individually ($P<0.05$), but not in response to treatment in arm 1. Among the patients in arm 1 with a BMI of 18.5–23, nyoshinsan had a significantly greater effect on those with higher BMI ($P<0.01$).

8. Conclusions

Nyoshinsan and the three major conventional Kampo medications for women (tokishakuyakusan, kamishoyosan, and keishibukuryogan) have similar effects on female climacteric disorder. Therefore proactive inclusion of nyoshinsan into treatment options is recommended.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no potentially problematic adverse effects.

11. Abstractor's comments

This study investigated and compared the effects of nyoshinsan for treatment of female climacteric disorder with those of tokishakuyakusan, kamishoyosan, and keishibukuryogan, which are considered the three major conventional Kampo medications for women. Although it was a randomized controlled trial that did not take pattern identification into account, it is worth noting that 66.7% of the effects of nyoshinsan, tokishakuyakusan, kamishoyosan, and keishibukuryogan were confirmed. The finding of greater effectiveness in women with relatively high BMI suggests that effectiveness could be increased by prescribing these medications on the basis of Kampo diagnosis of deficiency/excess pattern. However, to compare the results for nyoshinsan with the results for the three major conventional Kampo medications for women, by using the results from this four-group comparative study, undeniably presents the problem of multiplicity: essentially, the study requires randomization between two groups, nyoshinsan and the three major conventional Kampo medications for women. Further study offers some promise.

12. Abstractor and date

Ushiroyama T, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Ushiroyama T, Ikeda A, Kakuma K, et al. Comparing the effects of estrogen and an herbal medicine on peripheral blood flow in post-menopausal women with hot flashes: hormone replacement therapy and gui-zhi-fu-ling-wan (keishibukuryogan), a Kampo medicine. *The American Journal of Chinese Medicine* 2005; 33: 259-67. CENTRAL ID: CN-00528621, Pubmed ID: 15974485

1. Objectives

To compare the efficacy of keishibukuryogan (桂枝茯苓丸) and hormone replacement therapy (HRT) for relief of hot flashes and chills.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College.), Japan

4. Participants

Three-hundred and fifty-two postmenopausal patients with hot flashes untreated with HRT in the past 3 months and without past history of chronic diseases, aged 46–58 years. Patients with coronary artery anomaly, thrombotic diseases, cerebral infarction, hypertension, renopathy, and allergic conditions were excluded.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Keishibukuryogan (桂枝茯苓丸) (TJ-25) t.i.d. (daily dose 7.5 g).

Arm 2: oral administration of 0.625 mg of Premarin and 2.5 mg of Provera s.i.d. (i.e., HRT).

6. Main outcome measures

Peripheral blood flow, measured pre- and post-administration by a laser Doppler velocimeter at 3 sites (jaw, finger tips, and toes).

7. Main results

Both HRT and keishibukuryogan reduced blood flow in the jaw and finger tips. Blood flow in the toes was increased by keishibukuryogan but unchanged by HRT.

8. Conclusions

Keishibukuryogan is effective for chills, especially in the legs, in patients with hot flashes. HRT is ineffective for chills. Although both HRT and keishibukuryogan are effective for hot flashes, the latter is more effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is a controlled trial of HRT and keishibukuryogan. It ensures objectivity by measuring hot flashes and chills in terms of blood flow. It would also be interesting to investigate how well these medicines change blood flow in patients without hot flashes.

12. Abstractor and date

Nakata H, 1 April 2008.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**References**

Matsuo A, Koike K, Hoshina Y, et al. Study of the efficacy of unkeito for depressive and anxiety symptoms during menopause that are refractory to hormone replacement therapy. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2005; 22: 70-4 (in Japanese). Ichushi Web ID: 2005235338

Koike K. A slight advantage of Kampo treatment for gynecological disease 4: Menopausal depressed mood and the herbal medicine Unkei-to. *Sanfujinka Chiryō (Obstetrical and Gynecological Therapy)* 2006; 92: 784-6 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the usefulness of Kampo medicine for treatment of depressive patients refractory to hormone replacement therapy (HRT).

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

None (the authors belonged to the Department of Obstetrics and Gynecology, Kanazawa University School of Medicine), Japan.

4. Participants

Twenty-four depressive outpatients who visited the menopause clinic and were unresponsive to 6 months of HRT.

5. Intervention

Arm 1: HRT combined with TSUMURA Unkeito (温経湯) 7.5 g t.i.d. for 6 months. Washout for one month. Then HRT combined with TSUMURA Tokishakuyakusan (当帰芍薬散) 7.5 g t.i.d. for 6 months (n=12).

Arm 2: HRT combined with TSUMURA Tokishakuyakusan (当帰芍薬散) 7.5 g t.i.d. for 6 months. Washout for one month. Then, HRT combined with TSUMURA Unkeito (温経湯) 7.5 g t.i.d. for 6 months (n=12).

Hormone replacement therapy (HRT): Continuous use of transdermal estradiol (1 patch/2 days) and medroxyprogesterone (5 mg/day for 10 days).

6. Main outcome measures

Changes in Self-Rating Depression Scale (SDS) and State Trait Anxiety Inventory (STAI) scores after 6-month treatment with the unkeito or tokishakuyakusan combination.

7. Main results

In arm 1, SDS depression score was significantly decreased ($P<0.01$, testing method not indicated). STAI state and trait anxiety scores were significantly improved ($P<0.01$, testing method not indicated).

8. Conclusions

HRT + unkeito combination therapy is effective for relief of HRT-refractory depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper is based on the previously published "Koike K, Ohno S, Takahashi N, et al. Efficacy of the herbal medicine Unkei-to as an adjunctive treatment to hormone replacement therapy for postmenopausal women with depressive symptoms. *Clinical Neuropharmacology* 2004; 27: 157-62." This study demonstrated the efficacy of unkeito for depressive and anxiety symptoms refractory to HRT administered as treatment for climacteric disorders. However, something seems wrong with the definition of "depressive and anxiety symptoms refractory to hormone replacement therapy." Kampo medicine as treatment of depressive and anxiety symptoms would be better assessed in comparison with antidepressants and anxiolytics. In addition, the statement in the text that 3-month oral administration produced an effect lasting 6 months raises the concern that a 1-month washout in the cross-over comparison is sufficient. Future research is expected.

12. Abstractor and date

Nakata H, 1 April 2008, 8 April 2009, 1 June 2010, 31 December 2013.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Ushiroyama T, Sakuma K, Nosaka S. Comparison of effects of vitamin E and wen-jing-tang (unkei-to), an herbal medicine, on peripheral blood flow in post-menopausal women with chilly sensation in the lower extremities: a randomized prospective study. *The American Journal of Chinese Medicine* 2006; 34: 969-79. CENTRAL ID: CN-00577271, Pubmed ID: 17163586

1. Objectives

To compare the effects of unkeito (温経湯) and vitamin E on peripheral blood flow.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine, Japan.

4. Participants

One hundred and eighty post-menopausal women (42–61 years old) with chilly sensation in the lower extremities and no treatment by hormone replacement within 3 months.

5. Intervention

Arm 1: administration of unkeito (温経湯) (TSUMURA Unkeito Extract Granules 7.5 g/day) for 8 weeks (60 patients; of these, 58 were included for analysis).

Arm 2: administration of vitamin E (tocopherol nicotinate 600 mg/day) for 8 weeks (60 patients; of these, 55 were included for analysis).

Arm 3: no treatment for 8 weeks (60 patients; of these 48 were included for analysis).

6. Main outcome measures

Items evaluated by questionnaire on a 4-point scale and submandibular, middle finger, and middle toe blood flow measured by Doppler.

7. Main results

Chilly sensation evaluated by questionnaire was significantly improved in arm 1. Doppler blood flow evaluation revealed improved peripheral blood flow in the lower extremities in arm 1 and arm 2. While vitamin E significantly increased middle finger blood flow, unkeito suppressed blood flow (that was originally too high) and increased poor blood flow.

8. Conclusions

Unkeito is superior to vitamin E in improving blood flow and reducing chill.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No special problems noted.

11. Abstractor's comments

This paper compared the ability of unkeito and vitamin E to improve peripheral blood flow. It concluded that unlike vitamin E, unkeito improves chill by increasing poor circulation and improves hot flushes by decreasing excessive blood flow, well characterizing the Kampo medicine.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010.

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Yasui T, Irahara M, Aono T. Studies on treatment with the combination clomiphene citrate and toki-shakuyaku-san. *Nippon Funin Gakkai Zasshi (Japanese Journal of Fertility and Sterility)* 1995; 40: 83-91 (in Japanese).

1. Objectives

To compare the effects of clomiphene monotherapy with those of tokishakuyakusan (当帰芍薬散) plus clomiphene for infrequent menses, anovular menstrual cycle, and amenorrhea.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The Department of Obstetrics and Gynecology of Tokushima University Hospital and related hospitals (13 institutions), Japan.

4. Participants

Ninety-three outpatients seen at the above institutions and diagnosed with infrequent menses, anovular menstrual cycle, or amenorrhea between January 1992 and March 1994.

5. Intervention

Arm 1: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle + TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=41).

Arm 2: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=52).

6. Main outcome measures

Ovulation and pregnancy as determined by confirmation of a period of high basal body temperature lasting 10 or more days, or increased progesterone level (≥ 10 ng/mL) in mid-luteal phase. Improvement in endocrine condition as indicated by blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone. Assessments were made after treatments for 3 or more cycles.

7. Main results

There were no significant between-group differences in the ovulation rates evaluated for each treatment arm at each cycle, as well as in the pregnancy rate for each arm. In patients who became pregnant, the number of cycles until pregnancy was significantly lower in the combination therapy group (1.86 cycles) than in the monotherapy group (3.82 cycles) ($P < 0.05$). There were also no significant between-group differences during any treatment cycle in pituitary hormone and estradiol levels, the number of growing ovarian follicles, cervical mucus volume, endometrial thickness in the mid-luteal phase, and the period of high basal body temperature. Both the progesterone level and progesterone/estradiol concentration ratio in the preovulatory period were higher in the clomiphene monotherapy group than in the combination therapy group ($P < 0.05$).

8. Conclusions

In patients with infrequent menses, anovular menstrual cycle, or amenorrhea, combination therapy, as compared with monotherapy, did not improve ovulation rate but did facilitate pregnancy, suggesting the normalizing effects of tokishakuyakusan on sex hormones in the ovary.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present study compared the efficacy of combination therapy with tokishakuyakusan with the efficacy of clomiphene (used as a positive control with proven effects on abnormal menstrual cycles). The conclusion is that tokishakuyakusan could shorten the time until pregnancy and is therefore clinically applicable. From the point of view of western medicine, more detailed classification of the primary disease would be useful for the determination of indications for tokishakuyakusan in women with abnormal menstrual cycles who want to become pregnant. To compare the physiological and endocrine data, the combination therapy group should be subgrouped on the basis of *sho* (証, pattern). Subgroup analysis of the data is expected.

12. Abstractor and date

Ushiroyama T, 28 August 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**Reference**

Takushima Y, Michigami F. Clinical study of saireito on gestational edema and upper gastrointestinal symptoms. *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2010; 64: 709–15 (in Japanese). Ichushi Web ID: 2011072703 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effectiveness of saireito (柴苓湯) combined with either sojutsu (蒼朮, *Atractylodes Lancea* Rhizome) or byakujutsu (白朮, *Atractylodes* Rhizome) as constituent crude drugs for lower limb edema and functional dyspepsia-like gastrointestinal symptoms.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One hospital, Japan.

4. Participants

Fifty women in the latter stage of pregnancy with lower limb edema not associated with hypertension requiring drug therapy, and gastrointestinal symptoms such as appetite loss.

5. Intervention

Arm 1: saireito (柴苓湯) extract granules (manufacturer not identified) 3.0 g t.i.d. combined with sojutsu (蒼朮, *Atractylodes Lancea* Rhizome) for 4 weeks (n=25).

Arm 2: saireito (柴苓湯) extract granules (manufacturer not identified) 4.05 g b.i.d. combined with byakujutsu (白朮, *Atractylodes* Rhizome) for 4 weeks (n=25).

6. Main outcome measures

Ankle edema (ankle circumference), plantar edema (plantar circumference), gastrointestinal symptoms (questionnaire).

7. Main results

Ankle circumference began to improve significantly 2 weeks after saireito administration in both arms 1 and 2 ($P<0.05$). Improvement of plantar circumference after 4 weeks was significant in Arm 2 but not in Arm 1. Epigastralgia and bloating after meals at the end of the 4-week period of administration ($P<0.05$), epigastric heat sensation after treatment for 3 weeks ($P<0.01$), heaviness in the stomach after treatment for 3 weeks ($P<0.05$), and upper gastrointestinal symptoms overall (including gastrointestinal symptoms) after treatment for 3 weeks ($P<0.05$) were significantly improved in Arm 2 only.

8. Conclusions

Saireito combined with sojutsu and saireito combined with byakujutsu are both effective for lower limb edema in pregnancy. Of these combinations, only saireito + byakujutsu improve epigastric symptoms significantly.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

This is a quasi-randomized controlled trial in which medications were allocated in order of patient presentation. It is a significant clinical trial that compared the effects of byakujutsu or sojutsu with saireito for lower limb edema and epigastric symptoms in pregnancy. Before-after comparison demonstrated that only saireito combined with byakujutsu is effective for epigastric symptoms. This was probably a reflection of byakujutsu's capacity to promote gastrointestinal function. Therefore, the two different saireito formulae appear to be indicated for different patterns. A further study is recommended for comparison of groups in a randomized trial that includes a placebo group.

12. Abstractor and date

Okabe T, 1 December 2012.

15. Ante/Post-partum Diseases**References**

Ushiroyama T, Araki R, Sakuma K, et al. Efficacy of the kampo medicine xiong-gui-jiao-ai-tang, a traditional herbal medicine, in the treatment of threatened abortion in early pregnancy. *American Journal of Chinese Medicine* 2006; 34: 731-40. CENTRAL ID: CN-00457564, Pubmed ID: 17080540

Ushiroyama T, Sakuma K, Nosaka S, et al. Clinical efficacy of kyukikyogaito for imminent abortion with uterine hemorrhage*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2006; 23: 100-3 (in Japanese). Ichushi Web ID: 2006303253

1. Objectives

To evaluate the efficacy of kyukikyogaito (キユウ婦膠艾湯) as a therapeutic drug for imminent abortion in patients with uterine hemorrhage.

2. Design

Randomized controlled trial (RCT).

3. Setting

None. (The authors belonged to the Department of Obstetrics and Gynecology, Osaka Medical College and the Department of Obstetrics and Gynecology, Takatsuki Red Cross Hospital.), Japan.

4. Participants

Seventy-two patients who visited the hospital with a complaint of uterine hemorrhage and were given a diagnosis of imminent abortion.

5. Intervention

Arm 1: bed rest and administration of 2.5 g of TSUMURA Kyukikyogaito (キユウ婦膠艾湯) Extract Granules (TJ-77) t.i.d. (n=36).

Arm 2: bed rest and administration of human chronic gonadotropin (hCG) (alternate-day administration of 5,000 U) (n=36).

6. Main outcome measures

EFS (echo free space), number of days to hemostasis.

7. Main results

Statistical analysis was carried out using the chi-square test and Wilcoxon's signed-rank test. Significantly fewer days were required for hemostasis and for EFS disappearance in arm 1 (both $P < 0.0001$). EFS on day 7 of treatment was significantly smaller in arm 1 ($P < 0.0001$).

8. Conclusions

Kyukikyogaito (TJ-77) shortens the time to hemostasis in patients with imminent abortion and uterine hemorrhage.

9. From Kampo medicine perspective

The explanation of the efficacy of kyukikyogaito for imminent abortion is based on the blood replenishing effect of toki, shakuyaku, and senkyu as well as the hemostatic effect of akyo and gaiyo.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper shows that EFS disappears significantly earlier in patients with imminent abortion after treatment with a Kampo medicine. Considering that in principle, bed rest is the only treatment for imminent abortion with no effective therapeutic method having been established, the effects of kyukikyogaito are worthy of attention. However, without significant differences in the final outcome of fetal mortality, kyukikyogaito is reasonably considered to have limited efficacy and to contribute to better patient QOL through a reduction in length of hospital stay, etc.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**References**

Mizuno M, Sato K, Mori T, et al. Clinical evaluation of TSUMURA Tokishakuyakusan and ritodrine hydrochloride combination therapy in the management of threatened premature delivery*. *Sanka to Fujinka (Obstetrics and Gynecology)* 1992; 59: 469–80 (in Japanese).

1. Objectives

To objectively evaluate the usefulness of tokishakuyakusan (当帰芍薬散) combined with ritodrine hydrochloride in the management of threatened premature labor.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Thirty-six facilities nationwide including the Department of Obstetrics and Gynecology, University of Tokyo Hospital, Japan.

4. Participants

One hundred and forty-seven patients diagnosed with threatened premature labor (24 weeks to less than 37 weeks of pregnancy) at the above facility between June 1989 and August 1990 with a cervical dilation of <3.5 cm and effacement of <80%.

5. Intervention

Arm 1: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals, started before or at the start of ritodrine hydrochloride (Utemerin; UT) (pretreatment group; n=78).

Arm 2: TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals, started after the occurrence of adverse reactions to UT (post-treatment group; n=69).

6. Main outcome measures

Improvement in uterine contraction and prolongation of gestation evaluated on a 5-point scale; effect on maternal heart rate, fetal heart rate, and adverse drug reactions to UT evaluated on a 5-point scale; safety evaluated on a 3-point scale based on intrapartum, neonatal, and puerperal findings and laboratory findings; and usefulness with regard to clinical efficacy and safety evaluated on a 5-point scale.

7. Main results

The pretreatment, compared with the posttreatment, allowed the UT drip rate to be significantly raised. The pretreatment significantly suppressed uterine contraction at 1 hr of UT administration. There were no significant between-arm differences in symptoms of threatened premature labor. At 2 hr of UT administration, significantly more pretreated patients ($\geq 20\%$) than posttreated patients (10%) had no UT-associated palpitation ($P < 0.0001$). Similarly, significantly fewer pretreated patients had increased heart rate, tremor, decreased blood pressure, headache, and facial flushing. Full term delivery occurred in 71.8% of the pretreatment group and 62.5% of the posttreatment group. There was no between-arm difference in style of delivery and neonatal or puerperal findings.

8. Conclusions

Tokishakuyakusan relieves the adverse reactions to ritodrine hydrochloride, thereby enabling administration of more ritodrine hydrochloride to suppress uterine contraction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although their incidence and severity are not mentioned, adverse drug reactions associated with UT administration were relieved in 86% and 90% of patients receiving tokishakuyakusan pretreatment and posttreatment, respectively.

11. Abstractor's comments

This study demonstrated that tokishakuyakusan (a drug traditionally used to prevent abortion) relieves or suppresses the adverse drug reactions to ritodrine hydrochloride (a representative western medicine used for tocolysis to prevent abortion), thereby allowing maintenance therapy with ritodrine hydrochloride at higher levels. It shows that the fusion of oriental and western medicine can contribute to clinical practice. However, in principle, a tocolytic Kampo medicine should be started when pregnancy is diagnosed. Moreover, the effect of tokishakuyakusan should have been weak in patients who had already passed the stage of *mibyō* (未病, predisposition of disease) and been clinically diagnosed with threatened premature labor. Therefore, future studies should use a protocol starting in the first trimester and have an RCT design.

12. Abstractor and date

Ushiroyama N, 10 September 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**Reference**

Takushima Y, Inoguchi H, Study on usefulness of kyukichoketsuin for control of puerperium – comparison with methylergometrine maleate (1st report) *. *Progress in Medicine* 2001; 21: 1535-42 (in Japanese). Ichushi Web ID: 2002032923 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the usefulness of kyukichoketsuin (キユウ婦調血飲) for control of puerperium.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

None (authors belong to the Department of Obstetrics and Gynecology, Yamato Municipal General Hospital), Japan.

4. Participants

Forty-seven puerperants, who had a vaginal delivery after the 36th week of pregnancy and no abnormal bleeding of more than 1,000 mL, were randomized to receive either kyukichoketsuin or methylergometrine maleate.

5. Intervention

Arm 1: oral administration of 1 sachet (2.0 g) of TAIKODO Kyukichoketsuin (キユウ婦調血飲) Extract Granules (EK-230) t.i.d. (n=23)

Arm 2: oral administration of 1 tablet (0.125 mg) of Metenarin t.i.d. (n=24)

6. Main outcome measures

Uterine volume, length of uterine fundus, lower abdominal pain score, and amount of lactation during 1 to 5 days postpartum. Improvement in outcome measures compared between groups.

Adverse drug reactions: described symptoms.

7. Main results

Statistical analysis used *t*-test, chi-square test, and Wilcoxon's signed-rank test. There was no significant between-group difference in uterine volume or length of uterine fundus. Lower abdominal pain was significantly less frequent in patients receiving kyukichoketsuin on postpartum days 1 ($P<0.0028$), 2 ($P<0.0005$), and 4 ($P<0.0232$). Patients receiving kyukichoketsuin secreted significantly more milk on postpartum days 3 ($P<0.0345$), 4 ($P<0.0368$), and 5 ($P<0.0177$). Regarding safety, pain associated with uterine contraction was so severe in patients receiving Metenarin as to preclude continued treatment in 2 patients, whereas no adverse drug reactions occurred in the kyukichoketsuin group.

8. Conclusions

Kyukichoketsuin could be an alternative medication to methylergometrine maleate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Treatment was discontinued in two patients receiving methylergometrine maleate because of severe lower abdominal pain (associated with uterine contraction), whereas no adverse drug reactions occurred in the kyukichoketsuin group.

11. Abstractor's comments

The routine use of postpartum methylergometrine maleate has been criticized and is now limited only to cases such as uterine subinvolution. Therefore, this paper highlighting the effect of kyukichoketsuin, which is associated with few adverse drug reactions, is meaningful. However, since this paper does not address the effect of suckling stimulation and breast massage on uterine contraction and lactation promotion, further investigation of the effectiveness of oral kyukichoketsuin is expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**References**

Sakuma K, Ushiroyama T, Akise D, et al. Clinical efficacy of kyukichoketsuin for regulation of puerperal psychosomatic functions. *Sanfujinka no Shinpo (Advances in Obstetrics and Gynecology)* 2002; 54: 80-6 (in Japanese with English abstract). Ichushi Web ID: 2002151144 [MOL](#), [MOL-Lib](#)

Ushiroyama T, Sakuma K, Souen H, et al. Therapeutic effects of kyuki-choketsu-in in restoring postpartum physical condition. *The American Journal of Chinese Medicine* 2003; 31: 437-44. CENTRAL ID: CN-00457564, Pubmed ID: 12943174

1. Objectives

To evaluate the efficacy and safety of kyukichoketsuin (キユウ婦調血飲) for puerperal psychosomatic disorder.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital and associated facilities, Japan.

4. Participants

One-hundred and seventy-one women who had a normal delivery.

5. Intervention

Arm 1: daily administration of 6.0 g/day of Kanebo Kyukichoketsuin (キユウ婦調血飲) Extract Fine Granules for up to 1 month from the day of delivery (n=85).

Arm 2: administration of 0.375 mg/day of ergometrine (n=86).

6. Main outcome measures

Length of uterine fundus, blood hemoglobin concentration, body temperature, and amount of lactation measured 1 to 6 days postpartum.

Lochia, lactation, and mental state evaluated by questionnaire.

7. Main results

In arm 1, uterine contraction on postpartum day 5 was significantly greater, blood hemoglobin concentration was significantly higher, and mean amount of lactation was significantly increased from postpartum day 4 onward. The number of patients with subjectively rated depression in arm 1 was approx. half that in arm 2.

8. Conclusions

Kyukichoketsuin is more effective than ergometrine for some patients with puerperal psychosomatic symptomatology.

9. From Kampo medicine perspective

The crude-drug components of kyukichoketsuin associated with oxytocic, lactogenic, or psychotropic activity are mentioned in the discussion.

10. Safety assessment in the article

No adverse drug reactions occurred in either arm.

11. Abstractor's comments

In Japan, randomization by the RCT-envelope method tends not to be maintained. This study suggests the partial efficacy of kyukichoketsuin for some patients with puerperal psychosomatic symptoms. Kyukichoketsuin is also known by a name of kyukihoketsuto and considered to be effective for various postpartum symptoms including *qiketsukyoson* (気血虚損, qi and blood deficiencies), *hiikyojaku* (脾胃虚弱, hypofunctioning of the spleen and stomach), *orofugyo* (悪露不行, lochiometra), *kyoketsukata* (去血過多, hypermenorrhea), *inshokusissetsu* (飲食失節, crapula), and *dokisoshu* (怒気相衝, anger) (In: *Wanbinghuichun* [萬病回春]: *Recovery from All Ailments*).

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Wada H, Wada K, Motoyama K. Usefulness in postpartum control by kyukichoketsuin. *Sanfujinka no Sekai (World of Obstetrics and Gynecology)* 2003; 55: 1057-61. Ichushi Web ID: 2004022822

1. Objectives

To evaluate the clinical usefulness of kyukichoketsuin (キユウ婦調血飲) for “postpartum restoration”

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single facility (Wada Obstetric and Gynecologic clinic), Japan.

4. Participants

Sixty multiparas who visited the above facility between January and the end of December 2001 and had a normal delivery.

5. Intervention

Arm 1: administration of Kanebo Kyukichoketsuin (キユウ婦調血飲) Extract Granules (EK-230) 2.0 g t.i.d. (before meals) from immediately to 2 weeks postpartum in 30 patients.

Arm 2: administration of methylergometrine maleate (MME) 0.125 mg t.i.d. (after meals) from immediately to 5 days postpartum in 30 patients.

6. Main outcome measures

Uterine subinvolution: evaluated based on the length of the uterine fundus at 1 and 4 days postpartum and the amount of lochia at 1 month postpartum.

Amount of lactation: evaluated based on the amount of lactation at 4 days postpartum and the amount of lactation expressed as a percentage of the lactation amount after the previous delivery.

Clinical symptoms: complaint of afterpains evaluated by interview.

Drug compliance: evaluated on a 4-point scale by interview.

7. Main results

There was no between-group difference in the length of uterine fundus (11.4 ± 0.7 cm [kyukichoketsuin] vs 11.8 ± 2.8 cm [MME]) at 4 days postpartum and lactation at 4 days postpartum. The lactation index (i.e., amount of lactation in relation to the amount for the previous delivery of 100) was 81.7 ± 15.0 with MME and 136.7 ± 71.0 with kyukichoketsuin, showing a lactation-promoting effect of kyukichoketsuin, although the difference was not significant. There were more complaints of afterpains in the MME group (46.7%) than in the kyukichoketsuin group (23.3%). Drug compliance was significantly higher in patients receiving kyukichoketsuin ($P < 0.001$).

8. Conclusions

Compared with MME, kyukichoketsuin (“a medicine for postpartum restoration”) is a better restorer of postpartum health and some physiological functions in puerperants.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This study follows up a randomized study published in 2002 that verified the efficacy of kyukichoketsuin for “postpartum restoration” as described in *Wanbinghuichun* (萬病回春, *Recovery from All Ailments*) using objective parameters. The present results showing that kyukichoketsuin has clinical efficacy support the results of the previous study. The psychosomatic condition of postpartum health is referred to as “*qiketsukyoson* (気血虚損, qi and blood deficiencies)” in Kampo medicine, for which kyukichoketsuin is indicated. It is hoped that “*qiketsukyoson*,” a Kampo medical pathology, will be scientifically elucidated based on objective clinical parameters as in the present study.

12. Abstractor and date

Ushiroyama T, 1 April 2008, 8 August 2009, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**Reference**

Narimatsu A, Ito A, Usefulness of kyukichoketsuin during puerperium. *Rinsho Iyaku (Journal of Clinical Therapeutics & Medicine)* 2001; 17: 1329-35 (in Japanese with English abstract). Ichushi Web ID: 2002057351 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the clinical usefulness of kyukichoketsuin (キユウ婦調血飲) during puerperium.

2. Design

A randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Ogori-Daiichi General Hospital, Japan.

4. Participants

Eighty women who had normal vaginal delivery at the above facility between July 2000 and March 2001.

5. Intervention

Arm 1: postpartum administration of an oral antibiotic for 5 days + kyukichoketsuin (キユウ婦調血飲) (manufacturer not specified) 2.0 g t.i.d. before meals for 4 weeks, n=40.

Arm 2: postpartum administration of an oral antibiotic and methylergometerine maleate for 5 days, n=40.

6. Main outcome measures

Incidence of poor uterine contraction at 4 weeks postpartum, amount of milk sucked at 2 days postpartum, percentage of participants with ≥ 15 g/day of lactation, total amount of milk sucked, and incidences of “maternity blues” and depression at 5 days postpartum.

7. Main results

No poor uterine contraction or intrauterine infection occurred in either arm. Those receiving Kampo medicine suffered significantly less afterbirth pains ($P < 0.05$). Kampo medicine suppressed the decrease in newborn weight in all participants, especially in primiparas ($P < 0.05$). Postpartumly, kyukichoketsuin significantly reduced the frequency of hot flushes and twilight state. There was no between-arm difference in the incidence of maternity blues and no incidence of depression in either arm.

8. Conclusions

Kyukichoketsuin safely promotes the physical and mental restoration of puerperants, ultimately contributing to growth of newborns.

9. From Kampo medicine perspective

The increase in lactation is due to the ingredients of kyukichoketsuin (jio [地黄], toki [当帰], kobushi [香附子], chinpi [陳皮], and uyaku [烏薬]), which are also involved in nutritional fortification and physical reconditioning. In addition, kobushi and uyaku have a *qi*-conditioning effect and prevent postpartum depression.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This study verified the efficacy of kyukichoketsuin for “restoration of the postpartum psychosomatic condition” as described in *Wanbinghuichun* (萬病回春, *Recovery from All Ailments*). Although difference in uterine contraction should have been evaluated by measuring the length of the uterine fundus, the study should be praised for evaluating lactation by accurately measuring the amount of sucked milk. Biological evidence of the contribution of mental and physical factors to the restoration of puerperants should be sought. Scientific verification of the efficacy of kyukichoketsuin in various combinations (frequent in *Manbyokaishun*) is desired.

12. Abstractor and date

Ushiroyama T, 12 December 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases

Reference

Ushiroyama T, Sakuma K, Souen H, et al. Xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, stimulates lactation with increase in secretion of prolactin but not oxytocin in the postpartum period. *The American Journal of Chinese Medicine* 2007; 35: 195-202. CENTRAL ID: CN-00609546, Pubmed ID: 17436360

1. Objectives

To evaluate the postpartum lactation-promoting effect and safety of kyukichoketsuin (キユウ帰調血飲).

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital, Japan.

4. Participants

Eighty-two women who had normal spontaneous delivery.

5. Intervention

Arm 1: TAIKODO Kyukichoketsuin (キユウ帰調血飲) Extract Granules (Kanebo) 2.0 g t.i.d. for 6 days, n=41.

Arm 2: methylergometerine maleate 0.375 mg/day in 3 divided doses for 6 days, n=41.

6. Main outcome measures

Amount of lactation, blood prolactin concentration.

7. Main results

The amount of lactation was significantly increased in arm 1 on day 4 to 276.5±21.4 g (compared with 155.3±61.2 g in arm 2; $P<0.042$), on day 5 to 342.6±43.6 g (compared with 245.5±59.4 g in arm 2; $P<0.038$), and on day 6 to 413.7±68.1 g (compared with 293.3±98.5 g in arm 2; $P<0.046$). In addition, blood prolactin concentration was significantly elevated in arm 1 (compared with arm 2) on day 1 ($P<0.037$) and 6 ($P<0.0024$) after delivery.

8. Conclusions

Kyukichoketsuin may increase postpartum lactation.

9. From Kampo medicine perspective

Mentioned in discussion.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

While in Japan the RCT-envelope method of allocation often fails to maintain randomization, this study can suggest that kyukichoketsuin increases postpartum lactation. Kyukichoketsuin, also known as kyukihoketsuto, is considered to be effective for various postpartum symptoms including *qiketsukyoson* (気血虚損, qi and blood deficiencies), *hiikyojaku* (脾胃虚弱, hypofunctioning of spleen and stomach), *orofugyo* (悪露不行, lochiometra), *kyoketsukata* (去血過多, hypermenorrhea), *inshokusissetsu* (飲食失節, crapula), and *dokisoshō* (怒気相衝, anger) (In: *Wanbinghuichun* [萬病回春], *Recovery from All Ailments*).

12. Abstractor and date

Okabe T, 27 November 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**Reference**

Kawakami S, Nishimura J, Umeki M, et al. Kampo therapy for feeling of lactation deficiency*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2003; 20: 140-3 (in Japanese). Ichushi Web ID: 2004068785

1. Objectives

To evaluate a Kampo medicine effective for relieving the feeling of lactation deficiency.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (authors belong to the Department of Obstetrics and Gynecology, Fukuda Hospital), Japan.

4. Participants

Seventy-two puerperants who complained of feeling of lactation deficiency at 4 to 6 days postpartum between September 2002 and February 2002.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules t.i.d.

Arm 2: oral administration of 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules t.i.d.

Arm 3: oral administration of 2.5 g of Kanebo Kyukichoketsuin (キユウ婦調血飲) Extract Fine Granules t.i.d.

Arm 4: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of TSUMURA Juzentaihoto (十全大補湯) Extract Granules combined t.i.d.

Arm 5: oral administration of 2.5 g of TSUMURA Kakkonto (葛根湯) Extract Granules and 2.5 g of Kanebo Kyukichoketsuin (キユウ婦調血飲) Extract Fine Granule combined t.i.d.

Arm 6: oral administration of 2.5 g of TSUMURA Kikyoto (桔梗湯) Extract Granules t.i.d.

Arm 7: breast massage.

6. Main outcome measures

Total score from a questionnaire evaluating the amount of breast milk, degree of breast engorgement, milk supplementation, and satisfaction on a 10-point scale.

7. Main results

At 3 weeks after treatment, the score in the juzentaihoto monotherapy group was significantly higher than those in the kyukichoketsuin monotherapy, kakkonto + juzentaihoto combination therapy, and kikyoto monotherapy groups, but not significantly different from that in the breast massage group.

8. Conclusions

Juzentaihoto is effective treatment for feeling of lactation deficiency.

9. From Kampo medicine perspective

Administration according to “*sho* (証, pattern)” is recommended.

10. Safety assessment in the article

Not mentioned.

11. Abstractor’s comments

This study is valuable because it demonstrates the differing effects among Kampo prescriptions on lactation after birth and the importance of therapy according to *sho*. However, given that there was no significant effect on lactation deficiency and no difference between juzentaihoto and breast massage, the present data fail to provide evidence for an effect of juzentaihoto as a stimulant of lactation. Further investigations including combined use with breast massage are expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

15. Ante/Post-partum Diseases**Reference**

Fushiki H, Saeki A, Shiozaki A. Attempt to reduce adverse reactions associated with oral iron preparation for anemia in pregnancy by combination with rikkunshito (TJ-43)*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 2003; 20: 138-9 (in Japanese). Ichushi Web ID: 2004068784

1. Objectives

To evaluate whether rikkunshito (六君子湯) combined with oral iron can improve hemoglobin level and reduce adverse reactions associated with the administration of iron for anemia in pregnant women.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (one obstetrics and gynecology clinic), Japan.

4. Participants

One hundred and twenty pregnant women (duration of pregnancy \geq 5 months) with a hemoglobin (Hb) level of less than 11.0 g/dL, a hematocrit (Ht) of less than 33%, and a mean corpuscular volume (MCV) of less than 85 μm^3 .

5. Intervention

Arm 1: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d., and rikkunshito (六君子湯) 2.5 g t.i.d. for 14 days in patients with a mean age of 28.2 (20 - 42) years and a mean gestational age of 28.7 (18 - 38) weeks.

Arm 2: treatment with sodium ferrous citrate (50 mg) 1 tablet b.i.d. for 14 days in patients with a mean age of 28.8 (20 - 38) years and a mean gestational age of 28.4 (18 - 37) weeks.

6. Main outcome measures

Post-treatment Hb level.

7. Main results

Increase in Hb from the pre-treatment level was significantly greater after the sodium ferrous citrate plus rikkunshito therapy (arm 1; 0.8 [2.4 to -0.9] g/dL) than after sodium ferrous citrate monotherapy (arm 2; 0.3 [2.1 to -1.2] g/dL) ($P=0.002$). Also, oral administration of sodium ferrous citrate was better tolerated in arm 1.

8. Conclusions

It was suggested that rikkunshito combined with oral iron for anemia in pregnancy is effective for reducing adverse reactions associated with the administration of iron.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse reactions to rikkunshito treatment.

11. Abstractor's comments

Oral iron preparations are commonly associated with gastrointestinal adverse reactions. Thus, many patients stop the treatment. Great clinical relevance is suggested by the present results, which showed that treatment with iron could be continued in combination with rikkunshito. Although this study was classified as an RCT because of the random assignment, data necessary for the assessment of bias, including the presence or absence of blinding, were inadequate, and further assessment cannot be made. Further studies are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

15. Ante/Post-partum Diseases**Reference**

Ushiroyama T, Sakuma K, Ueki M, Efficacy of the Kampo medicine xiong-gui-tiao-xue-yin (kyuki-chouketsu-in), a traditional herbal medicine, in the treatment of maternity blues syndrome in the postpartum period. *The American Journal of Chinese Medicine* 2005; 33: 117-26. CENTRAL ID: CN-00515344, Pubmed ID: 15844839

1. Objectives

To confirm the efficacy of kyukichoketsuin (キユウ帰調血飲) for the “maternity blues.”

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Osaka Medical College Hospital and associated facilities, Japan.

4. Participants

Two-hundred and sixty-eight puerperants who had a normal single delivery and no pregnancy toxemia, diabetes mellitus, premature rupture of the membrane, etc. They were randomized to either kyukichoketsuin group or control group.

5. Intervention

Arm 1: administration of 2.0 g of Kanebo Kyukichoketsuin (キユウ帰調血飲) t.i.d., n=134.
Arm 2: control group without treatment, n=134.

6. Main outcome measures

Four items (including mood swings, crying over 5 min, and irritation) as judged by questionnaire.
Depressive symptoms as judged on the Edinburgh Postpartum Depression Scale.
Maternity blues as judged on a self-rating maternity blues scale.

7. Main results

Within 3 weeks postpartum, the kyukichoketsuin group had significantly decreased incidences of moderate or severe depressive symptom, crying lasting over 5 minutes, irritation, and maternity blues. During 3 to 6 weeks postpartum, there was no significant difference between arms. The incidence of maternity blues, especially within 3 days postpartum, was decreased in the kyukichoketsuin group.

8. Conclusions

Kyukichoketsuin can be used to stabilize postpartum mood.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

This study provides objective evidence for efficacy of kyukichoketsuin in the treatment of classic postpartum maternity blues. Maternity blues disappear within 3 weeks postpartum and are followed up without treatment in clinical practice. Thus, in emphasizing importance of postpartum care, this study seems significant. Further study results are expected.

12. Abstractor and date

Nakata H, 1 April 2008, 1 June 2010.

18. Symptoms and Signs**Reference**

Nishizawa Y, Nishizawa Y, Yoshioka F, et al. Beneficial effect of Chinese traditional herbal medicine, mai-men-don-tang (Japanese name: bakumondo-to) on acute pain in patients with acute internal medical disease: antitussive effect on elderly patients with post infectious persistent coughs, prospective, multicenter, randomized comparative trial between mai-men-dong-tang and forminoben hydrochloride. *Itami to Kampo (Pain and Kampo Medicine)* 2003; 13: 12-21 (in Japanese with English abstract). Ichushi Web ID: 2006247201

1. Objectives

To evaluate the efficacy of bakumondoto (麦門冬湯) for persistent cough after infection in the elderly.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two hospitals and three clinics, Japan.

4. Participants

Two-thousand and sixty-nine patients with intense dry cough persisting for 3 weeks or more after common cold syndrome, aged ≥ 65 years.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract granules 3.0 g t.i.d. between meals (n=1,039).

Arm 2: administration of fominoben hydrochloride 160 mg in three divided doses between meals (n=1,030).

6. Main outcome measures

Antitussive effect
Salivation degree, skin temperature, joint pain
Pain improvement rating
Global improvement rating

7. Main results

The antitussive effect and reduction in sputum expectoration (as measured on a visual analogue scale [VAS]) was superior in arm 1 than arm 2. Improvement in the following items after treatment, compared with baseline, was significant only in arm 1: the amounts of salivation and lacrimation determined by Saxon's test and Schirmer's test; joint pain judged on a VAS; and skin temperature measured with an upper and lower extremity-patch-type skin temperature indicator.

On the global scale, improvement, principally in cough, was better in arm 1 than arm 2. The condition of 89.5% of patients in arm 1 and 46.9% in arm 2 was rated "improved or better," showing the significantly higher efficacy of bakumondoto.

8. Conclusions

Bakumondoto is effective for not only cough but other symptoms in the elderly.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The "total-disease-related symptoms," a scale for acute pain severity developed by the present authors, is not described but referenced to their previous paper. This, however, should be detailed since the title refers to pain severity. In addition, except for the global improvement rating, the specific numbers of patients are not indicated, except in the graphs, making evaluation of the efficacy for pain impossible.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 1 June 2010.

18. Symptoms and Signs

References

Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. *Kampo to Meneki Arerugi (Kampo and Immuno-Allergy)* 2008; 22: 43-55 (in Japanese with English abstract).

Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form (SF-36) v2*. *Progress in medicine* 2010; 30: 100-1 (in Japanese).
[MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy of bakumondoto (麦門冬湯) on improvement in cough after lung cancer surgery.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

One hospital, Japan.

4. Participants

Thirty-two outpatients with prolonged cough for more than three weeks after lung cancer surgery, who were recruited between November 2005 and December 2007. Patients with apparent respiratory disease or antitussive drug use were excluded.

5. Intervention

The duration of administration was 4 weeks.

Arm 1: Tsumura Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9.0 g/day, n=17.

Arm 2: Medicon (dextromethorphan) 90 mg/day, or Astomine (dimemorfan) 60 mg/day, n=15.

6. Main outcome measures

Cough points, QOL score (36-Item Short Form [SF-36] v2 Health Survey).

7. Main results

Cough points showed significant decrease after 5 days of administration in arm 2, and after 3 days in arm 1 ($P<0.05$). Also, cough frequency was significantly less in arm 1 compared to arm 2 after 6 days of treatment until the end of the 4-week observation period ($P<0.05$). As for effect of improvement in cough, cough points decreased from 7 to 3.76 in arm 1, and from 7.2 to 4.58 in average after 4 weeks of administration. Cough disappeared in 3 patients in arm 1. Of 5 non-responders in arm 1, 3 showed improvement with proton pump inhibitor (PPI). QOL scores of the patients at the baseline were much lower than that of national standard. After the treatment, arm 2 showed improvement only in physical components, whereas arm 1 showed statistical improvements in general health, in both physical and mental components; mental health was significantly better in Arm 1 compared to arm 2.

8. Conclusions

Bakumondoto is effective in improving not only prolonged cough after lung cancer surgery, but also mental health components in QOL, when compared with Medicon or Astomine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Tsunezuka (2008) demonstrated that bakumondoto not only has efficacy in reducing cough frequency in cases of prolonged cough after lung cancer surgery but also has efficacy in reducing psychological stress. Bakumondoto treatment eliminated the symptoms of cough in 3 patients and use of PPI improved cough in 3 patients; the high rates were interesting. Another report by Tsunezuka (2010) based on this study, which added three months to the registration period and two patients to arm 2, also shows the same efficacy.

12. Abstractor and date

Fujisawa M, 1 June 2010, 14 January 2011, 31 December 2013

18. Symptoms and Signs**Reference**

Irifune K, Hamada H, Ito R, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients. *Phytomedicine* 2011; 18: 630–3. CENTRAL ID: CN-00790677, Pubmed ID: 21514123

1. Objectives

To evaluate the combined effects of bakumondoto (麦門冬湯) and a bronchodilator for prolonged cough following common cold.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT - envelope).

3. Setting

Six hospitals including Ehime University Hospital, Japan.

4. Participants

Twenty-seven adult patients who presented between February 2007 and March 2009 with prolonged cough for more than 3 weeks following a common cold. Patients whose prolonged cough was not attributable to common cold, and patients currently taking β 2 stimulants or anti-cholinergic drugs were excluded.

5. Intervention

Ultimately, 20 patients were registered after exclusions for adverse events and allocation errors.

Arm 1: TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. before or between meals, and 50 μ g Meptin[®] (n=9).

Arm 2: Meptin[®] 50 μ g b.i.d. after breakfast and before bed (n=10).

Patients with severe cough received Medicon[®], if requested.

6. Main outcome measures

Cough intensity on a 5-point scale and timing recorded in a cough diary, VAS (visual analogue scale) score for cough intensity and frequency, and sleep quality questionnaire.

7. Main results

A significant antitussive effect (based on cough diary data: arm 1, 11 subjects; arm 2, 8 subjects) was observed in arm 1 four and five days after administration ($P<0.05$). There was no significant difference between groups for sleep quality (questionnaire) or cough improvement (VAS).

8. Conclusions

Additional treatment with bakumondoto achieves earlier antitussive results in cases of prolonged cough that do not respond to centrally acting antitussives.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Meptin[®] (50 μ g) caused palpitations or tremors in 6 participants and bakumondoto extract granules caused rash in 1.

11. Abstractor's comments

Irifune et al. cite the assertion by Fujimori et al. (1997) that bakumondoto is effective for prolonged cough after common cold, whereas standard antitussive drugs are not. They also conducted a trial to compare the antitussive effects of Medicon[®] and bakumondoto, finding that bakumondoto has more rapid effects. The present study is the first randomized controlled trial (RCT) to clarify bakumondoto's antitussive effects. The use of central antitussives containing codeine for long periods is not recommended because of their adverse effects. Thus, using bakumondoto, which has few adverse effects, is apparently advantageous. Meptin[®] (50 μ g) results in frequent adverse effects when taken in combination, so further investigation into dosage, etc. is required.

12. Abstractor and date

Fujisawa M, 31 December 2012.

18. Symptoms and Signs**Reference**

Nishi K, Takata K, Asano S, et al. Effects of goreisan suppository on vomiting in children - comparison with domperidone suppository - . *Nihon Byoin Yakuzashikai Zasshi (Journal of Japanese Society of Hospital Pharmacists)* 1998; 34: 1173-6 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effects of goreisan (五苓散) suppository compared with domperidone suppository on vomiting in children.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single institution (Hokuriku Central Hospital), Japan.

4. Participants

Twenty children who visited the outpatient department with a chief complaint of vomiting. Patients who required fluid resuscitation were excluded.

5. Intervention

Arm 1: intrarectal administration of goreisan (五苓散) (via suppository consisting of TSUMURA Goreisan [五苓散] Extract Granules [1 g] + VOSCO H-15 base [1 mL]) in patients who underwent examination on the second or fourth week of the month (n=13).

Arm 2: intrarectal administration of domperidone (via suppository containing 10–30 mg dependent on the body weight) in patients who underwent the examination on the first, third, or fifth week of the month (n=7).

6. Main outcome measures

Presence or absence of nausea and vomiting 30 minutes after the administration.

7. Main results

Improvement rates of nausea and vomiting were 92.3% in arm 1 and 71.4% in arm 2.

8. Conclusions

The effects of goreisan on vomiting in children are suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions did not occur.

11. Abstractor's comments

This paper compares the effect of goreisan suppository with the effect of domperidone suppository on vomiting in children. It is generally difficult to conduct a clinical study in children. This study of the effects of the authors' original preparation of goreisan suppository is valuable because it was conducted in children. A definite conclusion was not drawn because the study design was not strictly an RCT and the number of patients enrolled was small. So future studies are expected to include a larger number of patients and employ a more sophisticated design.

12. Abstractor and date

Oikawa T, 19 September 2008, 6 January 2010, 1 June 2010.

18. Symptoms and Signs

References

Yoshida M, Mizuno T, Mizoguchi F, et al. Efficacy of goreisan suppositories for vomiting in young children (2nd report) – a double-blind study of the hochuekkito suppository*. *Wakan Iyaku Gakkaishi (Journal of Medical and Pharmaceutical Society for WAKAN-YAKU)* 1991; 7: 506-7 (in Japanese). Ichushi Web ID: 1993089053

Yoshida M. Efficacy of goreisan suppository for vomiting in young children*. *Toyoigaku (Japanese Journal of Oriental Medicine)* 2000; 28: 36-8 (in Japanese).

Yoshida M. Efficacy of goreisan suppository*. *Nihon Syhoni Toyo Igakkaishi (The Japan Pediatric Society for Oriental Medicine)* 2003; 19: 13-7. Ichushi Web ID: 2005266312

1. Objectives

To evaluate the efficacy and safety of goreisan (五苓散) for vomiting in young children.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

A single facility (the department of pediatrics of a hospital), Japan.

4. Participants

Thirty-five patients who vomited three or more times within 24 hr before visiting the pediatric department and experienced vomiting/nausea during the visit. One of these patients ejected the medicine immediately after insertion and was excluded, resulting in the inclusion of 34 patients (21 males and 13 females, aged 1 – 9 years with a mean of 3.9 years) for analysis.

5. Intervention

Arm 1: administration of a home-prepared suppository containing 1 g of TSUMURA Goreisan (五苓散) Extract Granules (n=16, 10 males and 6 females).

Arm 2: administration of a home-prepared suppository containing 1 g of TSUMURA Hochuekkito (補中益気湯) Extract Granules (n=18, 11 males and 7 females).

6. Main outcome measures

Complete response (disappearance of both vomiting and nausea); partial response (presence of nausea without vomiting); and no response (vomiting of supplied water).

7. Main results

The distribution of baseline characteristics (age, sex, underlying disease, frequency of vomiting, and complication with diarrhea) were similar between arms. Complete response, partial response, and no response were achieved in 12 (75%), 2, and 2 patients receiving goreisan, and in 5 (28%), 2, and 11 patients receiving hochuekkito, respectively. The difference between arm 1 and arm 2 was statistically significant ($P<0.05$).

8. Conclusions

Goreisan suppository reduces vomiting and nausea in young children more effectively than hochuekkito suppository.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

Goreisan is generally indicated for thirst, decreased urine output, and gastrointestinal diseases such as watery diarrhea and acute gastroenteritis with nausea, vomiting abdominal pain, headache, or edema. This study demonstrated the efficacy of goreisan suppository (in-home formulation) for reducing acute vomiting in young children. The usefulness has also been demonstrated in a multicenter, double-blind study, as mentioned below. Since the study period was in winter, the target diseases included common-cold-associated dyspepsia, winter diarrhea, vomiting, and common cold. Since it is generally difficult to administer a medicine orally or by drip infusion to young children with vomiting, the suppository is considered to be a clinically useful alternative dosage form. Therefore, it is very meaningful that this study demonstrated usefulness. However, this paper does not describe the methods of randomization and statistical analysis, which should be specified. In addition, another Kampo medicine and not a true placebo was used as the control, therefore it would be useful in the future to conduct a placebo-controlled study. Future development is expected. Notably, the formulation of goreisan extract is only approved for oral use, not for use in suppositories.

In the article by Yoshida (2003), a multicenter, case-series study with the same design and evaluation methods has also reported. The study population consisted of 87 patients (43 males and 44 females, aged 0 – 9 years with a mean of 2.4 years). Complete response was achieved in 72 patients (83%), and partial response in 2 patients. No difference in efficacy for underlying diseases was shown; complete response was achieved in 43 (88%) of 49 patients with winter infantile diarrhea, 22 (76%) of 29 patients with common-cold-associated diarrhea, and 5 (83%) of 5 patients with acute gastroenteritis. No difference in baseline characteristics was shown; there was no statistically significant difference in age, frequency of vomiting, complication with diarrhea, and use of enema between patients with complete or partial response, and patients with no response.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 8 April 2009, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**References**

Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. *Kampo Igaku (Science of Kampo Medicine)* 2010; 34: 12–3 (in Japanese).

Seike J, Sawada T, Kawakita N, et al. A new candidate supporting drug, rikkunshito, for the QOL in advanced esophageal cancer patients with chemotherapy using docetaxel/ 5-FU/ CDDP. *International Journal of Surgical Oncology* 2011; 2011: 1-7. DOI: 10.1155/2011/715623.

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Thoracic, Endocrine Surgery and Oncology, Tokushima University Hospital, Japan.

4. Participants

Nineteen patients to receive DFP (docetaxel+5-FU+cisplatin) therapy for advanced esophageal cancer (mainly stage II–III).

5. Intervention

Two-week administration.

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. (n=9).

Arm 2: no administration (n=10).

6. Main outcome measures

Grade of anorexia and nausea/vomiting (Common Terminology Criteria for Adverse Events [CTC-AE] ver. 3.0), QOL score (the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs [QOL-ACD]-based original questionnaire).

7. Main results

One of the participants in arm 1 was ineligible because of age violation and excluded from the analysis. Anorexia, nausea, and vomiting occurred as adverse drug reactions by 14 days after the start of chemotherapy in 3 (37.5%), 3 (37.5%), and 1 (12.5%) subject, respectively, in arm 1, and 7 (70%), 8 (80%) and 4 (40%) subjects, respectively, in arm 2, but there was no significant between-group difference. The change in mean vomiting score was 0 in both arms by day 8, but was 0.13 in arm 1 and 0.90 in arm 2 on day 14. Nausea score increased from day 8 and day 5 to 0.50 and 1.80 on day 14 in arm 1 and arm 2, respectively, showing significant difference on day 14 ($P<0.05$). Likewise, anorexia score reached 0.75 in arm 1 and 1.70 in arm 2 on day 14, showing a tendency toward lower score after rikkunshito administration. Rikkunshito also prevented significant suppression of depressed mood and decreased activities of daily living (both $P<0.05$).

8. Conclusions

Rikkunshito significantly suppresses anorexia and nausea/vomiting caused by chemotherapy (DFP therapy) for advanced esophageal cancer, and thereby prevents significant decline in QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The paper includes a section on adverse events and mentions that there was no adverse event associated with rikkunshito.

11. Abstractor's comments

This study is highly valued because it demonstrated by RCT that rikkunshito significantly relieves nausea and prevents QOL score from decreasing after chemotherapy. It is possible that the mechanism for improvement of anorexia is mediated by blood ghrelin. The 2010 paper in Japanese mentioned blood ghrelin analysis, but the 2011 paper in English makes no mention of blood ghrelin at all, perhaps because the widely scattered measurement results were an issue. The authors should conduct a large-scale clinical trial to find out whether it significantly alleviates vomiting and anorexia.

12. Abstractor and date

Motoo Y, 30 December 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Ohno T, Yanai M, Ando H, et al. Rikkunshito, a traditional Japanese medicine, suppresses cisplatin-induced anorexia in humans. *Clinical and Experimental Gastroenterology* 2011; 4: 291–6.
Pubmed ID: 22235173

1. Objectives

To verify the effects of rikkunshito (六君子湯) on cisplatin-induced anorexia in gastric cancer patients.

2. Design

Crossover randomized controlled trial (RCT-crossover).

3. Setting

Gunma University Hospital, Japan.

4. Participants

Ten unresectable or relapsed gastric cancer patients.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for three weeks (same period as S-1), two-weeks withdrawal, then the next course¹⁾ without rikkunshito (n=5).

Arm 2: first course without rikkunshito; then after five weeks, the next course with TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. for three weeks, the same period as S-1 (n=5).

¹⁾ One course consists of three-weeks of S-1 and two weeks withdrawal, making a total of five weeks, with a cisplatin IV infusion on the eighth day.

6. Main outcome measures

Plasma acyl-ghrelin before and three hours after administration of cisplatin; amount of oral food intake at each meal during hospitalization for five days after cisplatin (scored on a 10-point scale by a nurse); grade of anorexia (using CTC-AE ver. 3.0), nausea, and vomiting; and time to treatment failure (defined as time from administration of cisplatin to vomiting, or time to antiemetic usage).

7. Main results

Plasma acyl-ghrelin level before administration of cisplatin remained unchanged after administration in the rikkunshito-on period, but tended to decrease after administration of cisplatin in the rikkunshito-off period. The mean amount of oral food intake score was significantly higher during the rikkunshito-on period than the -off period ($P=0.0496$). The grade of anorexia was significantly lower during the rikkunshito-on period than the -off period ($P=0.0441$). The grade of nausea tended to be lower during the rikkunshito-on period, but the grade of vomiting was unchanged. There was no significant difference in the number of cases considered to be treatment failures between the rikkunshito-on period (n=5) and -off period (n=9).

8. Conclusions

Rikkunshito reduces cisplatin-induced anorexia in gastric cancer patients.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

Particular attention was paid to the possible occurrence of pseudoaldosteronism, however, no adverse event occurred in either arm.

11. Abstractor's comments

This is a valuable study and the first to clinically demonstrate by RCT that rikkunshito reduces cisplatin-induced anorexia in gastric cancer patients. The findings agree with the results of animal experiments (Takeda H, Sadakane C, Hattori T, et al. Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT₂ receptor antagonism. *Gastroenterology* 2008; 134: 2004–13.). However, the study found that rikkunshito had no significant effect on plasma acyl-ghrelin level, and on preventing or reducing nausea or vomiting. Hopefully the authors will conduct a large-scale RCT in Japan based on these results, as the authors mention in the discussion.

12. Abstractor and date

Motoo Y, 31 December 2013.

18. Symptoms and Signs**Reference**

Igarashi I. Clinical study of traditional Chinese medicine therapy for post-operative or post-traumatic swelling in lower extremities. *Seikeigeka (Orthopedic Surgery)* 1993; 44: 127–31 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of saireito (柴苓湯) for posttraumatic or postoperative swelling in the lower extremities.

2. Design

Randomized controlled trial (RCT).

3. Setting

The department of orthopedic surgery of one hospital, Japan.

4. Participants

Sixty-four inpatients receiving treatment for trauma or edema in the lower extremities.

5. Intervention

Arm 1: oral administration of TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. between or before meals (n=38).

Arm 2: no administration of Kampo medicine (n=26).

Analgesics were used as appropriate, but anti-swelling drugs were not used.

6. Main outcome measures

Swelling ratios calculated using circumferences of bilateral thighs, lower limbs and feet, and the number of days required for swelling disappearance.

7. Main results

Swelling resolution required 13–105 days after surgery or trauma (mean, 59.4 days) in arm 2, and 0–64 days (mean, 15.8 days) in arm 1. Swelling ratio was significantly smaller in arm 1 than in arm 2 at 1–6 weeks postoperatively (postoperative 1–6 weeks, $P<0.05$; 2–5 weeks, $P<0.01$). Nineteen patients in arm 1 who started saireito preoperatively required 0–56 days (mean, 9.5 days) for postoperative swelling resolution, and 10 of them did not develop swelling.

8. Conclusions

Saireito is effective for posttraumatic or postoperative swelling in the lower extremities.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Saireito administration was not associated with adverse reactions or electrolyte imbalance.

11. Abstractor's comments

This clinically useful, interesting study investigated the efficacy of saireito for swelling in the lower extremities after trauma or surgery. However, some patients in arm 1 had no swelling. Furthermore, 10 of 19 patients who started saireito preoperatively did not develop swelling, indicating that 10 of 38 patients in arm 1 had no swelling at the beginning of the study. In contrast, all patients in Arm 2 had swelling at the beginning of the study. This suggests a considerable between-arm difference in the baseline distribution of patients who had swelling. Preoperative patients without swelling or postoperative patients with swelling should have been allocated appropriately to meet the study objectives. Nevertheless, the focus of this study is excellent, and increasing sample size and dividing subjects into appropriate groups at the start will improve the study.

12. Abstractor and date

Goto H, 13 September 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Yoshida M, Kitaoka H, Masui Y, et al. Effects of shakuyaku-kanzo-to on muscle cramp in diabetics. *Shinkei Chiryogaku (Neurological Therapeutics)* 1995; 12: 529-34 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for preventing muscle cramps in diabetic patients.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One university hospital and multiple general hospitals, Japan.

4. Participants

Fifteen patients with non-insulin-dependent diabetes mellitus (NIDDM) in relatively good glycemic control who complained of muscle cramps two or more times a week.

5. Intervention

Arm 1: treatment with shakuyakukanzoto (芍薬甘草湯) extract granules (manufacturer, not specified) 7.5 g/day for 4 weeks (n=10).

Arm 2: treatment with eperisone hydrochloride 150 mg/day for 4 weeks (n=5).

Patients were followed up for 4 weeks after the completion of treatment; total follow-up period was 10 weeks.

6. Main outcome measures

Muscle cramps: improvement in frequency of muscle cramps was rated on a 5-point scale based on the post-treatment/pre-treatment ratio of the frequency; improvement in severity of muscle cramps was rated on a 5-point scale based on the change in pain scores (on a 4-point scale).

7. Main results

The improvement in the frequency of muscle cramps was “marked” in 20%, “moderate” in 70%, and “mild” in 10% for arm 1, and “moderate” in 60% and “no change” in 40% for arm 2. The improvement in the severity of muscle cramps was “marked” in 10%, “moderate” in 40%, “mild” in 30%, and “no change” in 20% for arm 1, and “mild” in 40% and “no change” in 60% for arm 2.

8. Conclusions

Shakuyakukanzoto is effective for preventing muscle cramps in diabetic patients and its efficacy is comparable or superior to that of eperisone hydrochloride.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred in shakuyakukanzoto-treated patients.

11. Abstractor's comments

It is clinically significant that a multicenter RCT was attempted, although the sample size was small. However, the between-group comparison of improvement was insufficient. As for adverse drug reactions, the number of patients analyzed was limited in this study and therefore reevaluation in a larger population is desired.

12. Abstractor and date

Kogure T, 8 August 2008.

18. Symptoms and Signs

References

Kumada T, Kumada H, Yoshiba M, et al. Effects of Shakuyaku-kanzo-to (Tsumura TJ-68) on muscle cramps accompanying cirrhosis in a placebo-controlled double-blinded parallel study. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicine)* 1999; 15: 499-523 (in Japanese with English abstract). Ichushi Web ID: 1999184114 [MOL](#), [MOL-Lib](#)

Kumada T, Kiriyaama I, Sone Y, et al. EBM-based Kampo therapy for gastrointestinal diseases 3. Efficacy of shakuyakukanzoto for “muscle cramps in the calves” associated with hepatic cirrhosis*. *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2003; 54: 536-8 (in Japanese) [CiNii](#)

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for relief of muscle cramp.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

A total of 23 nationwide facilities including university hospitals (departments of internal medicine and gastroenterology), Japan.

4. Participants

One-hundred and twenty-six patients with 2 or more episodes of muscle cramp weekly during the observation period (4 or more bi-weekly), aged ≥ 20 years and ≤ 70 years. These patients were also taking other drugs for a variety of problems including serious hepatic, renal, and cardiac diseases, pregnancy, hepatic failure, complications of hepatocellular carcinoma, electrolyte abnormality, and hypertension. After excluding 12 ineligible patients and 13 with incomplete data, 101 patients were included for statistical evaluation.

5. Intervention

Arm 1: administration of 7.5 g/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules in 3 divided doses (before meals) for 2 weeks following a 2-week observation period (n=65).

Arm 2: administration of the same dose of placebo granules at the same frequency for 2 weeks following a 2-week observation period (n=61).

6. Main outcome measures

Frequency of episodes of muscle cramp, duration of each episode, severity of pain (at completion of the study compared with baseline values determined during the observation period).

7. Main results

The percentage of patients with frequency of muscle cramp episodes rated “improved” or higher was significantly larger in the shakuyakukanzoto group than in the placebo group (67.3% vs 37.5%, respectively). The percentage of patients with improved final global rating, which takes duration of each episode and severity of pain into account, was significantly larger in the shakuyakukanzoto group (69.2% vs 28.6%, respectively). The percentage of patients with a utility rating of “useful” or higher was also significantly larger in the shakuyakukanzoto group (63.3% vs 34.1%, respectively).

8. Conclusions

Shakuyakukanzoto is a clinically useful Kampo formulation with excellent efficacy and safety for muscle cramp.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reactions occurred in 7 patients (14.3%) receiving shakuyakukanzoto and 2 patients (4.9%) receiving placebo. The main adverse drug reaction was pseudoaldosteronism in the shakuyakukanzoto group and gastrointestinal symptoms in the placebo group. No serious adverse drug reactions occurred.

11. Abstractor’s comments

This original article re-evaluates shakuyakukanzoto. The larger total amount of kanzo, contained in shakuyakukanzoto, is associated with higher incidence of pseudoaldosteronism. Since in the present study incidence of adverse drug reactions tended to be higher in the shakuyakukanzoto group, although there was no significant between-group difference in incidence, reduction in the dose is recommended in the future.

12. Abstractor and date

Arai M, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Nishizawa Y, Nishizawa Y, Amemori Y, et al. A randomized paralleled group comparison in multicenter cooperation: analgesic effect and safety with gosha-jinki-gan and shakuyaku-kanzo-to in the treatment of painful muscle cramps in patients with cirrhosis. *Itami to Kampo (Pain and Kampo Medicine)* 2000; 10: 13-8 (in Japanese with English abstract). Ichushi Web ID: 2002242334

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) for muscle cramps in the calves.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned, Japan.

4. Participants

Seventy-five patients with painful muscle cramps in the calves (PMC) associated with hepatic cirrhosis.

5. Intervention

Arm 1: oral administration of TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules (GJG) 30 mg/kg t.i.d. for 12 consecutive weeks, n=38.

Arm 2: oral administration of 50 mg/kg/day of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (SKT) in 3 divided doses for 12 consecutive weeks, n=37.

6. Main outcome measures

PMC rating (overall QOL, visual analog scale pain [VAS-P], face rating scale), QOL (modified health assessment questionnaire [MHAQ]), overall well-being (quality of well-being score), and psychological well-being (face scale).

7. Main results

GJG was significantly superior to SKT in improving the PMC rating and various QOL measures. The number of days until resolution of PMC was significantly shorter in the GJG group than in the SKT group.

8. Conclusions

Goshajinkigan is effective and safe for PMC associated with hepatic cirrhosis and is superior to shakuyakukanzoto in efficacy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse drug reaction symptoms and laboratory test abnormalities (increased AST, LDH, and CPK) were noted in 0 patients receiving goshajinkigan and 4 patients receiving shakuyakukanzoto, but these resolved after discontinuation of treatment.

11. Abstractor's comments

This paper suggests that goshajinkigan may be the first-choice drug for PMC associated with hepatic cirrhosis.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

18. Symptoms and Signs**Reference**

Yoshikawa H, Ikeuchi T, Kai Y. Clinical effects of kyuki-kyogai-to and sairei-to for essential microscopic hematuria. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 1997; 6: 55-8 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of kyukikyogaito (芎歸膠艾湯) and saireito (柴苓湯) for essential microscopic hematuria.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the authors belong to Showa University Fujigaoka Hospital and Ryokuseikai Yokohama General Hospital), Japan.

4. Participants

Sixty-eight female patients with essential microscopic hematuria who had no subjective symptoms, showed hematuria on analysis of urine obtained by urethral catheterization (according to the criteria proposed by Kai et al.), and had no abnormal findings on urological examinations.

5. Intervention

Arm 1: treatment with TSUMURA Kyukikyogaito (芎歸膠艾湯) Extract Granules 3.0 g t.i.d. for 4 weeks (n=26).

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 4 weeks (n=19).

Arm 3: no treatment (n=23).

6. Main outcome measures

The degree of microscopic hematuria induced by urethral catheterization.

7. Main results

The improvement in hematuria was “marked” in 34.6%, “moderate” in 38.5%, “unchanged” in 23.1%, and “worse” in 3.8% of patients in arm 1, compared with 0, 26.1, 52.2, and 21.7%, respectively, in arm 3; the improvement was significantly greater in arm 1 ($P<0.0002$). The improvement in arm 2 (26.3, 31.6, 42.1, and 0%) was significantly greater than that in arm 3 ($P<0.0045$). There was no significant difference in the improvement of hematuria between arm 1 and arm 2.

8. Conclusions

Kyukikyogaito and saireito are suggested to improve essential microscopic hematuria in women.

9. From Kampo medicine perspective

This issue was referred to in the discussion section.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor’s comments

This is a valuable controlled clinical trial that demonstrated the effects of kyukikyogaito and saireito on essential microscopic hematuria in women. As the authors point out, each prescription for two different *sho* (証, pattern) has a different mechanism of action. A higher efficacy will probably be demonstrated in an RCT of the treatment according to *sho*.

12. Abstractor and date

Okabe T, 26 August 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

Reference

Suzuki Y, Machida T, Onodera S, et al. Clinical effects of sairei-to for essential hematuria. *Hinyoki Geka (Japanese Journal of Urological Surgery)* 1994; 7: 325–7 (in Japanese). Ichushi Web ID: 1994241013

1. Objectives

To evaluate the clinical efficacy of saireito (柴苓湯) for essential hematuria.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Urology and 2nd Department of Internal Medicine, Jikei University School of Medicine, and two other facilities, Japan.

4. Participants

Eighty-two outpatients seen in the above hospitals with a chief complaint of hematuria and diagnosed with essential hematuria.

5. Intervention

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 9.0 g/day group for 28 days (n=50).
Arm 2: control group (no treatment) (n=32).

6. Main outcome measures

Urinary sediments evaluated on a 5-point scale: 3+, 2+, 1+, ±, and –.

7. Main results

A significantly greater improvement was noted in arm 2 than in arm 1 ($P<0.01$).

8. Conclusions

Saireito is expected to exert a hemostatic effect in hematuria.

9. From Kampo medicine perspective

Association with shosaikoto (小柴胡湯), an anti-inflammatory agent, is mentioned.

10. Safety assessment in the article

One patient complained of nausea.

11. Abstractor's comments

This paper suggests the possible efficacy of saireito for essential hematuria, but no therapeutic regimen has been established. However, considering the clinical significance of asymptomatic hematuria, an investigation of the possible efficacy of saireito for nephritis prevention would make this study more meaningful. Future results are expected.

12. Abstractor and date

Nakata H, 10 January 2009, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**References**

Shimizu Y, Yoshimura K, Soda T, et al. The effects of gosha-jinki-gan, a blended herbal medicine, and furosemide for nocturnal polyuria with elevated B-type natriuretic peptide: a crossover trial. *Neurourology and Urodynamics* 2010; 29: 833–4. CENTRAL ID: CN-00766683

Yoshimura K, Shimizu Y, Masui K, et al. Furosemide versus gosha-jinki-gan, a blended herbal medicine, for nocturnal polyuria: a randomized crossover trial. *Lower Urinary Tract Symptoms* 2012; 4: 77-81.

1. Objectives

To evaluate the effectiveness of goshajinkigan (牛車腎気丸) for nocturnal polyuria with elevated B-type natriuretic peptide (BNP).

2. Design

Crossover randomized controlled trial (RCT – cross over).

3. Setting

No information about location of the trial (the first author belongs to the Department of Urology, Kyoto University), Japan.

4. Participants

Twenty-four patients over 50 years with a nocturia frequency of more than three times/night, a nocturnal polyuria index of more than 35%, and serum BNP level of over 20 pg/mL.

5. Intervention

Arm 1: goshajinkigan (牛車腎気丸) (manufacturer not identified) 2.5 g t.i.d. for 4 weeks, then furosemide 20 mg q.d. (p.m.) for 4 weeks (n=14).

Arm 2: furosemide 20 mg once/day (p.m.) for 4 weeks, then goshajinkigan (牛車腎気丸) (manufacturer not identified) 2.5 g t.i.d. for 4 weeks (n=10).

6. Main outcome measures

International Prostate Symptom Score (IPSS), Pittsburgh Sleep Quality Index (PSQI), frequency volume chart (FVC), blood pressure, serum BNP, and total body water assessed before and after each administration.

7. Main results

Mean age of participants was 73.8 years (54–85 years). Nocturia frequency and volume decreased significantly with furosemide administration compared to goshajinkigan administration (both $P<0.05$). However, IPSS-7, IPSS-QOL, and nocturia frequency improved significantly with both goshajinkigan and furosemide in before/after comparisons ($P<0.05$, $P<0.01$, $P<0.05$ for the three measures respectively with goshajinkigan, and $P<0.01$ for all three measures with furosemide). IPSS-total and nocturia volume improved significantly only with furosemide (both $P<0.01$). Nocturia volume decreased markedly with furosemide administration but only slightly with goshajinkigan administration. PSQI scores and subjective sleep scores improved significantly only with furosemide (both $P<0.05$).

8. Conclusions

Furosemide is more effective for nocturnal polyuria associated with elevated BNP, but goshajinkigan may be almost as effective.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical study investigated the effectiveness of goshajinkigan for nocturnal polyuria associated with elevated B-type natriuretic peptide. By classifying the causes of subjects' condition (nocturnal polyuria), effective condition for using goshajinkigan can be identified. The paper subsequently published by Yoshimura et al (2012) includes 36 participants and reports similar results, but it describes in detail the research methods they employed. Goshajinkigan may be effective for patients with slight nocturnal polyuria symptoms or patients who cannot take furosemide due to its adverse effects, which include electrolyte disturbance. It is, therefore, a highly significant clinical study.

12. Abstractor and date

Goto H, 31 December 2012, 31 December 2013.

18. Symptoms and Signs

Reference

Sekiguchi Y, Miyai K, Noguchi K, et al. Study of effects of anti-heat shock protein 60 antibody by ba wei di huang wan and qing xin lian zi yin (II). *Wakan Iyakugaku Zasshi (Journal of Traditional Medicines)* 1998; 15: 326-7 (in Japanese). [CiNii](#)

1. Objectives

To determine the effects of hachimijiogan (八味地黄丸) and seishinrenshiin (清心蓮子飲) on anti-heat shock protein (HSP) 60 antibody.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Not mentioned (the authors are in the Department of Urology, Yokohama City Kowan Hospital), Japan.

4. Participants

Twelve patients with normal urinalysis who chiefly complained of urinary frequency, pain on urination, or incomplete emptying.

5. Intervention

Arm 1: treatment with TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules (dose, not specified) orally for 2 weeks → treatment with TSUMURA Hachimijiogan (八味地黄丸) Extract Granules (dose, not specified) orally for 2 weeks (n=7).

Arm 2: treatment with TSUMURA Hachimijiogan (八味地黄丸) Extract Granules (dose, not specified) orally for 2 weeks treatment with TSUMURA Seishinrenshiin (清心蓮子飲) Extract Granules (dose, not specified) orally for 2 weeks (n=5).

6. Main outcome measures

General subjective symptoms and urinary symptoms were evaluated using the International Prostate Symptom Score (IPSS) questionnaire. The titer of anti-HSP60 antibody was measured in blood samples.

7. Main results

The titer of anti-HSP60 IgG1 antibody was significantly reduced compared with the pre-treatment level both in arms 1 and 2. No change was observed in the titer of anti-HSP60 IgG2 antibody in both arms. Overall, although there was no change in urinary subjective symptoms score after treatment in both arms, gender-specific analysis of these ratings showed significant improvements after treatment of the male patients of arm 1 and female patients of arm 2. The outcomes were compared between patients with subjective symptoms lasting one month or more and patients with subjective symptoms lasting less than one month. The titer of anti-HSP60 IgG1 antibody declined significantly from pre-treatment level both in arms 1 and 2 in patients with urinary frequency lasting one month or more, but not in patients with urinary frequency lasting less than one month. Then, the association between general subjective symptoms and anti-HSP60 antibody (IgG1) were examined. The anti-HSP60 antibody (IgG1) titer was significantly higher in patients who self-reported nervousness than in patients who didn't ($P=0.028$) and in patients who reported early waking than in patients who didn't ($P=0.0074$). Similarly, the anti-HSP60 antibody (IgG1) titer was significantly lower in patients who reported having a good night's sleep than in patients who didn't ($P=0.0300$), and in patients who reported stiff back ($P=0.0390$) or cold hands ($P=0.0472$) than in patients who didn't.

8. Conclusions

The reduction of the titer of anti-HSP60 antibody (IgG1) after the hachimijiogan and seishinrenshiin treatments varies depending on the gender and the duration of urinary tract symptoms.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This clinical study evaluated the effects of hachimijiogan and seishinrenshiin treatments on anti-HSP60 antibody. It is the only study to examine the association between anti-HSP60 antibody and urological symptoms. However, the paper was published in abstract form, and many details are omitted. One of the points that might significantly influence the results is wash-out period, which was not specified. The authors stated "the titer of anti-HSP60 IgG1 antibody was significantly reduced compared with the pre-treatment level both in arms 1 and 2". If the drugs were switched without wash-out, the anti-HSP60 IgG1 titer would remain low because the first drug is still present and active at the time of cross-over. So the length of the wash-out period needs to be stated. In addition, the authors found "significant improvements in male patients of arm 1 and female patients of arm 2 after the treatment", but this remarkable result might not be fully appreciated because details, including male/female ratio, are not available. Publication of the details of this study is needed to obtain further valuable insights into the association between Kampo medicine and anti-HSP60 antibody.

12. Abstractor and date

Goto H, 17 September 2008, 6 January 2010, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Matsushita S, Ueda S, Ouchi Y, et al. Usefulness of Chotosan (TJ-47) for relieving the accompanying symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension. *Geriatric Medicine* 1995; 33: 1333-41 (in Japanese). Ichushi Web ID: 1996118416

1. Objectives

To evaluate the efficacy and safety of chotosan (釣藤散) for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Geriatrics, The University of Tokyo Hospital; Department of Geriatrics, Nippon Medical School Hospital; and five hospitals, Japan.

4. Participants

Twenty-two patients with sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension, and the accompanying symptoms, such as headache, heaviness of head, and dizziness.

5. Intervention

Arm 1: treatment with TSUMURA Chotosan (釣藤散) Extract Granules 2.5 g t.i.d. orally between meals for 12 weeks (n=11).

Arm 2: treatment with dilazep hydrochloride 50 mg t.i.d. orally between meals for 12 weeks (n=11).

6. Main outcome measures

Subjective symptoms (headache, heaviness of head, dizziness, stiff shoulders, palpitation, chest distress, hot flashes, tinnitus, numbness, cold extremities, and fatigue), psychiatric symptoms (disorientation, loss of memory, bad mood, depression, anxiety and irritation, deranged speech, and decreased motivation), and blood pressure measured at baseline and 4, 8, and 12 weeks from the start of the study.

7. Main results

Because one patient in arm 2 withdrew due to a staggering walk, 11 patients in arm 1 and 10 in arm 2 were included in the analysis of results. Headache, heaviness of head, dizziness, stiff shoulders, depression, and anxiety and irritation were significantly improved in arm 1 compared to arm 2. Blood pressure in the sitting position was lowered significantly from 156/91 mmHg at baseline to 142/84 mmHg at 12 weeks in arm 1. In contrast, no significant change in blood pressure was observed in arm 2 (149/84 mmHg at baseline to 146/82 mmHg at 12 weeks) and there was no between-arm difference. When the change in blood pressure was subjectively rated on a 4-point scale (1: lowered - 4: elevated), the improvement at 12 weeks was significantly better in arm 1 than in arm 2.

8. Conclusions

Chotosan, compared with dilazep hydrochloride, is more effective for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension, as well as for lowering blood pressure.

9. From Kampo medicine perspective

To determine which pattern (*kyo-sho* [虚証, deficiency pattern], *chukan-sho* [中間証, intermediate pattern], or *jitsu-sho* [実証, excess pattern]) each participant had, diagnoses were made using the *jitsu-sho* scoring system of the *kyo-jitsu* assessment. All the participants were diagnosed as having *kyo-sho*, making it impossible to determine the efficacy of chotosan for these three different patterns. In addition, no correlation was revealed by stratified analysis of global improvement ratings according to the indication of chotosan, including severity measures of headache, heaviness of head, dizziness, stiff shoulders, palpitation, choking feeling in the chest, hot flashes, tinnitus, disorientation, memory decline. There was no correlation between the degree of blood pressure lowering and the *jitsu-sho* score or the *sho*-related measures.

10. Safety assessment in the article

One patient in arm 1 developed mild elevation of lactose dehydrogenase (LDH) after 12 weeks of treatment. One patient in arm 2 discontinued the treatment due to staggering walk.

11. Abstractor's comments

This is an innovative clinical study that attempted to evaluate the efficacy of chotosan based on a consideration of *sho*, and determined objectively the efficacy of chotosan for relieving the symptoms and sequelae of cerebrovascular disease, chronic cerebrovascular insufficiency, or hypertension. However, each arm included only 11 patients and even fewer patients were included in the analysis of symptom improvement. This may explain why a significant difference was not detected. Furthermore, dilazep hydrochloride, which was used as a control, may cause, although uncommonly, adverse reactions such as headache, dizziness, and palpitation. The selection of this drug as a control would seem to be inappropriate because its adverse reactions are also among the variables used to measure outcome. Yet this is a remarkable clinical study that demonstrated the efficacy of chotosan in spite of the small number of patients.

12. Abstractor and date

Goto H, 18 September 2008, 1 June 2010.

18. Symptoms and Signs**Reference**

Nishizawa Y, Nishizawa Y, Fushiki S. Analgesic effects on headache in patients with spinal cord injury. *Nippon Zutsu Gakkaishi (Japanese Journal of Headache)* 1997; 25: 23-6. Ichushi Web ID: 2000154079

1. Objectives

To evaluate the efficacy and safety of chotosan (釣藤散) for relieving headache in patients with spinal cord injury.

2. Design

Double-blinded randomized controlled trial (DB-RCT).

3. Setting

Not mentioned (the first author belongs to a clinic), Japan.

4. Participants

Two hundred and fifty-one patients who complained of moderate or severe headache persisting for at least 6 months after spinal cord injury; had normal cognitive and communicative abilities; and had no other pain than headache.

5. Intervention

Arm 1: treatment with clonidine (9–13.5 µg) (n=33).

Arm 2: treatment with tizanidine (120–180 µg) (n=31).

Arm 3: treatment with chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=30).

Arm 4: treatment with loxoprofen (3.6–4.8 mg) (n=34).

Arm 5: treatment with clonidine (9–13.5 µg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=31).

Arm 6: treatment with tizanidine (120–180 µg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=29).

Arm 7: treatment with loxoprofen (3.6–4.8 mg) + chotosan (釣藤散; manufacturer, not specified) (90–120 mg) (n=32).

Arm 8: treatment with lactose (90–120 mg) (n=31).

Test drugs were administered orally in capsules, 3 hours before meals, for 6 months. Other details, including the frequency of administration, were not available.

6. Main outcome measures

Headache evaluated on a Visual Analogue Scale for pain (VAS-P) for 8 hours starting from 30 minutes before the administration. After 6 months of treatment, pain and quality of life (QOL) determined using the McGill Pain Questionnaire and evaluated using a VAS and verbal descriptor scale. Clonidine concentrations in cerebrospinal fluid and plasma measured only in patients who received this drug.

7. Main results

A total of 221 (30 in arm 1, 29 in arm 2, 28 in arm 3, 25 in arm 4, 28 in arm 5, 27 in arm 6, 24 in arm 7, and 30 in arm 8) out of 251 participants were included in the efficacy analysis. VAS-P and QOL were significantly improved only in arms 1 and 5 compared with the control ($P < 0.01$). Furthermore, the improvements in arm 5 were significantly greater than those in arm 1.

8. Conclusions

Chotosan enhances analgesic effect of clonidine for headache in patients with spinal cord injury.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse effects of clonidine were mentioned in the results section, but no details were given. Although 30 patients appear to have withdrawn during the 6-month treatment, no details were given either.

11. Abstractor's comments

This clinical study determined the effects of various drugs on headache due to spinal cord injury in 250 patients, and provided meaningful results which can be directly applied to clinical practice. The value of the paper would have been increased by inclusion of detailed descriptions of the administration method, adverse drug reactions, etc. As for study design, many ineffective control drugs were used in this study. From the perspective of ethics, the effects of those drugs should have been observed in a shorter-term study. Although this study was reported to be a “double blind test”, the numbers of capsules administered varied between arms and some problems with blinding are suspected. Furthermore, results from the clinical evaluation of various drugs were reported along with the correlation of blood clonidine concentration and pain. Preferably, these results should have been described clearly and separately in the methods and results sections. Nonetheless, this is a meaningful clinical study that provided a lot of valuable data and clarified the efficacy of chotosan combination therapy.

12. Abstractor and date

Goto H, 22 September 2008, 6 January 2010, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**References**

Seki H, Tateyama M, Sahara M, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization using the sealed-envelope method)*. *Shinryo to Shinyaku (Medical Consultation & New Remedies)* 1991; 28: 573–6 (in Japanese). Ichushi Web ID: 1992103222

Seki H, Okita N, Takase S, et al. Pain-relieving effect of goshuyuto on chronic headache: comparison with keishininjinto (with randomization carried out using the sealed-envelope method)*. *Pharma Medica* 1993; 11: 288–91 (in Japanese). Ichushi Web ID: 1994170314

1. Objectives

To evaluate the efficacy and safety of goshuyuto (呉茱萸湯) for relieving chronic headache using keishininjinto (桂枝人參湯) as a control.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The department of neurology of one hospital, Japan.

4. Participants

Eighty-eight patients with chronic headache.

5. Intervention

Arm 1: oral administration of goshuyuto (呉茱萸湯) (manufacturer unknown) 2.5 g t.i.d. for 4 weeks (n=44).

Arm 2: oral administration of keishininjinto (桂枝人參湯) (manufacturer unknown) 2.5 g t.i.d. for 4 weeks (n=44).

6. Main outcome measures

Headache severity rated on a 4-point scale.

7. Main results

Headache severity was at least moderately improved in 56.8% and 38.6% of patients and at least slightly improved in 79.5% and 61.4% of patients in the goshuyuto (呉茱萸湯) group and keishininjinto (桂枝人參湯) group, respectively.

8. Conclusions

The effect of goshuyuto on chronic headache is comparable to that of keishininjinto.

9. From Kampo medicine perspective

Goshuyuto was expected to be effective in patients prone to obesity and constipation and with cold limbs, whereas keishininjinto was expected to be effective in lean patients prone to loose stool.

10. Safety assessment in the article

Mild increase in gamma-glutamyltranspeptidase (γ -GTP), glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) or prickly heat rash was noted in 3 patients in arm 1.

11. Abstractor's comments

This clinical study investigated the efficacy of goshuyuto for chronic headache using keishininjinto as a control and is excellent because it reviewed the *sho* (証, pattern) of the responsive group with the intention of elucidating the pathology of chronic headache according to Kampo concepts. Unfortunately, the results were not statistically significant. The failure to demonstrate a significant between-arm difference may be due to the use of only one measure of headache severity. Evaluating headache frequency, time to resolution, and frequency of use of as-needed drugs might have revealed differences in the efficacy of goshuyuto and keishininjinto. The names of the drug combinations and drug manufacturers should also have been specified. In addition, the *sho* (証, pattern) should have been used to identify the indications for goshuyuto and keishininjinto rather than to compare the indications for these medicines. Nevertheless, this clinical study is valuable because it considered the difficulty of using a placebo in patients with clinical complaints. The article by Seki et al (1991) was the interim report for this study.

12. Abstractor and date

Goto H, 14 September 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs

References

Odaguchi H, Hanawa Y. Complementary alternative medicine in headache treatment*. *Igaku no Ayumi (Journal of Clinical and Experimental Medicine)* 2005; 215: 1137-40 (in Japanese) [MOL](#), [MOL-Lib](#)
Odaguchi H, Wakasugi A, Ito H, et al. The efficacy of goshuyuto, a typical Kampo (Japanese herbal medicine) formula, in preventing episodes of headache. *Current Medical Research and Opinion* 2006; 22: 1587-97. CENTRAL ID: CN-00571314, Pubmed ID: 16870083

1. Objectives

To evaluate the efficacy of goshuyuto (呉茱萸湯) for relief of chronic headache and to evaluate the associated adverse drug reactions.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Three university-associated outpatient headache clinics, Japan.

4. Participants

Fifty-three patients with chronic headache that responded to goshuyuto orally administered for 4 weeks.

5. Intervention

Arm 1: oral administration of 7.5 g/day of TSUMURA Goshuyuto (呉茱萸湯) Extract Granules for 12 weeks (n=28).

Arm 2: oral administration of the same dose of placebo granules indistinguishable in appearance, taste, and odor from goshuyuto for 12 weeks (n=25).

6. Main outcome measures

Headache severity, headache frequency, and severity of cold, menstrual cramps, and shoulder stiffness evaluated in all participants.

Surface temperature of fingers and toes, skin blood flow, deep body temperature, brain and femoral oxygen saturation, rigidity of the trapezius muscle, and blood serotonin concentration evaluated in some participants.

7. Main results

After a 12-week treatment, the number of days with headache was significantly decreased from baseline by 2.6 in arm 1 but remained unchanged in arm 2 (decreased by 0.3), showing significantly greater improvement in arm 1 than in arm 2. In addition, the number of doses of an analgesic taken was significantly decreased from baseline by 2.2 in arm 1 but remained unchanged (decreased by 1.4) in arm 2, indicating no between-arm difference. Comparison limited to migraine disclosed the same trend. There were no significant changes in the other parameters in both arms.

8. Conclusions

Goshuyuto decreases the frequency of headache episodes in patients with chronic headache, thereby reducing the number of analgesic doses.

9. From Kampo medicine perspective

This study considers *sho*, since its first stage involved selection of only goshuyuto-responders as “*sho* for goshuyuto,” and these were enrolled in a double-blind, randomized controlled trial at the second stage.

10. Safety assessment in the article

No adverse drug reactions occurred except for increases in ALT, AST and γ -GTP in 1 patient receiving goshuyuto. These reactions persisted 3 months after drug discontinuation, suggesting possible development of fatty liver.

11. Abstractor's comments

In this study, goshuyuto was administered to 91 patients with chronic headache at its first stage to select responders (n=53) for a double-blind, randomized controlled trial at its second stage. Thus, it may be a groundbreaking study in that it focused on “*sho*.” Besides headache, menstrual cramps and shoulder stiffness also tended to be improved by treatment with goshuyuto, warranting investigation with a larger sample size to clarify “goshuyuto-*sho*.” More clinical studies in oriental medicine such as the present study are expected in the future.

12. Abstractor and date

Goto H, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Hasegawa K, Mizutani Y, Kuramoto H, et al. The Effect of L-glutamine and shakuyaku-kanzo-to for paclitaxel-induced myalgia/arthralgia. *Gan to Kagaku Ryoho (Japanese Journal of Cancer and Chemotherapy)* 2002; 29: 569-74 (in Japanese with English abstract). Ichushi Web ID: 2002217069 [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the efficacy and safety of shakuyakukanzoto (芍薬甘草湯) and L-glutamine for paclitaxel-induced myalgia and arthralgia.

2. Design

Crossover randomized controlled trial (RCT-crossover).

3. Setting

Department of Obstetrics and Gynecology, Okayama University Medical School, Japan.

4. Participants

Fifteen patients with ovarian (n=13), cervical (n=1), or vulva (n=1) cancer who: 1) had received chemotherapy including paclitaxel (TXL) in December 1999 through July 2000; 2) had developed myalgia and arthralgia; and 3) were scheduled for 2 or more cycles of chemotherapy. The data from twelve of these patients were analyzed.

5. Intervention

Arm 1: TXL treatment combined with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day (three divided doses) in the second cycle and with L-glutamine 2.0 g/day (three divided doses) in the third cycle, in 7 patients.

Arm 2: TXL treatment combined with L-glutamine 2.0 g/day (three divided doses) in the second cycle and with shakuyakukanzoto (芍薬甘草湯) 7.5 g/day (three divided doses) in the third cycle, in 8 patients.

The first cycle (TXL monotherapy), in which pain occurred, was considered to be a control.

Shakuyakukanzoto (芍薬甘草湯) and L-glutamine were orally administered from 1 week before the TXL treatment until the pain resolved.

A single dose of an NSAID (Voltaren: 25 mg) was given if the effects of test drugs were poor. The washout period was at least one week

6. Main outcome measures

The efficacy was evaluated based on: 1) sum of pain scores; 2) duration of myalgia and arthralgia; 3) duration of grade 2 or greater myalgia and arthralgia; 4) number of analgesics used; and 5) final subjective impressions.

7. Main results

Twelve patients were evaluated in the final analysis. Reductions of the duration of myalgia and arthralgia were significantly different between the control and the L-glutamine-treated patients. Reductions of the duration of grade 2 or greater myalgia and arthralgia in the shakuyakukanzoto- and the L-glutamine-treated patients differed significantly from that of the control patients. No significant differences occurred in any variable between the shakuyakukanzoto- and the L-glutamine-treated patients.

8. Conclusions

Shakuyakukanzoto and L-glutamine have no dramatic effects on paclitaxel-induced myalgia and arthralgia, except for the reduction of the duration of grade 2 or greater pain.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One L-glutamine-treated patient reported nausea and one shakuyakukanzoto-treated patient could not take the drug for an unspecified reason.

11. Abstractor's comments

Shakuyakukanzoto is effective for pains associated with smooth and skeletal muscle spasm. In contrast, arthralgia (a paclitaxel-induced adverse reaction) is not included as an indication for treatment with shakuyakukanzoto. However, excellent responses were reported in the present study. The efficacy of this drug for this indication might be confirmed in the future by increasing the number of patients, as well as by identifying candidate patients for this treatment from an analysis of responders and non-responders.

12. Abstractor and date

Okabe T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Satoh N, Sakai S, Kogure T, et al. A randomized double-blind placebo-controlled clinical trial of hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness, N of one and responder restricted design. *Phytomedicine* 2005; 12: 549-54. CENTRAL ID: CN-00524047, Pubmed ID: 16121514

1. Objectives

To evaluate the efficacy of hochuekkito (補中益氣湯) for the elderly with weakness.

2. Design

Double-blind, randomized controlled trial (DB-RCT) in combination with N-of-1 trial restricted to hochuekkito-responders.

3. Setting

Five hospitals associated with Toyama Medical and Pharmaceutical University (now Toyama University), Japan.

4. Participants

Fifteen elderly patients (3 males and 12 females; age [mean \pm SD], 78.4 \pm 7.8 years) with weakness satisfying the following 4 inclusion criteria: (1) complaint of discomfort and anorexia due to chronic debilitating disease; (2) no history of infection or vascular disorder within 1 month before the start of the trial; (3) no malignant diseases; and (4) aged \geq 60 years and $<$ 90 years.

5. Intervention

Responders during the 2-week run-in period were randomly assigned to the following 3 arms:

Arm 1: administration of Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of placebo at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Arm 2: administration of placebo (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=5).

Arm 3: administration of Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Responders had to meet criterion (1) and one of the three other criteria (2) to (4): (1) good drug compliance; (2) subjective overall evaluation improved; (3) clinical symptoms improved; or (4) symptoms other than chief complaint improved.

6. Main outcome measures

36-item short-form health survey (SF36), profile of mood states (POMS), natural killer (NK) activity, interleukin (IL)-2-producing activity of peripheral lymphocytes, lymphocyte-proliferating activity, and lymphocyte cell-surface antigens.

7. Main results

PCS (physical component summary) of SF36 was significantly improved in the hochuekkito group ($P<0.05$). There were significant among-arm differences in 4 (anger-hostility, fatigue, tension-anxiety, confusion) of 6 subscales of the POMS ($P<0.01$, $P<0.05$, $P<0.01$, $P<0.05$, respectively). Lymphocyte cell-surface antigens, CD3-positive cells, and CD3/CD4 double-positive cells were significantly increased in the hochuekkito group ($P<0.05$).

8. Conclusions

Hochuekkito improves the QOL of elderly patients with weakness and activated their immune systems.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred.

11. Abstractor's comments

The design of this study is very interesting, being a combination of RCT and N-of-1 trial. The authors mention that 15 candidates were registered and none dropped out; however, the actual number was 13 (four participants in arm 1, five in arm 2, and four in arm 3). The authors treated the participants as one group, with a washout period separating the interventions in each arm, and proceeded on a two-group basis by converting to a hochuekkito (補中益氣湯) group (17 participants), and a placebo group (nine participants). The authors argue that they added an N-of-1 trial to a small-scale RCT; however, there is no before-after comparison for the N-of-1 trial, and it rather resembles a crossover trial (DB-RCT-crossover). Interpreting results from a complex design is difficult. Hopefully the authors will further develop their approach.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Jeong JS, Ryu BH, Kim JS, et al. Bojungikki-tang for cancer-related fatigue: A pilot randomized clinical trial. *Integrative Cancer Therapies* 2010; 9: 331–8. CENTRAL ID: CN-00770648, Pubmed ID: 21059621

1. Objectives

To evaluate the effectiveness of hochuekkito (補中益氣湯) for cancer-related fatigue.

2. Design

Randomized controlled trial (RCT).

3. Setting

East-West Neo Medical Center, Kyung Hee University, Republic of Korea.

4. Participants

Forty patients with cancer-related fatigue (May to October 2009).

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益氣湯) Extract Granules 7.5 g/day for 2 weeks (n=20).

Arm 2: no treatment, course monitored for 2 weeks (n=20).

6. Main outcome measures

Primary outcome measure: Visual Analogue Scale of Global Fatigue (VAS-F)

Secondary outcome measures: Functional Assessment of Cancer Therapy-General (FACT-G), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Trial Outcome Index-Fatigue (TOI-F).

7. Main results

Eighteen patients were included in each group for evaluation. Significant improvements were observed in arm 1 compared to arm 2 for before/after changes in all measures, VAS-F ($P=0.040$), FACT-G ($P=0.047$), FACT-F ($P=0.025$), and TOI-F ($P=0.049$).

8. Conclusions

Hochuekkito improves cancer-related fatigue.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood tests (aspartate amino transferase [AST], alanine aminotransferase [ALT], creatinine, blood urea nitrogen [BUN]) were performed before and after administration, and participants were asked about subjective symptoms using a questionnaire based on version 2.0 of the NCI-CTC-AE questionnaire. Although these results showed no significant change in liver or kidney function, two participants complained of grade 1 stomach discomfort.

11. Abstractor's comments

While fatigue is the most commonly known indication for hochuekkito, this study is valuable for having verified its effectiveness and safety for cancer patients through an RCT. Yet, the inclusion criteria included a two-month gap since chemo- or radiotherapy, which raises questions about whether their influence could really be ruled out. Furthermore, a placebo effect cannot be completely ruled out because no treatment was administered in arm 2, and the administration period was only two weeks. In future, such a study would hopefully give the control group a placebo, or increase the number of subjects, for treatment over a longer period.

12. Abstractor and date

Motoo Y, 31 December 2012.

18. Symptoms and Signs

Reference

Ohno S, Suzuki T, Asaoka T, et al. Effects of Oriental medicine on lymphoid cells. *Kampo to Meneki-Allergy (Kampo and Immunoallergy)* 1995; 9: 78-86 (in Japanese with English abstract). Pubmed ID: 21724872

1. Objectives

To evaluate the effect of hochuekkito (補中益氣湯) on lymphocytes.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

One center: the Second Department of Internal Medicine, Saitama Medical University Hospital, Japan.

4. Participants

Thirty people who presented at an Oriental medicine outpatient clinic with fatigue.

5. Intervention

Arm 1: TSUMURA Hochuekkito (補中益氣湯) Extract Granules group (n=15).

Arm 2: TSUMURA Hachimijiogan (八味地黄丸) Extract Granules group (n=15).

6. Main outcome measures

Changes in leukocyte, neutrophil, and lymphocyte counts; response of lymphocytes to phytohemagglutinin (PHA) and concanavalin A (ConA) stimulation.

7. Main results

No changes in leukocyte or neutrophil count were observed. Lymphocyte count increased significantly in arm 1 ($P<0.05$). Lymphocyte count decreased with PHA and ConA stimulation in arm 2, and, conversely, lymphocyte count (particularly large-granular lymphocyte count) increased with ConA stimulation in arm 1.

8. Conclusions

Hachimijiogan and hochuekkito have different effects on the lymphocyte system *in vivo*.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One participant taking hochuekkito suffered constipation and three taking hachimijiogan suffered stomach discomfort, but no serious adverse effects were observed.

11. Abstractor's comments

While the significant increase in lymphocyte count in the hochuekkito group is the starting point for this study, the lymphocyte counts prior to treatment in the control group (hachimijiogan group) were widely scattered, which might explain the lack of any significant difference between the groups (Fig. 6 and Fig. 7). Increasing the number of participants in a future study may reduce between-group differences. Accordingly, it would be better to make the control group a no-treatment group, rather than a hachimijiogan group. Interestingly, the increase in the lymphocyte count (particularly large-granular lymphocyte count) and NK activity in the hochuekkito group suggests hochuekkito has an effect on tumor immune cells. Hopefully the authors will conduct a further study into the question of whether hachimijiogan and hochuekkito have similar activities, with an increased number of participants.

12. Abstractor and date

Nakata H, 31 December 2013.

18. Symptoms and Signs**Reference**

Ishioka T. Comparison of the efficacy of goreisan and saireito for mild edema of the dorsum of the foot in elderly subjects stratified by physical strength*. *Kampo no Rinsho (Journal of Kampo Medicine)* 1997; 44: 1091-5 (in Japanese).

1. Objectives

To compare the efficacy of goreisan (五苓散) and saireito (柴苓湯) for mild edema of the dorsum of the foot in the elderly.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

A special nursing home, Japan.

4. Participants

Forty-three patients who were admitted to the nursing home, had no serious cardiac diseases, had a serum creatinine level within normal limits, and complained of mild persistent edema of the dorsum of the foot (9 males and 34 females, aged 66-94 years, mean age 83.1 years). Of these 43 patients, 21 were placed into a "moderate physical strength" subgroup and 22 into a "low physical strength" subgroup, on the basis of strength demonstrated during a balloon volleyball game played in the nursing home.

5. Intervention

Arm 1: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. for 2 weeks, then switched, with no wash-out, to TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 2 weeks. The sample size was not reported.

Arm 2: treatment with TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 2 weeks, then switched, with no wash-out, to TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d. for 2 weeks. The sample size was not reported.

6. Main outcome measures

Disappearance of edema after 2 weeks of treatment was rated as "moderate response"; marked reduction of edema as "mild response"; no change as "no response"; and symptomatic exacerbation requiring diuretics after 1 week, or marked exacerbation after 2 weeks of treatment as "worsening". The two drugs were considered as "having comparable efficacy" when the extent of symptomatic changes during the first and the second 2 weeks were similar.

7. Main results

One patient was hospitalized with bronchitis on day 3 of the saireito treatment following the goreisan treatment. Consequently, the efficacy of goreisan but not saireito was evaluated in this patient. As a result, efficacy analysis population included 43 patients for goreisan and 42 for saireito. A "mild" or better response was obtained in 67% of the goreisan-treated and 62% of the saireito-treated patients; the difference was not significant. In the subgroup with moderate physical strength, there was no significant difference in the rate of response to goreisan (57%) and saireito (62%). In contrast, the rate of response to goreisan (77%) tended to higher than that to saireito (62%; $P < 0.1$) in the subgroup with low physical strength.

8. Conclusions

Both goreisan and saireito results in a "mild" or better response in 60% or more of the elderly patients with mild edema of the dorsum of the foot. Notably, patients with low physical strength tended to be more responsive to goreisan.

9. From Kampo medicine perspective

The author argued that the classification "low physical strength" is almost identical to the definition of weak constitution in the clinical guidelines for the reevaluation of Kampo extract preparations, and that "low physical strength" and weak constitution are consistent with the Kampo concept of *kyo-sho* (虚証, deficiency pattern).

10. Safety assessment in the article

Although no individual patients developed abnormalities while taking the test drugs, a decrease in potassium level in all patients and an elevated serum creatinine level in the subgroup with low physical strength were observed. Subjective or objective symptoms were not reported.

11. Abstractor's comments

This study was a cross-over trial conducted in a special nursing home. There are some problems with the study design, such as the absence of wash-out period and the non-blinded design. The development of further studies is expected.

12. Abstractor and date

Tsuruoka K, 25 April 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Kishida Y, Miki H, Nishii T, et al. Therapeutic effects of Saireito (TJ-114), a traditional Japanese herbal medicine, on postoperative edema and inflammation after total hip arthroplasty. *Phytomedicine* 2007; 14: 581-6. CENTRAL ID: CN-00609214, Pubmed ID: 17292595

1. Objectives

To investigate the efficacy and safety of saireito (柴苓湯) on postoperative edema and inflammation after total hip arthroplasty (THA).

2. Design

Randomized controlled trial (RCT).

3. Setting

Two departments (Department of Kampo Medicine and Department of Orthopaedic Surgery) of Osaka University, and one hospital, Japan.

4. Participants

Female patients who underwent THA because of unilateral osteoarthritis, n=17.

5. Intervention

Arm 1: Tsumura Saireito (柴苓湯) Extract Granules 9.0 g/day for 2 days before surgery and for 2 weeks after surgery, n=8.

Arm 2: no administration, n=9.

6. Main outcome measures

The circumference of the lower limb at three locations (the lower leg, ankle, and forefoot), Merle d'Aubigne hip score for clinical evaluation including pain, and serum C-reactive protein (CRP) level.

7. Main results

At three weeks after surgery, the circumference of the lower leg was less in arm 1 than in arm 2. The serum CRP level became negative by 2 weeks after surgery in 6 of 8 patients in arm 1 and in 0 of 9 patients in arm 2 ($P<0.001$).

8. Conclusions

Administration of saireito is suggested to reduce postoperative lower leg edema and inflammation after THA.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were reported in arm 1 and documented in arm 2.

11. Abstractor's comments

This study suggests the efficacy of saireito for postoperative lower leg edema after THA. In this trial, all patients had a pneumatic foot compression device and wore compression stockings concurrently to prevent postoperative lower leg swelling. This study also indicated that saireito is effective in decreasing postoperative inflammation. All patients received an intravenous infusion of prophylactic antibiotics for 4 days, subsequently oral antibiotics for 4 days, and nonsteroidal anti-inflammatory drugs (NSAIDs) for 1 week after surgery. However, CRP level remained positive in all subjects in arm 2, two weeks after surgery. In general, a few days' treatment with antibiotics should lead to a negative CRP level by two weeks after surgery. Further clinical studies with more patients and fewer concomitant therapies for knee replacement arthroplasty and bipolar hip arthroplasty are awaited and anticipated.

12. Abstractor and date

Okabe T, 11 December 2008, 1 June 2010, 31 December 2013.

18. Symptoms and Signs**Reference**

Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2010; 61: 78–83 (in Japanese with English abstract). Ichushi Web ID: 2010110656
[J-STAGE](#)

1. Objectives

To evaluate the efficacy of preoperative administration of hochuekkito (補中益気湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Okayama University Hospital and 8 related facilities, Japan.

4. Participants

Fifty-one patients undergoing laparotomy for advanced gastric/colon cancer in the period between February and December 2004.

5. Intervention

Medication taken for 7 consecutive days preoperatively to the day before surgery.

Arm 1: hochuekkito (補中益気湯) extract granules (manufacturer not indicated) 2.5 g t.i.d. (n=24).

Arm 2: no administration (n=27).

6. Main outcome measures

Serum cortisol level and soluble interleukin (IL)-2 receptor (sIL-2R) level immediately before and at 1 day after the operation; white blood cell (WBC) count and differential WBC count before and 1 and 7 days after the operation; C-reactive protein (CRP) level before and 1, 3, and 7 days after the operation; body temperature/pulse rate from the day before to 14 days after the operation; use of antibiotics until 14 days after the operation.

7. Main results

The analysis population consisted of 48 patients (after 2 and 1 patient dropped out in arm 1 and arm 2, respectively). There was no significant between-arm difference in preoperative serum cortisol level, but a tendency toward lower preoperative sIL-2R level in the hochuekkito group ($P=0.08$). The percent decline in cortisol level from preoperative baseline to postoperative day 1 value was significantly greater in arm 1 than in arm 2 ($P=0.04$), while there was no significant between-arm difference in the decline in sIL-2R level, WBC count, differential WBC count, or CRP level before and 1 and 7 days after the operation. The pre- to postoperative declines in mean body temperature and mean pulse rate were significantly greater in arm 1 ($P=0.0002$ and $P=0.03$, respectively). Fewer patients used second-line antibiotics postoperatively in the hochuekkito group than in the control group ($P=0.05$).

8. Conclusions

Preoperative administration of hochuekkito significantly suppresses the postoperative inflammatory response to surgical wounding.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study is significant because it demonstrates by RCT that preoperative 1-week administration of hochuekkito significantly suppresses postoperative SIRS, while focusing on the characteristics of Kampo medicine for treating *mibyō* (未病, subclinical state). The use of antibiotics, mentioned in the last section of the results, was said to be “significantly different between arms” even though $P=0.05$. The criterion for significance, indicated in the text, was $P < 0.05$. Preoperative administration of hochuekkito reduced postoperative complications and duration of hospitalization, which is medically and economically beneficial. Furthermore, administration of hochuekkito may raise the awareness of patients and prepare them for surgery.

12. Abstractor and date

MotooY, 30 December 2010.

18. Symptoms and Signs

References

Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san, an oriental herbal medicine, in obese Japanese women with impaired glucose tolerance. *Clinical and Experimental Pharmacology and Physiology*, 2004; 31: 614-9. CENTRAL ID: CN-00505762, Pubmed ID: 15479169

Hioki C, Yoshimoto K, Yoshida T. Efficacy of bofu-tsusho-san in obese Japanese women with IGT. *Rinsho Kampo Yakuri Kenkyukai Kaishi (Journal of the Society for Clinical Kampo Pharmacology)*, 2004; 100th Memorial Issue: 19-22. Ichushi Web ID: 2006163538

Hioki C. The first randomized trial of bofutsushosan in obese patients with IGT. *Pharma Medica* 2007; 25: 43-8 (in Japanese) Ichushi web ID: 2008035994, MOL, MOL-Lib

Hioki C, Arai M. Bofutsushosan use for obesity with IGT: search for scientific basis and development of effective therapy with Kampo medicine. *Journal of Traditional Medicine* 2007; 24: 115-27. *Journal of Traditional Medicine* 2007; 24: 115-27. J-STAGE

1. Objectives

To evaluate the efficacy and safety of bofutsushosan (防風通聖散) in obese Japanese women with impaired glucose tolerance.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

An university hospital (Kyoto Prefectural University of Medicine), Japan.

4. Participants

Eighty-one obese women (mean body mass index, 36.5 kg/m²) with impaired glucose tolerance were included. Patients with kidney, heart and/or liver disease, any metabolic or endocrine disease, psychiatric disorders, or cancer were excluded.

5. Intervention

Arm 1: treatment with TSUMURA Bofutsushosan (防風通聖散) Extract Granules for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (44 patients; of these, 41 were included for analysis).

Arm 2: treatment with placebo for 24 weeks + low-calorie diet (1,200 kcal) + exercise therapy (300 kcal) (41 patients; of these, 40 were included for analysis).

6. Main outcome measures

Body weight, the proportion of body fat (% weight), visceral and subcutaneous fat accumulation, systolic and diastolic blood pressure, heart rate, biochemical data (triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, uric acid, glycosylated hemoglobin (HbA1c), and fasting glucose), and waist and hip circumference were measured before treatment, and after 12 and 24 weeks of treatment. Values for 2-h oral glucose tolerance test (OGTT) glucose, glucose area under the curve (AUC) 120, fasting insulin, insulin AUC120, and homeostasis model assessment of insulin resistance (HOMA-IR) were measured or calculated after 24 weeks.

7. Main results

Waist circumference decreased in both arms after 12- and 24-week treatment compared with before treatment. The decrease was significantly greater after 24 weeks in Arm 1 compared with Arm 2. There were significant differences in more measures after 24 weeks than after 12 weeks in both arms. In Arm 2, body weight, body fat (%), and subcutaneous fat decreased only after 24 weeks; systolic and diastolic blood pressure, triglyceride, and total cholesterol reduced after 12 and 24 weeks. In Arm 1, body weight, body fat (%), visceral and subcutaneous fat, systolic and diastolic blood pressure, biochemical data (LDL cholesterol, HDL cholesterol, uric acid, and insulin [fasting and AUC120]), 2-h OGTT glucose, and HOMA-IR improved after 24 weeks. The decrease in body weight in Arm 1 was associated with decreased visceral and subcutaneous fat but not with a decrease in adjusted resting metabolic rate, whereas the weight loss in Arm 2 was not associated with decreased visceral fat.

8. Conclusions

Bofutsushosan is useful in the treatment of obese patients with impaired glucose tolerance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was no effect on cardiovascular or central nervous system in the two arms. Although no subject had steatorrhea, 3 subjects in the bofutsushosan arm discontinued treatment and withdrew from the study because of diarrhea. One subject in the placebo arm dropped out of the study owing to noncompliance.

11. Abstractor's comments

This DB-RCT (examining the efficacy and safety of bofutsushosan in obese Japanese women with impaired glucose tolerance) provides a high quality of evidence. Although body weight tended to decrease between 12 and 24 weeks of treatment in the placebo arm, it can still be concluded that the anti-obesity effect of bofutsushosan combined with diet and exercise therapies is more likely to persist potently. Further studies should be conducted to evaluate the effect of bofutsushosan monotherapy without diet and exercise therapies. Investigations with Kampo diagnostic considerations are also needed.

12. Abstractor and date

Namiki T, 15 September 2007, 1 April 2008, 13 March 2009, 1 June 2010, 31 December 2013.

19. Extrinsic Injuries/Diseases**Reference**

Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. *Kampo to Rinsho (Journal of Kampo Medicine)* 2010; 1: 128–32 (in Japanese). Ichushi Web ID: 2010218384

1. Objectives

To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.

2. Design

Randomized controlled trial (RCT).

3. Setting

One orthopedic clinic, Japan.

4. Participants

Thirty-five outpatients with grade III fresh ATFL isolated injury who received conservative therapy from April 2008 to March 2009.

5. Intervention

Treatment lasted approximately two weeks.

Arm 1: TSUMURA Jidabokuippo (治打撲一方) Extract Granules 2.5–7.5 g/day (n=17 [17 legs]).

Arm 2: loxoprofen sodium 60–180 mg/day (n=18 [18 legs]).

The dose was calculated per kg of body weight.

6. Main outcome measures

Pain (visual analogue scale [VAS]), swelling (average circumference at 5-cm centrally and peripherally from the ATFL rupture site).

7. Main results

Of 17 patients in arm 1, the pain had resolved within three weeks of trauma in 11 patients, within four weeks in 4, within six weeks in 1, and within 12 weeks in 1, and of 18 patients in arm 2, within three weeks in 12, within four weeks in 2, within six weeks in 2, and within 12 weeks in 2. The swelling had resolved within three weeks in 12 patients, within four weeks in 2, within six weeks in 2, and within 12 weeks in 1 in arm 1 and within three weeks in 9, within four weeks in 4, within six weeks in 3, and within 12 weeks in 2 in arm 2. A tendency toward earlier resolution of swelling was found in arm 1 at 2 weeks after trauma, and eventually disappeared.

8. Conclusions

The efficacy of the Western medicine and the Kampo medicine (jidabokuippo) for pain and swelling in grade III fresh ATFL isolated injury is comparable. The jidabokuippo treatment tends to resolve swelling earlier.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Clinical testing was not carried out and there were no adverse events.

11. Abstractor's comments

This paper is clinically significant because it compares the efficacy of loxoprofen sodium with that of jidabokuippo for pain and swelling in grade III fresh ATFL isolated injury in an RCT. Unfortunately, statistical analysis between groups was not sufficiently powerful to distinguish between the groups. However, from the viewpoint of primary care for grade III fresh lateral ligament injury of the ankle joint, the results of this paper are clinically quite significant, and further clinical study is anticipated.

12. Abstractor and date

Kogure T, 6 January 2011, 31 December 2013.

19. Post-anesthesia and Postoperative Pain**Reference**

Otake T, Kato I, Saito S, et al. The prophylactic effect of "gosyuyu-to" and "gorei-san" for post-spinal headache. *Pain Clinic* 1991; 12: 648-52 (in Japanese).

1. Objectives

To evaluate the efficacy of goshuyuto (呉茱萸湯) and goreisan (五苓散) for post-lumbar puncture headache (PLPH).

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the authors were affiliated with the Department of Anesthesiology, Isesaki Municipal Hospital), Japan.

4. Participants

Two hundred and ninety-five American Society of Anesthesiologists (ASA) PS I or II patients who underwent lumbar anesthesia.

5. Intervention

Arm 1: treatment with TSUMURA Goreisan (五苓散) Extract Granules 2.5 g orally 4 times, at night after surgery and in the morning, at noon, and in the evening of the following day (n=88).

Arm 2: treatment with TSUMURA Goshuyuto (呉茱萸湯) Extract Granules 2.5 g orally 4 times, at night after surgery and in the morning, at noon, and in the evening of the following day (n=93).

Arm 3: no treatment with Kampo medicine (n=114).

Indomethacin suppository was the only drug used for relieving postoperative wound pain.

6. Main outcome measures

Post-lumbar puncture headache (PLPH) severity was evaluated using a 5-point scale on days 1 (24 hours after the lumbar puncture), 2, 3, and 7.

7. Main results

The incidence of PLPH in all patients was 21.4%. Two-arm comparisons of the ratings of PLPH revealed significantly greater relief in arm 2 than arm 3 only on day 1 ($P<0.05$). Sex-specific analysis showed significantly greater relief in the female patients of arm 2 than of arm 3 on day 1 ($P<0.05$).

8. Conclusions

Goshuyuto seems to be effective for preventing and relieving headache after lumbar anesthesia or after intrathecal puncture during epidural block anesthesia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is an interesting clinical study of the efficacy of goshuyuto and goreisan for relieving PLPH. It is a well-designed study with appropriate consideration given to clinical details including patient characteristics, interactions with indomethacin, type of puncture needle, and patient position. Since the incidence of PLPH is low and decreases over time, the small sample size may have contributed to the lack of a statistically significant difference in the outcome. In addition, if Kampo medicines had been administered for the duration of PLPH (about a week), differences among the three arms might have appeared on other days besides day 1. Despite the limited number of cases, this clinical study demonstrated the efficacy of goshuyuto. Future consideration of sample size and treatment duration would help to further clarify the efficacy of Kampo medicines for PLPH.

12. Abstractor and date

Goto H, 15 September 2008, 1 June 2010, 31 December 2013.

19. Anesthesia, Postoperative Pain**Reference**

Isai H. Successful control of postoperative pain and hyperhidrosis by Kampo medicine after thoracotomy for pulmonary disease. *Itami to Kampo (Pain and Kampo Medicine)* 1997; 7: 29-32 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of keishikajutsubuto (桂枝加朮附湯) and shakuyakukanzoto (芍薬甘草湯) on postoperative pain and hyperhidrosis following thoracotomy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital, Japan.

4. Participants

Twenty patients who underwent thoracotomy for pulmonary disease (lung cancer in 19 patients and spontaneous pneumothorax in 1 patient).

5. Intervention

All patients were given 4-6 mg of epidural morphine daily for 5 days after surgery. In addition, indomethacin, diclofenac sodium, or buprenorphine hydrochloride suppository was used at the discretion of each patient. Kampo medicine was administered for 4 weeks beginning on postoperative day 7.

Arm 1: control group (no Kampo medicine) (n=7).

Arm 2: TSUMURA Keishikajutsubuto (桂枝加朮附湯) Extract Granules 2.5 g t.i.d. (n=7).

Arm 3: TSUMURA Keishikajutsubuto (桂枝加朮附湯) Extract Granules 2.5 g t.i.d. + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g t.i.d. (n=6).

6. Main outcome measures

Dose of analgesics, wound pain, hyperhidrosis.

7. Main results

The dose of analgesic suppositories tended to decrease over the first 3 postoperative weeks in all 3 groups, but leveled out in Arm 1 and continued to decrease in Arms 2 and 3 at Weeks 4 and 5, resulting in a significantly higher level in Arm 1 than in Arms 2 and 3. Wound pain was well controlled in all 3 groups including Arm 1, where pain could be controlled by high doses of analgesics. Hyperhidrosis was almost resolved at Week 4 in Arm 2 and at Week 5 in Arm 3, but occurred significantly more often in Arm 1 than in Arms 2 and 3.

8. Conclusions

Kampo preparations administered after thoracotomy, particularly keishikajutsubuto plus shakuyakukanzoto, reduces the use of analgesics as well as the severity of hyperhidrosis. Therefore, this Kampo preparation is recommended after thoracotomy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were reported.

11. Abstractor's comments

In the Discussion, it was stated that while keishikajutsubuto is effective for wound pain, shakuyakukanzoto is effective for hyperhidrosis. This was also shown graphically.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010.

19. Post-anesthesia and Postoperative Pain**Reference**

Miyazaki M, Yasui M, Ikenaga M, et al. The effect of Shakuyaku-kanzo-to (Tsumura TJ-68) on pain after hemorrhoidectomy – a prospective randomized study –. *Journal of the Japan Society of Coloproctology* 2012; 65: 313–7 (in Japanese with English abstract).

1. Objectives

To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) for pain after hemorrhoidectomy

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the first author belonged to the Department of Coloproctology, Dojinkai Dojin Hospital & the Department of Surgery, Osaka National Hospital), Japan.

4. Participants

Thirty-nine patients with hemorrhoids or mucosal prolapse who had undergone semi-closed hemorrhoidectomy.

5. Intervention

Arm 1: after hemorrhoidectomy, diclofenac sodium 25 mg t.i.d. plus TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 mg t.i.d. taken orally (n=18).

Arm 2: after hemorrhoidectomy, diclofenac sodium 25 mg t.i.d. alone taken orally (n=21).

In cases of poor analgesic action, both groups were permitted intramuscular injection of the painkillers pentazocine 15 mg plus hydroxyzine pamoate 25 mg, diclofenac sodium 50 mg suppository, or single-use loxoprofen sodium orally.

6. Main outcome measures

Pain score (maximum score for the day on a 10-point visual analog scale), type of pain (when resting, when defecating, when mobile), number of days till pain score fell below three, number of days till pain disappeared when resting, waking in the night due to pain, use of painkiller injection, additional use of nonsteroidal anti-inflammatory drugs (NSAIDs) by suppository or by mouth.

7. Main results

Excluding the day of surgery, pain scores were significantly lower in arm 1 compared to arm 2 on each day from the first to the ninth day after surgery ($P<0.05$). “Type of pain” results were not reported in the original paper. Significant differences between arm 1 and arm 2 were noted in the mean number of days till the pain score fell below three (2.1 vs 5.2; $P<0.05$) and use of painkiller injections (three times [17%] vs ten times [48%]; $P<0.05$) but not in the number of days till pain disappeared when resting, additional use of non-steroidal anti-inflammatory drugs (NSAIDs), or waking in the night due to pain.

8. Conclusions

Administration of shakuyakukanzoto in addition to NSAIDs is effective in improving pain after hemorrhoidectomy.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

No adverse effects of shakuyakukanzoto were observed.

11. Abstractor’s comments

This clinical study investigated the effectiveness of shakuyakukanzoto in addition to NSAIDs for pain after hemorrhoidectomy. While hemorrhoidectomy is excellent therapy, it is avoided because of the postoperative pain. This very interesting clinical study is intended to investigate whether that complication can be alleviated based on the unique idea of physicians. On the other hand, the pain score graphs imply that pain began to decrease in the shakuyakukanzoto group the day after surgery, even though there was no significant difference, which suggests a problem with the participant allocation method. Furthermore, while the mean pain scores were not significantly different immediately after surgery (5.7 without shakuyakukanzoto and 5.1 with shakuyakukanzoto), the difference was significant on the eighth day (2.4 and 2.1, respectively). It is also possible that variation had decreased by the eighth day; the mention of not just mean values but standard deviation suggests the possibility of deliberate emphasis on statistical differences. However, as the authors mention in the discussion, their treatment methods were relatively simple and potentially could alleviate pain, and should be further evaluated in a large-scale multi-center study.

12. Abstractor and date

Goto H, 31 December 2013.

19. Post-anesthesia and Postoperative Pain**Reference**

Watanabe Y, Asai S, Hida A, et al. Regarding the utility of saireito against keloid and hypertrophic scars following surgery and injury. *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2012; 67: 245–9 (in Japanese). Ichushi Web ID: 2012256652, [J-STAGE](#)

1. Objectives

To evaluate the effectiveness and safety of saireito (柴苓湯) for keloid and hypertrophic scars following surgery, burn injury, and wound injury.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Department of Plastic and Reconstructive Surgery, Chukyo Hospital (1 center), Japan.

4. Participants

Fifty patients with confirmed subjective/objective symptoms including itchiness, tenderness, spontaneous pain, flushing, induration, or swelling of keloid and hypertrophic scars following surgery, burn injury, or wound injury.

5. Intervention

Allocation proceeded alternately in the order of consultation.

Arm 1: Kracie Saireito (柴苓湯) Extract Fine Granules 8.1 g/day in three divided doses orally before meals for at least 12 weeks (n=29).

Arm 2: no administration of saireito (柴苓湯) (n=21).

Compression, external preparations, and patches were applied depending on the symptom, but internal medicines such as tranilast were not given. Ointments containing steroids were used as appropriate in all patients. Compression gear was used for patients who had keloid and hypertrophic scars around limb joints.

6. Main outcome measures

Scar height and subjective/objective symptoms (itchiness, tenderness, spontaneous pain, flushing, induration, and swelling) were measured/evaluated on a 4-point scale (3: severe, 2: moderate, 1: mild, 0: none) at the start and in week 2, 4, 8 and 12 of the study.

7. Main results

The analysis included all 50 patients except those who took anti-allergy medicine during the study. In comparison to arm 2, arm 1 had significantly improved scores for itchiness and flushing starting on week 8 (week 8: $P<0.05$; week 12: $P<0.01$) and significantly improved scores for scar height, tenderness, spontaneous pain, induration, and swelling ($P<0.01$).

8. Conclusions

Saireito improves symptoms of keloid and hypertrophic scars following surgery, burn injury, or wound injury.

9. From Kampo medicine perspective

Not mentioned.

10. Safety assessment in the article

No adverse effects of saireito were observed.

11. Abstractor's comments

This clinical study investigated the effectiveness of saireito for keloid and hypertrophic scars following surgery and injury. It is an advanced study that attempted to investigate the effects of saireito on pathological conditions with no effective therapy and which occur in large numbers of plastic surgery patients. The authors mention the number of patients whose results were analyzed but not the initial number of participants. Given that patients who took anti-allergy drugs were excluded from the analysis, the authors should have given the initial number of participants and the reasons for exclusion. Furthermore, because compression, external preparations, and patches were also used (depending on the symptom), mentioning the number of such cases would have clarified the details of the study. Additionally, the patient background table shows that 11 participants in the saireito group and only one in the no treatment group had scars due to wound injury. Since hypertrophic scars improve more readily than keloid scars, the authors should have considered whether any bias was attributable to the primary disease. Moreover, scar height improved from 1.5 mm to 0.5–1.0 mm; unless centimeters were misreported as millimeters, this is an extremely small change. Thus, the authors should have described their measurement methods. Yet, this clinical study is praiseworthy for being based on past reports and for detecting an effect of saireito on a pathological condition with no established treatment. Hopefully the authors will further evaluate its effectiveness in a multicenter study.

12. Abstractor and date

Goto H, 31 December 2013.

21. Others

Reference

Saruwatari J, Hisaeda S, Higa Y, et al. The *in-vivo* effect of Bakumondoto (TJ-29), a traditional Japanese medicine used for treatment of chronic airway disease, on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activity in man. *Journal of Pharmacy and Pharmacology* 2004; 56: 1171-7. CENTRAL ID: CN-00490887, Pubmed ID: 15324486

1. Objectives

To evaluate the effect of bakumondoto (麦門冬湯) on cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (university), Japan.

4. Participants

Twenty-six healthy university students.

5. Intervention

Arm 1: administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 3.0 g t.i.d. for 1 week followed by administration of the same dose of placebo at the same frequency for 1 week, with 2-week washout between both administration periods (n=13).

Arm 2: administration of placebo 3.0 g t.i.d. for 1 week followed by administration of the same dose of TSUMURA Bakumondoto (麦門冬湯) Extract Granules at the same frequency for 1 week, with 2-week washout between both administration periods (n=13).

6. Main outcome measures

Urinary cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities (determined by a caffeine test).

7. Main results

There were no significant differences in urinary cytochrome p450 1A2, xanthine oxidase, and N-acetyltransferase 2 activities on days 1 and 7 from baseline in either arm.

8. Conclusions

Caffeine test is a safe and noninvasive screening test for herb-drug interaction measuring the ratio of urinary caffeine metabolites (cytochrome p450 1A2, xanthine oxidase, N-acetyltransferase 2). Bakumondoto did not affect cytochrome p450 1A2 (a hepatic enzyme metabolizing theophylline), xanthine oxidase, or N-acetyltransferase 2 activity, suggesting the unlikeliness of interaction.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions occurred in the subjects receiving bakumondoto.

11. Abstractor's comments

Rather than examining data on the direct clinical effects of bakumondoto (麦門冬湯) extract granules, this study examines data on the effect of bakumondoto on urinary caffeine metabolites. The increase in Kampo medicine usage has raised interest in the interaction of Kampo with Western medicines. Hopefully this kind of research will progress further.

12. Abstractor and date

Fujisawa M, 15 June 2007, 1 April 2008, 31 December 2013.

21. Others

References

Ohnishi N, Yonekawa Y, Fumihara T, et al. Studies on interactions between traditional herbal and Western medicines, II. Lack of pharmacokinetic interaction between shoseiryu-to and carbamazepine in healthy volunteers. *TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)* 1999; 16: 399-404. Ichushi Web ID: 2000070928 [MOL](#), [MOL-Lib](#)

Yonekawa Y, Ohnishi N, Kitano N, et al. Drug interaction with Kampo medicines (2): kinetic characteristics of carbamazepine combined with shoseiryuto in healthy volunteers. *TDM Kenkyu (Japanese Journal of Therapeutic Drug Monitoring)* 1999; 16: 191-2. [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effect of shoseiryuto (小青竜湯) on blood carbamazepine concentration.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

None (authors belong to the Department of Hospital Pharmacy, Kyoto Pharmaceutical University), Japan.

4. Participants

Four healthy adult males.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Arm 1: administration of 9.0 g/day of TSUMURA Shoseiryuto (小青竜湯) Extract Granules in 3 divided doses before meals for 7 days and 200 mg of carbamazepine in the morning of day 4 (n=4).

Arm 2: administration of 200 mg of carbamazepine (n=4).

A two-week period intervened between the changeover from the arm 1 intervention to the arm 2 intervention.

6. Main outcome measures

Concentrations of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood sampled before, and 1.5, 4, 8, 24, 48, and 72 hr after administration of carbamazepine.

7. Main results

Combination with shoseiryuto did not affect the following parameters of carbamazepine and its metabolite carbamazepine-10,11-epoxide in blood: the maximum blood concentration; time to reach the maximum blood concentration; slope of the elimination phase; elimination half-life; area under the plasma concentration-time curve; and mean residence time.

8. Conclusions

Oral administration of shoseiryuto does not affect blood carbamazepine concentration.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study objectively demonstrated that combination of shoseiryuto does not affect blood carbamazepine concentration, which is susceptible to the effects of various drugs. This study does not evaluate the efficacy of the Kampo medicine, but is considered meaningful, given that Western and Kampo medicines are commonly combined in clinical practice.

12. Abstractor and date

Goto H, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Isobe H, Yamamoto K, Cyong JC. Effects of hachimi-jio-gan (ba-wei-di-huang-wan) on blood flow in the human central retinal artery. *The American Journal of Chinese Medicine* 2003; 31: 425-35. CENTRAL ID: CN-00457563, Pubmed ID: 12943173

1. Objectives

To evaluate the effect of hachimijiogan (八味地黄丸) on human central retinal artery.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (the University of Tokyo), Japan.

4. Participants

Twelve healthy volunteers (6 males and 6 females; mean age, 26.0 years).

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Arm 1: single-dose administration of 27 g of Uchida no Hachimigan M (八味地黄丸) (n=12).

Arm 2: single-dose administration of 27 g of placebo (lactose) (n=12).

6. Main outcome measures

Systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity, and vascular resistance of the central retinal artery, measured by ultrasonic diagnosis device before administration and every 15 min after administration for 60 min.

7. Main results

In arm 2, there were no changes from baseline in systolic blood flow velocity, diastolic blood flow velocity, mean blood flow velocity or vascular resistance of the central retinal artery. In arm 1, although vascular resistance did not change, there were increases in systolic velocity at 15 and 45 min, diastolic velocity at 45 min, and mean velocity at 30, 45, and 60 min. Group comparison revealed significantly higher systolic blood flow velocity at all postdose time points until 60 min, higher diastolic blood flow velocity at 45 min, and significantly higher mean blood flow velocity in the time period from 30 to 60 min in arm 1.

8. Conclusions

This study provides evidence that hachimijiogan increases the blood flow velocity of the central retinal artery.

9. From Kampo medicine perspective

When compared with hachimijiogan-non-responders (with unsuitable *sho*, n=9), hachimijiogan-responders (with suitable *sho*, n=3) had higher systolic, diastolic, and mean flow rates in the time period from 15 to 60 min (statistical analysis not performed due to the small sample size).

10. Safety assessment in the article

None.

11. Abstractor's comments

It was reported some time ago that hachimijiogan acts on the central nervous system to improve hypobulia in the elderly, and to improve eye symptoms. The present report showed an increase in blood flow rate of the central retinal artery, providing evidence for efficacy in improving visual acuity. Moreover, it was shown that intracerebral blood flow may also increase, suggesting effects on the central nervous system. Also, this report provides a valuable discussion from a Kampo medicine perspective of increased blood flow velocity in responders. However, a larger sample size will be necessary in the future. Another problem is that the systemic blood pressure was not indicated, making it impossible to determine whether the increase in blood flow velocity is attributable to a systemic or local reaction. Furthermore, since this RCT did not evaluate clinical efficacy and used single-dose administration, it is hoped that clinical research examining the persistent effects of long-term oral administration will be conducted.

12. Abstractor and date

Namiki T, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Hamazaki K, Sawazaki S, Itomura M, et al. No effect of a traditional Chinese medicine, hochu-ekki-to, on antibody titer after influenza vaccination in man: a randomized, placebo-controlled, double-blind trial. *Phytomedicine* 2007; 14: 11-4. CENTRAL ID: CN-00576087, Pubmed ID: 16644196

1. Objectives

To assess the efficacy and safety of hochuekkito (補中益氣湯) on antibody production after influenza vaccination.

2. Design

Double-blind, randomized, controlled trial (DB-RCT).

3. Setting

No description of the setting is available; the authors belong to the Division of Clinical Application, Institute of Natural Medicine, University of Toyama, Japan.

4. Participants

Of the 49 healthy males aged between 20 and 60 years who volunteered to enter this trial of hochuekkito, 36 were enrolled. None of the 36 had been taking any herbal medicine, hormone therapy, or anti-inflammatory drugs.

5. Intervention

Arm 1: administration of Kanebo Hochuekkito (補中益氣湯) Extract Fine Granules 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.

Arm 2: administration of placebo (consisted mainly of cane sugar) 3.75 g b.i.d. before breakfast and supper for 14 days until the day prior to influenza vaccination, n=18.

6. Main outcome measures

Blood samples were taken at weeks 0, 1, 2, 4, and 12. Hemagglutination inhibition (HI) was used to measure influenza antibody titer, and a chromium (Cr)-release assay was used to measure natural killer (NK) activity.

7. Main results

Three subjects in arm 2 (because of common cold and diarrhea) and one subject in arm 1 (for a personal reason) dropped out of the study. There were no significant between-arm differences in postvaccination titer and NK activity.

8. Conclusions

Oral administration of hochuekkito for 14 days before influenza vaccination does not affect postvaccination antibody production.

9. From Kampo medicine perspective

Subjects not intending to use hochuekkito, as well as subjects with easy fatigability, a high susceptibility to colds, slow recovery from colds, a high susceptibility to other infections like herpes and wound infection, poor appetite, loose bowels, and somnolence especially after meals, were excluded from the study.

10. Safety assessment in the article

No adverse effects were observed.

11. Abstractor's comments

This is a high-quality, well-designed, and double-blind clinical trial to assess the effect of hochuekkito on antibody production after influenza vaccination. A similar report (Yamaguchi H et al., Assessment of the effect of hochuekkito extract on antibody response to influenza vaccination. *Kampo to Saishin-chiryō [Kampo & the Newest Therapy]* 2006; 15: 235-7 [in Japanese]) concluded similarly that oral administration of hochuekkito for 1 week after the vaccination has no effect on antibody production. On the other hand, as mentioned in the discussion of this paper, Takagi et al. reported that hochuekkito increased antibody production in old mice (Takagi et al. Antibody response of Kampo-hozai after influenza B immunization in old mice. *The Japanese Society for Vaccinology* 2002; 6: 72 [abstract in Japanese]). Considering that all the clinical trials were conducted with healthy subjects, further investigation in the elderly with decreased ability to produce antibodies is awaited. The design of this clinical trial, based on the result from basic studies, should be emulated by researchers who conduct clinical trials of Kampo medicines.

12. Abstractor and date

Goto H, 21 November 2008, 1 June 2010.

21. Others**Reference**

Terashima Y, Hamazaki K, Itomura M, et al. Effect of a traditional Chinese medicine, maobushisaishinto, on the antibody titer after influenza vaccination: A randomized, placebo-controlled, double-blind trial. *Journal of Traditional Medicines* 2007; 24: 59-66. Ichushi Web ID: 2007258196 [J-STAGE](#)

1. Objectives

To evaluate the effect of maobushisaishinto (麻黄附子細辛湯) on antibody titer after influenza vaccination.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Two university hospitals, Japan.

4. Participants

One hundred and six healthy subjects aged 20–71 years.

5. Intervention

Maobushisaishinto (麻黄附子細辛湯) and placebo capsules were donated by Kotaro Pharmaceutical Co., Ltd. The following drugs were orally administered from day –14 to –1 of influenza vaccination (A/H1N1, A/H3N2, B). All subjects were vaccinated in late November, before the influenza season.

Arm 1: Kotaro Maobushisaishinto (麻黄附子細辛湯) Extract Capsules (6 capsules/day), n=23.

Arm 2: placebo capsules, n=24.

6. Main outcome measures

Serum hemagglutination inhibition titers were measured at weeks 0, 1, 2, 4, and 12.

7. Main results

After excluding 57 subjects with antibody titers of more than 1:80 and 2 subjects diagnosed with influenza during the study period (one in each arm), 23 and 24 subjects were enrolled for analysis. There was no significant between-arm difference in antibody titer against A/New Caledonia/20/99(H1N1), A/New York/55/2004(H3N2), and B/Shanghai/361/2002. However, anti-H3N2 virus antibody titer was significantly higher in arm 2 than in arm 1 at week 4. Subgroup comparisons (smokers vs non-smokers and older subjects [≥ 40 years old] vs younger subjects [< 40 years old]) found no significant between-arm differences in antibody titers.

8. Conclusions

No adjuvant effect of maobushisaishinto on antibody titer after influenza vaccination is observed.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Previous studies have shown the adjuvant effect of maobushisaishinto on influenza vaccination in animals and in elderly subjects. This paper aims to verify this effect.

12. Abstractor and date

Fujisawa M, 15 January 2009, 1 June 2010.

21. Others

Reference

Sato Y, Katagiri F, Itoh H, et al. Bushi-richu-to raises calcitonin gene-related peptide, substance P, somatostatin, and vasoactive intestinal polypeptide levels in human plasma. *Journal of Health Science* 2007; 53: 615-21. Ichushi Web ID: 2008127570 [J-STAGE](#)

1. Objectives

To elucidate the mechanism of bushirichuto (附子理中湯) activity in raising gut-regulated peptide levels.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Department of Clinical Pharmacy, Oita University Hospital, Japan.

4. Participants

Five healthy male volunteers recruited at the facility mentioned above, n=5.

5. Intervention

Arm 1: Kanebo Bushirichuto (附子理中湯) Extract Fine Granules (EK-410) 4.5 g was orally administered with 100 mL of water for 4 weeks.

Arm 2: placebo was orally administered with 100 mL of water for 4 weeks.

Each subject was administered these drugs with an interval of four weeks.

6. Main outcome measures

Blood samples were obtained before administration, and at 20, 40, 60, 90, 120, 180, and 240 min after administration of the test substances, and plasma levels of calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and motilin-like immunoreactive substance (IS) were measured by enzyme immunoassay (EIA).

7. Main results

One dose of bushirichuto significantly increased CGRP, somatostatin, and VIP levels (which peaked at 40–60 min) and significantly increased substance P level (which peaked at 180 min). CGRP level increased 5.7-fold at 40 min (85.2 ± 58.7 pg/mL in arm 1 vs. 14.9 ± 1.9 pg/mL in arm 2) ($P < 0.01$), somatostatin level increased 2.1-fold at 60 min (20.2 ± 6.1 pg/mL in arm 1 vs. 9.8 ± 2.1 pg/mL in arm 2) ($P < 0.01$), VIP level increased 2-fold at 60 min (16.9 ± 7.0 pg/mL in arm 1 vs. 8.3 ± 1.4 pg/mL in arm 2) ($P < 0.01$), and substance P increased 2-fold at 180 min (68.5 ± 18.7 pg/mL in arm 1 vs. 34.3 ± 17.9 pg/mL in arm 2) ($P < 0.01$). On the other hand, plasma motilin-like IS level was unaffected during observation for 240 min after administration.

8. Conclusions

Administration of bushirichuto may reduce sensitivity to cold, gastrointestinal discomfort, and gastrointestinal dysfunction *via* increasing plasma levels of CGRP, somatostatin, VIP, and substance P.

9. From Kampo medicine perspective

The authors suggest that the taste and smell of bushirichuto may affect the kinetics of gut-regulated peptides.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

Although this investigation had only a small number of subjects, the results helped us to reveal the mechanism of bushirichuto activity. As bushirichuto is an “*onchu-sankan*” (温中散寒) medicine which contains herbs (Aconiti tuber [附子] and Zingiberis siccaturum rhizome [乾姜]) with strong anti-coldness (“*sankan*”) activity, it is used for patients with “*hie*” (or a feeling of coldness in the body). However, the authors did not reveal whether the male volunteers had *kan-sho* (寒証, cold pattern). Most subjects treated with bushirichuto in clinical practice are frail women. From that point of view, to minimize the discrepancy between bushirichuto use in actual clinical practice and experimental study, clinical studies of “*sho*” in women with and without symptoms, and having the same study design as this trial, are awaited.

12. Abstractor and date

Ushiroyama T, 19 December 2008, 1 June 2010, 31 December 2013.

21. Others**Reference**

Takahashi H, Nakao R, Hirasaka K, et al. Effects of single administration of Rokumi-gan (TJ-87) on serum amino acid concentration of 6 healthy Japanese male volunteers. *Journal of Medical Investigation* 2007; 54: 91-8. Ichushi Web ID: 2007295608 [J-STAGE](#)

1. Objectives

To evaluate effects of rokumigan (六味丸) on serum amino acid concentrations.

2. Design

Randomized crossover controlled trial (RCT-cross over).

3. Setting

Department of Internal Medicine, the Komatsushima Hospital, Japan.

4. Participants

Six healthy men (mean age 35.5 years), n=6.

5. Intervention

Arm 1: lactose 5 g administered once at 9:00, n=6.

Arm 2: Asahi amino GET 5 tablets (contains a similar amount of amino acids as 10 g of Tsumura Rokumigan (六味丸) Extract Granules) administered once at 9:00, n=6.

Arm 3: Tsumura Rokumigan (六味丸) Extract Granules (TJ-87) 10 g administered once at 9:00, n=6.

There was a washout period of 3 months between treatments.

6. Main outcome measures

Serum amino acid concentrations before and at 1, 2, 4, and 6 h after the intervention.

7. Main results

In arm 1, concentrations of Ala, Gly, and Ile were significantly decreased from pretreatment levels at 6 h, and Arg, Glu, His, Leu, Lys, Phe, Ser, and Val levels were unchanged. In arm 2, concentrations of Ala, Glu, Gly, Ile, Leu, and Ser were significantly decreased at 6 h, but Arg, His, Lys, Phe, and Val levels remained unchanged. In arm 3, the levels of Ala at 2 h and Gly and Ser at 1 h were significantly increased, but Arg, Glu, His, Ile, Leu, Lys, Phe, and Val levels remained unchanged. In all three arms, serum levels of Asn, Cys, Gln, Met, Pro, Thr, Trp, and Tyr were not determined, and Asp were undetectable.

8. Conclusions

Serum amino acid concentrations are higher after administration of rokumigan than after administration of a supplement containing a similar amount of amino acids.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

This interesting well-designed cross-over clinical trial investigates the entry of amino acids from rokumigan into the blood. Changes in the concentration of amino acids after rokumigan administration were compared with those after administration of lactose or an amino acid mixture containing almost the same amount of amino acids. Amino acid levels (e.g., the pretreatment Ala level) were widely dispersed in all three arms, suggesting possible measurement errors in serum level for some amino acids. To adjust for dispersion in the data, relative changes in amino acid concentrations were calculated and are shown in Fig. 1. However, symbols a, b, and c are not defined. Also, the amino acid mixture administered in arm 2 contains several ingredients besides amino acids such as beer yeast, and their influence on absorption should be considered. Importantly, this study found that administration of rokumigan increased amino acid levels in blood and suppressed the gradual decrease observed in other arms. This observation may have important pharmacologic implications. Further studies on several Kampo medicines are anticipated.

12. Abstractor and date

Goto H, 27 November 2008, 1 June 2010, 31 December 2013.

21. Others**Reference**

Qi J, Toyoshima A, Honda Y, et al. Pharmacokinetic study on acetaminophen: interaction with a Chinese medicine. *Journal of Medical and Dental Sciences* 1997; 44: 31-5. CENTRAL ID: CN-00145359, Pubmed ID: 9385040

1. Objectives

To evaluate the effect of kakkonto (葛根湯) on the pharmacokinetics of acetaminophen.

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

No study site was specified (authors affiliated with the Department of Preventive Medicine, Division of Social Medicine, Medical Research Institute, Tokyo Medical and Dental University), Japan.

4. Participants

Nineteen healthy volunteers.

5. Intervention

Arm 1: single oral dose of PL granules containing 150 mg of acetaminophen) in combination with TSUMURA Kakkonto (葛根湯) Extract Granules (containing 1250 mg of extract) (n=19).

Arm 2: single oral dose of PL (containing 150 mg of acetaminophen) (n=19).

There was a 1-week washout period.

6. Main outcome measures

Blood concentrations of acetaminophen (APAP) and APAP glucuronide (measured by high performance liquid chromatography [HPLC] before and 0.5, 1, 2, 3, and 4 hours after administration of APAP) were used to calculate the maximum blood concentration (C_{max}), time to C_{max} (t_{max}), half-life in blood ($t_{1/2}$), and area under the blood concentration curve (AUC).

7. Main results

There were no between-arm differences in C_{max} , t_{max} , $t_{1/2}$, or AUC of APAP or APAP glucuronide.

8. Conclusions

The pharmacokinetics of acetaminophen is not affected by concomitant administration of kakkonto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were reported.

11. Abstractor's comments

This study measured blood acetaminophen concentration after coadministration of kakkonto with acetaminophen (which are commonly co-administered in clinical practice). Adverse reactions to acetaminophen were not affected by administration of kakkonto in combination with PL. In another study involving volunteers, however, it was reported that the blood APAP concentration was higher after co-administration of kakkonto (5 g; use of granules or extract bulk powder, not specified) in combination with APAP (12 mg/kg). In rats that received APAP (10 mg/kg) plus kakkonto (100 or 200 mg/day) for 1 week, the APAP level was significantly higher in the kakkonto (200 mg/day) group than in the distilled water group only at 0.25 hour after APAP administration. Therefore, since drug interaction may affect the blood acetaminophen concentration depending on the dose and/or treatment duration of kakkonto and acetaminophen, a randomized clinical study might have been more useful if co-administration was frequent. Nevertheless, the study was very valuable because it showed that the blood acetaminophen concentration was not affected by a single co-administration at commonly used doses.

12. Abstractor and date

Goto H, 19 September 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Shimakura K, Mineshita S, Sanaka M, et al. Effects of kakkonto on the pharmacokinetics of phenacetin in human serum and saliva*. *Rinsho Yakuri (Japanese Journal of Clinical Pharmacology and Therapeutics)* 1994; 25: 229–30 (in Japanese).

1. Objectives

To evaluate the effects of kakkonto (葛根湯) on the pharmacokinetics of phenacetin.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

One university hospital, Japan.

4. Participants

Eleven healthy subjects.

5. Intervention

Arm 1: phenacetin 12 mg/kg (n=6).

Arm 2: phenacetin 12 mg/kg + TSUMURA Kakkonto (葛根湯) Extract Granules 2 sachets (containing 1250 mg of kakkonto dry extract / sachet) (n=5).

Crossed over with a 7-day or longer washout period between arms.

6. Main outcome measures

Blood and saliva concentrations of phenacetin and its metabolites, acetaminophen and glucuronide.

7. Main results

There were no between-arm significant differences in C_{max} (post-dose maximum blood concentration) and AUC (area under the blood concentration-time curve: a measure of efficacy reflecting the percent drug absorption or bioavailability) of acetaminophen in either blood or saliva. The time-course of acetaminophen concentration showed a tendency toward higher concentration in saliva in arm 2 than in arm 1, but no between-arm difference in concentration in blood.

8. Conclusions

Kakkonto seems to only slightly affect the pharmacokinetics of phenacetin, acetaminophen, or glucuronide.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This study would have been probably designed to demonstrate kakkonto combined with phenacetin increases the concentration of acetaminophen, a metabolite of phenacetin. Since the authors states that “at present, combination Kampo medicines containing western cold remedies and Kampo medicines such as kakkonto extract are commercially available, and some studies report the usefulness of Kampo medicines for drug efficacy of western medicines.” In this study, concentration in saliva was measured because it was the focus of therapeutic drug monitoring at that time.

12. Abstractor and date

Fujisawa M, 15 October 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Fukushima M. Profiles of effects of traditional oriental herbal medicines on the central nervous system in humans - assessment of saiboku-to and saiko-ka-ryukotsu-borei-to using EEG and pharmacokinetics of herbal medicine-derived ingredients as indices -. *Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica)* 1997; 99: 355-69 (in Japanese with English abstract).

1. Objectives

To evaluate the effects of saibokuto (柴朴湯) and saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) on the central nerve system in humans.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single-center study in Department of Neuropsychiatry, Kansai Medical University, Japan.

4. Participants

Twelve healthy adult men.

5. Intervention

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 7.5 g q.d. for 1 day followed by 2.5 g t.i.d. for 8 days.

Arm 2: TSUMURA Saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) 7.5 g q.d. for 1 day and 2.5 g t.i.d. for the following 8 days

Arm 3: lactose (placebo) 3 g q.d. for 1 day followed by 2.5 g t.i.d. for 8 days.

There was a washout period of 2 weeks or more between treatments.

6. Main outcome measures

Electroencephalogram (EEG) global field power (GFP) spectrum change.

7. Main results

For each individual, placebo-controlled data on GFP were used to calculate change due to treatment (i.e., the difference in GFP between before and after treatment). In Arm 1, there was an increase of 3.24 in the δ band 1 hour after administration ($P<0.01$) and an increase of 3.20 in the α_3 band 3 hours after administration ($P<0.01$). In Arm 2, there was no significant change in GFP 1, 3, or 6 hours after administration.

8. Conclusions

Saibokuto may have an effect on the central nervous system.

9. From Kampo medicine perspective

Mentioned in section "Subjects and Administration Method".

10. Safety assessment in the article

Not documented.

11. Abstractor's comments

In this article, saibokuto changed the EEG global field power in healthy adult men. This indicates that the GFP may be used as an objective measure of the central effect of saibokuto. In addition, the authors stated that the response to saibokuto varied among individuals. Further studies based on *sho* (証, pattern.syndrome) are awaited to validate the results of this study.

12. Abstractor and date

Okabe T, 29 August 2008, 1 June 2010, 31 December 2013.

21. Others**Reference**

Hasegawa T, Yamaki K, Nadai M, et al. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. *International Journal of Clinical Pharmacology and Therapeutics* 1994; 31: 57-61. CENTRAL ID: CN-00102144, Pubmed ID: 8004359

1. Objectives

To evaluate the effect of Kampo medicines on bioavailability of ofloxacin (OFLX) in healthy volunteers.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single institution (Nagoya University School of Medicine), Japan.

4. Participants

Seven healthy male volunteers (age 23–30 years).

5. Intervention

Arm 1: treatment with OFLX 200 mg.

Arm 2: treatment with OFLX 200 mg + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g.

Arm 3: treatment with OFLX 200 mg + TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g.

Arm 4: treatment with OFLX 200 mg + TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g.

Test drugs were administered orally with 150 mL of water at 8:30 a.m. at one-week intervals.

6. Main outcome measures

Blood concentration of OFLX and the percentage of OFLX excreted in 24-hour urine at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the administration; pharmacokinetic analysis.

7. Main results

There were no significant between-arm differences in bioavailability. The percentage of OFLX excreted in 24-hour urine in arm 1 (mean±SEM, 80.6±3.9%) was not significantly different from that after OFLX co-administration with shosaikoto (arm 2; 79.7±5.1%), rikkunshito (arm 3; 76.8±2.3%), or saireito (arm 4; 80.3±5.3%).

8. Conclusions

Kampo medicines have no significant effect on bioavailability of ofloxacin in healthy volunteers.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It was speculated that those Kampo medicines studied don't have much effect on metabolism of quinolones and therefore can be safely co-administered with those agents. However, since this was an evaluation in healthy volunteers, it should be kept in mind that Kampo medicines might affect bioavailability in certain circumstances, such as in the disease state.

12. Abstractor and date

Namiki T, 29 December 2008, 6 January 2010, 1 June 2010, 31 December 2013.

21. Others

References

Niitsuma T, Fukuda T, Yamamoto S, et al. Effects of saibokuto and other saiko-zai (saiko-drugs) on prednisolone metabolism. *Kampo to Meneki-Arerugi (Kampo and Immuno-allergy)* 1993; 7: 43–52 (in Japanese).

Homma M, Oka K, Ikeshima K, et al. Different effects of traditional Chinese medicines containing similar herbal constituents on prednisolone pharmacokinetics. *Journal of Pharmacy and Pharmacology* 1995; 47: 687–92. CENTRAL ID: CN-00120671, Pubmed ID: 8583374

1. Objectives

To evaluate the effects of shosaikoto (小柴胡湯), saibokuto (柴朴湯), and saireito (柴苓湯) on prednisolone metabolism.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Department of Clinical Pharmacology, Tokyo University of Pharmacy and Life Science, 3rd Department of Internal Medicine, Tokyo Medical University, Japan.

4. Participants

Twenty-two nonsmoking healthy males who took no drug that could affect glucocorticoid metabolism.

5. Intervention

Since allocation of patients by administration pattern to these treatment arms is not known, the treatment arms are described in terms of treatment regimen.

Study 1

Arm 1: TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for 3 days. On the third study day, 10 mg prednisolone was administered orally in combination with the test preparation (n=6).

Arm 2: prednisolone 10 mg (n=6).

Age, 21.8±1.2 years; body weight, 63.8±6.8 kg

Study 2

Arm 1: TSUMURA Saibokuto (柴朴湯) Extract Granules 2.5 g t.i.d. for 3 days. On the third study day, 10 mg prednisolone was administered orally in combination with the test preparation (n=9).

Arm 2: prednisolone 10 mg (n=9).

age, 23.5±1.5 years; body weight, 61.3±4.5 kg

Study 3

Arm 1: TSUMURA Saireito (柴苓湯) Extract Granules 3.0 g t.i.d. for 3 days (n=7)

Arm 2: prednisolone 10 mg (n=7)

Age, 22.4±1.9 years; body weight, 62.0±7.1 kg

Following a 2-week washout period, subjects were crossed over to the opposite arm.

6. Main outcome measures

Areas under the time-blood concentration curve (AUC) of prednisolone and prednisone, measured before and 1, 2, 4, and 6 h after treatment.

7. Main results

After the intervention, the AUC of prednisolone was significantly decreased to 0.94–0.78 mgL⁻¹ in the shosaikoto group ($P<0.05$), significantly increased to 0.92–1.06 mgL⁻¹ in the saibokuto group, and unchanged in the saireito group. After the intervention, the AUC ratio of prednisolone to prednisone, which reflects the activity of 11 β -hydroxysteroid dehydrogenase (11-HSD), an *in vivo* steroid metabolic enzyme, was increased in the shosaikoto group ($P<0.01$), decreased in the saibokuto group ($P<0.01$), and unchanged in the saireito group.

8. Conclusions

Different types of saiko drugs affect steroid pharmacokinetics differently. 11-HSD activity is decreased, unaffected, and increased by saibokuto, saireito, and shosaikoto, respectively.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Kampo formulations have been used to stabilize medical conditions treated with steroids, with the aim of decreasing the use of steroids. This valuable study examined the effect of each saiko drug on steroid pharmacokinetics. An RCT in steroid-treated patients, but not healthy subjects as in the present study, would clarify the meaning of the present results.

12. Abstractor and date

Tsuruoka K, 26 April 2008, 1 June 2010, 31 December 2013.

21. Others

Reference

Hasegawa T, Yamaki K, Muraoka I, et al. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. *Antimicrobial Agents and Chemotherapy* 1995; 39: 2135-37. CENTRAL ID: CN-00119767, Pubmed ID: 8540731

1. Objectives

To determine the pharmacokinetics of levofloxacin (Cravit[®]) when coadministered with hochuekkito (補中益氣湯), rikkunshito (六君子湯), or juzentaihoto (十全大補湯), and to gain insights into the interactions between them.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Second Department of Internal Medicine, Nagoya University School of Medicine, Japan.

4. Participants

Eight male volunteers with no abnormal findings on medical history, routine blood biochemistry, and urinalysis.

5. Intervention

Since allocation of patients to these treatment arms is not described, the treatment arms are described in terms of treatment regimen.

Arm 1: treatment with levofloxacin 200 mg alone.

Arm 2: treatment with levofloxacin 200 mg + TSUMURA Hochuekkito (補中益氣湯) Extract Granules 2.5 g.

Arm 3: treatment with levofloxacin 200 mg + TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g.

Arm 4: treatment with levofloxacin 200 mg + TSUMURA Juzentaihoto (十全大補湯) Extract Granules 2.5 g.

All the 8 patients underwent arm 1 through arm 4 treatments, with a wash-out period of 7 days between treatments.

6. Main outcome measures

Concentrations of levofloxacin in blood and urine (determined by high-performance liquid chromatography).

7. Main results

All three Kampo formulations studied had no effect on metabolism of levofloxacin.

8. Conclusions

Kampo medicines have no effect on the pharmacokinetics of levofloxacin. Further investigations, including investigations of other Kampo formulations, are needed.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events occurred.

11. Abstractor's comments

This paper describes the effect of Kampo medicines on the pharmacokinetics of a typical antibiotic. It has been reported that Kampo medicines have considerable effects on the intestinal environment. The demonstration of no effect on the pharmacokinetics of at least one antibiotic in this study is of great significance, considering that western prescription medications and Kampo medicines are commonly coadministered in current clinical practice.

12. Abstractor and date

Nakata H, 10 January 2009, 31 December 2013.

21. Others

Reference

Ohnishi M, Hitoshi K, Katoh M, et al. Effect of a Kampo preparation, byakkokaninjinto, on the pharmacokinetics of ciprofloxacin and tetracycline. *Biological & Pharmaceutical Bulletin* 2009; 32: 1080–4. CENTRAL ID: CN-00704915, Pubmed ID: 19483319 [J-STAGE](#)

1. Objectives

To evaluate the effects of co-administered byakkokaninjinto (白虎加人参湯) on pharmacokinetics and renal excretion of antibiotics (tetracycline or ciprofloxacin).

2. Design

Randomized controlled cross-over trial (RCT-cross over).

3. Setting

Department of Pharmacy and Pharmacokinetics, Aichi Medical University and Faculty of Pharmacy, Meijo University, Japan.

4. Participants

Twenty healthy male volunteers (aged 23–36, mean 29.3 years).

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

Study 1

Arm 1: oral ciprofloxacin (Ciproxan tablet) 200 mg alone.

Arm 2: oral ciprofloxacin (Ciproxan tablet) 200 mg + byakkokaninjinto (白虎加人参湯) 3 g.

Each subject took Ciproxan immediately after taking byakkokaninjinto (白虎加人参湯) with 180 mL of water. After a 7-day wash-out period, the treatments were switched.

Study 2

Arm 1: oral tetracycline (Achromycin V capsule) 250 mg alone.

Arm 2: oral tetracycline (Achromycin V capsule) 250 mg + byakkokaninjinto (白虎加人参湯) 3 g.

The dosing and cross-over were performed in the same manner as Study 1.

The number of subjects in each arm is not specified.

6. Main outcome measures

Plasma and urinary concentrations of tetracycline and ciprofloxacin were measured by HPLC.

7. Main results

The peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of tetracycline and ciprofloxacin were significantly decreased by co-administration of byakkokaninjinto. The decrease in bioavailability of ciprofloxacin (15%) was smaller compared with that of tetracycline (30%). The co-administration of byakkokaninjinto significantly decreased urinary excretion rate of tetracycline, but not that of ciprofloxacin. Byakkokaninjinto had no effect on renal clearance of either antibiotic.

8. Conclusions

Byakkokaninjinto appears to reduce the absorption of tetracycline and ciprofloxacin.

9. From Kampo medicine perspective

In this study, it was assumed that byakkokaninjinto was used for treating heat exhaustion and febrile disease.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This highly suggestive study noted that co-administered byakkokaninjinto may reduce the absorption of tetracyclines and new quinolone agents (e.g., ciprofloxacin). The authors stated that this reduction may be due to the formation of chelates with Ca^{2+} contained in byakkokaninjinto. There remain some problems in the study design, such as small number of participants, inclusion of male subjects only, and no description of the number of subjects assigned to each arm. Yet the results of this study, if confirmed, mean that the co-administered byakkokaninjinto may delay the cure of infectious diseases, and therefore will have a strong impact on clinical practice. An RCT of byakkokaninjinto in patients with infectious diseases is desirable, but ethical aspects of such a trial must be considered. Alternatively, retrospective studies, including studies with a case-control design, might be of some help. Further studies on this topic are expected.

12. Abstractor and date

Tsuruoka K, 1 June 2010, 31 December 2013.

21. Others**Reference**

Ogawa H, Xu F, Uebaba K, et al. Antioxidative potentiality of a Kampo formulation measured by an ex vivo study. *The Journal of Alternative and Complementary Medicine* 2009; 15: 267–74.

1. Objectives

To evaluate the antioxidative effect of bofutsushosan (防風通聖散) in healthy adults using the lag time of low-density lipoprotein (LDL) oxidation as the main yardstick.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

University of Toyama, Japan.

4. Participants

Eighteen healthy males (aged 22±3 years) selected from 38 males. The inclusion criteria were total cholesterol ≥180 and ≤220 mg/dL, triglyceride ≤170 mg/dL, high-density lipoprotein (HDL) cholesterol ≥40 mg/dL, LDL cholesterol ≤140 mg/dL). The subjects were randomly assigned to the following three arms.

5. Intervention

Arm 1: bofutsushosan (防風通聖散; Kanebo) 7.5 g/day.

Arm 2: placebo of bofutsushosan (防風通聖散; Kanebo) 7.5 g/day.

Arm 3: tablet containing a mixture of vitamin E (500 mg/day) and vitamin C (1000 mg/day).

6. Main outcome measures

Inhibitory effect on LDL oxidation induced by 2,2'-azobis (4-methoxy-2,4-dimethyl-valeronitrile); the lag time to oxidation (production of conjugated dienes), as a measure of antioxidative effect; plasma ephedrine, plasma baicalin, serum lipid peroxide, serum free fatty acids, urinary 8(OH)dG/creatinine levels, blood pressure, and heart rate.

7. Main results

The lag time tended to be longer, though not significantly longer, in arm 1 than arm 2 ($P=0.08$). There were no significant changes in levels of urinary 8(OH)dG/creatinine and serum lipid peroxide. In arm 1, a sympathomimetic response to the pharmacological action of ephedrine was observed.

8. Conclusions

Although not confirmed, the systemic antioxidative effect of bofutsushosan is suggested by this study.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This double-blind randomized controlled trial (DB-RCT) demonstrated the potential antioxidative effect of bofutsushosan on lipids. Drug administration in arms 1 and 2 was double-blinded, whereas it was unblinded in arm 3. So the study is an incomplete DB-RCT. Yet the outcomes are clinically highly suggestive. In the future, RCTs that involve patients with hyperlipidemia, compare Kampo medicines with standard medications, and use true endpoints to assess outcome are expected to be conducted.

12. Abstractor and date

Tsuruoka K, 1 June 2010.

21. Others

Reference

Yasui T, Yamada M, Uemura H, et al. Changes in circulating cytokine levels in midlife women with psychological symptoms treated with selective serotonin reuptake inhibitors and Japanese traditional medicine. *Maturitas* 2009; 62: 146–52.

1. Objectives

To compare the effects of kamishoyosan (加味逍遙散) and paroxetine in improving anxiety and depression as menopausal symptoms.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Obstetrics and Gynecology, Tokushima University Hospital, Japan.

4. Participants

Seventy-six women with menopausal, psychological symptoms (such as anxiety and mild depression) who were recruited from among patients visiting the outpatient clinic of the Department of Obstetrics and Gynecology between November 2005 and October 2007. Subjects with major depression were excluded.

5. Intervention

Arm 1: paroxetine (paroxetine [GlaxoSmithKline] 10 mg/day for 6 months) (n=38).

Arm 2: Kamishoyosan (Tsumura Kamishoyosan Extract Granules 7.5 g/day for 6 months), (n=38).

6. Main outcome measures

The main outcome measures were serum levels of cytokines (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, TNF- α , IFN- γ , MCP-1, and MIP-1 β) and climacteric symptoms assessed using Greene's climacteric scale.

7. Main results

The psychological, somatic, and vasomotor scores assessed using Greene's climacteric scale were improved in both arms, but improvement was greater in the paroxetine arm. Serum IL-6 levels decreased significantly compared with baseline in both arms, and showed significant positive correlations with Greene's climacteric scores. A significant decrease in IL-8, MIP-1 β , and MCP-1 levels was also observed in the paroxetine arm.

8. Conclusions

The mechanism of the drug action of both paroxetine and kamishoyosan may involve IL-6, which therefore may be a useful marker of treatment. Though useful in treating menopausal symptoms, kamishoyosan is less effective than paroxetine.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Six of the 38 women in the paroxetine arm dropped out of the study because of the following adverse effects: headache, nausea, and uncomfortable gastrointestinal tract symptoms. One woman in kamishoyosan arm dropped out of the study because of bitter taste in the mouth and diarrhea, and two women dropped out because of no response to the drug.

11. Abstractor's comments

Kamishoyosan is often prescribed along with keishibukuryogan (桂枝茯苓丸) for treatment of menopausal symptoms. Although less effective than paroxetine, kamishoyosan was useful. Clinically, kamishoyosan and keishibukuryogan are prescribed based on *Kampo* findings, and the effectiveness of these drugs might be demonstrated if the subjects are treated on the basis of *Kampo* findings. However, it is interesting that improvement in somatic and psychological symptoms was correlated with serum IL-6 level. This correlation suggests a role of IL-6 in the mechanism of kamishoyosan.

12. Abstractor and date

Nakata H, 1 June 2010.

21. Others**Reference**

Inotsume N, Fukushima S, Hayakawa T, et al. Pharmacokinetics of Ephedrine and Pseudoephedrine after oral administration of kakkonto to healthy male volunteers. *Rinsho Yakuri (Japanese Journal of Clinical Pharmacology and Therapeutics)* 2009; 40: 79-83. Ichusi Web ID: 2009308892

1. Objectives

To evaluate the pharmacokinetic profiles of serum ephedrine and pseudoephedrine after oral administration of kakkonto (葛根湯), and changes in biokinetics after different administered doses.

2. Design

Randomized controlled trial (cross over) (RCT-cross over)

3. Setting

One university, Japan.

4. Participants

Ten healthy male volunteers aged 23-26 years.

5. Intervention

Since allocation of patients to these treatment arms is not mentioned, the treatment arms are described in terms of treatment regimen.

To examine the actual absorption under the conditions of administration after meals, following an overnight fast, kakkonto was given 1 hour after breakfast, and lunch was served 4 hours later. Blood samples were obtained before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug ingestion. The regimen was repeated in cross-over design after an interval of 2 weeks. Daily dose (7.5 g) of kakkonto contained 14.43 mg of ephedrine and 5.73 mg of pseudoephedrine.

Arm 1: Kanebo (now Kracie) Kakkonto (葛根湯) Extract Granule 2.5 g.

Arm 2: Kanebo (now Kracie) Kakkonto (葛根湯) Extract Granule 3.75 g.

6. Main outcome measures

Indices of the blood level-time curve of ephedrine and pseudoephedrine (maximum concentration [C_{max}]), time to maximum serum concentration (t_{max}), area under the serum concentration-time curve (AUC), mean residence time (MRT), and terminal elimination rate constant (κ).

7. Main results

Serum ephedrine and pseudoephedrine concentrations were measured using a gas chromatograph-mass spectrometer. Standard curves were constructed based on quantitative analysis of deuterium labeled epinephrine and pseudoephedrine.

In Arm 1, the mean values of C_{max} (ng/mL), t_{max} (h), AUC (ng · h/mL), MRT (h), and κ (/h) of ephedrine were 22.0, 3.0, 238.5, 9.8, and 0.1, respectively, and those of pseudoephedrine were 8.1, 3.0, 66.8, 7.4, and 0.2, respectively. The mean C_{max} values of ephedrine and pseudoephedrine were 1.50- and 1.58-fold higher in Arm 2 compared with Arm 1, although the t_{max} did not differ significantly. The mean AUC values of ephedrine and pseudoephedrine in Arm 2 were 1.31- and 1.48- fold higher, respectively, than those in Arm 1, while the mean MRT and κ did not differ significantly.

8. Conclusions

The kinetic behavior of ephedrine and pseudoephedrine are largely linear at the doses examined.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a basic study evaluating the pharmacokinetics of ephedrine and pseudoephedrine contained in kakkonto in human serum. They were determined using high precision measurements such as gas chromatography, mass spectrometry, and deuterium labeling.

12. Abstractor and date

Fujisawa M, 1 June 2010, 31 December 2013.

21. Others

Reference

Munekage M, Kitagawa H, Ichikawa K, et al. Pharmacokinetics of daikenchuto, a traditional Japanese medicine (Kampo) after single oral administration to healthy Japanese volunteers. *Drug Metabolism and Disposition* 2011; 39: 1784-8. Pubmed ID: 21724872

1. Objectives

To analyze the blood kinetics of indicator components in daikenchuto (大建中湯).

2. Design

Randomized controlled trial (cross over) (RCT-cross over).

3. Setting

Surgery Department, Kochi Medical School Hospital, Japan.

4. Participants

Nineteen healthy volunteers (including three volunteers who did not meet the criteria and were excluded).

5. Intervention

Groupings by administration pattern were not indicated, so the arms are described in terms of drug groups.

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 2.5 g group (n=15).

Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules 5 g group (n=16).

Arm 3: TSUMURA Daikenchuto (大建中湯) Extract Granules 10 g group (n=16).

6. Main outcome measures

Hydroxyl- α -sanshool, hydroxyl- β -sanshool, 6-shogaol, 10-shogaol, ginsenoside Rb1, and ginsenoside Rg1 blood kinetics (AUC, C_{max} , $t_{1/2}$, t_{max}).

7. Main results

Hydroxyl- α -sanshool, hydroxyl- β -sanshool, 6-shogaol, and 10-shogaol reached t_{max} in 0.2–0.5 hours and were rapidly eliminated from the blood; however, ginsenoside Rb1 and ginsenoside Rg1 reached t_{max} in 1–4 hours and were more slowly eliminated from the blood. Increases in blood concentrations of hydroxyl- α -sanshool, hydroxyl- β -sanshool, 6-shogaol, and 10-shogaol were dosage dependent, but increases in blood concentrations of ginsenoside Rb1 and ginsenoside Rg1 were dosage independent.

8. Conclusions

Of the six indicator components in daikenchuto, increases in the blood concentrations of the sansho- and kankyo-derived components are dose dependent but increases in those of ginseng-derived components are dose independent.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Six adverse events (abnormal laboratory values) occurred in four participants, but a causal relationship with daikenchuto was excluded.

11. Abstractor's comments

The blood kinetics of six indicator components in daikenchuto extract were analyzed in this study. There are distinct differences between the blood kinetics of low molecular weight compounds such as hydroxyl- α -sanshool, hydroxyl- β -sanshool, 6-shogaol, and 10-shogaol, and high molecular weight compounds such as ginsenoside Rb1 and ginsenoside Rg1, which points to the complexity of the blood kinetics of Kampo preparations with their wide arrays of components. This paper suggests the possibility that prescriptions considered to be deficiency-pattern treating formulae or *hozai* (補劑) (because they contain a wide array of high molecular weight compounds) do not act in a dosage dependent manner.

12. Abstractor and date

Nakata H, 31 December 2013.

21. Others

Reference

Takayama S, Okitsu R, Iwasaki K, et al. The effect of warming the abdomen with herbal medicine or thermal therapy on superior mesenteric artery blood flow. *Kampo to Saishin Chiryō (Kampo & the Newest Therapy)* 2011; 20: 253-8 (in Japanese with English abstract). Ichushi Web ID: 2011349495

1. Objectives

To evaluate the effect of daikenchuto (大建中湯) and abdominal thermotherapy on blood flow through the superior mesenteric artery.

2. Design

Randomized controlled trial (RCT).

3. Setting

No mention of participating centers (the authors belong to the Advanced Course in Kampo Medicine, Department of Traditional Asian Medicine, Tohoku University), Japan.

4. Participants

Forty-three healthy volunteers with no cardiovascular or gastrointestinal disease.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (5 g) + distilled water (50 mL) group (n=14).

Arm 2: Abdominal warming group (n=15).

Arm 3: Distilled water (50 mL) group (n=14).

6. Main outcome measures

Comparison of changes in superior mesenteric artery blood flow monitored using a heat conduction control device at commencement of abdominal warming for 20 minutes, at oral administration of daikenchuto, and every 10 minutes (up to 50 minutes) after oral administration of distilled water.

7. Main results

Superior mesenteric artery blood flow was significantly increased in arms 1 and 2 compared to arm 3 ($P < 0.01$ in both) but was not significantly different between arms 1 and 2.

8. Conclusions

The traditional medical therapy of abdominal warming increases superior mesenteric artery blood flow to the same extent as oral daikenchuto.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

It is significant that this study demonstrated with objective indicators that warm tonification (the Kampo medical concept of warming the body and tonifying qi) and warming (the therapeutic method used in acupuncture and moxibustion) both have the characteristic of increasing superior mesenteric artery blood flow. Further study is warranted to determine the significance of this increase.

12. Abstractor and date

Nakata H, 31 December 2013.

21. Others**Reference**

Arai M, Sato H, Shirota F. An investigation into the relief of colonoscopy pain provided by shakuyaku-kanzo-to. *Nihon Toyo Igaku Zasshi (Japanese Journal of Oriental Medicine)* 1994; 44: 385-90 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) for relieving pain during colonoscopy.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Thirty-eight patients (30–60 years old) who underwent total colonoscopy.

5. Intervention

Arm 1: oral administration of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5.0 g before the examination (n=18).

Arm 2: no treatment (n=20).

Diazepam 10 mg was injected intramuscularly 5 minutes before the examination in both arms.

6. Main outcome measures

Subjective symptoms (visual pain score: VPS), systolic blood pressure, heart rate, and examination time.

7. Main results

VPS was significantly lower in arm 1 (4.89 ± 0.42 vs. 6.20 ± 0.34 ; $P < 0.05$). There were no between-arm differences in the systolic blood pressure, heart rate, and examination time.

8. Conclusions

Shakuyakukanzoto relieves pain during colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper is of clinical significance in that it demonstrated the efficacy of shakuyakukanzoto for relieving pain during colonoscopy in an RCT. The study would be more meaningful if it employed a design involving administration of placebo, such as lactose, instead of no-treatment.

12. Abstractor and date

Kogure T, 8 August 2008.

21. Others

References

Imazato S, Kai S, Koizumi K, et al. A Clinical Study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. *Therapeutic Research* 1997; 18: S505-10 (in Japanese). MOL, MOL-Lib

Imazato S, Kai S, Koizumi K, et al. A clinical study of shakuyaku-kanzo-to (Kampo) as a preparation for double contrast barium enema. *Kampo Igaku (Science of Kampo Medicine)* 1998; 22: 87-92 (in Japanese).

1. Objectives

To evaluate the effectiveness of Shakuyakukanzoto (芍薬甘草湯) for complaints and distress related to pre-enema treatment.

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Sixty patients who visited the hospital to undergo an enema X-ray examination..

5. Intervention

Arm 1: modified Brown method + TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 2.5 g before evening meal and sleep on the day before examination, and in the morning before examination (n=30).

Arm 2: modified Brown method (n=30).

6. Main outcome measures

Subjective symptoms (questionnaire).

7. Main results

Subjective symptom scores in arm 1 and arm 2 were 96.7% and 46.7% (respectively) for “not so much” abdominal pain the night before; 86.7% and 6.7% for “usual” sleep the night before; 90% and 66.7% for “no problems” referring to distress associated with enema examination pretreatment when visiting the hospital; and 66.7% and 0% for “easier than last time” referring to a previous occasion. Daily stool frequency was reduced in arm 1 (time range: 0~6 AM).

8. Conclusions

Shakuyakukanzoto reduces distress associated with enema examination pretreatment.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned. The examination itself was reported to have no ill effects and barium adhesion was reported to be satisfactory in arm 1.

11. Abstractor’s comments

This RCT is worthy of praise for having evaluated the effects of shakuyakukanzoto on pain and distress associated with pretreatment for the barium enema X-ray examination using a large number of participants. The evidence could have been made easier to understand by giving subjective symptoms numerical values and by comparing the two groups in greater detail.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010, 31 December 2012.

21. Others**Reference**

Yokota H, Kanazawa H, Kondo T, et al. New colon preparation using the Kampo herb method (daio-kanzo-to). *Therapeutic Research* 1989; 10: 1637–43 (in Japanese with English abstract).

1. Objectives

To clinically evaluate the efficacy of a new colon preparation for colonoscopy using daiokanzoto (大黃甘草湯).

2. Design

Randomized controlled trial (RCT).

3. Setting

One general hospital, Japan.

4. Participants

Sixty patients undergoing colonoscopy for lower gastrointestinal complaints.

5. Intervention

Arm 1: TSUMURA Daiokanzoto (大黃甘草湯) Extract Granules 7.5 g/day from 2 days before colonoscopy (n=30).

Arm 2: modified Brown method (n=30).

6. Main outcome measures

Degree of colonic irrigation (3-point scale), comprehensive evaluation (physician's impression, 4-point scale).

7. Main results

The degree of colonic irrigation was good in 90% and 30%, fair in 10% and 60%, and poor in 0% and 10% of patients in arm 1 and arm 2, respectively. Comprehensive evaluation was excellent in 83.3%, good in 6.7%, fair in 10% and poor in 0% of patients in arm 1.

8. Conclusions

Daiokanzoto is superior to the modified Brown method of colonic preparation for colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No patients in arm 1 had nausea, vomiting, or abdominal pain but 1 patient had bloated feeling, while 6, 2, 6, and 1 patient in arm 2 had nausea, vomiting, abdominal pain, and bloated feeling, respectively.

11. Abstractor's comments

This study deserves praise for developing a new pretreatment method for colonoscopy using daiokanzoto and performing an RCT that compared it with the conventional method. However, statistical analysis of the data is warranted since the study's between-arm comparison was insufficient.

12. Abstractor and date

Kogure T, 8 August 2008, 1 June 2010.

21. Others

Reference

Saida Y, Takase M, Okumura C, et al. Efficacy of combined use of shakuyakukanzoto in pretreatment for large bowel endoscopy – prospective randomized trial*. *Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)* 2003; 20: 34-7 (in Japanese). Ichushi Web ID: 2005123565

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) combined with polyethylene glycol solution (PEG) in pretreatment for large bowel endoscopy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

None (authors belong to the Department of Colon and Rectal Surgery, Tohokamagaya Hospital), Japan.

4. Participants

Seventy patients who were scheduled to undergo large bowel endoscopy between November 2000 and March 2001 and gave informed consent to participate in this trial.

5. Intervention

Arm 1: oral administration of shakuyakukanzoto (芍薬甘草湯) (2.5 g t.i.d.) starting from lunchtime on the day before endoscopy (n=37).

Arm 2: non-treatment (n=33).

Endoscopy was performed by an experienced specialist.

6. Main outcome measures

Frequency of defecation on the day of endoscopy, time until defecation, presence or absence and severity of abdominal pain associated with pretreatment, presence or absence and severity of nausea, pretreatment condition (residue), and time required to reach cecum.

7. Main results

Frequency of defecation and time until defecation were 6.9 ± 2.5 times and 234 ± 36 min, respectively, in arm 1 and 7.6 ± 3.4 times and 171 ± 30 min, respectively, in arm 2, showing reduced frequency and extended time until defecation in arm 1, although there were no significant differences between arms. The incidence and score of abdominal pain were 11% and 0.6 ± 0.4 , respectively, in arm 1 and 12% and 0.5 ± 0.4 , respectively, in arm 2, showing no difference between arms. Nausea was more prevalent in arm 1 with the incidence of 33%, compared with 12% in arm 2, although there was no difference in nausea score between arms. Pretreatment score and time required to reach cecum were 0.9 ± 0.8 and 7.9 ± 5.4 min, respectively, in arm 1 and 0.7 ± 0.8 and 7.9 ± 5.5 min, respectively, in arm 2, showing no difference between arms.

8. Conclusions

Shakuyakukanzoto combined with PEG tends to slightly suppress the cleansing of the bowel needed prior to large bowel endoscopy and may induce nausea, suggesting its ineffectiveness in such pretreatments.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

To achieve adequate intestinal lavage in preparation for large intestine endoscopy, a large amount of PEG has to be swallowed. In terms of efficacy and patient satisfaction, however, currently available pretreatments are not always useful. Focusing on this issue, the present study is meaningful. To further enhance the quality of this clinical research, however, the control should be a placebo that has no effect on bowel motility rather than no treatment. With no other useful concomitant drugs available, it is hoped that new drugs and useful approaches will be investigated.

12. Abstractor and date

Arai M, 23 February 2007, 30 October 2007, 1 June 2010.

21. Others**Reference**

Ai M. Assessment of the antispasmodic effect of peppermint oil and Shakuyaku-kanzon-to (TJ-68); a Chinese herbal medicine on the clonic wall. *Medical Tribune Online (Digestive Disease Week: DDW)* 2005: 10-1 (in Japanese).

1. Objectives

To evaluate the efficacy of directly sprayed shakuyakukanzoto (芍薬甘草湯) on large bowel spasm.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (university), Japan.

4. Participants

One-hundred and thirty-one patients scheduled to undergo large bowel endoscopy for polyp surveillance, etc.

5. Intervention

Arm 1: shakuyakukanzoto (芍薬甘草湯) group (0.5 g of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extra Granules dissolved in physiological saline to make 50 mL [concentration: 10 g/L]).

Arm 2: peppermint oil group (0.4 mL of peppermint oil and 0.05 g of sorbitan fatty acid ester dissolved in water to make 50 mL [concentration: 8 mL/L]).

Arm 3: Physiological saline group.

In all arms, conventional fluoroscopy (CF) was performed in the left lateral position, and the contraction ring in the gastric antrum was sprayed, kept 1 cm from the tip of the endoscope inserted 20–25 cm from the anus.

6. Main outcome measures

Contraction ring lumen area (presented as the number of pixels on videotaped digital images of contraction-relaxation motions of the contraction ring during the 3-min period beginning before and ending after each drug was sprayed), and area under the expanded area-time curve.

7. Main results

Lumen area was significantly larger in the shakuyakukanzoto group and peppermint oil group than in the physiological saline group. The area under the expanded area-time curve was also significantly larger in both treatment groups than in the physiological saline group. There was no difference in outcome measures between the shakuyakukanzoto group and peppermint oil group.

8. Conclusions

Shakuyakukanzoto and peppermint oil have comparable large intestinal wall-relaxing activity.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Direct spray of large intestinal wall with shakuyakukanzoto may be applicable as an antispastic in the CF test.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008, 31 December 2013.

21. Others

Reference

Sugihara N. Effectiveness of shakuyaku-kanzo-to as a pretreatment for upper digestive tract endoscopic examination. *Kampo Shinryo* 1999; 18: 17-9 (in Japanese).

1. Objectives

To evaluate the efficacy of pretreatment with shakuyakukanzoto (芍薬甘草湯) for upper gastrointestinal tract endoscopy.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

Single facility (clinic), Japan.

4. Participants

Fifty-eight subjects who underwent endoscopy.

5. Intervention

Arm 1: shakuyakukanzoto (芍薬甘草湯) group (oral administration of 80 mg of dimethicone syrup followed by 5.0 g of shakuyakukanzoto (芍薬甘草湯) extract granules) (n=11).

Arm 2: anticholinergic drug group (oral administration of 80 mg of dimethicone syrup followed by subcutaneous injection of 40 mg of scopolamine butylbromide) (n=28).

6. Main outcome measures

Symptoms during endoscopy (pain evaluated subjectively on a visual analogue scale), peristalsis (Niwa's classification).

7. Main results

Among those under 70 years, the anticholinergic drug was significantly superior to shakuyakukanzoto in suppression of peristalsis, but was more frequently associated with experience of pain/discomfort.

8. Conclusions

Shakuyakukanzoto provides as much pain relief as the anticholinergic drug.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

Of 58 subjects, only 39 were actually assigned to either group (arm 1, n=11; arm 2, n=28). This sample size seems to be slightly too small to evaluate efficacy.

12. Abstractor and date

Kogure T, 15 June 2007, 1 April 2008.

21. Others

Reference

Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, a herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Digestive Endoscopy* 2005; 17: 50-3. CENTRAL ID: CN-00575598, Ichushi Web ID: 2006000780

1. Objectives

To evaluate the efficacy of daikenchuto (大建中湯) combined with polyethylene glycol solution (PG solution) in pretreatment for large bowel endoscopy.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

None (authors belong to the 3rd Department of Surgery, Toho University School of Medicine), Japan.

4. Participants

Two-hundred and eighty-five patients who underwent total large bowel endoscopy between January and December 2001, gave informed consent to participate in this trial, and remained after excluding those under 18 years old, pregnant women, and other ineligible patients.

5. Intervention

Arm 1: combination of PG solution and TSUMURA Daikenchuto (大建中湯) Extract Granules (oral administration of 2.5 g each at 12:00 and 21:00 on the day before and 7:00 on the day of large bowel endoscopy) (n=144).

Arm 2: PG solution alone (n=141).

Endoscopy was performed by an experienced specialist.

6. Main outcome measures

Frequency of defecation on the day of endoscopy, time until defecation, presence or absence of abdominal pain, abdominal score, presence or absence of nausea, nausea score, pretreatment score, and time required to reach the ileocecal area.

7. Main results

The PG solution/daikenchuto combination group and PG solution group defecated 7.9 ± 3.1 times and 7.7 ± 3.6 times, respectively, and required 3.3 ± 1.6 hr and 3.0 ± 1.5 hr until defecation, respectively. The incidence of abdominal pain (score) was 17% (0.17 ± 0.38) and 15% (0.15 ± 0.35), respectively, and the incidence of nausea (score) was 24% (0.28 ± 0.55) and 21% (0.21 ± 0.43), respectively. Thus, there were no significant between-group differences in these parameters. Pretreatment score was significantly improved in the PG solution/daikenchuto combination group (0.28 ± 0.52 vs 0.81 ± 0.77 in the PG solution group; $P < 0.01$). The time required to reach the ileocecal area was also significantly reduced in the PG solution/daikenchuto combination group (6.4 ± 3.6 min vs 7.3 ± 4.0 min in the PG solution group; $P = 0.04$).

8. Conclusions

PG solution/daikenchuto pretreatment for large bowel endoscopy is a more patient-friendly effective method for facilitating insertion (compared with pretreatment with PG solution alone) and does not increase the level of uncomfortable symptoms such as abdominal pain, nausea, and frequent defecation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This randomized controlled trial demonstrated that daikenchuto combined with PG solution is superior to PG alone in the preparation of the large intestine for endoscopy. This study has a large sample size and is well designed, but fails to explain pretreatment score and abdominal pain score. It has been presented in a previous report "Saida Y. The 15th Surgery and Kampo Medicine Study Meeting 1. Efficacy of combined use of daikenchuto in pretreatment for large bowel endoscopy - 6 prospective studies - . *Progress in Medicine* 2005; 25: 3058-9 (in Japanese)."

12. Abstractor and date

Arai M, 10 March 2007, 30 October 2007, 1 June 2010, 31 December 2013.

21. Others

Reference

Ai M, Yamaguchi T, Odaka T, et al. Objective assessment of the antispasmodic effect of Shakuyaku-kanzo-to (TJ-68), a Chinese herbal medicine, on the colonic wall by direct spraying during colonoscopy. *World Journal of Gastroenterology* 2006; 12: 760-4. CENTRAL ID: CN-00563124, Pubmed ID: 16521190

1. Objectives

To evaluate the efficacy and safety of direct spraying of shakuyakukanzoto (芍薬甘草湯) on the colonic mucosa for suppression of bowel movement during colonoscopy.

2. Design

A randomized controlled trial (RCT).

3. Setting

Not specifically mentioned (the authors belong to one university hospital), Japan.

4. Participants

One-hundred and ten patients with suspected intestinal hemorrhage, acute abdomen due to acute enteritis, inflammatory bowel disease, or a history of abdominal surgery, and treated with an oral drug affecting bowel movement, who visited our hospital between July 2002 and March 2004.

5. Intervention

Arm 1: spray of 0.5 g/50 mL of a solution of TSUMURA Shakuyakukanzo (芍薬甘草湯) Extract Granules in physiological saline maintained at 36°C over the area of spasms in the intestine, 10 mm apart (n=51).

Arm 2: spray of physiological saline maintained at 36°C in the same manner as arm 1.

Colon preparation involved oral administration of Magcorol (59 g/250 mL) on the day before colonoscopy and 2 L of Niflec on the day of colonoscopy. No sedatives were used during colonoscopy (n=50).

Five patients in arm 1 and 4 patients in arm 2 were excluded from the study population because of poor or incomplete bowel preparation.

6. Main outcome measures

Lumen area (pixels) × time (min), determined before and after spraying over the area of spasms.

7. Main results

Before spraying, there was no significant difference between arms. After spraying, the area × time value was significantly larger in arm 1.

8. Conclusions

Direct spray of shakuyakukanzoto is effective for suppression of bowel movement during colonoscopy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no complications throughout the study period.

11. Abstractor's comments

This is an excellent study because it quantifies bowel movement by monitoring digital images over time, enabling objective evaluation.

12. Abstractor and date

Kogure T, 27 January 2009.

21. Others

Reference

Mizukami T, Maruyama K, Yamauchi H, et al. Assessment of antispasmodic effect of herbal medicine, Shyakuyakukanzoto (TJ-68) on colonoscopy – Using colonoscopy insertion technique “collapsing method” –. *Kampo to Saishin-chiryō (Kampo & the Newest Therapy)* 2006; 15: 69-76 (in Japanese). Ichushi Web ID: 2006142071

1. Objectives

To evaluate the efficacy of shakuyakukanzoto (芍薬甘草湯) solution in preparation for colonoscopy used with the water method of distension.

2. Design

A quasi-randomized controlled trial (quasi-RCT).

3. Setting

Not mentioned (the authors belong to one specialty hospital), Japan.

4. Participants

Forty-two males undergoing colonoscopy who gave consent to participate in the study.

5. Intervention

Arm 1: intrarectal injection of a solution of TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules (1.25 g/100 mL) instead of water used in preparation for colonoscopy used with the water method, simultaneously performed with colonoscopy insertion (n=21).

Arm 2: intramuscular injection of butylscopolammonium bromide (Buscopan) (20 mg/mL/A), simultaneously performed with colonoscopy insertion (n=21).

One patient in each arm was considered unresponsive because of failure to achieve spasmolysis during the test and was excluded.

6. Main outcome measures

Duration of spasmolysis determined by measuring the time between the first and second appearance of colonic ring contractions.

Pulse rate measured before and 10 min after endoscope insertion.

Pain evaluated on a 5-point scale.

7. Main results

There was no significant difference in duration of spasmolysis or pain scale score between arms. Percent increase in pulse rate from before to 10 min after insertion was significantly larger in arm 2. Spasmolytic effect persisted until completion of the test in 68.8% of subjects in arm 1 and 25.0% of subjects in arm 2, showing a significant between-arm difference.

8. Conclusions

Shakuyakukanzoto solution in preparation for colonoscopy, used with the water method, prolongs spasmolysis.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This excellent paper suggests the potential of a Kampo medicine as a bowel pretreatment for colonoscopy. Evaluation of spasmolysis by colonoscopy is limited to the visual field. Combined use of fluoroscopy may enable observation to be extended to the whole intestine. Studies on the effects of distension methods other than the water method during colonoscopy are expected.

12. Abstractor and date

Kogure T, 26 January 2009, 1 June 2010.

21. Others

Reference

Saida Y, Nagao J, Nakamura Y, et al. Dai-kenchu-to and mosapride in combination with precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)* 2005; 22: 145-8 (in Japanese). Ichushi Web ID: 2007146750

1. Objectives

To evaluate the bowel cleansing effect of precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage solution (PG solution) combined with daikenchuto (大建中湯) and mosapride.

2. Design

Randomized controlled trial (RCT).

3. Setting

None (the authors belong to the Third Department of Surgery, Toho University School of Medicine and/or Tohokamagaya Hospital), Japan.

4. Participants

Two hundred and twenty-two patients (155 males and 67 females) who underwent colonoscopy between April 2004 and October 2004 and gave informed consent, including consent to disclose relevant information.

5. Intervention

Arm 1: treatment with 2 L of polyethylene glycol (PG) solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) (n=116).

Arm 2: treatment with 2 L of PG solution plus daikenchuto (大建中湯) (7.5 g; manufacturer, not specified) and mosapride (15 mg; 3 tablets) (n=106).

PG solution was administered orally for about 2 hours, at least 6 hours prior to the colonoscopy. Daikenchuto (大建中湯) and mosapride were administered in three divided doses, starting at noon one day before colonoscopy.

6. Main outcome measures

Number of bowel movements, duration time of defecation, presence and severity of abdominal pain and nausea, ease/difficulty of taking the combined medication, adequacy of bowel preparation, and cecal intubation time.

7. Main results

The mean number of bowel movements was significantly higher in arm 2 (7.8) than in arm 1 (7.0). Defecation time tended to be slightly longer in arm 2 (3 h 18 min) than in arm 1 (2 h 59 min). No between-arm differences in abdominal pain (13% of patients in arm 1 and 17% in arm 2) and nausea (24% and 25%, respectively) were observed. The percentage of patients who reported that taking the combined medication was "difficult" or "slightly difficult" was significantly higher in arm 2 (38%) than in arm 1 (28%). No between-arm differences in mean bowel preparation scores (0.9 in both arms) and median cecal intubation times at colonoscopy (6 minutes in both arms) were observed.

8. Conclusions

The addition of mosapride offers no benefit to precolonoscopy bowel preparation with PG solution plus daikenchuto alone.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper follows up a previous paper that discussed the efficacy of precolonoscopy bowel preparation with PG solution plus daikenchuto: Saida Y, Sumiyama Y, Nagao J, et al. Dai-kenchu-to, an herbal medicine, improves precolonoscopy bowel preparation with polyethylene glycol electrolyte lavage: results of a prospective randomized controlled trial. *Digestive Endoscopy* 2005; 17: 50-3. The present trial had a large sample size and was well-designed. There are yet some drawbacks, including the following: 1) possible dependence of some results on skills of the colonoscopist is not mentioned; and 2) the method used for scoring bowel preparation quality was not described. Further studies, like this one, are anticipated.

12. Abstractor and date

Arai M, 19 January 2009, 1 June 2010.

21. Others

Reference

Arai J, Nakajima S, Fujinuma S, et al. A comparative study of bowel preparation for barium enema using divided administrations of powdered magnesium citrate with mosapride or DAIKEN CHUTOU. *Nihon Daicho Kensa Gakkai Zasshi (Journal of the Japan Society of Colon Examination)* 2002; 19: 170-3 (in Japanese). Ichushi Web ID: 2003041591

1. Objectives

To evaluate the effectiveness of daikenchuto (大建中湯) in bowel preparation for barium enema X-ray study.

2. Design

Randomized crossover controlled trial (RCT).

3. Setting

Ohashi Hospital, Toho University School of Medicine, Japan.

4. Participants

Forty-five patients who underwent barium enema X-ray study on an outpatient basis between March and August 2001.

5. Intervention

Arm 1: conventional bowel preparation plus oral administration of daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. on the day before the X-ray examination (n=24).

Arm 2: conventional bowel preparation plus oral administration of mosapride citrate 10 mg t.i.d. on the day before the X-ray examination (n=21).

6. Main outcome measures

The number and amount of fecal residues and the adherence of barium.

7. Main results

No significant between-arm differences were observed in the number and amount of fecal residues or in the adherence of barium.

8. Conclusions

Daikenchuto is suggested to be as effective as mosapride citrate in bowel preparation for barium enema X-ray study.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This paper compares the effectiveness of daikenchuto with that of mosapride citrate in bowel preparation for barium enema X-ray study. Prokinetic agents combined with conventional bowel preparation for barium enema X-ray decreases the number and amount of fecal residues and improves the adherence of barium. The authors of the present paper concluded that daikenchuto is as effective as a prokinetic agent. The effectiveness of daikenchuto in preparation for lower gastrointestinal endoscopy has been suggested in a previous report and the usefulness of shakuyakukanzoto has already been demonstrated. The use of Kampo medicines in this field is expected to increase in the future.

12. Abstractor and date

Oikawa T, 31 December 2008, 1 June 2010.

21. Others

References

Fujinami H. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): randomized placebo-controlled trial. *Nikkei Medical (Supplement)* 2010; 8: 34 (in Japanese).

Fujinami H, Kudo T, Nakayama Y, et al. Assessment of diminished peristalsis using Shakuyakukanzoto (TJ-68) as premedication for endoscopic retrograde cholangiopancreatography (ERCP): a randomized, placebo-controlled trial. *Gastrointestinal Endoscopy* 2010; 71: AB227.

1. Objectives

To evaluate the effectiveness of shakuyakukanzoto (芍薬甘草湯) as premedication for ERCP in suppressing duodenal peristalsis.

2. Design

Randomized controlled trial (RCT).

3. Setting

No. 3 Department of Internal Medicine, Toyama University Hospital, Japan.

4. Participants

Thirty patients undergoing ERCP (20 males, 10 females; mean age 66.5 years).

5. Intervention

Arm 1: shakuyakukanzoto group: TSUMURA Shakuyakukanzoto (芍薬甘草湯) Extract Granules 5.0 g dissolved in 50 mL warm water (n=10).

Arm 2: anticholinergic group: scopolamine butylbromide solution 20 mg/mL intravenous injection (n=10).

Arm 3: placebo group: warm (37°C) water 50 mL (n=10).

The liquids in arm 1 and arm 3 were sprayed directly into the duodenum through an endoscope.

6. Main outcome measures

Assessment by DVD image analysis of the time required to stop peristalsis (RT: seconds) and period of cessation of peristalsis (DT: minutes).

7. Main results

Peristalsis stopped in 8/10 patients in arm 1, 10/10 in arm 2, and 0/10 in arm 3. RT was 76.0 ± 23.9 in arm 1 and 42.4 ± 6.1 in arm 2. DT was 11.3 ± 4.2 in arm 1 and 14.9 ± 5.3 in arm 2. There was no significant difference in RT and DT between these groups.

8. Conclusions

Shakuyakukanzoto is effective as premedication for ERCP in suppressing duodenal peristalsis. Its effects are similar to scopolamine butylbromide solution 20 mg/mL intravenous injection.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

In clinical terms, this is a highly significant clinical trial because it assessed peristalsis in three groups during actual ERCP. Anticholinergics are generally used to reduce peristaltic action for upper gastrointestinal endoscopy and ERCP, but they are contraindicated for patients with ischemic heart disease, prostatic hypertrophy, glaucoma, etc. Such patients cannot take anticholinergics. Shakuyakukanzoto appears to be a very safe premedication that will reliably suppress peristalsis in such patients.

12. Abstractor and date

Kogure T, 31 December 2012.

21. Others**Reference**

Kita T, Sumino M. The effect of dosage frequency of ethical Kampo extract formulations on drug compliance – a comparison of twice a day and three times a day prescriptions. *Igaku to Yakugaku (Japanese Journal of Medicine and Pharmaceutical Science)* 2011; 66: 117–22 (in Japanese). Ichushi Web ID: 2011300492 [MOL](#), [MOL-Lib](#)

1. Objectives

To assess whether differences in ethical Kampo extract formulation dosage and dosing frequency have an effect on compliance and patient satisfaction.

2. Design

Crossover randomized controlled trial (RCT – cross over).

3. Setting

Not specified (the authors are from the Center for Environment, Health and Field Sciences, Chiba University.), Japan.

4. Participants

One hundred and five outpatients who had been taking ethical Kampo extract formulation for chronic disease or symptoms for more than one month, whose condition had stabilized, and who gave their consent.

5. Intervention

Kracie KB - stick packages (twice a day) and Kracie EK - stick packages (three times a day) containing the same ethical Kampo extract formulation as currently being taken. Administered for one week each.

Arm 1: three times a day for the first week, then twice a day for the second week (n=54).

Arm 2: twice a day for the first week, then three times a day for the second week (n=55).

6. Main outcome measures

Questionnaire on dosing circumstances (timing, whether dosing was missed, and how often dosing was missed), patients' satisfaction with frequency and dosage (5-step scale: satisfied, slightly satisfied, no change, slightly dissatisfied, dissatisfied), and lifestyle (which suits lifestyle better, twice a day or three times a day) during each period.

7. Main results

In arm 1, dosing was missed in 36 of 54 participants during the first week (three times a day) and 15 of 54 participants in the second week (twice a day), which meant a significant difference ($P<0.0001$). Similarly, there was a significant difference in missed dosing in arm 2 ($P<0.001$). The mean amount and proportion of left-over medication was 2.0 ± 2.2 packages and $9.4\pm 10.4\%$, respectively, during the three-times-a-day period and 0.4 ± 0.8 and $2.8\pm 6.0\%$ respectively during the twice-a-day period. There was a significant difference in the proportion of left-over medication between the periods ($P<0.0001$). Participants missed their medication most often around midday (63 participants, 87.5%) during the three-times-a-day period. Thirty-nine participants (72.2%) were satisfied or slightly satisfied in arm 1, where dosage frequency decreased in the second week, while 36 participants (65.5%) were satisfied or slightly satisfied in arm 2, where dosage frequency increased in the second week. Ninety-four participants (86.2%) chose the twice-a-day medication for consistency with lifestyle, while 6 participants chose the three-times-a-day medication (5.5%) and 9 (8.3%) were indifferent.

8. Conclusions

Reducing the frequency of Kampo extract preparation dosing from three to two times a day decreases missed dosing, and therefore is an effective means of improving compliance.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This RCT employed different dosing frequencies in the intervention and measured outcomes in terms of dosing compliance and satisfaction. This trial is, therefore, very instructive in that it demonstrates that such an approach can be used in an RCT. It also has great clinical significance in the sense that doctors' prescribing behavior can change patients' dosing compliance. Researchers should be encouraged to develop further research along these lines, perhaps by including symptoms among the outcomes.

12. Abstractor and date

Tsuruoka K, 31 December 2012.

21. Others

Reference

Ueda T, Yamashita K, Nakamori Y, et al. Study of the MRSA carriage-preventing effect of Hochuekkito (TJ-41): 1st report*. *Progress in Medicine* 1999; 19: 1000-3 (in Japanese). [MOL](#), [MOL-Lib](#)

1. Objectives

To evaluate the effects of hochuekkito (補中益気湯) on prevention of MRSA carriage, prevention of *Pseudomonas aeruginosa* carriage, prevention of infection development, neutrophil count, and C-reactive protein (CRP) value.

2. Design

Randomized controlled trial (RCT).

3. Setting

Single facility (Osaka University Hospital ER), Japan.

4. Participants

Twenty patients with trauma (aged 16 years or older) who were hospitalized in the above facility for at least 1 week.

5. Intervention

Arm 1: hochuekkito group (補中益気湯) (n=8 [2/10 enrolled were excluded]; male: female = 3:1; mean age, 46.8 years; injury severity score [ISS], 26.1).

Arm 2: non-treatment group (n=12; male: female = 3:1; mean age, 31.2 years; ISS, 24.0).

6. Main outcome measures

Incidences of MRSA and *Pseudomonas aeruginosa* colonization and infection, CRP level, and neutrophil count.

Bacteriological examination of nasopharyngeal swabs, sputum, midstream urine, feces, and wound scraping was performed on the 1st, 3rd and, 7th day of hospitalization.

7. Main results

There was no significant between-arm difference in neutrophil count and CRP level. Meningitis occurred in 0 of 2 treated patients and 4 of 5 untreated patients. There was no difference in the incidence of pneumonia. MRSA was detected in 1 of 8 treated patients and 4 of 12 untreated patients, although the difference was not significant. *Pseudomonas aeruginosa* was detected in 1 of 8 treated patients.

8. Conclusions

Hochuekkito tends to prevent MRSA carriage and infections in trauma patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

This is a valuable RCT performed in an emergency setting. As admitted by the authors in the text, the timing of hochuekkito administration varied. Specification of the method, duration of hochuekkito administration, and presence or absence of blinding, would increase the reliability of this assessment. More results from their study, now underway with a new protocol, are expected.

12. Abstractor and date

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010.

21. Others

Reference

Fujii S, Fukushi Y, Yamaguchi E, et al. A study of the addition of tokishakuyakusan during in-vitro fertilization cycles*. *Sanfujinka Kampo Kenkyu no Ayumi (Recent Progress of Kampo Medicine in Obstetrics and Gynecology)* 1997; 14: 121-5 (in Japanese).

1.

Objectives

To evaluate the effect of ovarian stimulation by tokishakuyakusan (当帰芍薬散) (used during in vitro fertilization and embryo transfer [IVF-ET] cycles) on follicular growth, luteal function, pregnancy rate, and abortion rate.

2.

Design

Randomized controlled trial (RCT).

3.

Setting

Single institution (Department of Obstetrics and Gynecology, Hirosaki University Hospital), Japan.

4.

Participants

Ninety-three patients who were diagnosed as infertile at the above-mentioned institution between April 1995 and September 1996 and underwent ovarian stimulation using gonadotropin-releasing hormone (GnRH) agonist (long protocol).

5.

Intervention

Arm 1: IVF-ET with ovarian stimulation using GnRH agonist (long protocol) and hMG, combined with oral administration of TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals.

6.

Arm 2: IVF-ET with ovarian stimulation using GnRH agonist (long protocol) and human menopausal gonadotropin (hMG).

Main outcome measures

The following measures were compared between two arms: number of dosing days and total dose of hMG as an ovarian stimulant, endometrial thickness at the last dose of hMG, number of retrieved oocytes, number of fertilized oocytes, fertilization rate, number of transferred embryos, number of cancelled transfer cycles per oocyte retrieval, pregnancy rate, abortion rate per pregnancy; blood concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), estradiol (E), and progesterone (P); and P/E ratio.

7.

Main results

There were no between-arm differences in the number of dosing days and total dose of hMG as an ovarian stimulant, endometrial thickness at the last dose of hMG, number of retrieved oocytes, number of fertilized oocytes, and fertilization rate. There were trends toward higher number of transferred embryos and lower number of cancelled transfer cycles per oocyte retrieval in arm 2. There were no between-arm differences in pregnancy rate per oocyte retrieval and abortion rate per pregnancy. The blood estradiol concentration was relatively high in arm 2 throughout the treatment cycles. No significant differences were observed in the blood concentrations of PRL and progesterone and P/E ratio. The blood FSH concentration was significantly higher in arm 2 at the time of oocyte retrieval ($P < 0.01$).

8.

Conclusions

During IVF-ET cycles (GnRH agonist-long protocol), oral tokishakuyakusan was not found to have a clear clinical significance, but it reduced the total dose of hMG required to induce follicular growth, suggesting that this drug may stimulate secretion of FSH at the times of human chorionic gonadotropin (hCG) administration and oocyte retrieval.

9.

From Kampo medicine perspective

None.

10.

Safety assessment in the article

Not mentioned.

11.

Abstractor's comments

The authors of this paper concluded that during IVF-ET cycles, combined tokishakuyakusan has no clear clinical significance. Yet it is noteworthy that, in IVF-ET, which we can consider an example of highly-advanced medical technology, tokishakuyakusan significantly reduced the dose of the drug used for ovarian stimulation, tended to reduce the rate of cancelled embryo transfer cycles per oocyte retrieval (to one fifth), and increased the number of transferred embryos. In this study, a sufficient number of cycles for clinical evaluation were administered, but rates of pathological conditions that require oral tokishakuyakusan were not compared between the two arms. Subgroup analyses would have been needed for, at least, cases with *oketsu* (瘀血, static blood) and *suidoku* (水毒, disorder of body fluid metabolism). I hope that the true clinical value of tokishakuyakusan-combined therapy will be found in future prospective studies that compare the effects according to the pathological conditions (with or without *ketsu-kyo* [血虚, blood deficiency], *oketsu*, or *suidoku*) with rigorous oriental medical diagnoses.

12.

Abstractor and date

Ushiroyama T, 10 September 2008, 1 June 2010, 31 December 2013.

13. Structured Abstract

(1 abstract describing a meta-analysis)

15. Ante/Post-partum Diseases

Reference

Koinuma M, Narikawa H, Kamei M, et al. Meta-analysis on the usefulness in postpartum control by kyukichoketsuin with methylergometrine maleate as control. *Nihon Toyo Igaku Zasshi (Kampo Medicine)* 2006; 57: 45-55 (in English with Japanese abstract). Ichushi Web ID: 2006097925 [CiNii](#)

1. Objectives

To evaluate the efficacy of kyukichoketsuin (キユウ帰調血飲) (KCL) in puerperal care in comparison with methylergometrine maleate (MME) by conducting a meta-analysis.

2. Data source

Articles in *Igaku Chuo Zasshi (Japana Centra Revuo Medicina)* (1983 – 2004) and Medline (1966 – 2004) were searched and collected using key words such as kyukichoketsuin, etc.

3. Selection of study

Inclusion criteria: 1) RCT; 2) original article; 3) study population consisting of puerperal primipara and pluripara who had normal delivery; 4) use of KCL as an intervention drug and MME as control; and 5) indices of therapeutic effect including length of uterine fundus, amount of lactation, and severity of afterbirth pains.

4. Data extraction

Data extraction was performed independently of data integration by a different researcher. Extracted data were baseline characteristics of subjects, sample size, method of randomization, method of blinding, method of administering the investigational and control drugs, dosage, number of daily doses, number of days of administration, concomitant drugs, and study endpoints. If study end points data were shown just graphically without numerical values, points on the graph with calipers were measured and converted graphical values to numerical values. The quality of selected RCTs was evaluated using the Chalmers' scoring system.

5. Main results

Of 44 RCTs gathered, 5 satisfied the selection criteria. One of these 5 overlapped and was excluded, leaving 4 RCTs for analysis. These RCTs were equivalent in quality. Analysis of three RCTs evaluating breast pain revealed that KCL significantly attenuated afterbirth pains compared with MME (combined odds ratio: 0.32 [95%CI, 0.17 – 0.60]). On day 5 after delivery, there was statistically significant difference in the length of the uterine fundus between groups treated with KLC and MME in 1 trial, but no difference based on the combined data from all 4 trials. On day 4 after delivery, neither data from individual trials nor the combined data showed significant differences in the length of the uterine fundus, suggesting comparable effect of KCL and MME on involution of the uterus. Combined data from 2 contradictory articles compared the amount of lactation on day 4 after delivery, one showed no difference and another showed that both KCL and MME increased the amount of lactation, demonstrated significantly less lactation with KCL (combined odds ratio: -8.20 [95%CI, -16.17 to -0.23]). Combined data on day 5 after delivery revealed that KCL increased the amount of lactation, although not significantly, showing the efficacies of KCL and MME for inducing lactation were similar.

6. Conclusions

Compared to MME, KCL is more effective in attenuating afterbirth pains. Analysis of safety is necessary.

7. From Kampo medicine perspective

None.

8. Safety assessment in the article

Not mentioned.

9. Abstractor's comments

The authors deserve praise for conducting a meta-analysis of RCTs restricted to Kampo medicine. As the point of meta-analysis is to gather data from all related studies, it would be better to provide the details of the gathering process; for example, whether the search was exhaustive and included a hand-search of textbooks, reference books, and specialists' opinions. Considering current movement towards evidence based medicine (EBM) in Kampo field, the authors' meta-analysis is epoch-making. It is expected that this study will stimulate further meta-analyses and systematic reviews of Kampo medicine studies.

10. Abstractor and date

Tsuruoka K, 19 February 2009, 1 June 2010.