Evidence Reports of Kampo Treatment (EKAT)

Appendix 2020

漢方治療エビデンスレポート(EKAT) Appendix 2020

31 Jan 2022

Task Force for Evidence Report (ER -TF) Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

ver.1.0　2022.1.31

History of version upgrades

31 Jan. 2022: Kampo Chiryo Ebidensu Repoto, Appendix 2020 (Evidence Reports of Kampo Treatment, Appendix 2020)

1 Sep. 2021: Kampo Chiryo Ebidensu Repoto, 2019 (Evidence Reports of Kampo Treatment, 2019: 512 Randomized Controlled Trials)

1 June 2020: Kampo Chiryo Ebidensu Repoto, Appendix 2018 (Evidence Reports of Kampo Treatment, Appendix 2018)

18 May 2020: Kampo Chiryo Ebidensu Repoto, Appendix 2017 (Evidence Reports of Kampo Treatment, Appendix 2017)

1 Nov. 2018: Kampo Chiryo Ebidensu Repoto, 2016 (Evidence Reports of Kampo Treatment, 2016)

31 Mar. 2017: Kampo Chiryo Ebidensu Repoto, Appendix 2015 (Evidence Reports of Kampo Treatment, Appendix 2015)

6 June 2015: Kampo Chiryo Ebidensu Repoto, Appendix 2014 (Evidence Reports of Kampo Treatment, Appendix 2014)

31 Dec. 2013: Kampo Chiryo Ebidensu Repoto, 2013 – 402 no RCT (Evidence Reports of Kampo Treatment, 2013: 402 Randomized Controlled Trials)

31 Dec. 2012: Kampo Chiryo Ebidensu Repoto, Appendix 2012 (Evidence Reports of Kampo Treatment, Appendix 2012)

1 Oct. 2011: Kampo Chiryo Ebidensu Repoto, Appendix 2011 (Evidence Reports of Kampo Treatment, Appendix 2011)

1 June 2010: Kampo Chiryo Ebidensu Repoto, 2010 – 345 no RCT (Evidence Reports of Kampo Treatment, 2010: 345 Randomized Controlled Trials)

1 June 2009: Kampo Chiryo Ebidensu Repoto, 2009 – 320 no RCT (Evidence Reports of Kampo Treatment, 2009: 320 Randomized Controlled Trials)

1 Apr. 2008: Kampo Chiryo Ebidensu Repoto, Dai 2-han – RCT 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 June 2007: Kampo Chiryo Ebidensu Repoto, Dai 2-han –RCT wo Shu ni Shite- Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment, 2nd edition - Focusing on RCTs- Interim Report 2007)

20 July 2005: Kampo Chiryo niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (Nihon Toyo Igaku Zasshi [Kampo Medicine] 2005: 56, EBM supplementary issue)

20 Sept. 2002: Kampo Chiryo 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
2022.1.31	Evidence Reports of Kampo Treatment, Appendix 2020 (EKAT Appendix 2020)	From EKAT 2019 2019	639[2)]	533[1),2)]	225[2)]
2021.9.1	Evidence Reports of Kampo Treatment, 2019 - 512 Randomized Controlled Trials (EKAT 2019)	1986-2018	616	512[1)]	216
2020.6.1	Evidence Reports of Kampo Treatment, Appendix 2017 (EKAT Appendix 2018)	From EKAT 2017 2017	594[3)]	493[1), 3)]	203[3)]
2020.5.18	Evidence Reports of Kampo Treatment, Appendix 2017 (EKAT Appendix 2017)	From EKAT 2016 2016	578[4)]	478[1), 4)]	188[4)]
2018.11.1	Evidence Reports of Kampo Treatment, 2016 - 467 Randomized Controlled Trials (EKAT 2016)	1986-2015	567	467[1)]	181

2017.3.31	Evidence Reports of Kampo Treatment, Appendix 2015 (EKAT Appendix 2015)	From EKAT 2014 2014	545[5)]	447[1), 5)]	177[5)]
2015.6.6	Evidence Reports of Kampo Treatment, Appendix 2014 (EKAT Appendix 2014)	From EKAT 2013 2013 (First half)	513[6)]	418[1), 6)]	167[6)]
2013.12.31	Evidence Reports of Kampo Treatment, 2013 - 402 Randomized Controlled Trials (EKAT 2013)	1986-2012 (First half)	494	403[1)]	159
2012.12.31	Evidence Reports of Kampo Treatment, Appendix 2012 (EKAT Appendix 2012)	From EKAT 2011 2011 (First half)	457[7)]	379[1), 7)]	150[7)]
2011.10.1	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT Appendix 2011)	From EKAT 2010 2010 (First half)	432[8)]	360[1), 8)]-	-
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 ver.1.1	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 at least 1 meta-analysis

2) Total of all references added or removed in EKAT 2019 and EKAT Appendix 2020.

3) Total of all references added or removed in EKAT 2016, EKAT Appendix 2017 and EKAT Appendix 2018.

4) Total of all references added or removed in EKAT 2016 and EKAT Appendix 2017.

5) Total of all references added or removed in EKAT 2013, EKAT Appendix 2014 and EKAT Appendix 2015.

6) Total of all references added or removed in EKAT 2013 and EKAT Appendix 2014.

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

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

Notes on the current version

Since 2007, the Task Force for Evidence Reports (ER -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 Chiryo Ebidensu Repoto (Evidence Reports of Kampo Treatment: EKAT). As indicated in the "Version History upgrades" on the previous page, the "Evidence Reports of Kampo Treatment, 2019 -512 RCTs (EKAT 2019) was published on 1 September 2021. The EKAT 2019 presented the results of 502 RCTs and 10 meta-analyses performed between 1986, when the current quality specifications for Kampo formulations for medical use were established, and 2018.

This EKAT Appendix 2020 contains SAs (19 RCTs and 1 meta-analysis) of 20 of the RCT reports published within approximately one year after the publication of EKAT Appendix 2019. Furthermore, the committee prepared and published an SA for one RCT that had been excluded in the past. Although the website itself has not been updated since the publication of EKAT 2019, the Google search engine available on the website allows users to access all SAs in both EKAT 2019 and EKAT Appendix 2020.

The ER-TF carried out a search for RCT reports for the present EKAT in April 2020, to prepare SAs of RCT reports published in most medical journals in 2019. Although publication of EKAT 2020 was planned in 2020, it was actually published in 2022 due to a delay in the publication of EKAT 2019. However, it is expected that the ER-TF will carry out its search for RCT reports in April of each year and publish the EKAT within the fiscal year going forward.

The next EKAT is also scheduled to be published as an appendix.

Sixth Phase (June 2019 – June 2021)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)
Organization

Notes: The information below was as of June 2021, and may differ from the current status.

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

Toshiaki KOGURE Department of Japanese Oriental Medicine, Gunma Chuo Hospital

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

Ichiro ARAI Graduate School of Pharmaceutical Sciences, Nihon Pharmaceutical University

Yasuhito KATO Department of Obstetrics and Gynaecology, Asahikawa Medical University

Masamichi KITAGAWA Academic Information Center, The Jikei University School of Medicine

Hiroshi KOIKE Department of Family Medicine, Division of Comprehensive Patient Care, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Hirozo GOTO Department of Kampo Medicine, Hokusei Hospital

Nami KONDO Department of Breast Oncology, Saitama Medical University International Medical Center (April 2020 -)

Hiroki TAKUMA Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba

Hideyuki NAKATA Kampo Internal Medicine/Health Medical Center, Nerima General Hospital

Miyuki MINARI Subcommittee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association (- August 2020)

Hiroyasu MIWA Subcommittee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association (August 2020 -)

Adviser

Kiichiro TSUTANI Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

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

Yoshiharu MOTOO Department of Medical Oncology, Komatsu Sophia Hospital (Trustee in charge of Committee for EBM, JSOM)

Seventh Phase (June 2021 -)
Task Force for Evidence Reports (ER - TF)
Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)
Organization

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

Toshiaki KOGURE Department of Japanese Oriental Medicine, Gunma Central General Hospital

Members (9 persons, listed in order of the Japanese syllabary):

Ichiro ARAI Graduate School of Pharmaceutical Sciences, Nihon Pharmaceutical University

Yasuhito KATO Department of Obstetrics and Gynecology, Asahikawa Medical University

Masamichi KITAGAWA Academic Information Center, The Jikei University School of Medicine

Hiroshi KOIKE Department of Family Medicine, Division of Comprehensive Patient Care, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Hirozo GOTO Department of Kampo Medicine, Hokusei Hospital

Nami KONDO Department of Breast Oncology, Saitama Medical University International Medical Center

Hiroki TAKUMA Acupuncture and Physical Therapy Teacher Training School, University of Tsukuba

Hiroyasu MIWA Subcommittee to Assess the Efficacy of Kampo Formulations, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association

Akino WAKASUGI Center for Evidence-Based-Medicine, Oriental Medicine Research Center, Kitasato University

Adviser

Kiichiro TSUTANI Faculty of Health Sciences, Tokyo Ariake University of Medical and Health Sciences

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

Yoshiharu MOTOO Department of Medical Oncology, Komatsu Sophia Hospital (Trustee in charge of Committee for EBM, JSOM)

Lists of Structured Abstracts
(structured abstract and included references list)

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

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C15.9	To evaluate the effectiveness and safety of rikkunshito (六君子湯) for delayed nausea and vomiting in patients with esophageal cancer receiving highly emetogenic chemotherapy.	rikkunshito (六君子湯)	Hamai Y, Yoshiya T, Hihara J, et al. Traditional Japanese herbal medicine rikkunshito increases food intake and plasma acylated ghrelin levels in patients with esophageal cancer treated by cisplatin-based chemotherapy. *Journal of Thoracic Disease* 2019; 11(6): 2470-8.	RCT-cross over	C	8
C16.9	To evaluate the effect of concomitant use of hochuekkito (補中益気湯) in postoperative adjuvant chemotherapy (S-1) for gastric cancer on reducing adverse events and improving treatment completion rates.	hochuekkito (補中益気湯)	Okabe H, Kinjo Y, Obama K. et al. A Randomized Phase II Study of S-1 Adjuvant Chemotherapy With or Without Hochu-ekki-to,a Japanese Herbal Medicine, for Stage II/III Gastric Cancer: The KUGC07 (SHOT) Trial. *Frontiers in Oncology* 2019 Apr 17;9:294. doi: 10.3389/fonc.2019.00294.	RCT	C	9
C18.9	To compare hangeshashinto (半夏瀉心湯) and oral alkalinization for diarrhea due to FOLFIRI.3 in patients with colorectal cancer.	hangeshashinto (半夏瀉心湯)	Yamazaki K, Ariyoshi N, Miyauchi H, et al. A randomized controlled, open-label early phase II trial comparing incidence of FOLFIRI.3-induced diarrhoea between Hangeshashinto and oral alkalization in Japanese patients with colorectal cancer. *Journal of Clinical Pharmacy and Therapeutics* 2019; 44(6): 946-51.	RCT	N	10
C18.9	To validate the effectiveness and safety of ninjin'yoeito (人参養栄湯) for oxaliplatin-induced cumulative peripheral neuropathy.	ninjin'yoeito (人参養栄湯)	Motoo Y, Tomita Y, Fujita H. Prophylactic efficacy of ninjin' yoeito for oxaliplatin-induced cumulative peripheral neuropathy in patients with colorectal cancer receiving postoperative adjuvant chemotherapy: a randomized, open-label, phase 2 trial (HOPE-2). *International Journal of Clinical Oncology* 2020; 25(6): 1123-9.	RCT	N	11
C18.9	To evaluate the effectiveness and safety of perioperative oral administration of daikenchuto (大建中湯) on nutritional status after laparoscopic surgery for colorectal cancer.	daikenchuto (大建中湯)	Fujita F, Torashima Y, Inoue Y, et al. Daikenchuto improved perioperative nutritional status of the patients with colorectal cancer: A prospective open-labeled randomized exploratory study. *Interventional Medicine & Applied Science* 2019; 11(2): 84-8.	RCT	N	12
C34.9 R63.0	To evaluate the effectiveness and safety of rikkunshito (六君子湯) for vomiting and anorexia in patients treated with chemotherapy for lung cancer.	rikkunshito (六君子湯)	Yoshiya T, Mimae T, Ito M, et al. Prospective, randomized, cross-over pilot study of the effects of Rikkunshito, a Japanese traditional herbal medicine, on anorexia and plasma-acylated ghrelin levels in lung cancer patients undergoing cisplatin-based chemotherapy. *Investigational New Drugs* 2020; 38(2): 485-92.	RCT-cross over	C	13
C80.0	To evaluate the efficacy and safety of hangeshashinto (半夏瀉心湯) mixed with honey for intraoral discomfort events in terminally ill cancer patients.	hangeshashinto (半夏瀉心湯)	Murakami S, Igarashi A, Miyano K, et al. Investigation of the efficacy of gargling a mixture of hangeshashinto (半夏瀉心湯) and honey for intraoral discomfort events in terminally ill cancer patients. *Palliative Care Research* 2019; 14(3): 159-67.	RCT-envelope	I	14
E66.9	To evaluate the effects of bofutsushosan (防風通聖散) on obese and obesity-prone women.	bofutsushosan (防風通聖散)	Hayashida M, Kaneko T, and Miyata A. Fat-reducing effect of Shokansen (生漢煎)® bofutsushosan (防風通聖散) (type-2 OTC drugs). *Advanced Medicine for Health and Beauty* 2019; 6(1): 14-21.	RCT	I	15
G30.9	To evaluate the effectiveness of kihito (帰脾湯) on cognitive function in Alzheimer's disease.	kihito (帰脾湯)	Watari H, Shimada Y, Matsui M, et al. Kihito, a Traditional Japanese Kampo Medicine, Improves Cognitive Function in Alzheimer's Disease Patients. *Evidence-Based Complementary and Alternative Medicine* 2019 May 14;2019:4086749. doi: 10.1155/2019/4086749.	RCT-cross over	N	16
I50.9	To evaluate the effectiveness of goreisan (五苓散) in elderly patients with heart failure.	goreisan (五苓散)	Tamano M, Toyoda S, Kato S, et al. A long-term prognostic benefit of Tolvaptan plus goreisan (五苓散) in elderly patients with heart failure. *Progress in Medicine* 2019; 39(7): 753-60.	RCT	I	17
I50.9	To evaluate the effectiveness and safety of mokuboito (木防已湯) for acute exacerbations of chronic heart failure.	mokuboito (木防已湯)	Ezaki H, Ayaori M, Sato H, et al. Effects of Mokuboito, a Japanese Kampo medicine, on symptoms in patients hospitalized for acute decompensated heart failure - A prospective randomized pilot study. *Journal of Cardiology* 2019; 74(5): 412-7.	RCT	N	18
I62.0	To evaluate the effect of the timing of goreisan (五苓散) and saireito (柴苓湯) use on the incidence of chronic subdural hematoma after unruptured cerebral aneurysm clipping, and to compare the efficacy of goreisan (五苓散) and saireito (柴苓湯).	goreisan (五苓散) saireito (柴苓湯)	Kawase T, Teranishi T, Miyatani K, et al. Chronic subdural hematoma associated with postoperative unruptured cerebral aneurysm: a prospective study of the timing of postoperative use of goreisan (五苓散) and saireito (柴苓湯). *Neurosurgery and Kampo* 2019; 5: 63-5.	RCT	I	19
J02.9	To validate the effectiveness and safety of kikyoto (桔梗湯) for sore throat in acute upper respiratory inflammation.	kikyo-to (桔梗湯)	Ishimaru N, Kinami S, Shimokawa T, et al. Kikyo-to vs. placebo on sore throat associated with acute upper respiratory tract infection : A randomized controlled trial. *Internal Medicine* 2019; 58(17): 2459-65.	DB-RCT	N	20
J69.0	To evaluate the effectiveness and safety of hangekobokuto (半夏厚朴湯) for aspiration pneumonia in patients after cardiovascular surgery.	hangeshokanto (半夏厚朴湯)	Kawago K, Nishibe T, Shindo S, et al. A Double-Blind Randomized Controlled Trial to Determine the Preventive Effect of Hangekobokuto on Aspiration Pneumonia in Patients Undergoing Cardiovascular Surgery. *Annals of Thoracic and Cardiovascular Surgery* 2019; 25(6): 318-25.	DB-RCT	N	21

K30	To evaluate the effectiveness and safety of rikkunshito (六君子湯) treatment of gastrointestinal symptoms and gastrointestinal motility in patients with functional dyspepsia (FD) in Belgium.	rikkunshito (六君子湯)	Masuy I, Carbone F, Holvoet L, et al. The effect of rikkunshito on gastrointestinal symptoms and gastric motor function: The first study in a Belgian functional dyspepsia population. *Neurogastroenterol Motil* 2020 Feb; 32(2): e13739. doi: 10.1111/nmo.13739.	DB-RCT-cross over	N	22
K64.9	To evaluate the effectiveness and safety of otsujito (乙字湯) for defecation management and symptom control in patients with hemorrhoids and anal fissure.	otsujito (乙字湯)	Kurihara H, Akase T, Nakamura K, et al. Effectiveness of otsujito (乙字湯) for defecation management in patients with hemorrhoids and anal fissure. *Phil Kampo* 2019; 74: 12-3.	quasi-RCT	I	23
N46	To evaluate the effectiveness of antioxidant supplements for male infertility with hochuekkito (補中益気湯) as a control.	hochuekkito (補中益気湯)	Terai K, Horie S, Fukuhara S, et al. Combination therapy with antioxidants improves total motile sperm counts: A Preliminary Study. *Reproductive Medicine and Biology* 2020; 19(1): 89-94.	RCT	N	24
R63.3	To investigate the efficacy of standard and double-dose rikkunshito (六君子湯) for increasing the dose of calories in patients on enteral nasogastric tube feeding.	rikkunshito (六君子湯)	Doi M, Miyamoto K, Shimaoka T, et al. The effect of standard and high dose of rikkunshito on achievement of enteral nutrition target in critically ill patients: a pilot randomized controlled trial. *Acute Medicine & Surgery* 2020; 7: e442. doi: 10.1002/ams2.442.	RCT	N	25
T14.1	To evaluate the effectiveness of hochuekkito (補中益気湯) in patients with refractory chronic skin wounds.	hochuekkito (補中益気湯)	Akita S, Namiki T, Kawasaki Y, et al. The beneficial effect of traditional Japanese herbal (Kampo) medicine, Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), for patients with chronic wounds refractory to conventional therapies: A prospective, randomized trial. *Wound Repair and Regeneration* 2019; 27(6): 672-9.	RCT	C	26

[Meta-analysis]

K91.9	To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative gastrointestinal dysfunction by meta-analysis in patients with gastrointestinal cancer.	daikenchuto (大建中湯)	Hosaka M, Arai I, Ishiura Y, et al. Efficacy of daikenchuto, a traditional Japanese Kampo medicine, for postoperative intestinal dysfunction in patients with gastrointestinal cancers: meta-analysis. *International Journal of Clinical Oncology* 2019; 24(11): 1385-96.	meta-analysis	N	27

[Addition of articles that had been excluded in the past]

F03	To evaluate the effectiveness of yokukansan (抑肝散) (TJ-54) on neurotransmitters in patients with dementia.	yokukansan (抑肝散)	Takeyoshi K, Kurita M, Nishino S, et al. Yokukansan improves behavioral and psychological symptoms of dementia by suppressing dopaminergic function. *Neuropsychiatric Disease and Treatment* 2016; 12: 641-9.	RCT	C	28

[Correction of structured abstracts that had already been listed]

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	
K59.0	To evaluate the effectiveness and safety of daikenchuto (大建中湯) for constipation in post-stroke patients.	daikenchuto (大建中湯)	Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine Daikenchuto improves functional constipation in poststroke patients. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/231258	RCT	C&N	29
			Numata T, Takayama M, Iwasaki K, et al. A prospective controlled clinical trial using daikenchuto (大建中湯) for constipation symptoms in patients with cerebrovascular accident sequelae. *Kampo medicine and the Newest Therapy* 2015; 24: 145-52.	RCT-envelope	I&N	
			Arita R, Numata T, Takayama S, et al. Responder Analysis of Daikenchuto Treatment for Constipation in Poststroke Patients: A Subanalysis of a Randomized Control Trial. *Journal of Evidence-Based Integrative Medicine* 2019; 24: 2515690X19889271.	RCT-envelope	C	
Z04.8	To evaluate the equivalence of shoseiryuto (小青竜湯) extract and decoction.	shoseiryuto (小青竜湯)	Chikafumi Horii, Akira Okonogi, Toshiki Okubo, et al. A study on the equivalence of shoseiryuto (小青竜湯) extract and decoction (I). *The Japanese journal of pharmacology* 2014; 68(2): 65-9.	RCT-cross over	I&N	30
			Chikafumi Horii, Akira Okonogi, Ryuji Takahashi, et al. A study on the equivalence of shoseiryuto (小青竜湯) extract and decoction (II). The Japanese journal of pharmacology 2019; 73(2): 73-83.	RCT-cross over	I	

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Hamai Y, Yoshiya T, Hihara J, et al. Traditional Japanese herbal medicine rikkunshito increases food intake and plasma acylated ghrelin levels in patients with esophageal cancer treated by cisplatin-based chemotherapy. *Journal of Thoracic Disease* 2019; 11(6): 2470-8. CENTRAL ID: CN-01960953, Pubmed ID: 31372284, UMIN ID: UMIN000010747

1. Objectives

To evaluate the effectiveness and safety of rikkunshito (六君子湯) for delayed nausea and vomiting in patients with esophageal cancer receiving highly emetogenic chemotherapy.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

A single department of surgery, university hospital.

4. Participants

Advanced esophageal cancer patients receiving at least two cycles of cisplatin (CDDP)-based chemotherapy (CDDP + 5-fluorouracil [FU] or CDDP + 5-FU + docetaxel [DOC]) every 3 weeks (20 patients).

5. Intervention

Arm 1: cycle 1: Tsumura Rikkunshito (六君子湯) Extract Granules 2.5 g three times a day before meals for 2 weeks from the day of start of chemotherapy, and after 1 week of wash-out; cycle 2: rikkunshito (六君子湯) not administered (10 patients).

Arm 2: cycle 1: rikkunshito not administered; cycle 2: Tsumura Rikkunshito (六君子湯) Extract Granules 2.5 g three times a day before meals for 2 weeks from the day of start of chemotherapy (10 patients).

6. Main outcome measures

The primary end point was the rate of change in dietary (caloric) intake between cycles of treatment with and without rikkunshito (六君子湯); the secondary endpoints were the appetite visual analog scale (VAS) score; grade of nausea and vomiting based on the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0; taste disturbance grade; and plasma acyl-ghrelin (AG) levels.

7. Main results

One patient withdrew from the study due to renal insufficiency and another patient, due to a brain hemorrhage. Although total daily calorie intake was significantly reduced after the start of chemotherapy for both cycles, the median percentage reduction in dietary intake during the period from Day 4 to Day 6 was significantly lower in the cycle with rikkunshito (六君子湯) than in the cycle without rikkunshito (六君子湯)(P =0.02). Appetite VAS scores, nausea and vomiting, and taste disturbance grades did not differ significantly between the two cycles. There was a trend toward a higher increase in plasma AG levels from Day 3 to Day 8 in cycles with rikkunshito (六君子湯) than in cycles without rikkunshito (六君子湯) (68% vs 48%, P=0.08); however, the difference was not significant.

8. Conclusions

Rikkunshito (六君子湯) attenuates late dietary intake loss caused by CDDP-based chemotherapy in patients with advanced esophageal carcinoma.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No rikkunshito (六君子湯)-associated adverse event was observed.

11. Abstractor's comments

This is the first report to analyze the effect of rikkunshito (六君子湯) on caloric intake and plasma AG levels in esophageal cancer patients receiving highly emetogenic chemotherapy. As standard antiemetic therapy can control nausea and vomiting for up to Day 5 but is ineffective for anorexia, it is significant that this study shows that cycles of rikkunshito (六君子湯) may improve symptoms particularly late anorexia. There were no significant differences in the VAS score for anorexia, and moreover, it is disappointing that there was no significant difference in the plasma AG level, which is important for rikkunshito's (六君子湯) mechanism of action, although the rate of increase in plasma AG level from Day 3 to Day 8 tended to be higher during cycles with rikkunshito (六君子湯). As plasma AG level was measured only on Day 1, Day 3, and Day 8 of chemotherapy, validation of the measurements may be needed. The authors performed a similar analysis in lung cancer and they say in the discussion that they obtained similar results. We expect that they will obtain more reliable results in larger samples, including samples from multicenter collaborative studies in the future.

12. Abstractor and date

Motoo Y, 14 December 2020.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Okabe H, Kinjo Y, Obama K. et al. A Randomized Phase II Study of S-1 Adjuvant Chemotherapy With or Without Hochu-ekki-to, a Japanese Herbal Medicine, for Stage II/III Gastric Cancer : The KUGC07 (SHOT) Trial. *Frontiers in Oncology* 2019 Apr 17;9:294. doi: 10.3389/fonc.2019.00294. CENTRAL ID: CN-02003292, Pubmed ID: 31058092, UMIN ID: UMIN000004701

1. Objectives

To evaluate the effect of concomitant use of hochuekkito (補中益気湯) in postoperative adjuvant chemotherapy (S-1) for gastric cancer on reducing adverse events and improving treatment completion rates.

2. Design

Randomized controlled trial (RCT).

3. Setting

Twenty-five institutions, including university hospital departments of surgery.

4. Participants

Gastric cancer patients (Stage II/III) after curative resection who were able to start oral administration of S-1 and hochuekkito (補中益気湯) within 8 weeks after surgery (113 patients).

5. Intervention

Arm 1: Each cycle consisted of S-1 80 mg/m^2/day orally administered for 4 weeks and 2 weeks of rest and the entire course was continued for 1 year.
Tsumura Hochuekkito (補中益気湯) Extract Granules 7.5 g/day was orally administered for the same period of time (56 patients).

Arm 2: Each cycle consisted of S-1 80 mg/m ^{2}/day (divided into 2 portions) orally administered for 4 weeks and 2 weeks of rest and the entire course was continued for 1 year (57 patients).

6. Main outcome measures

Primary endpoint: Completion rate of S-1 oral administration.

Secondary endpoints: Relative dose intensity (RDI), adverse event, relapse-free survival (RFS), overall survival (OS).

7. Main results

A total of 55 patients in each group were included in the analysis, excluding 2 who did not meet the enrollment criteria and one who had a prescribing error. The completion rates for S-1 were 54.5% for Arm 1 and 50.9% for Arm 2 (P=0.35). The median RDI was 89.2% for Arm 1 and 71.9% for Arm 2 (P=0.33), and the percentages achieving 90% RDI were 47.3% and 30.7% (P=0.08), respectively. Grade 3 or 4 adverse events were identified in 45.5% and 54.5% of patients of Arm 1 and Arm 2, respectively (P=0.446). At 3 years of enrollment, there was no significant difference in RFS and OS between the two groups (P=0.271 and P=0.140, respectively), but there was a trend toward more relapses and deaths in the hochuekkito (補中益気湯) group.

8. Conclusions

The use of hochuekkito (補中益気湯) in combination with S-1 oral administration tends to increase the S-1 completion rate and improve RDI, as well as reduce adverse events.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Hochuekkito (補中益気湯) did not cause any apparent side effects.

11. Abstractor's comments

The assumption that higher S-1 completion rate contributes to RFS and OS was reversed, i.e., there were more relapses and deaths in the hochuekkito (補中益気湯) group. The authors attributed this to the higher proportion of TNM classification T3 or N4 cases in the hochuekkito (補中益気湯) group. Further validation is expected in light of the limitation that the study was not double-blind and did not take into account the diagnosis of Kampo medicine.

12. Abstractor and date

Kondo N, 9 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Yamazaki K, Ariyoshi N, Miyauchi H, et al. A randomized controlled, open-label early phase II trial comparing incidence of FOLFIRI.3-induced diarrhoea between Hangeshashinto and oral alkalization in Japanese patients with colorectal cancer. *Journal of Clinical Pharmacy and Therapeutics* 2019; 44(6): 946-51. Pubmed ID: 31407827, UMIN ID: UMIN000024219

1. Objectives

To compare hangeshashinto (半夏瀉心湯) and oral alkalinization for diarrhea due to FOLFIRI.3 in patients with colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single university.

4. Participants

Patients with unresectable advanced colorectal cancer receiving FOLFIRI.3 therapy (30 patients).

5. Intervention

Arm 1: Tsumura Hangeshashinto (半夏瀉心湯) Extract Granules (2.5 g per dose three times daily before meals, from 3 days before the start of FOLFIRI.3 therapy to the end of FOLFIRI. 3 therapy) (15 patients).

Arm 2: Oral alkalinization group (0.6 g of sodium bicarbonate [baking soda], 100 mg of ursodeoxycholic acid [UDCA], and 250 mg of magnesium oxide [MgO], taken three times daily after meals from Day 1 through Day 5 of each cycle of FOLFIRI. 3 therapy) (15 patients).

6. Main outcome measures

The primary endpoint was the frequency of delayed diarrhea (diarrhea after 24 h of CPT-11 administration, a key component of FOLFIRI.3 therapy) during FOLFIRI.3 therapy (all grades according to CTC-AE v3.0); secondary endpoints were the response rate (RECIST, v1.1), medication compliance, frequency of adverse events other than diarrhea, the frequency of use of antidiarrheal drugs such as loperamide, and the duration of FOLFIRI.3 therapy.

7. Main results

A patient in the hangeshashinto (半夏瀉心湯) group declined to receive several oral medications, including hangeshashinto (半夏瀉心湯) and antiemetics, and withdrew from the study. The frequency of delayed diarrhea of grade 3 or above (and all grades) did not differ significantly between the two groups. Additional endpoints that did not differ significantly between the two groups included the frequency of loperamide use; frequencies and grades of neutropenia and thrombocytopenia; response rate; and the duration of FOLFIRI.3.

8. Conclusions

Hangeshashinto (半夏瀉心湯) is comparable to oral alkalinization for the prevention of delayed diarrhea with FOLFIRI.3 therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not stated.

11. Abstractor's comments

Although delayed diarrhea in FOLFIRI.3 results from the impaired intestinal mucosal barrier function associated with SN-38, which is an activated metabolite of CPT-11, oral (intestinal) alkalinization with a combination of baking soda, UDCA, and MgO is an insured method of treatment. This RCT is the first report to directly compare hangeshashinto (半夏瀉心湯) with oral alkalinization. As a result, no significant difference in effectiveness was observed between the two groups, and the authors suggest that hangeshashinto (半夏瀉心湯) could substitute oral alkalinization for the prevention of FOLFIRI.3-induced delayed diarrhea. As the authors state that the sample size is still small, a sufficient number of enrolled patients will be needed in future research to validate superiority or noninferiority. The basis for this study was the fact that some patients refuse oral alkalinization because of the bad taste of baking soda. At the same time, consideration should also be given to the fact that a certain percentage of patients complain that Kampo medicines, including hangeshashinto (半夏瀉心湯), are difficult to drink because of their taste or smell. If hangeshashinto (半夏瀉心湯) did not cause interstitial pneumonitis or hepatic dysfunction when added to FOLFIRI.3, we would have liked to see the safety of the drug mentioned in the paper. Further studies are expected.

12. Abstractor and date

Motoo Y, 8 December 2020.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Motoo Y, Tomita Y, Fujita H. Prophylactic efficacy of ninjin'yoeito for oxaliplatin-induced cumulative peripheral neuropathy in patients with colorectal cancer receiving postoperative adjuvant chemotherapy: a randomized, open-label, phase 2 trial (HOPE-2). *International Journal of Clinical Oncology* 2020; 25(6): 1123-9. Pubmed ID: 32232692, UMIN ID: UMIN000012745

1. Objectives

To validate the effectiveness and safety of ninjin'yoeito (人参養栄湯) for oxaliplatin-induced cumulative peripheral neuropathy.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single university hospital.

4. Participants

Fifty-two patients with colorectal cancer (pathologic stage 3) treated with adjuvant chemotherapy.

5. Intervention

Arm 1: Tsumura Ninjin'yoeito (人参養栄湯) Extract Granules for ethical use, 9 g per day orally administered (divided into two or three portions, given before meals) (26 patients).

Arm 2: Tsumura Ninjin'yoeito (人参養栄湯) Extract Granules (for ethical use) not administered (26 patients).

Chemotherapy (XELOX) performed in both arms: capecitabine (2400 mg/m^2, day 1-14) + oxaliplatin (130 mg/m^2, day 1) given every 3 weeks for 8 cycles.

6. Main outcome measures

The primary endpoint: Cumulative peripheral neuropathy (Grade) at the end of 8 cycles.

Secondary endpoints: Relative dose intensity of oxaliplatin, relapse-free survival, and overall survival.

7. Main results

In all, 40 patients (20 patients in Arm 1 and 20 patients in Arm 2) completed 8 cycles of chemotherapy and 12 patients (6 patients in each Arm) discontinued the treatment. There were adverse events in 8 patients (4 patients in each Arm), recurrence in 2 patients (1 patient in each Arm), withdrawn in 1 patient (Arm 1), and ischemic stroke in 1 patient (Arm 2).

A significantly lower number of patients in the ninjin'yoeito (人参養栄湯) group had Grade 2 or worse accumulating peripheral nerve injury (2 patients [10%] in the ninjin'yoeito [人参養栄湯] group vs 11 patients [55%] in the control group; $P<0.01$). Oxaliplatin-related relative dose intensity was significantly higher in the ninjin'yoeito (人参養栄湯) group (83.3 ± 3.3%) than in the control group (72.3 ± 3.3%) ($P=0.02$). Significantly more patients in the ninjin'yoeito (人参養栄湯) group had a relative dose intensity of 100% (8 patients [40%] in the ninjin'yoeito [人参養栄湯] group vs 1 patient [5%] in the control group; $P<0.05$). The relapse-free survival and overall survival were both longer in the ninjin'yoeito (人参養栄湯) group than in the control group, but the differences were not significant.

8. Conclusions

Ninjin'yoeito (人参養栄湯) is effective for oxaliplatin-induced cumulative peripheral neuropathy in adjuvant colorectal cancer chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There was one patient with hypokalemia and edema, possibly due to ninjin'yoeito (人参養栄湯), but this patient withdrew after 4 cycles due to anorexia and fatigue caused by chemotherapy. Aside from this case, there was no adverse event with ninjin'yoeito (人参養栄湯).

11. Abstractor's comments

Oxaliplatin-induced cumulative peripheral nerve injury is intractable and has not been addressed by western medicine. This landmark paper presents findings from an RCT showing the effectiveness of ninjin'yoeito (人参養栄湯) for peripheral nerve injury induced by oxaliplatin-based therapy in patients treated with XELOX as adjuvant colorectal cancer chemotherapy. Previous RCTs have tested the effectiveness of goshajinkigan (牛車腎気丸), but the efficacy remains questionable, with some studies showing a preventive effect and others showing a lack of effect. In this context, the results of this study provide sufficient support for further development and we look forward to the accumulation of additional cases.

12. Abstractor and date

Kogure T, 8 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Fujita F, Torashima Y, Inoue Y, et al. Daikenchuto improved perioperative nutritional status of the patients with colorectal cancer：A prospective open-labeled randomized exploratory study. *Interventional Medicine & Applied Science* 2019; 11(2): 84-8. Pubmed ID: 32148910, UMIN ID: UMIN000006413

1. Objectives

To evaluate the effectiveness and safety of perioperative oral administration of daikenchuto (大建中湯) on nutritional status after laparoscopic surgery for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single university hospital (department of surgery).

4. Participants

Twenty patients undergoing laparoscopic surgery for colorectal cancer.

5. Intervention

Arm 1: Tsumura Daikenchuto (大建中湯) Extract Granules treatment group, administered from 2 days before surgery to 12 weeks after surgery (10 patients).

Arm 2: Tsumura Daikenchuto (大建中湯) Extract Granules non-treatment group (10 patients).

6. Main outcome measures

The primary endpoints were weight gain, Gastrointestinal Symptom Rating Scale (GSRS) score, and serum biochemical parameters (levels of serum albumin, serum total protein, pre-albumin, and total cholesterol).

7. Main results

One patient in Arm 1 was unable to take the drug because of the taste and 2 patients in Arm 2 were ineligible and withdrew from the study.

Weight gain was significantly higher in Arm 1 than in Arm 2 (the control) at weeks 2, 4, and 12 ($P<0.05$), and GSRS was lower, but not significantly so, in Arm 1 than in Arm 2 at all times. With regard to serum biochemistry, no statistically significant difference was observed except that serum total protein was significantly lower in Arm 1 than Arm 2 on day 3 after surgery.

8. Conclusions

Oral perioperative administration of daikenchuto (大建中湯) significantly restores weight after laparoscopic surgery for colorectal cancer.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Daikenchuto (大建中湯)-associated adverse events were not observed.

11. Abstractor's comments

This report analyses the effect of perioperative oral administration of daikenchuto (大建中湯) on body weight, gastrointestinal symptoms, and serum biochemical parameters after laparoscopic surgery in patients with colorectal cancer. The results showed that patients in the daikenchuto (大建中湯) group did not lose weight after surgery, suggesting that daikenchuto (大建中湯) might be useful as an aid to recovery after surgery. Although mechanisms that limit weight loss such as enhanced intestinal peristalsis and increased blood flow were suggested, further elucidation of mechanisms is needed. Also, although the dose dependency of daikenchuto (大建中湯)'s effect was discussed, the daily dose of daikenchuto (大建中湯) was not described in the methods. Although the usual dose of daikenchuto (大建中湯) was 15 g per day, patients may be treated with 7.5 g per day, so it is important to state the daily dose. Although the study was limited to laparoscopic cases, the lack of significant between-group differences in many endpoints was presumably related to the lower surgical invasiveness of laparoscopic surgery compared to open surgery. As the authors stated in their discussion, it is hoped that more robust results will be achieved in future studies with a larger sample size.

12. Abstractor and date

Kato Y, 1 February 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

18. Symptoms and signs

Reference

Yoshiya T, Mimae T, Ito M, et al. Prospective, randomized, cross-over pilot study of the effects of Rikkunshito, a Japanese traditional herbal medicine, on anorexia and plasma-acylated ghrelin levels in lung cancer patients undergoing cisplatin-based chemotherapy. *Investigational New Drugs* 2020; 38(2): 485-92. CENTRAL ID: CN-01979095, Pubmed ID: 31428894, UMIN ID: UMIN000010748

1. Objectives

To evaluate the effectiveness and safety of rikkunshito (六君子湯) for vomiting and anorexia in patients treated with chemotherapy for lung cancer.

2. Design

Randomized controlled trial (cross-over) (RCTcross-over).

3. Setting

A single university hospital.

4. Participants

Lung cancer patients aged 20-80 years scheduled to receive at least two sessions of cisplatin-containing chemotherapy.

5. Intervention

Arm 1: Patients were treated with Tsumura Rikkunshito (六君子湯) Extract Granules at 7.5 g/day (2.5 g three times daily) for 14 days at the start of the first chemotherapy session, and not treated with rikkunshito (六君子湯) during the second chemotherapy session (20 patients).

Arm 2: Patients were not treated with Tsumura Rikkunshito (六君子湯) Extract Granules at the start of the first chemotherapy session, and took Tsumura Rikkunshito (六君子湯) Extract Granules at 7.5 g/day (2.5 g three times daily) for 14 days with the start of the second chemotherapy session (20 patients).

6. Main outcome measures

The primary endpoint was the change in daily caloric intake. A key secondary endpoint is the plasma acyl ghrelin (AG) levels, while other secondary endpoints included activities of daily living assessed by the Functional Living Index-Emesis (FLIE) score, frequency of chemotherapy-induced nausea and vomiting (CINV), side effects, and changes in blood laboratory values.

7. Main results

A total of 31 patients were included in the analysis after excluding 1 patient with chemotherapy allergy and 8 patients who received only 1 dose of chemotherapy. There was a significantly lower reduction in calorie intake during the rikkunshito (六君子湯) treatment period compared to the non-treatment period (18% vs. 25%, P=0.025). As compared with the AG level on day 1 of both the rikkunshito (六君子湯) treatment period and non-treatment period, the level was significantly lower on day 3 (early phase) (P<0.001) and significantly higher on the day 5 (late phase) of the rikkunshito (六君子湯) treatment period (P=0.025), but no significant increase was observed during the non-treatment period. Except for 1 patient whose FLIE score could not be recorded, 30 patients showed no significant difference in CINV, but a tendency toward lower FLIE score on days 3-5 (late phase) of the rikkunshito (六君子湯) treatment period than the control treatment period (P=0.074).

8. Conclusions

Rikkunshito (六君子湯) reduces the loss of appetite caused by chemotherapy with cisplatin in patients with lung cancer and increases plasma acyl ghrelin levels in the late phase.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

A safety analysis of 35 patients treated with rikkunshito (六君子湯) showed no adverse reactions to rikkunshito (六君子湯).

11. Abstractor's comments

This was an interesting clinical study that demonstrated the effectiveness of rikkunshito (六君子湯), which is frequently used to improve appetite, in reducing the loss of appetite caused by the side effects of cisplatin-containing chemotherapy, together with the ability of rikkunshito (六君子湯) to increase ghrelin levels. Although described by the authors as a pilot study, the study has shown the effectiveness of the small sample size, crossover design. It is possible that the effects of chemotherapies for a greater variety of cancers could be verified using a similar method, and further research is expected to be developed in the future.

12. Abstractor and date

Koike H, 31 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Murakami S, Igarashi A, Miyano K, et al. Investigation of the efficacy of gargling a mixture of hangeshashinto (半夏瀉心湯) and honey for intraoral discomfort events in terminally ill cancer patients. *Palliative Care Research* 2019; 14(3): 159-67. Ichushi Web ID: 2020082563, J-STAGE

1. Objectives

To evaluate the efficacy and safety of hangeshashinto (半夏瀉心湯) mixed with honey for intraoral discomfort events in terminally ill cancer patients.

2. Design

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

3. Setting

A single municipal hospital (palliative medicine department).

4. Participants

Terminally ill cancer patients who complained of oral discomfort and agreed to participate in this study were included (22 patients).

5. Intervention

Arm 1: Patients who continued 3 to 5 gargles with 2.5 g Tsumura Hangeshashinto (半夏瀉心湯) Extract Granules for 2 weeks (13 patients).

Arm 2: Patients who continued 3 to 5 gargles with mixture of 2.5 g Tsumura Hangeshashinto (半夏瀉心湯) Extract Granules and 5 g honey for 2 weeks (9 patients).

6. Main outcome measures

Oral dryness was measured using an oral moisture meter (Mukus ®), halitosis-related three kinds of sulfur compounds were measured using a gas meter (Oralchroma ®), stomatitis was assessed based on the Common Terminology Criteria for Adverse Events Ver.3.0, and intraoral discomfort was assessed based on the severity of subjective symptoms and signs graded using the four-step Verbal Rating Scale.

7. Main results

Two patients in Arm 1 discontinued, and 20 patients were included in the analysis. In both Arm 1 and Arm 2, compared with the baseline, oral dryness was improved (P<0.05) and the levels of hydrogen sulfide (H_2S) in exhaled breath were reduced (P<0.05). Subjective and objective symptoms (oral discomfort self-perceived symptoms) showed only a tendency to improve with oral administration of hangeshashinto (半夏瀉心湯). The addition of honey did not improve both compliance and symptoms.

8. Conclusions

Hangeshashinto (半夏瀉心湯) improves intraoral dryness and reduces the levels of exhaled hydrogen sulfide in patients with terminal cancer. Mixture with honey does not change the effectiveness of gargling with hangeshashinto (半夏瀉心湯).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In one patient, gargling was discontinued at the patient's request due to the onset of pruritus, but the symptoms disappeared promptly after gargling was discontinued.

11. Abstractor's comments

In this paper, the effect of using honey in combination with hangeshashinto (半夏瀉心湯) did not change either patient compliance or treatment efficacy. Hangeshashinto (半夏瀉心湯) is a highly bitter formula, and its bitterness cannot be eliminated by adding honey. The effect was not enhanced by the addition of honey, but it is necessary to keep a considerable amount of honey in the mouth for a long time in order for the osmotic effect of honey to prevent bacterial growth, and the fact that the addition of a small amount of honey did not improve the symptoms in this study is considered a reasonable result. However, the findings that hangeshashinto (半夏瀉心湯) improves intraoral dryness and reduces the levels of exhaled hydrogen sulfide may lead to the elucidation of action mechanisms for improving stomatitis.

12. Abstractor and date

Nakata H, 14 February 2021; Motoo Y, 8 June 2025.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

4. Metabolism and Endocrine Diseases

Reference

Hayashida M, Kaneko T, and Miyata A. Fat-reducing effect of Shokansen (生漢煎)® bofutsushosan (防風通聖散) (type-2 OTC drugs). *Advanced Medicine for Health and Beauty*2019; 6(1): 14-21. Ichushi Web ID: 2019201180

1. Objectives

To evaluate the effects of bofutsushosan (防風通聖散) on obese and obesity-prone women.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single site.

4. Participants

Obese and obesity-prone Japanese women aged 20-49 years who are interested in dieting. The following persons were excluded from the study: persons who might have allergic symptoms to the ingredients of the study drug, persons receiving hormone replacement therapy, pregnant or lactating persons, persons taking medications that might affect the results of the study, persons who regularly consume health foods that might affect the results of the study, persons who had aesthetic medicine treatments that might affect the study site, persons who were currently participating in trials involving the use of other medications or in trials involving cosmetics or drugs, and persons deemed inappropriate by the principal investigator (29 patients).

5. Intervention

Arm 1: One packet of Shokansen® (生漢煎) bofutsushosan (防風通聖散) was taken three times daily for 8 weeks (15 patients).

Arm 2: Not treated (14 patients).

6. Main outcome measures

Weight, body mass index (BMI), body fat percentage, and upright umbilicus and coccygeal circumference were assessed. Changes in quality-of-life (QOL) were assessed by questionnaire on a nine-point score scale: (1) stool status, (2) body coldness, (3) changes in the size of clothes, (4) skin impression, (5) fatigue, (6) feeling refreshed, (7) being able to move dynamically, (8) being able to sleep soundly, and (9) feeling light.

7. Main results

Twenty-two subjects (12 patients in the bofutsushosan (防風通聖散) group and 10 patients in the non-treatment group) were included in the analysis, after excluding the 7 patients who discontinued the study. Patients in Arm 1 experienced significantly reduced body weight, BMI, body fat percentage, and upright umbilicus and coccygeal circumference compared with the baseline ($P<0.01$, $P<0.01$, $P<0.05$, $P<0.01$, and $P<0.01$, respectively). Patients in Arm 2 showed significant reductions in BMI and upright coccygeal circumference compared with baseline ($P<0.05$), but changes in weight, body fat percentage, and upright umbilicus circumference were not significant. A comparison of the change in Arm 1 and Arm 2 from before the start of oral administration to 8 weeks after treatment showed significant reductions in body weight, BMI, body fat percentage, and upright periumbilical circumference in Arm 1 ($P<0.01$, $P<0.01$, $P<0.05$, and $P<0.05$, respectively). A significantly improved quality of life for (1), (3), (5), (7), (8), and (9) in Arm 1 ($P<0.01$, $P<0.05$, $P<0.05$, $P<0.01$, $P<0.05$, and $P<0.05$, respectively) and for (1) and (7) in Arm 2 ($P<0.05$ and $P<0.01$).

8. Conclusions

Bofutsushosan (防風通聖散) has a lipid-reducing effect and improves women's quality of life.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no side effects of bofutsushosan (防風通聖散).

11. Abstractor's comments

Bofutsushosan (防風通聖散) is a Kampo preparation commonly used for dieting. This interesting clinical study actually evaluated the effects of bofutsushosan (防風通聖散) in a randomized controlled trial. It is particularly meaningful that this study evaluated not only the fat-reducing effect of bofutsushosan (防風通聖散) but also its QOL improving effect at the same time. However, there are points to consider, such as the lack of description of the preparation method of the test drug, errors in the units of weight (mg → g) in Table 1, and the relevance of the QOL questionnaire to the non-treated group. In addition, because of the small size of this study, future clinical studies with a larger number of patients are desirable to confirm reproducibility and to evaluate the safety.

12. Abstractor and date

Koike H, 19 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

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

Reference

Watari H, Shimada Y, Matsui M, et al. Kihito, a Traditional Japanese Kampo Medicine, Improves Cognitive Function in Alzheimer's Disease Patients. *Evidence-Based Complementary and Alternative Medicine* 2019 May 14;2019:4086749. doi: 10.1155/2019/4086749. Pubmed ID: 31217803, UMIN ID: UMIN000023509

1. Objectives

To evaluate the effectiveness of kihito (帰脾湯) on cognitive function in Alzheimer's disease.

2. Design

Randomized controlled trial (cross-over) (RCT cross-over).

3. Setting

A single university hospital (department of neuropsychiatry).

4. Participants

Adults in Toyama Prefecture who had been diagnosed with Alzheimer's disease from cognitive tests and imaging tests between July 2016 and March 2018, who had taken a cholinesterase inhibitor (Aricept, Reminyl, or Rivastach) for at least six months, and who had a score of at least 15 on the pre-study Mini-Mental State Examination (MMSE) (16 patients).

5. Intervention

Arm 1: A cholinesterase inhibitor (Aricept, Reminyl, or Rivastach)
alone for 16 weeks, and then a cholinesterase inhibitor (Aricept, Reminyl, or Rivastach) + Tsumura Kihito (帰脾湯) Extract Granules for 16 weeks (5 patients).
No washout period, Tsumura Kihito (帰脾湯) Extract Granules dose of 7.5 g per day, three times daily before or between meals.

Arm 2: A cholinesterase inhibitor (Aricept, Reminyl, or Rivastach) + Tsumura Kihito (帰脾湯) Extract Granules for 16 weeks, and then a cholinesterase inhibitor (Aricept, Reminyl, or Rivastach) alone for 16 weeks (5 patients).

6. Main outcome measures

The following cognitive function tests are assessed before and after 16 and 32 weeks of administration.
1) Japanese versions of the MMSE (MMSE-J)
2) Japanese versions of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS-J)

7. Main results

Five patients were excluded because they did not meet criteria such as MMSE-J score less than 15.
Arm 1: A total of 6 patients were enrolled, but 1 patient was excluded due to the use of other drugs during the study. Significant improvement in both the MMSE-J and RBANS-J was observed after taking kihito (帰脾湯) compared to not taking kihito (帰脾湯). ($P<0.05$)

8. Conclusions

In the present study, it was found that kihito (帰脾湯) improves cognitive function (MMSE-J, RBANS-J) in Alzheimer's patients. Based on our findings, we consider the use of kihito (帰脾湯) to be beneficial for the treatment of dementia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no kihito (帰脾湯)-associated adverse events or other adverse events . No safety assessment was described for the non-treated group.

11. Abstractor's comments

This is the first report to show that kihito (帰脾湯) improves cognitive function in patients with Alzheimer's disease. The fact that not only the MMSE-J but also the cognitive function test RBANS-J showed a trend towards improvement with the use of kihito (帰脾湯) suggests that kihito (帰脾湯) may be a potential treatment for cognitive decline associated with Alzheimer's disease in the future. It is hoped that the number of cases will be increased in the future and that more reliable results will be achieved.

12. Abstractor and date

Kato Y, 1 February 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

9. Cardiovascular Diseases

Reference

Tamano M, Toyoda S, Kato S, et al. A long-term prognostic benefit of Tolvaptan plus goreisan (五苓散) in elderly patients with heart failure. *Progress in Medicine* 2019; 39(7): 753-60. Ichushi Web Web ID: 2019367726

1. Objectives

To evaluate the effectiveness of goreisan (五苓散) in elderly patients with heart failure.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single hospital.

4. Participants

Elderly patients with heart failure who received oral furosemide and were hospitalized for acute exacerbation of chronic heart failure. Patients who were switched to intravenous furosemide 40-80 mg/day for two days after hospitalization and who did not show improvement in symptoms or physical findings were also given Tolvaptan 7.5 mg/day starting on Day 3 (28 patients).

5. Intervention

Arm 1: Patients who were responders to Tolvaptan and received oral doses of 7.5 mg of Tolvaptan and 5 to 7.5 g of TSUMURA Goreisan (五苓散) Extract Granules per day (10 patients).

Arm 2: Patients who were non-responders to Tolvaptan and received oral doses of 7.5 mg of Tolvaptan and 5 to 7.5 g of TSUMURA Goreisan (五苓散) Extract Granules per day (8 patients).

Arm 3: Patients who were responders to Tolvaptan and received oral doses of 7.5 mg of Tolvaptan per day (10 patients).

All groups were followed for 2 years after discharge.

6. Main outcome measures

A comparison was made between the frequency of rehospitalization for worsening heart failure, improvement in severity of heart failure as measured by New York Heart Association (NYHA) classification and B-type natriuretic peptide (BNP) level at discharge, and 1 year and 2 years after discharge, and changes in renal function as measured by estimated glomerular filtration ratio (eGFR).

7. Main results

The frequency of rehospitalization for worsening heart failure 2 years after discharge (mean + /-standard deviation) was significantly reduced for Arm 1 (1.9±0.8) and Arm 2 (2.0±1.3) compared with Arm 3 (3.8±0.8) (P<0.05). Two years after discharge as compared at admission, BNP levels in Arm 1 and Arm 2 were significantly improved (230±212 pg/ml and 245±185 pg/ml, respectively) compared with Arm 3 (465±380 pg/ml) (P<0.05). NYHA score was also significantly reduced in Arm 1 and Arm 2 (2.5±0.7 and 2.2±0.4, respectively) compared with in Arm 3 (1.6±0.6; P<0.05). Changes in eGFR did not differ between the groups. No cardiac deaths were observed in any of the three groups during follow-up.

8. Conclusion

Among elderly patients with heart failure, the combination of Tolvaptan and goreisan (五苓散) may improve the long-term prognosis of both Tolvaptan responders and non-responders with heart failure.

9. From Kampo medicine perspective

Goreisan (五苓散) is a prescription for curing the maldistribution of water and is thought to correct the maldistribution of water in the organs and tissues in heart failure.

10. Safety assessment in the article

Not described.

11. Abstractor's comments

This is a valuable clinical study of elderly patients with heart failure who were followed for two years. The authors have already reported the effects of goreisan (五苓散) for one year, and the present study is an expansion of that study. As already noted in the previous report, however, although it is stated that no cardiac deaths were observed in both groups during follow-up, there is no mention of other dropout cases. Also, as the study has not been blinded, when studying the frequency of readmissions, it is important to clarify the criteria for admission and to describe whether no additional medications were given. Although there are points that require further investigation, this is a clinical study that suggests that goreisan (五苓散) may be effective in treatment of heart failure in elderly patients, and we would like to see more cases in the future.

12. Abstractor and date

Goto H, 10 December 2020.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

9. Cardiovascular Diseases

Reference

Ezaki H, Ayaori M, Sato H, et al. Effects of Mokuboito, a Japanese Kampo medicine, on symptoms in patients hospitalized for acute decompensated heart failure - A prospective randomized pilot study. *Journal of Cardiology* 2019; 74(5): 412-7. Pubmed ID: 31272834, UMIN ID: UMIN000026621

1. Objectives

To evaluate the effectiveness and safety of mokuboito (木防已湯) for acute exacerbations of chronic heart failure.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single hospital (cardiology department).

4. Participants

Forty patients ≥20 years of age with acute exacerbation of chronic heart failure who required hospitalization.

5. Intervention

Arm 1: Standard of care + Tsumura Mokuboito (木防已湯) Extract Granules 7.5 g per day orally (in 3 divided doses, to be taken before meals) (21 patients).

Arm 2: Standard treatment only (19 patients).

6. Main outcome measures

The primary outcome: Changes in performance status (shortness of breath, edema, fatigue, and anorexia) measured using visual analog scales (VASs [100-mm scales]). Secondary end points: Changes in serum B-type natriuretic peptide concentration, biochemical and echocardiography parameters, weight loss and peripheral edema. Assessment at Day 10 in each case and at the day of discharge if discharged before Day 10.

7. Main results

There were no significant differences in age, gender, or heart failure severity between the two groups, but ischemic heart disease/hypertension/diabetes mellitus were significantly more common in Arm 2. There were no significant differences in the administration of renin angiotensin system inhibitors, mineralocorticoid receptor inhibitors, beta-antagonists, diuretics, digitalis preparations, and PDE-III inhibitors, whereas the administration of vasopressin antagonists was significantly greater in Arm 2. One patient in Arm 2 died on day 11 of hospitalization due to exacerbation of heart failure, while 39 patients were discharged walking.

ΔVAS for systemic status was significantly greater in Arm 1 (Arm 1: -62.2±25.4, Arm 2: -33.0±30.6; $P<0.01$). On the other hand, no significant differences were obtained between the two groups in changes in body weight, edema, and biochemical and echocardiographic parameters.

8. Conclusions

Oral mokuboito (木防已湯) is effective treatment for the systemic symptoms of acute exacerbation of chronic heart failure (shortness of breath, edema, fatigue, and anorexia).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events attributed to mokuboito (木防已湯) were not observed.

11. Abstractor's comments

This is a clinically significant paper that evaluates the effectiveness of mokuboito (木防已湯) in an RCT in patients with acute exacerbations of chronic heart failure requiring inpatient care. Although positioned as a pilot study by the authors, mokuboito (木防已湯) significantly reduced systemic symptoms due to heart failure and the result is sufficiently promising for future development. Further analysis of the subject groups by severity of disease would provide suggestions for future designs. However, the statistical analysis focused on pre- and post-comparisons for each group and comparison of the amount of change for each group, which is disappointing because it does not provide adequate comparison between the two groups.

At any rate, this is a clinically relevant paper and we look forward to further validation.

12. Abstractor and date

Kogure T, 8 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

9. Cardiovascular Diseases

Reference

Kawase T, Teranishi T, Miyatani K, et al. Chronic subdural hematoma associated with postoperative unruptured cerebral aneurysm: a prospective study of the timing of postoperative use of goreisan (五苓散) and saireito (柴苓湯). *Neurosurgery and Kampo* 2019; 5: 63-5. Ichushi Web ID: 2020054846

1. Objectives

To evaluate the effect of the timing of goreisan (五苓散) and saireito (柴苓湯) use on the incidence of chronic subdural hematoma after unruptured cerebral aneurysm clipping, and to compare the efficacy of goreisan (五苓散) and saireito (柴苓湯).

2. Design

A randomized controlled trial (RCT). Randomization was performed within the goreisan (五苓散) group and saireito (柴苓湯) group, respectively. Randomization was not performed between the goreisan (五苓散) and saireito (柴苓湯) groups.

3. Setting

University hospital affiliated facilities.

4. Participants

A total of 184 patients who underwent unruptured cerebral aneurysm clipping from January 2016 to August 2017 were included in the in the goreisan (五苓散) group, and 129 patients who underwent unruptured cerebral aneurysm clipping from September 2017 to September 2018 were included in the saireito (柴苓湯) group. An RCT of the effect of goreisan (五苓散) intake timing on chronic subdural hematoma incidence was conducted in the former group while an RCT of the effect of saireito (柴苓湯) intake timing on chronic subdural hematoma incidence was conducted within the latter group.

5. Intervention

Goreisan (五苓散)

Arm 1: Goreisan (五苓散) 7.5 g/day (taken orally for 1 week beginning the day after surgery) (72 patients).

Arm 2: Goreisan (五苓散) 7.5 g/day (taken orally for 1 week beginning 1 week after surgery) (84 patients).

Saireito (柴苓湯)

Arm 3: Saireito (柴苓湯) 7.5 g/day (taken orally for 1 week beginning the day after surgery) (66 patients).

Arm 4: Saireito (柴苓湯) 7.5 g/day (taken orally for 1 week beginning 1 week after surgery) (63 patients).

6. Main outcome measures

Incidence of chronic subdural hematoma (CSDH).

7. Main results

A total of 258 patients were included in the analysis, after excluding 28 who withdrew from Arm 2. In both goreisan (五苓散) groups (Arm 1 and Arm 2) and saireito (柴苓湯) groups (Arm 3 and Arm 4), arms that took medications orally for 1 week beginning 1 week after surgery (Arm 2 and Arm 4) showed a significantly lower incidence of chronic subdural hematoma ($P<0.05$). There was no significant difference in incidence between groups beginning treatment 1 week after surgery (i.e., between the goreisan [五苓散] group [Arm 2] and the saireito [柴苓湯] group [Arm 4].

8. Conclusions

For prevention of chronic subdural hematoma after clipping of unruptured cerebral aneurysm, goreisan (五苓散) or saireito (柴苓湯) should be taken 1 week after the surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No particular problems were noted.

11. Abstractor's comments

A number of articles have described the effectiveness of goreisan (五苓散) and saireito (柴苓湯) for preventing the development of chronic subdural hematoma. A number of previous reports have indicated that patients continue to take goreisan (五苓散) or saireito (柴苓湯) for a period after surgery. Based on the idea that it is appropriate to use oral medications at the minimum necessary level, it is significant that this study investigated a defined period of 7 days of oral administration starting one week after surgery. Also, although goreisan (五苓散) and saireito (柴苓湯) are often used without distinction, the difference between goreisan (五苓散) and saireito (柴苓湯) is significant in terms of cost. Therefore, the confirmation that there is no difference in chronic subdural hematoma occurrence is significant from a medical economics point of view.

12. Abstractor and date

Nakata H, 15 February 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Ishimaru N, Kinami S, Shimokawa T, et al. Kikyo-to vs. placebo on sore throat associated with acute upper respiratory tract infection : A randomized controlled trial. *Internal Medicine* 2019; 58(17): 2459-65. Pubmed ID: 31178508, UMIN ID: UMIN000030239, J-STAGE

1. Objectives

To validate the effectiveness and safety of kikyoto (桔梗湯) for sore throat in acute upper respiratory inflammation.

2. Design

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

3. Setting

A single hospital (internal medicine department).

4. Participants

Seventy patients who visited as outpatients with a complaint of sore throat and were diagnosed with acute upper respiratory inflammation.

5. Intervention

Arm 1: A single oral dose of 2.5 g of Tsumura Kikyoto (桔梗湯) Extract Granules dissolved in plain hot water (35 patients).

Arm 2: A single oral dose of 2.5 g of placebo dissolved in plain hot water (35 patients).

6. Main outcome measures

Primary end point: Change in sore throat assessed using the visual analog scale (VAS; 100 mm method).

A secondary end point: Percentage of patients with moderate to severe sore throat (in the all severity: none, mild, moderate, and severe).

Each was assessed 10 minutes after oral administration.

7. Main results

There were no significant differences between the two groups in age, gender, severity of sore throat, and trigger for sore throat (e.g., Flu). There were no dropouts and all 35 patients in each Arm were eligible for assessment.

Δ VAS for sore throat was 14.40±10.55 in the kikyoto (桔梗湯) group and 17.00±14.50 in the placebo group, with no significant difference between the two groups (P=0.394). Also, the percentage of patients with moderate to severe sore throat was 8/35 (22.9%) in the kikyoto (桔梗湯) group and 14/35 (40.0%) in the placebo group, with no significant difference between the two groups (P=0.20).

8. Conclusions

A single dose of kikyoto (桔梗湯) extract does not reduce pharyngeal pain in acute upper respiratory inflammation.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events attributed to kikyoto (桔梗湯) extract were not observed.

11. Abstractor's comments

As this is the first paper to validate the effectiveness of a single oral dose of kikyoto (桔梗湯) for sore throat due to acute upper respiratory inflammation in a DB-RCT, the completion of this study is commendable. It is disappointing that the authors did not obtain significant results from their evaluation of the efficacy of a 2.5 g medical extract 10 min after orally intake. The design of this study is limited to oral administration and commendable because some previous case-control studies of kikyoto (桔梗湯) have reported some cases of gargling without taking the medicine orally. Additionally, it is important to note that the paper clearly states that the placebo is lactose (in some cases, the content of the placebo is not stated). However, whether it can truly be considered a placebo is debatable.

Although Kampo preparations such as kikyoto (桔梗湯) are considered to be fast-acting in everyday clinical practice, it is common practice to give them for more than one day, and the patients might need to be given multiple doses and evaluated for an extended period of observation, as the authors state. As 2-day follow-up is expected to be labor-intensive for physicians and patients, however, the need for additional clinical trials should be carefully considered.

12. Abstractor and date

Kogure T, 8 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Kawago K, Nishibe T, Shindo S, et al. A Double-Blind Randomized Controlled Trial to Determine the Preventive Effect of Hangekobokuto on Aspiration Pneumonia in Patients Undergoing Cardiovascular Surgery. *Annals of Thoracic and Cardiovascular Surgery* 2019; 25(6): 318-25. Pubmed ID: 31316037, UMIN ID: UMIN000017390, J-STAGE

1. Objectives

To evaluate the effectiveness and safety of hangekobokuto (半夏厚朴湯) for aspiration pneumonia in patients after cardiovascular surgery.

2. Design

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

3. Setting

A single university hospital (cardiovascular surgery department).

4. Participants

Outpatients who underwent cardiovascular surgery at our study site between August 2014 and August 2015. Patients 20 years of age or older who were able to take hangekobokuto (半夏厚朴湯) orally and who were informed about the study and consented. Patients were excluded if they took additional oral medications or planned to take oral medications, were pregnant or planned to be pregnant, were breastfeeding, were taking other Kampo medicines or were scheduled to take them, or were susceptible to Parkinson's disease, stroke, or aspiration pneumonia (34 patients).

5. Intervention

Arm 1: Hangekobokuto (半夏厚朴湯) Extract Granules (JPS Corporation) 7.5 g per day was taken orally before or between meals for 14 days from the end of surgery (16 patients).

Arm 2: Lactose similar to Hangekobokuto (半夏厚朴湯) Extract Granules was taken orally before or between meals for 14 days from the end of surgery (18 patients).

6. Main outcome measures

A primary end point was frequency of aspiration pneumonia, which was diagnosed according to the Japanese Respiratory Society guidelines for the management of hospital-acquired pneumonia in adults by (1) the presence of alveolar infiltrate shadow on a chest X-ray or chest CT; (2) two or more of the following symptoms: fever of 37.5°C or higher, elevated C-reactive protein (CRP) level, or elevated white blood cell count of 9,000/μL or higher, and (3) suspicion of aspiration. A secondary endpoint was recovery from disordered swallowing and coughing, which were assessed by symptoms, salivary substance P levels, white blood cell count, CRP levels, length of stay after surgery, and duration of antibiotic use.

7. Main results

One patient refused the oral test drug because it tasted bad, 2 patients wanted to discontinue internal administration because of cardiac failure, and 1 patient discontinued oral medication because of an accident unrelated to the study. Thirty of 34 patients (Arm 1,13 patients; Arm 2, 17 patients) were included in the analysis. Aspiration pneumonia was significantly less frequent in Arm 1 than in Arm 2 (0% vs. 35%; P=0.017). The postoperative dysphagia on Day 14 post-surgery tended to be less frequent in Arm 1 than in Arm 2 (53.9% vs 82.4%; P=0.091). Both white blood cell counts and CRP levels on Day 3 post-surgery were significantly lower in Arm 1 than in Arm 2 (P=0.004, 0.006).

8. Conclusion

Hangekobokuto (半夏厚朴湯) can prevent the development of aspiration pneumonia in patients after cardiovascular surgery.

9. From Kampo medicine perspective

Not described.

10. Safety assessment in the article

Although congestive heart failure developed in two patients, hangekobokuto (半夏厚朴湯) is not likely to be involved.

11. Abstractor's comments

This interesting clinical study examined the effectiveness of hangekobokuto (半夏厚朴湯) for aspiration pneumonia that commonly develops in patients after cardiovascular surgery. Hangekobokuto (半夏厚朴湯) is also an effective strategy in terms of side effects and cost effectiveness. The authors state in their introduction that dysphagia occurs in 3-4% of patients after cardiovascular surgery. In contrast, the control group in the current clinical study had a higher incidence of aspiration pneumonia (35%) and dysphagia frequency (82.4%). Although this may be partly due to the large number of elderly participants, further study with a larger number of cases would be desirable. However, the results are highly promising, as aspiration pneumonitis did not occur in patients taking hangekobokuto (半夏厚朴湯).

12. Abstractor and date

Goto H, 14 December 2020.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Masuy I, Carbone F, Holvoet L, et al. The effect of rikkunshito on gastrointestinal symptoms and gastric motor function: The first study in a Belgian functional dyspepsia population. *Neurogastroenterol Motil* 2020 Feb; 32(2): e13739. doi: 10.1111/nmo.13739. Pubmed ID: 31608532

1. Objectives

To evaluate the effectiveness and safety of rikkunshito (六君子湯) treatment of gastrointestinal symptoms and gastrointestinal motility in patients with functional dyspepsia (FD) in Belgium.

2. Design

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

3. Setting

A single university hospital research center (Belgium).

4. Participants

FD patients (age: 18-75 years) who complained of postprandial fullness and met Rome III criteria (34 patients).

5. Intervention

Arm 1: After a 2-week run-in period, Cycle 1: one dose of 2.5 g of Tsumura Rikkunshito (六君子湯) Extract Granules (dissolved in 200 ml of lukewarm water; the same applies hereafter), three times daily before meals for 4 weeks; and after a 4-week wash-out, Cycle 2: placebo for 4 weeks (17 patients).

Arm 2: After a 2-week run-in period, Cycle 1: placebo for 4 weeks; and after a 4-week wash-out, Cycle 2: Tsumura Rikkunshito (六君子湯) Extract Granules 2.5 g per dose three times daily before meals for 4 weeks (17 patients).

6. Main outcome measures

The primary endpoint was intragastric pressure (measured with a high-resolution manometer attached to a nasogastric tube). Secondary endpoint was gastrointestinal symptom scores on a questionnaire.

7. Main results

A total of 11 patients dropped out and 23 were assessed. Reasons for dropout included comorbidities in 5, pain distress in 2, and lack of time in 2. Intragastric pressure decreased with rikkunshito (六君子湯) treatment compared with baseline and placebo treatment, but the difference was not significant. After rikkunshito (六君子湯) treatment, there were significant reductions from baseline in early satiety during meals (P=0.017), satiety after meals (P=0.041), abdominal fullness (P=0.007), epigastric pain (P=0.036), nausea (P=0.021), and eructation (P=0.028), but those declined similarly after placebo treatment (P-values omitted). There was no significant difference between the rikkunshito (六君子湯) and placebo treatment.

8. Conclusions

Rikkunshito (六君子湯) can also be used safely in Belgian patients with FD and significantly improves gastrointestinal symptom scores after treatment, but with greater placebo effect.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Rikkunshito (六君子湯)-associated adverse events were not observed.

11. Abstractor's comments

This study is significant in that it is the first double-blind RCT in Europe (Belgium) using a Japanese rikkunshito (六君子湯) extract formulation. Although rikkunshito (六君子湯) resulted in a non-significant decrease in intragastric pressure and significant improvement in gastrointestinal symptoms, the results were similar to those obtained with placebo and there were no differences between the two groups. Based on the results, the authors concluded that there was a substantial placebo effect in the clinical efficacy of rikkunshito (六君子湯). The authors point out the following issues: the sample size was small; the taste of the placebo was different from that of the active drug; as the study was conducted in tertiary hospitals, it is unclear whether it can be applied to primary care clinics and other settings; and the treatment duration was as short as 4 weeks. We hope that the efficacy of rikkunshito (六君子湯) will be verified, especially overseas, with a design that addresses these issues.

12. Abstractor and date

Motoo Y, 9 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Kurihara H, Akase T, Nakamura K, et al. Effectiveness of otsujito (乙字湯) for defecation management in patients with hemorrhoids and anal fissure. *Phil Kampo* 2019; 74: 12-3. Ichushi Web ID: 2019141050

1. Objectives

To evaluate the effectiveness and safety of otsujito (乙字湯) for defecation management and symptom control in patients with hemorrhoids and anal fissure.

2. Design

Quasi-randomized controlled trial (quasi-RCT).

3. Setting

A single hospital (specialized in anal and colorectal diseases).

4. Participants

A total of 60 patients with hemorrhoids or anal fissure with constipation who were considered to be appropriate for conservative treatment and presented as outpatients between April and July 2017.

5. Intervention

Arm 1: Kracie otsujito (乙字湯) Extract Fine Granules was given twice daily, 3.0 g per dose for 2 weeks.
Arm 2: No treatment given.
All patients in each group received Tribenoside/Lidocaine ointment. The use of Kampo medicines other than otsujito (乙字湯) and laxatives were prohibited.
(Although the number of patients allocated to each arm is not stated, it is assumed to be 30 in each Arm based on the statement “allocated to the two groups in the order of arrival.”)

6. Main outcome measures

Frequency of defecation and subjective symptoms (pain, bleeding, and stool condition) were assessed on a four-point symptom scale (0-3).

7. Main results

Twenty-three patients who could be followed up after 2 weeks (9 in the otsujito [乙字湯] group and 14 in the non-treatment group after 37 dropped out) were analyzed. Pain, bleeding, frequency of defecation ($P<0.05$), and stool condition ($P<0.01$) were significantly improved in the otsujito (乙字湯) group at week 2 compared with the beginning of the treatment. The change in scores showed significant improvement in stool condition and frequency of defecation in the otsujito (乙字湯) group compared to the non-treated group ($P<0.01$). Although there were no significant differences in pain or bleeding, the otsujito (乙字湯) group had a greater change in scores.

8. Conclusions

The effectiveness of otsujito (乙字湯) for bowel management of hemorrhoids and anal fissure was suggested.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events such as diarrhea and abdominal pain due to otsujito (乙字湯) were not observed.

11. Abstractor’s comments

This is the first quasi-randomized controlled trial to evaluate the effectiveness of otsujito (乙字湯) for conservative management of defecation in patients with hemorrhoids and anal fissure. Since the patients were not severely symptomatic to begin with, it would have been possible to extract changes in symptoms more clearly if the evaluation method had been more creative. It is difficult to grasp the actual condition of constipation by number of bowel movement and stool condition is more objective with the use of the Bristol Stool Form Scale. As constipation has been recognized as a symptom precipitating factor, confounding between constipation and other symptom scores should also be mentioned.Since not only defecation but also pain and bleeding were reduced after only two weeks of treatment with otsujito (乙字湯), we assume that the anti-inflammatory and analgesic effects of otsujito (乙字湯), as well as its laxative action including Daio (大黄), are involved. A similar study might further evaluate the utility of otsujito (乙字湯) for the treatment of anal diseases with western medical medicine as the control arm. As hemorrhoids and anal fissure are diseases that affect a large population and lead to a decreased quality of life, we look forward to seeing the results of future studies with a high level of evidence.

12. Abstractor and date

Kondo N, 9 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Terai K, Horie S, Fukuhara S, et al. Combination therapy with antioxidants improves total motile sperm counts: A Preliminary Study. *Reproductive Medicine and Biology* 2020; 19(1): 89-94. Pubmed ID: 31956290

1. Objectives

To evaluate the effectiveness of antioxidant supplements for male infertility with hochuekkito (補中益気湯) as a control.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single university hospital (urology department).

4. Participants

Male infertility patients aged 20-60 years in whom oligozoospermia (sperm concentration <15 million per milliliter) or asthenozoospermia (sperm motility <40%) was diagnosed (31 patients).

Patients were excluded if they: had azoospermia, severe oligozoospermia (sperm concentration <5 million/mL), severe sperm asthenia (sperm motility <5%), total active sperm count >30 million, had diseases such as varicocele or cryptorchidism that cause infertility, had a history of its surgery, a history of chemotherapy for malignant tumors, drug or other addictions, were users of androgens, antiandrogens, immunosuppressive drugs, or had severe renal disease, liver failure, or endocrine disorders.

5. Intervention

Arm 1: Antioxidant supplements (containing l-carnitine, zinc, astaxanthin, coenzyme Q_{10}, vitamin C, vitamin B12, and vitamin E) taken three times daily for 12 weeks orally (15 patients).

Arm 2: Hochuekkito (補中益気湯)(manufacturer, dosage not known), 3 times daily for 12 weeks orally)(16 patients).

6. Main outcome measures

Luteinizing hormone (LH) level, follicle-stimulating hormone (FSH) level, testosterone level, semen volume, sperm concentration, sperm motility, and total active sperm count were assessed before and 12 weeks after oral administration.

7. Main results

All 31 patients were included in the analysis without any dropouts. Total active sperm count was significantly increased in Arm 1 (P=0.04). There were no significant changes in LH level, FSH level, testosterone level, semen volume, sperm concentration, or sperm motility. Arm 2 did not show a significant increase in any of the semen parameters, but showed increasing trends in sperm concentration, sperm motility, and total active sperm count.

8. Conclusions

Antioxidant supplements increase total active sperm count.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not described.

11. Abstractor's comments

This is an interesting clinical study that evaluated the efficacy of antioxidant supplements for male infertility, an important contemporary problem, using hochuekkito (補中益気湯) as a control drug. In this study, neither the test drug supplement nor the control drug, hochuekkito (補中益気湯), showed significant effects, but this may have been due to the short duration of the study and the small sample size, and future re-studies are desirable. Also, the effectiveness of the supplements is obscured by the lack of a direct comparison between the group taking the supplements and the group taking hochuekkito (補中益気湯), and also by the lack of a comparison with a placebo that is clearly ineffective. Further research is desirable.

12. Abstractor and date

Koike H, 19 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

18. Symptoms and signs

Reference

Doi M, Miyamoto K, Shimaoka T, et al. The effect of standard and high dose of rikkunshito on achievement of enteral nutrition target in critically ill patients: a pilot randomized controlled trial. *Acute Medicine & Surgery* 2020; 7: e442. doi: 10.1002/ams2.442. Pubmed ID: 31988757, UMIN ID: UMIN000031466

1. Objectives

To investigate the efficacy of standard and double-dose rikkunshito (六君子湯) for increasing the dose of calories in patients on enteral nasogastric tube feeding.

2. Design

Randomized controlled trial (RCT).

3. Setting

University hospital mixed intensive care unit (ICU)

4. Participants

A total of 26 patients aged 20 years and over who were started on nasogastric tube feedings within 48 hours of admission to the ICU and were expected to remain on tube feeding for at least 5 days, were expected to survive for at least 48 hours, were not scheduled for gastric removal, had no allergy to rikkunshito (六君子湯), and had no anatomical abnormalities in the stomach or intestinal tract.

5. Intervention

Arm 1: No prescription.
Arm 2: Tsumura Rikkunshito (六君子湯) Extract Granules 7.5 g/day.
Arm 3: Tsumura Rikkunshito (六君子湯) Extract Granules, 15 g per day.

6. Main outcome measures

Daily caloric intake (enteral nutrition quantity); blood ghrelin level.

7. Main results

There was no significant between-group differences in caloric intake or blood ghrelin level.

8. Conclusions

Rikkunshito (六君子湯) does not contribute to an increase in intake more quickly during nasal tubal feeding than it does without it.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No particular problems were noted.

11. Abstractor's comments

Rikkunshito (六君子湯) has recently been frequently used for the management of functional dyspepsia (FD). This study was planned because it has been reported to enhance gastrointestinal digestive and excretory functions, and part of this effect is due to an increase in blood ghrelin level, however, the pathophysiology of FD, a chronic condition, is likely to differ from that of FD acutely treated in the ICU. As gastrointestinal function may also be associated with decreased basal metabolism, we would like to see changes in basal metabolism in the next trial.

12. Abstractor and date

Nakata H, 18 February 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

19. Injury, poisoning, and postoperative pain

Reference

Akita S, Namiki T, Kawasaki Y, et al. The beneficial effect of traditional Japanese herbal (Kampo) medicine, Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), for patients with chronic wounds refractory to conventional therapies : A prospective, randomized trial. *Wound Repair and Regeneration* 2019; 27(6): 672-9. CENTRAL ID: CN-01980967, Pubmed ID: 31350938, UMIN ID: UMIN000010613

1. Objectives

To evaluate the effectiveness of hochuekkito (補中益気湯) in patients with refractory chronic skin wounds.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two university hospitals (including a department of Japanese-oriental medicine and department of plastic surgery).

4. Participants

Patients with skin wounds that do not improve for ≥3 weeks with standard therapy (20 patients).

5. Intervention

Arm 1: In addition to continuing standard therapy,
Tsumura Hochuekkito (補中益気湯) Extract Granules three times daily, 2.5 g per dose before meals for 12 weeks (9 patients).
Arm 2: Continued standard therapy alone (11 patients).

6. Main outcome measures

Primary endpoint: Number of patients with DESIGN-R score improvement at 12 weeks after intervention.
Secondary endpoints: Total DESIGN-R score, trend in each individual item score, hematological test items
Wound healing was assessed by total DESIGN-R score as well as each item score (Depth, Exudate, Size, Inflammation/Infection, Granulation tissue, Necrotic tissue, Pocket).
The DESIGN-R score was assessed at the time of the intervention, at weeks 4, 8, and 12, while hematological parameters such as IgE, IL-6, IL-10, and TGF-β levels were measured at the same time.

7. Main results

Two patients in the control group dropped out, and analysis was done with 9 patients in each group. Although the causes and sites of wounds (postoperative fistula, pressure ulcer, etc.) were diverse, there were no significant differences in DESIGN-R score or hematological parameter levels at the time of intervention between the two groups. All patients in the hochuekkito (補中益気湯) group had improvement in total DESIGN-R scores at week 12, whereas only 3 patients in the control group showed improvement (P=0.009). After 8 weeks of treatment, patients in the hochuekkito (補中益気湯) group showed a significant improvement in total DESIGN-R score (P=0.04), whereas patients in the control group showed an inconsistent trend. Regarding each item score, there was significant improvement in Depth (P=0.02), Effusion (P=0.01), Size (P=0.01), and Granulation tissue (P=0.04) but only a trend toward improvement was observed in Inflammation/Infection/Necrotic tissue/Pocket. Of the hematological parameters, only albumin level at week 12 showed a significant improvement in the hochuekkito (補中益気湯) group (P=0.048).

8. Conclusions

Hochuekkito (補中益気湯) promotes healing of refractory wounds and improves nutritional status.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events of oral administration of hochuekkito (補中益気湯) were observed during the observation period.

11. Abstractor's comments

This study is significant for being the first RCT to demonstrate the effect of hochuekkito (補中益気湯) in promoting wound healing on treatment-resistant refractory wounds. Although the patient backgrounds and courses of treatment in the two groups were complex and not homogeneous, the fact that all patients in the hochuekkito (補中益気湯) group showed improvement was highly significant. While no significant improvement in inflammatory findings was observed, a trend toward improvement in C-reactive protein (CRP) and IL-6 levels was seen only in the hochuekkito (補中益気湯) group, and albumin levels, which are negatively correlated with CRP levels, showed significant improvement, although there was a delay in wound healing. Accordingly, not only the improvement in nutritional status but also the improvement in inflammatory findings can be assumed to be factors that promote wound healing with hochuekkito (補中益気湯). When considering further research, we suggest adding quality of life assessment along with examination of other survey items (e.g., prealbumin).

12. Abstractor and date

Kondo N, 9 January 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Hosaka M, Arai I, Ishiura Y, et al. Efficacy of daikenchuto, a traditional Japanese Kampo medicine, for postoperative intestinal dysfunction in patients with gastrointestinal cancers: meta-analysis. *International Journal of Clinical Oncology* 2019; 24(11): 1385-96. Pubmed ID: 31297704

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) for postoperative gastrointestinal dysfunction by meta-analysis in patients with gastrointestinal cancer.

2. Data sources

Data from the Structured Abstract 2013, 2014, and 2015 Appendices, prepared by the Evidence-based Medicine (EBM) Committee of the Japan Society for Oriental Medicine by searching the Cochrane Central Register of Controlled Trials (CENTRAL) and the web version of the Japan Medical Abstracts Society (JAMAs)'s Igaku Chuo Zasshi (Ichushi).

3. Study selection

Randomized controlled trials (RCTs) comparing a daikenchuto (大建中湯) treatment group to a non-treatment group for intestinal dysfunction after gastrointestinal cancer surgery were collected.

4. Data extraction

The authors of this paper extracted information (the author, year of publication, language, study design, cancer type, number of participants in the kampo group, number of participants in the control group, and outcomes) from the structured abstract prepared by the EBM Committee of the Japan Medical Abstracts Society, and two co-authors confirmed the progress and the extracted results.

5. Main outcome measures

The primary endpoint was time to first postoperative passage of flatus and defecation. Secondary endpoints were frequency of bowel obstruction, length of hospital stay after surgery, survival, quality of life, and side effects.

6. Main results

A meta-analysis of 9 RCTs was conducted. With regard to control groups, three trials included placebo groups and six trials included non-daikenchuto (大建中湯)-administered groups. One trial involved post-operative patients with esophageal cancer, 2 trials involved post-operative patients with gastric cancer, and 6 trials involved post-operative patients with colorectal cancer. As assessed in 6 studies, the primary endpoint of first postoperative passage of flatus was significantly shorter in the daikenchuto (大建中湯) group than in the control group (P=0.01). Time to first post-operative defecation was assessed in 6 studies and did not differ between the daikenchuto (大建中湯) group and the control group. A secondary endpoint of post-operative hospital stay was shorter in the daikenchuto (大建中湯) group than in the control group (P=0.01). In a subgroup analysis of RCTs of colorectal cancer, the first postoperative defecation was significantly shorter in the daikenchuto (大建中湯) group than in the control group (P=0.01). A significant difference in the time to the first post-operative passage of flatus was found between RCTs with no conflict-of-interest explanations and unblinded RCTs.

7. Conclusions

Daikenchuto (大建中湯) is effective for improving intestinal dysfunction in postoperative patients with gastrointestinal cancer. However, significant differences disappeared in RCTs with conflict-of-interest explanations and RCTs that were blinded to conflicts of interest.

8. From Kampo medicine perspective

None.

9. Safety assessment in the article

Adverse effects were not observed in 7 RCTs. Two RCTs did not describe side effects.

10. Abstractor's comments

This was a meta-analysis of daikenchuto (大建中湯), which is frequently used to improve intestinal peristalsis after gastrointestinal surgery. This report is important in showing that the results of the meta-analysis also demonstrated the efficacy of daikenchuto (大建中湯) and in proving the potential of Kampo medicine internationally. The fact that the effect varies by patient is useful in clarifying the target for the use of daikenchuto (大建中湯). On the other hand, the significant differences disappeared when limiting to RCTs with description of conflicts of interest and blindness. It is hoped that the accumulation of further RCTs will clarify the efficacy of daikenchuto (大建中湯).

11. Abstractor and date

Goto H, 19 December 2020.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

5. Psychiatric/Behavioral Disorders

Reference

Takeyoshi K, Kurita M, Nishino S, et al. Yokukansan improves behavioral and psychological symptoms of dementia by suppressing dopaminergic function. *Neuropsychiatric Disease and Treatment* 2016; 12: 641-9. Pubmed ID: 27042075, UMIN ID: UMIN000006146

1. Objectives

To evaluate the effectiveness of yokukansan (抑肝散) (TJ-54) on neurotransmitters in patients with dementia.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single psychiatric hospital

4. Participants

Patients who were hospitalized for dementia between January 2009 and August 2010 (90 patients).

Patients in whom the behavioral and psychological symptoms of dementia (BPSD) were no longer able to be managed in home care, nursing homes, or similar facilities and who came to this hospital to be treated for BPSD.

Exclusion criteria:

Participation in other drug trials within 4 weeks of study entry.

Hypersensitivity to risperidone, yokukansan (抑肝散), or fluvoxamine.

Presence of any type of severe or unstable disease that could interfere with the study.

5. Intervention

Arm 1: Yokukansan (抑肝散) treatment group, Tsumura Yokukansan (抑肝散) Extract Granules (2.5-7.5 g/day), 27 patients.

Arm 2: Risperidone treatment group (0.5 to 2.0 mg/day), 27 patients.

Arm 3: Fluvoxamine treatment group (25-200 mg/day), 27 patients.

Duration of administration: 8 weeks.

Dose adjustments were at the discretion of investigators according to patients' clinical response. Doses of yokukansan (抑肝散) 2.5 g/day, risperidone 0.5 or 1.0 mg/day, and fluvoxamine were increased in increments of 25 or 50 mg/day.

6. Main outcome measures

Risperidone, yokukansan (抑肝散), and fluvoxamine were equally effective in treating the behavioral and psychological symptoms of dementia (BPSD) in previous studies, and their mechanisms of action differ from each other. Monoamines have emerged as key players in mediating several behavioral or psychological symptoms through synaptic signaling. A primary objective of this study was to identify the monoamines that fluctuate with each drug treatment in patients with BPSD and to determine whether plasma levels of catecholamine metabolites are correlated with pharmacological treatment. Plasma homovanillic acid (HVA), a dopamine metabolite, and 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, were analyzed by high-performance liquid chromatography for comparison among the three groups and assessed at Week 0, 2, 4, 6, and 8.

BPSD and cognitive function were assessed using the neuropsychiatric inventory-nursing home (NPI-NH) rating scale and the Mini‐Mental State Examination (MMSE), respectively.

7. Main results

Eight patients were excluded based on selection criteria and 82 hospitalized patients were included. Finally, the data from 42 patients who completed 8 weeks of treatment (yokukansan [抑肝散]: 17 patients; risperidone: 9 patients; fluvoxamine: 16 patients) were analyzed. A significant reduction from baseline in plasma homovanillic acid levels was observed in the yokukansan (抑肝散) group ($P<0.05$). Conversely, the risperidone and fluvoxamine groups showed no significant change in plasma homovanillic acid level from baseline. The patients in all groups had substantially reduced NPI-NH sum scores and showed no significant change in MMSE scores.

8. Conclusions

Yokukansan (抑肝散) includes geissoschizine methyl ether, which is known to exert partial agonist effects on dopamine D2 receptors. Improvement in BPSD with yokukansan (抑肝散) intake has been suggested to result from suppression of dopaminergic functions, similar to the effects of aripiprazole. This study shows that yokukansan (抑肝散) improves the BPSD by suppressing dopamine release. NPI-NH sum scores were substantially reduced in all groups and MMSE scores were not significantly changed.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not described.

11. Abstractor's comments

As basic studies of the mechanism of action of yokukansan (抑肝散) for BPSD have reported, yokukansan (抑肝散) suppresses abnormal glutamate release in hippocampus in zinc deficiency models and has neuroprotective effects against glutamate-mediated excitotoxicity. In addition, patients with dementia show abnormalities in various nervous systems, including the cholinergic, serotonergic, dopaminergic, glutamatergic, and GABAergic nervous systems. Findings of this study demonstrate that yokukansan (抑肝散) suppresses dopamine release. As dopamine is a neurotransmitter closely associated not only with dementia but also with other psychiatric disorders, it is hoped that further research will be conducted to investigate the effects of yokukansan (抑肝散) on other psychiatric disorders.

12. Abstractor and date

Kato Y, 1 February 2021; Nagata Y, 8 June 2025.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Numata T, Takayama S, Tobita M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. *Evidence-Based Complementary and Alternative Medicine* 2014: 1-8. doi: 10.1155/2014/231258

Numata T, Takayama M, Iwasaki K, et al. A prospective controlled clinical trial using daikenchuto (大建中湯) for constipation symptoms in patients with cerebrovascular accident sequelae. *Kampo medicine and the Newest Therapy* 2015; 24: 145-52. Ichushi web ID: 2015271809

Arita R, Numata T, Takayama S, et al. Responder Analysis of Daikenchuto Treatment for Constipation in Poststroke Patients：A Subanalysis of a Randomized Control Trial. *Journal of Evidence-Based Integrative Medicine* 2019; 24: 2515690X19889271. CENTRAL ID: CN-02051186, Pubmed ID: 31823650

1. Objectives

To evaluate the effectiveness and safety of daikenchuto (大建中湯) for constipation in post-stroke patients.

2. Design

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

3. Setting

Six hospitals.

4. Participants

A total of 34 patients (17 women/17 men) diagnosed with functional constipation between September 2012 and December 2013 according to Roma III diagnostic criteria, who had suffered a cerebral hemorrhage, stroke, or subarachnoid hemorrhage, and whose condition had been stable for at least 6 months.

5. Intervention

Arm 1: Tsumura Daikenchuto (大建中湯) Extract Granules 5 g three times daily orally before meals or by tube administration for 4 weeks in addition to general constipation treatments such as laxatives, enemas, and stool extraction (17 patients).

Arm 2: General constipation treatments including laxatives, enemas, and stool extraction for 4 weeks (17 patients).

6. Main outcome measures

Constipation scoring system (CSS) score, gas volume score (GVS), calcitonin gene-related peptide (CGRP) blood concentration.

7. Main results

CSS score and GVS were statistically significantly reduced in Arm 1 compared with Arm 2 ($P<0.01$ and $P=0.03$, respectively). No significant between-Arm difference in blood levels of CGRP were observed.

8. Conclusions

Daikenchuto (大建中湯) is effective in improving constipation and abdominal gas accumulation in poststroke patients.

9. From Kampo medicine perspective

Daikenchuto (大建中湯) appeared effective for constipation with poor appetite and decreased digestive tract function.

10. Safety assessment in the article

No side effects were seen in the daikenchuto (大建中湯) group.

11. Abstractor's comments

This paper describes a clinical trial investigating the efficacy of daikenchuto (大建中湯) for constipation in post-stroke patients. Constipation and abdominal fullness are often a problem in post-stroke patients, and this paper is significant in showing that daikenchuto (大建中湯) is effective in such situations. In addition, while it has been hypothesized that the efficacy of daikenchuto (大建中湯) for constipation is mediated by CGRP, the negative data showing that there was no significant difference in CGRP despite clinical efficacy is also significant for future basic research. As noted in this article, other articles describe the ineffectiveness of daikenchuto (大建中湯) for constipation in patients in other settings. Studies to show how effective daikenchuto (大建中湯) is for constipation in a wider range of patients are desirable.

12. Abstractor and date

Koike H, 24 December 2015, 1 October 2018, 1 June 2021.

Note) The quality of this RCT has not been validated by the EBM committee of the Japan Society for Oriental Medicine.

21. Others

References

Chikafumi Horii, Akira Okonogi, Toshiki Okubo, et al. A study on the equivalence of shoseiryuto (小青竜湯) extract and decoction (I). *The Japanese journal of pharmacology* 2014; 68(2): 65-9. Ichushi Web ID: 2014173073 MOL, MOL-Lib

Chikafumi Horii, Akira Okonogi, Ryuji Takahashi, et al. A study on the equivalence of shoseiryuto (小青竜湯) extract and decoction (II). *The Japanese journal of pharmacology* 2019; 73(2): 73-83. Ichushi Web ID: 2019391256 MOL, MOL-Lib

1. Objectives

To evaluate the equivalence of shoseiryuto (小青竜湯) extract and decoction.

2. Design

Randomized controlled trial (cross over) (RCT cross-over).

3. Setting

University Hospital Medical Information Network (UMIN) research center, Clinical Trials Registry (CTR).

4. Participants

Six patients who responded to the call.

5. Intervention

As there is no mention of grouping, arms are used to describe the drug groups.

Arm 1: 6.0 g of Kracie Shoseiryuto (小青竜湯) Extract Fine Granules was administered, followed by decoction 2 weeks later.

Arm 2: After shoseiryuto (小青竜湯) decoction (3 g of ephedra, 3 g of peony, 3 g of Zingiber siccatum, 3 g of Glycyrrhiza, 3 g of cinnamon, 3 g of Asiasarum root, 3 g of Schisandra fruit, and 6 g of Pinellia tuber), extract fine granules were administered 2 weeks later.

6. Main outcome measures

The plasma concentrations were measured at 15, 30, 60, 120, 240, and 480 minutes after administration of ephedrine and pseudoephedrine in ephedra, peoniflorin in peony, gomisin A and schizandrin in Schisandra fruit, glycyrrhizic acid, liquiritin, and liquiritigenin in Glycyrrhiza, asarinin in Asiasarum root, and [6]-shogaol and zingerone in Zingiber siccatum.

7. Main results

According to reference (I), there were no significant differences in blood concentrations of ephedrine or pseudoephedrine at each time point between the decoction and extract formulation. Reference (II) suggested that gomisin A, schizandrin, liquiritin, [6]-shogaol, and asarinin might be indicator components useful for the assessment of equivalence.

8. Conclusions

The concentrations of the ephedra indicator components between the decoction and extract formulations of shoseiryuto (小青竜湯) are considered to be equivalent. For constituent crude drugs other than ephedra, some are presumed to be likely to be indicator components useful for equivalence assessment and others are presumed to be unavailable as indicator components.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No particular problems were noted.

11. Abstractor's comments

Ref. (I): Although this article states that there were no significant differences in the ephedra indicator components, it suggests that making comparisons that include peoniflorin in peony and asarinin in Asiasarum root, as well as data taking into account the effects of absorption and metabolism, would be more accurate. However, some of the medicinal properties of the extract can be considered to have been proven since at least the ephedra indicator components serve as characteristic constituents with which to evaluate the bioequivalence of the preparations.

Ref. (II): Taking reference (I) into consideration, the authors investigated indicator components other than ephedra indicator components, but appropriate selection of the indicator component is important in assessing the equivalence of Kampo medicinal prescriptions, which seems to be difficult to do.

12. Abstractor and date

references (I): Nakata H, 31 March 2017.

references (II): Wakasugi A, 28 September 2021.

List of Excluded References (Appendix 2020)

Abbreviations: C, The Cochrane Library (CENTRAL); I, Igaku Chuo Zasshi (Japana 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).

ICD-10	Research Question	Kampo Formula	References	Reason for exclusion	Source
F05.9	Effect of yokukansan for psychiatric symptoms in cancer patients undergoing high invasive surgery	yokukansan (抑肝散)	Wada S, Sadahiro R, Matsuoka Y, et al. Yokukansan for perioperative psychiatric symptoms in cancer patients undergoing high invasive surgery. J-SUPPORT 1605 (ProD Study): study protocol for a randomized controlled trial. *Trials* 2019; 20: 1-9.	5) Publication only includes protocol	C
F05.9	Evaluation of prevention of postoperative delirium in elderly patients planned to undergo an elective surgery through meta-analysis	yokukansan (抑肝散)	T L Janssen, A R Alberts, L Hooft, et al. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. *Clinical Interventions in Aging* 2019; 14: 1095-117.	6) Meta-analysis of major Western medicines (only one article on Yokukansan)	N
F05.9	Evaluation of the preventive effect of medicines on postoperative delirium through meta-analysis	yokukansan (抑肝散)	Yong Liu, Xiao-Jin Li, Yi Liang, et al. Pharmacological Prevention of Postoperative Delirium: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evidence-Based Complementary and Alternative Medicine* 2019; 1-10.	6) Meta-analysis of major Western medicines (only one article on Yokukansan)	N
F45.3	Comparison of the effects of anti-inflammatory agents and saibokuto on pharyngeal dysesthesia	saibokuto (柴朴湯)	Kobayashi H, Yamamoto K, Zusho H. Comparison of Antiphlogistics and Chinese Medicines as to Therapeutic Effects on Abnormal Sensation of Pharynx. *Jibi to rinsho* 1985; 31(3): 569-76.	3) Used Kampo preparations manufactured prior to 1985	I

G44.4	Evaluation of the efficacy of yokukansan for drug-induced headache	yokukansan (抑肝散)	Mitsufuji T, Araki N, Ito Y, et al. Protocol paper: Effects of yokukansan on medication-overuse headache. *Neurology and Clinical Neuroscience* 2019; 7(3): 119-21.	5) Publication only includes protocol	I
K30	The effect of rikkunshito on functional dyspepsia	rikkunshito (六君子湯)	Seok-Jae Ko, Jae-Woo Park, Jae-Hong Lee, et al. Herbal medicine Yukgunja-tang for functional dyspepsia protocol for a systematic review of randomized controlled trials. *Medicine* 2018; 97(40): 1-4.	5) Publication only includes protocol	N
K52.0	Effect of hangeshashinto for acute radiation-induced enteritis	hangeshashinto (半夏瀉心湯)	Murai T, Manabe Y, Shibamoto Y, et al. Efficacy of herbal medicine TJ-14 for acute radiation-induced enteritis: a multi-institutional prospective Phase II trial. *Journal of Radiation Research* 2020; 61(6): 140-5.	1) Not an RCT.	C
K58.9	Evaluation of effects of shigyakusan or probiotics for irritable bowel syndrome and medically unexplained physical symptoms	shigyakusan (四逆散)	Nakatani M. Effect of Shigyakusan Used for IBS and Medically Unexplained Physical Symptoms Diagnosed by Abdominal N Line Tenderness in Comparison with Probiotics. *International Medical Journal* 2019; 26(3): 204-8.	1) Not an RCT.	I
T81.8	Verification of the effects of Kampo medicines and acupuncture on general anesthesia complications	saireito (柴苓湯) jidabokuip po (治打撲一方)	Komazawa N, 105. Establishing a Comprehensive Preventive Approach for General Anesthesia Complications Using Kampo Medicine and Acupuncture. Research report from The Uehara Memorial Foundation. 2018;32: 1-4.	6) RCT of acupuncture	I