Evidence Reports of Kampo Treatment (EKAT)

Appendix 2021

漢方治療エビデンスレポート(EKAT) Appendix 2021

31 May 2022

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

ver.1.0 31 May 2022

History of version upgrades

31 May. 2022: Kampo Chiryo Ebidensu Repoto Appendix 2021 (Evidence Reports of Kampo Treatment Appendix 2021)
31 Jan. 2022: Kampo Chiryo Ebidensu Repoto Appendix 2020 (Evidence Reports of Kampo Treatment Appendix 2020)
1 Sep. 2021: Kampo Chiryo Ebidensu Repoto 2019 - 512 no RCT (Evidence Reports of Kampo Treatment 2019: 512 Randomized Controlled Trials)
1 Jun. 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 Jun. 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 Jun. 2010: Kampo Chiryo Ebidensu Repoto 2010 - 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)
1 Jun. 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 Jun. 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 Jul. 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
2022.5.31	Evidence Reports of Kampo Treatment Appendix 2021 (EKAT Appendix 2021)	From EKAT 2020 2020	651 [2]	544 [1), 2)]	234 [2]
2022.1.31	Evidence Reports of Kampo Treatment Appendix 2020 (EKAT Appendix 2020)	From EKAT 2019 2019	639 [3]	533 [1), 3)]	225 [3]
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 2018 (EKAT Appendix 2018)	From EKAT 2017 2017	594 [4]	493 [1), 4)]	203 [4]
2020.5.18	Evidence Reports of Kampo Treatment Appendix 2017 (EKAT Appendix 2017)	From EKAT 2016 2016	578 [5]	478 [1), 5)]	188 [5]
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 [6]	447 [1), 6)]	177 [6]
2015.6.6	Evidence Reports of Kampo Treatment Appendix 2014 (EKAT Appendix 2014)	From EKAT 2013 2013 (First half)	513 [7]	418 [1), 7)]	167 [7]
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 [8)]	379 [1), 8)]	150 [8)]
2011.10.1	Evidence Reports of Kampo Treatment Appendix 2011 (EKAT Appendix 2011)	From EKAT 2010 2010 (First half)	432 [9)]	360 [1), 9)]	-
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, EKAT Appendix 2020 and EKAT Appendix 2021
[3)] Total of all references added or removed in EKAT 2019, EKAT Appendix 2020
[4)] Total of all references added or removed in EKAT 2016, EKAT Appendix 2017 and EKAT Appendix 2018
[5)] Total of all references added or removed in EKAT 2016, EKAT Appendix 2017
[6)] Total of all references added or removed in EKAT 2013, EKAT Appendix 2014 and EKAT Appendix 2015
[7)] Total of all references added or removed in EKAT 2013, EKAT Appendix 2014
[8)] Total of all references added or removed in EKAT 2010, EKAT Appendix 2011 and EKAT Appendix 2012
[9)] Total of all references added in EKAT 2010 and EKAT Appendix 2011

Notes on the current version

The Task Force for Evidence Reports (ER-TF) of the Committee for Evidence-based Medicine (EBM), Japan Society for Oriental Medicine (JSOM), comprehensively gathers data obtained in randomized controlled trials (RCTs) of Kampo formulations in Japan, compiles structured abstracts (SAs), and then publishes them on the website of the Committee for Evidence-based Medicine as Evidence Reports of Kampo Treatment (EKAT). It has been doing this since 2007.

As indicated in the "History of version upgrades" on the previous page, the "Evidence Reports of Kampo Treatment 2019 - 512 RCTs" (EKAT 2019) was published on September 1, 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. On January 31, 2022, EKAT Appendix 2020 was published and additionally contained only SAs of RCT reports published approximately one year after the publication of EKAT 2019.

EKAT Appendix 2021 contains SAs for 11 RCT reports published within approximately one year after the publication of EKAT Appendix 2020. Even though the ER-TF website has not been updated since the publication of the EKAT 2019, the Google search engine available on the website allows users to access all SAs in EKAT 2019, EKAT Appendix 2020, and EKAT Appendix 2021.

The ER-TF carried out a search for RCT reports for the present EKAT in April 2021, to prepare SAs of RCT reports published in most medical journals in 2020. Although publication of EKAT Appendix 2021 was planned in 2021, it was actually published in 2022 due to a delay in the publication of EKAT 2019 and EKAT Appendix 2020. 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.

In the next revision, the ER-TF will carry out a full revision of the EKAT.

The Japan Society for Oriental Medicine (JSOM)

Seventh Phase (June 2021 －)
Committee for Evidence-based Medicine (EBM)
Task Force for Evidence Reports (ER-TF)

(Affiliations of the EBM Committee members in fiscal year 2021 may be different from those of the current members.)

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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, Hand searching Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C18.9	To evaluate the efficacy and safety of daikenchuto (大建中湯) on colorectal cancer patients with the potential risk of postoperative ileus	daikenchuto (大建中湯)	Wakasugi M, Suzuki Y, Tei M, et al. Effects of Daikenchuto on postoperative gastrointestinal motility in colorectal carcinoma patients with abdominal pain and distension: a prospective, randomized trial. *Surgery Today* 2020; 50(11): 1524-9.	RCT	C	8
C18.9 L27.1	To assess the efficacy of eppikajutsuto (越婢加朮湯) for preventing hand-foot syndrome (HFS) as a complication of postoperative adjuvant chemotherapy using capecitabine for colorectal cancer	eppikajutsuto (越婢加朮湯)	Watanabe K, Ishibe A, Watanabe J, et al. The effect of TJ-28 (Eppikajutsuto) on the prevention of hand-foot syndrome using Capecitabine for colorectal cancer：The Yokohama Clinical Oncology Group Study (YCOG1102). *Indian Journal of Gastroenterology* 2020; 39(2): 204-10.	RCT	C	9
C25.9 K31.9	To evaluate the efficacy of rikkunshito (六君子湯) on delayed gastric emptying (DGE) after pancreaticoduodenectomy (PD)	rikkunshito (六君子湯)	Yamaguchi H, Kimura Y, Imamura M, et al. Effect of rikkunshito, a traditional Japanese herbal medicine, on delayed gastric emptying and oral dietary intake after pancreaticoduodenectomy: a prospective, randomized, single-center, open-labeled study. *Clinical and Experimental Gastroenterology* 2020; 13: 577-87.	RCT	C	10
C76.0 K12.1	To assess hangeshashinto (半夏瀉心湯) mouthwash for prevention/treatment of chemotherapy-induced oral mucositis (OM)	hangeshashinto (半夏瀉心湯)	Taira K, Fujiwara K, Fukuhara T, et al. The effect of hangeshashinto on oral mucositis caused by induction chemotherapy in patients with head and neck cancer. *Yonago Acta Medica* 2020; 63(3): 183-7.	DB-RCT	C	11
I62.0	To evaluate the efficacy and safety of goreisan (五苓散) for the recurrence rate of chronic subdural hematoma (CSDH) after surgical treatment	goreisan (五苓散)	Fujisawa N, Oya S, Yoshida S, et al. A prospective randomized study on the preventive effect of Japanese herbal Kampo medicine goreisan for recurrence of chronic subdural hematoma. *Neurologia Medico-Chirurgica* 2021; 61(1): 12-20.	RCT	C	12
J44.9	To evaluate the efficacy and safety of ninjin'yoeito (人参養栄湯) in frailty or prefrailty patients with chronic obstructive pulmonary disease (COPD)	ninjin'yoeito (人参養栄湯)	Hirai K, Homma T, Matsunaga T, et al. Usefulness of Ninjin'yoeito for chronic obstructive pulmonary disease patients with frailty. *Journal of Alternative and Complementary Medicine* 2020; 26(8): 750-7.	RCT	N	13
M17.9	To evaluate the efficacy and safety of keishikajutsubuto (桂枝加朮附湯) in degenerative knee osteoarthritis (KOA)	keishikajutsubuto (桂枝加朮附湯)	Myung Kwan Kim, Jungtae Leem, Young Il Kim, et al. Gyejigachulbutang (Gui-Zhi-Jia-Shu-Fu-Tang, Keishikajutsubuto, TJ-18) in degenerative knee osteoarthritis patients：Lessons and responders from a multicenter randomized placebo-controlled double-blind clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2020; Article ID 2376581.	DB-RCT	N	14

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
N51	To evaluate the effects of goreisan (五苓散) on serum sodium levels and the occurrence of transurethral resection (TUR) syndrome in patients undergoing TUR of the prostate	goreisan (五苓散)	Fujiwara A, Nakahira J, Nakano S, et al. Efficacy of Goreisan in preventing transurethral resection syndrome in transurethral resection of the prostate: A randomized-controlled study. *Journal of Alternative and Complementary Medicine* 2020; 26(8): 738-42.	RCT	N	15
N95.1	To evaluate the efficacy and safety of kamishoyosan (加味逍遙散) in patients with menopausal symptoms	kamishoyosan (加味逍遙散	Takamatsu K, Ogawa M, Higuchi H, et al. Effects of kamishoyosan, a traditional Japanese medicine, on menopausal symptoms: a randomized, placebo-controlled, double-blind clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2020; Article ID 9285317.	DB-RCT	C	16
Z04.8	To evaluate whether it is possible to determine the bioequivalence of kakkonto（葛根湯） extract granules and tablets with ephedrine and pseudoephedrine as markers	kakkonto (葛根湯)	Hakamatsuka T, Kamakura H, Watanabe J, et al. Bioequivalence test between Kakkonto Extract Granules and Tablets in healthy volunteers. *Shoyakugaku Zasshi* (*The Japanese Journal of Pharmacognosy*) 2020; 74(2): 89-97. (in Japanese)	RCT-cross over	I	17
Z04.8	To evaluate the equivalence and changes in plasma concentration of hachimijiogan (八味地黄丸) decoction and extract preparation (medicinal use) when administered to humans	hachimijiogan (八味地黄丸)	Horii C, Okonogi A, Takahashi R, et al. Studies on bioequivalence of Hachimijiogan decoction and its extract preparation. *Shoyakugaku Zasshi* (*The Japanese Journal of Pharmacognosy*) 2020; 74(1): 46-57. (in Japanese)	RCT-cross over	I	18

[Revisions of Already Included References]

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
C25.9	To assess the efficacy of daikenchuto (大建中湯) for prevention of paralytic ileus after	daikenchuto (大建中湯)	Okada K, Kawai M, Hirono S, et al. Evaluation of the efficacy of daikenchuto (TJ-100) for the prevention of paralytic ileus after pancreaticoduodenectomy: a multicenter, double-blind, randomized, placebo-controlled trial. *Surgery* 2016; 159: 1333-41.	DB-RCT	C	19
			Maeda H, Okada KI, Fujii T, et al. Transition of serum cytokines following pancreaticoduodenectomy: A subsidiary study of JAPAN-PD. *Oncol Lett* 2018; 16: 6847-53.		C	
			Maeda H, Okada K, Fujii T, et al. No significant effect of daikenchuto (TJ-100) on peritoneal IL-9 and IFN-γ levels after pancreaticoduodenectomy. *Clin Exp Gastroenterol* 2020; 13: 461-6.		C	

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

Reference

Wakasugi M, Suzuki Y, Tei M, et al. Effects of Daikenchuto on postoperative gastrointestinal motility in colorectal carcinoma patients with abdominal pain and distension: a prospective, randomized trial. *Surgery Today* 2020; 50(11): 1524-9. CENTRAL ID: CN-02144161, PubMed ID: 32588153, Clinical Trial Registration No.: UMIN000008348

1. Objectives

To evaluate the efficacy and safety of daikenchuto (大建中湯) on colorectal cancer patients with the potential risk of postoperative ileus.

2. Design

Randomized controlled trial (RCT).

3. Setting

One hospital (Osaka Police Hospital), Japan.

4. Participants

Thirty-two colorectal cancer patients who were candidates for curative colonic resection and had preoperative constipation of at least CTCAE ver. 4 grade 1 with an abdominal pain and/or distention Gastrointestinal Symptom Rating Scale (GSRS) score of at least 3. Patients who underwent low anterior resection and those with colostomy were excluded from the study.

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules 5 g t.i.d., oral administration, from 2 weeks before surgery to the preoperative day, and from the postoperative day (POD) 2 to 28, n=16.

Arm 2: No treatment, n=16.

6. Main outcome measures

The primary endpoints were gastrointestinal symptoms (abdominal pain/distention) levels measured by Visual Analogue Scale (VAS); the sensation of incomplete bowel evacuation (yes/no); and POD of the first evacuation, postoperative time until first flatus, and the number of bowel movements per day. Secondary endpoints included quality of life evaluated by acid reflux, abdominal pain, indigestion, diarrhea, and constipation (assessed using the GSRS questionnaire).

7. Main results

One patient in Arm 1 was changed from laparoscopic surgery to laparotomy. There was no difference in VAS scores for abdominal pain and distention between the two Arms. The incidence of a sensation of incomplete bowel evacuation on PODs 3 (P=0.04) and 28 (P=0.05) was significantly lower in the Arm 1 compared with Arm 2. The number of evacuations per day on PODs 1 (P=0.01), 2 (P=0.01), and 6 (P=0.01) were also significantly lower in the Arm 1 than in the Arm 2. There were no differences between the Arms in the POD of the first evacuation and postoperative time until first flatus. Regarding GSRS scores for acid reflux, abdominal pain, indigestion, diarrhea, constipation, and total GSRS scores, there were no differences between the two Arms.

8. Conclusions

Daikenchuto may suppress the number of bowel movements per day and the sensation of incomplete bowel evacuation after colorectal surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

There were no adverse events related to daikenchuto treatment.

11. Abstractor's comments

This is clinical research of the effects of daikenchuto for gastrointestinal symptoms, etc. in postoperative colorectal cancer patients. Notably, transient improvement in the number of evacuations and incidence of sensation of incomplete bowel evacuation was demonstrated by an RCT, although the insufficient sample size seems to have made the results show a transient and limited effect. It is hoped that the sample size will be increased through multi-institutional joint research, etc., thereby further elucidating the efficacy of daikenchuto after colorectal cancer surgery.

12. Abstractor and date

Goto H. 18 Feb 2022.

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

Reference

Watanabe K, Ishibe A, Watanabe J, et al. The effect of TJ-28 (Eppikajutsuto) on the prevention of hand-foot syndrome using Capecitabine for colorectal cancer： The Yokohama Clinical Oncology Group Study (YCOG1102). *Indian Journal of Gastroenterology* 2020; 39(2): 204-10. CENTRAL ID: CN-02123518, Pubmed ID: 32406009, Clinical Trial Registration: UMIN000005899

1. Objectives

To assess the efficacy of eppikajutsuto (越婢加朮湯) for preventing hand-foot syndrome (HFS) as a complication of postoperative adjuvant chemotherapy using capecitabine for colorectal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two university hospitals, Japan.

4. Participants

Twenty-two Stage III colorectal cancer patients who have undergone radical resection and were chemotherapy-naïve could proceed to postoperative adjuvant chemotherapy with capecitabine. The participants were required to take part in the study within 8 weeks after surgery and had no history of myocardial infarction/unstable angina in the previous 6 months.

5. Intervention

Arm 1: TSUMURA Eppikajutsuto (越婢加朮湯) Extract Granules (TJ-28) 2500 mg t.i.d. taken orally every day during the capecitabine administration period (3 weeks/course × 8) (n=12).

Arm 2: Pyridoxine 20 mg t.i.d. taken orally every day during the capecitabine administration period (3 weeks/course × 8) (n=10).

6. Main outcome measures

The primary endpoint was the occurrence of grade ≥2 HFS, based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE). The secondary endpoints were time to observation of grade ≥2 HFS, time to the disappearance of HFS, and incidence of adverse events.

7. Main results

Efficacy was analyzed in 22 patients (12 in Arm 1 and 10 in Arm 2). The occurrence of grade ≥2 HFS was 50.0% (6/12 patients) in Arm 1 and 40.0% (4/10 patients) in Arm 2 (not statistically significant). Neither the time to observation of grade ≥2 HFS nor the time to the disappearance of HFS was significantly different between arms. Rest periods, dose reductions, and discontinuations were implemented in accordance with the study protocol. Relative dose intensity (RDI) was 76.2% in Arm 1 and 68.2% in Arm 2. There was no significant difference between arms for the occurrence of adverse events other than HFS, yet compared to the single patient who discontinued treatment in Arm 1 due to their own wish (8.3%), a total of 6 patients in Arm 2 discontinued treatment due to liver dysfunction, diarrhea, neutropenia, and own wish (60%) apart from the 2 cases of HFS, which meant the dropout rate was significantly lower in Arm 1 (P=0.020).

8. Conclusions

It is not clear whether eppikajutsuto (越婢加朮湯) has superior efficacy to pyridoxine in preventing the occurrence of HFS associated with capecitabine administration. It may, however, facilitate the continuation of chemotherapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

It is difficult to distinguish whether adverse events were due to the capecitabine or the eppikajutsuto (越婢加朮湯).

(There was no difference between the two arms, so they are believed to be due to the capecitabine.)

11. Abstractor's comments

This is the first study to assess the effects of a Kampo medicine on capecitabine-induced HFS in an RCT and is therefore groundbreaking. The authors, however, do not mention their reason for selecting eppikajutsuto, while case reports can be found elsewhere on hochuekkito (補中益気湯). It would also have been preferable for the authors to mention any apprehensions about the risks of adverse effects of the eppikajutsuto being masked by any adverse effects of the oral anti-cancer agent, and the risks of administering eppikajutsut, which is prescribed for people with comparatively robust physical fitness, together with an oral anti-cancer agent to patients within 8 weeks after surgery. The authors excluded patients who had had myocardial infarction/unstable angina in the previous 6 months, which suggests they were thinking of the constituent crude drug mao (ephedra herb), but unfortunately, there is no explanation of this in the paper. While the authors set the sample size at 50, their analysis is based on 22 patients, which makes references to statistical significance difficult. As the authors indicate, future studies with larger sample sizes are anticipated.

12. Abstractor and date

Kondo N, 30 March 2022.

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Yamaguchi H, Kimura Y, Imamura M, et al. Effect of rikkunshito, a traditional Japanese herbal medicine, on delayed gastric emptying and oral dietary intake after pancreaticoduodenectomy: a prospective, randomized, single-center, open-labeled study. *Clinical and Experimental Gastroenterology* 2020; 13: 577-87. CENTRAL ID: CN-02213554, PubMed ID: 33328753, Clinical Trial Registration No: UMIN000012052

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) on delayed gastric emptying (DGE) after pancreaticoduodenectomy (PD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Sixty patients aged 20 to 79 years with Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1 who were scheduled to undergo PD.

5. Intervention

Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules (TJ-43) 2.5 g t.i.d., from postoperative day (POD) 1 to POD 21, n=30.
Arm 2: No additional treatment, n=30.

6. Main outcome measures

The primary endpoint was the incidence of DGE diagnosed on the basis of International Study Group of Pancreatic Surgery (ISGPS) criteria. Secondary endpoints were short-term postoperative outcomes including oral dietary intake represented by total dietary intake (TDI), postoperative complications (Clavien-Dindo classification), and perioperative changes in levels of serum hormones such as ghrelin and leptin.

7. Main results

Twenty-six patients in each Arm completed the protocol treatment and were included in the analysis set (four patients in each Arm did not complete the study protocol). The overall incidence of DGE was not statistically different between Arm 1 and Arm 2 (30.8% vs 30.8%). There were no statistically significant differences in TDI up to POD 14 and POD 21, complications, and length of hospital stay. Total ghrelin level was significantly upregulated at POD 14 and 21 in Arm 1 (P<0.05) but not in Arm 2. Acyl-ghrelin level was also significantly upregulated at POD 14 and 21 in Arm 1 (P<0.01), but only at POD 21 in Arm 2 (P<0.05). Leptin levels were significantly lower than the preoperative level at POD 7 (P<0.05), 14 (P<0.05), and 21 (P<0.01) in Arm 1, but only at POD 21 in Arm 2 (P<0.05).

8. Conclusions

Rikkunshito treatment from POD 1 to 21 increases ghrelin and acyl-ghrelin levels and lowers leptin level, but does not reduce the incidence of DGE.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse events related to this study were observed.

11. Abstractor's comments

This is an important study investigating the efficacy of rikkunshito for gastrointestinal dysfunction after pancreaticoduodenectomy. The present study failed to demonstrate such efficacy of rikkunshito but reconfirmed its known ability to increase ghrelin and acyl-ghrelin levels and lower leptin level. As the efficacy of rikkunshito may be successfully demonstrated with design revisions such as more precise specification of the study population, as proposed by the authors, future studies are desired.

12. Abstractor and date

Koike H. 21Feb, 2022

2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)
11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Taira K, Fujiwara K, Fukuhara T, et al. The effect of hangeshashinto on oral mucositis caused by induction chemotherapy in patients with head and neck cancer. *Yonago Acta Medica* 2020; 63(3): 183-7. CENTRAL ID: CN-02161127, Pubmed ID: 32884437

1. Objectives

To assess hangeshashinto (半夏瀉心湯) mouthwash for prevention/treatment of chemotherapy-induced oral mucositis (OM).

2. Design

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

3. Setting

One university hospital, Japan.

4. Participants

Sixteen head and neck cancer (T2-T4a pharyngeal, laryngeal, oral, or maxillary sinus squamous cell carcinoma) patients receiving induction chemotherapy (first course of TPF).

~~5.~~ Intervention

Arm 1: TSUMURA Hangeshashinto (半夏瀉心湯) Extract Granules (TJ-14) mouthwash (2.5 g of TJ-14 dissolved in 100 ml water) used as a gargle (n=8).

Arm 2: Placebo mouthwash (2.5 g of lactose dissolved in 100 ml water) used as a gargle (n=8).

In both arms patients gargled (for 30 seconds then spat out the mouthwash) three times a day 30 minutes after each meal for 14 days after the start of chemotherapy and did not eat or drink for 30 minutes after gargling.

6. Main outcome measures

The primary endpoint was the duration of grade ≥2 OM. The secondary endpoints were incidence of OM overall, days to OM onset, total duration of OM, and incidence of other adverse events due to chemotherapy.

7. Main results

All 16 patients completed the treatment and were included in the analysis. The mean duration of grade ≥2 OM was significantly shorter in Arm 1 than in Arm 2 (1.3 days compared to 3.7 days, P=0.039). The incidence of grade ≥2 OM was 37.5% (3 patients) in Arm 1 and 50.0% (4 patients) in Arm 2 (not significantly different). The mean number of days to OM onset was 9.7 days in Arm 1 and 6.7 days in Arm 2 (not significantly different). The incidence of OM overall, total duration of OM, and incidence of adverse events associated with the chemotherapy did not differ significantly between the two treatment arms.

8. Conclusions

Hangeshashinto (半夏瀉心湯) (TJ-14) may shorten the duration of oral mucositis (grade ≥2) induced by chemotherapy in head and neck cancer patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reactions were observed in the hangeshashinto group.

11. Abstractor's comments

While hangeshashinto (半夏瀉心湯) has shown good results in radiation and chemoradiation therapy for other carcinomas as well as head and neck cancer. This is a clinical study to investigate whether hangeshashinto is effective for oral mucositis even when chemotherapy alone is used. The method of observing from the first day of chemotherapy to the complete remission of oral mucositis supports the reliability of the results, but the obtained results have no preventive effect, and the therapeutic effects were limited (while it did shorten the duration of grade ≥2 OM, it did not shorten the duration of OM overall). Considering that it is a study of a small number of cases, it is hoped that further studies will be conducted in the future. In that case, I hope that subjective evaluations (pain, etc.) and the validity of the mouthwash using lactose as a placebo are addressed.

12. Abstractor and date

Kondo N, 30 March 2022.

9. Cardiovascular Diseases

Reference

Fujisawa N, Oya S, Yoshida S, et al. A prospective randomized study on the preventive effect of Japanese herbal Kampo medicine goreisan for recurrence of chronic subdural hematoma. *Neurologia Medico-Chirurgica* 2021; 61(1): 12-20. CENTRAL ID: CN-02201206, Pubmed ID: 33208583 , Clinical Trial Registration No: UMIN000010006 , J-STAGE

1. Objectives

To evaluate the efficacy and safety of goreisan (五苓散) for the recurrence rate of chronic subdural hematoma (CSDH) after surgical treatment.

2. Design

Randomized controlled trial (RCT).

3. Setting

Not mentioned (the author belongs to the Department of Neurosurgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan).

4. Participants

Two hundred twenty-four patients who underwent initial burr hole surgery for CSDH. Patients with the following criteria were excluded: (1) age ≤18 years, (2) a history of craniotomy for hematoma and myelodysplastic syndrome, (3) an arachnoid cyst on the ipsilateral side of the CSDH, and (4) refusal to give consent to participate in this study.

5. Intervention

Arm 1: TSUMURA Goreisan (五苓散) Extract Granules 2.5 g t.i.d., oral administration, 3 months (administration was started within a few days after the surgery), n=112.

Arm 2: No medication, n=112 (one patient who took goreisan before surgery was excluded).

6. Main outcome measures

Primary outcome measure: Symptomatic recurrence of CSDH within 3 months postoperatively. Secondary outcome measures: Occurrence of wound infection and seizure. Risk stratification analysis was also performed on the basis of computed tomography (CT) images (Nakaguchi classification).

7. Main results

Of the randomized patients, 208 were included in the final analysis (104 patients for both Arm 1 and Arm 2; 16 patients were excluded from the analysis). The recurrence rate of Arm 1 was lower than that of Arm 2 (5.8% vs 12.5%, P=0.09), but the difference was not statistically significant. A significant preventive effect of goreisan was found in a stratified analysis of 145 patients with high-risk CT features (Arm 1, n=71; Arm 2, n=74), namely in patients with homogeneous and separated types (Arm 1: 5.6% vs Arm 2: 17.6%, P=0.04). The occurrence of wound infection and seizure was not significantly different between the two groups.

8. Conclusions

Goreisan may prevent recurrence of CSDH in a subset of high-risk patients whose hematoma shows homogeneous and separated patterns on CT images.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

In the goreisan-treated group, adverse events were observed in 3 patients (severe headache, diarrhea, and abdominal discomfort); one patient with headache was not able to tolerate and discontinued goreisan treatment.

11. Abstractor's comments

This article is admirable in that it evaluates the efficacy of goreisan for reducing the postoperative recurrence of CSDH and safety in an RCT. The postoperative recurrence rate tended to be lower in the goreisan group, although the difference was not statistically significant. However, CT image-based stratified analysis identified a significant preventive effect of goreisan for recurrence in patients with homogeneous and separated types of CSDHs. The results are considered clinically significant because there are no currently available drugs that decrease postoperative recurrence rate. As the authors state, the results should be carefully interpreted because of the small sample size and conduct of the study at a single center. Accordingly, further accumulation of clinical data in the future is desired.

12. Abstractor and date

Kogure T, 22 Feb, 2022.

10. Respiratory Diseases (including Influenza and Rhinitis)

Reference

Hirai K, Homma T, Matsunaga T, et al. Usefulness of Ninjin'yoeito for chronic obstructive pulmonary disease patients with frailty. *Journal of Alternative and Complementary Medicine* 2020; 26(8): 750-7. Pubmed ID: 32551796, Clinical Trial Registration No: UMIN000034582

1. Objectives

To evaluate the efficacy and safety of ninjin'yoeito (人参養栄湯) in frailty or prefrailty patients with chronic obstructive pulmonary disease (COPD).

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital, Japan.

4. Participants

Sixty-eight frail or prefrail patients with COPD. The inclusion criteria were (1) age ≥65 years; (2) diagnosis of COPD and initiation of bronchodilator therapy; (3) a history of smoking (Brinkman Index ≥200); and (4) presence of a state of frailty or prefrailty.

5. Intervention

Arm 1: Kracie Ninjin'yoeito (人参養栄湯) Extract Fine Granules 2.5 g t.i.d. before or between meals for 24 weeks (n=33).

Arm 2: continue conventional treatment (not specifically mentioned) (n=35).

6. Main outcome measures

Changes in the following assessment scores at week 24: Kihon checklist (KCL) scores, which reflect changes in frailty; Simplified Nutritional Appetite Questionnaire (SNAQ) scores, which reflect changes in appetite; COPD Assessment Test (CAT) scores, which reflect changes in quality of life (QOL) in patients with COPD; Hospital Anxiety and Depression Scale (HADS)-Anxiety scores, which reflect changes in anxiety; HADS-Depression scores, which reflect changes in depression.

7. Main results

Three patients in arm 2 withdrew before starting treatment. After allocation, in Arm 1, one patient developed lung cancer and another patient voluntarily discontinued outpatient visits, while one patient in Arm 2 voluntarily discontinued outpatient visits. Finally, 62 patients were included in the analysis (31 patients for each Arm).

KCL score tended to be improved in Arm 1 compared with Arm 2 (P=0.09). On the other hand, there was a significant difference in the changes in other scores (SNAQ [P=0.03], CAT [P=0.03], HADS-Anxiety [P<0.01], and HADS-Depression [P=0.02]) in favor of Arm 1 compared with Arm 2.

8. Conclusions

Ninjin'yoeito improves appetite, QOL, and mood disorders in frail, elderly patients with COPD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Although four patients in the ninjin'yoeito group had diarrhea requiring dose reduction (from 7.5 to 2.5 g), no serious side effects were observed in the ninjin'yoeito group during course of the study.

11. Abstractor's comments

This is valuable clinical research that followed up the effects of ninjin'yoeito in frail patients with COPD for as long as 24 weeks. As mentioned by the authors, the study's non-double-blind design would require caution in interpreting the effects on subjective symptoms. Moreover, with no details of treatment shown, it is unclear whether ninjin'yoeito had add-on effects to those of background therapies. However, while long-term administration of Kampo medicine in the elderly is usually associated with many dropouts due to treatment discontinuation, the present research minimized dropouts, showing the great efforts of the authors to promote the research. Conduct of a DB-RCT with a larger sample size is awaited.

12. Abstractor and date

Goto H. 18 Feb, 2022

13. Diseases of the Musculo Skeletal System and Connective Tissue

Reference

Myung Kwan Kim, Jungtae Leem, Young Il Kim, et al. Gyejigachulbutang (Gui-Zhi-Jia-Shu-Fu-Tang, Keishikajutsubuto, TJ-18) in degenerative knee osteoarthritis patients : Lessons and responders from a multicenter randomized placebo-controlled double-blind clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2020; Article ID 2376581 Pubmed ID: 33178309, Clinical Trial Registration No: KCT0003024

1. Objectives

To evaluate the efficacy and safety of keishikajutsubuto (桂枝加朮附湯) in degenerative knee osteoarthritis (KOA).

2. Design

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

3. Setting

One university hospital and one hospital, South Korea.

4. Participants

Eighty patients with KOA. The inclusion criteria were (1) age over 40 years old, (2) a visual analogue scale (VAS) score higher than 30 mm for knee pain during daily life, (3) Grade 2 or higher on the Kellgren–Lawrence Grading Scale, (4) voluntary decision to participate and sign the written informed consent form.

5. Intervention

Arm 1: TSUMURA Keishikajutsubuto (桂枝加朮附湯) Extract Granules 2.5 g t.i.d., 30 minutes after meals, for 4 weeks (n=40).

Arm 2: Placebo t.i.d., 30 minutes after meals, for 4 weeks (n=40).

Acetaminophen (maximum daily dose of 3000 mg or less, six tablets per day, 500 mg/tablet) was administered as a rescue medication and taken only when the pain was unbearable.

6. Main outcome measures

The change in the VAS score for knee pain, Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC), European Quality of Life Five Dimensions (EQ-5D) score from baseline to the 2nd, 4th, and 8th weeks. Exploratory subgroup analysis on the basis of BMI was also performed. The total amount of rescue medication consumption was recorded at each visit.

7. Main results

Seventy-two patients completed the study, and eight (3 patients in Arm 1, 5 patients in Arm 2) dropped out. There was no significant difference in VAS score, K-WOMAC, and EQ-5D score between Arm 1 and Arm 2. In subgroup analysis performed in subjects with a BMI lower than 25 kg/m^2, reduction in VAS score after 4 weeks was significantly larger in Arm 1 than in Arm 2 (P=0.0239). The dose of pain medication was significantly lower in Arm 1 than in Arm 2 after four weeks (P=0.016).

8. Conclusions

Four weeks of keishikajutsubuto intervention do not significantly improve knee pain, knee function, or quality of life of degenerative KOA patients compared to placebo, but may improve knee pain only in a those with BMI lower than 25. In addition, keishikajutsubuto may reduce rescue medicine consumption.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

During the study, 41 adverse events occurred: 24 in the keishikajutsubuto group and 17 in the placebo group. Of the 24 adverse events occurring in the keishikajutsubuto group, six adverse events were likely to have been caused by clinical trial drugs (abdominal distension, diarrhea, dry mouth, increased blood pressure, increased alanine aminotransferase, and abdominal discomfort), and 18 were unrelated. Of the 17 adverse events in the placebo group, three were possibly related to the clinical trial drug (abdominal discomfort, hypertension, and palpitations), and 14 were considered unrelated. Two severe adverse events of hypertension and back pain occurred in the placebo group, but the affected patients recovered. There were no serious adverse events in the keishikajutsubuto group.

11. Abstractor's comments

Knee osteoarthritis occurs when the articular cartilage wears down due to increased body weight and age, causing severe knee pain. This disease is prevalent in women, and its pathogenesis is considered to involve such factors as aging, obesity, and trauma. This article reports on the analysis of the effects of keishikajutsubuto, which suggested the possible effectiveness of keishikajutsubuto in the patient population with a BMI lower than 25. It is hoped that more reliable results will be obtained by increasing the sample size and the number of days of follow-up in the future.

12. Abstractor and date

Kato Y. 10 Feb, 2022.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Fujiwara A, Nakahira J, Nakano S, et al. Efficacy of Goreisan in preventing transurethral resection syndrome in transurethral resection of the prostate: A randomized-controlled study. *Journal of Alternative and Complementary Medicine* 2020; 26(8): 738-42. PubMed ID: 32609534, Clinical Trial Registration No: UMIN000017135

1. Objectives

To evaluate the effects of goreisan (五苓散) on serum sodium levels and the occurrence of transurethral resection (TUR) syndrome in patients undergoing TUR of the prostate.

2. Design

Randomized controlled trial (RCT).

3. Setting

One university hospital and one hospital, Japan.

4. Participants

Fifty-four men aged 20-90 years who were scheduled for TUR of the prostate with the use of monopolar cutting diathermy between 2015 and 2018.

5. Intervention

Arm 1: oral administration of 2.5 g of TSUMURA Goreisan (五苓散) Extract Granules on the night before surgery and on the morning of surgery (n=27).

Arm 2: no treatment (n=27).

6. Main outcome measures

Primary outcome measure: incidence of TUR syndrome; Secondary outcome measure: serum sodium levels.

7. Main results

After randomization, one patient in goreisan arm refused to participate in the study; surgery was canceled in another three patients. Finally, 50 patients completed the study and were included in the analysis (23 in Arm 1 and 27 in Arm 2).

With serum sodium levels remaining above 125 mmol/L in all patients, no patients strictly satisfied the criteria for TUR syndrome. Intraoperative serum sodium levels were significantly higher in goreisan arm than in no-treatment arm (P<0.001). Three patients in each arm experienced symptoms of TUR syndrome, resulting in no significant difference in the incidence between arms. Postoperative serum sodium levels did not differ significantly between arms. On the other hand, intraoperative (P=0.008) and postoperative (P=0.02) hemoglobin (Hb) levels were significantly higher in goreisan arm than in no-treatment arm.

8. Conclusions

Preoperative Goreisan administration can help maintain serum sodium levels in patients undergoing TUR of the prostate.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse drug reaction of goreisan was observed.

11. Abstractor's comments

TUR-P is associated with fluid overload, resulting in dilutional hyponatremia. TUR-P sometimes causes TUR syndrome with cardiovascular and neuropsychiatric symptoms, which are difficult to manage with modern medicine. The present RCT is a breakthrough in that it verified the efficacy of goreisan for prevention of these conditions. However, no patients satisfied a critical diagnostic criterion for TUR syndrome (hyponatremia with serum sodium level of 125 mmol/L or lower), and with three patients in each arm having symptoms, there was no significant difference in the incidence of TUR syndrome, which is the primary outcome measure, or symptoms of TUR syndrome. On the other hand, the goreisan arm had significantly higher serum sodium levels, the secondary outcome measure, and significantly higher intraoperative and postoperative Hb levels as well as hematocrit (Ht) values, suggesting potential effects of goreisan on the mechanism of dilutional hyponatremia. As described in the text, goreisan is associated with few side effects. In the present RCT as well, no side effects were observed with goreisan, as mentioned in discussion. As the occurrence of benign prostatic hypertrophy tends to be increasing in Japan as well, further verification with larger sample size is awaited.

12. Abstractor and date

Motoo Y. 10 Feb, 2022.

14. Genitourinary Tract Disorders (including Climacteric Disorders)

Reference

Takamatsu K, Ogawa M, Higuchi H, et al. Effects of kamishoyosan, a traditional Japanese medicine, on menopausal symptoms: a randomized, placebo-controlled, double-blind clinical trial. *Evidence-Based Complementary and Alternative Medicine* 2020; Article ID 9285317. CENTRAL ID: CN-02161686, Pubmed ID: 32733592, Clinical Trial Registration No: UMIN000005079

1. Objectives

To evaluate the efficacy and safety of kamishoyosan (加味逍遙散) in patients with menopausal symptoms.

2. Design

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

3. Setting

Four university hospitals and 9 related hospitals, Japan.

4. Participants

Two hundred and five patients aged 40-60 years with a chief complaint of climacteric disorders (hot flashes, insomnia, headache, and/or neurological symptoms). Patients with serious comorbidities (e.g., liver disease, kidney disease, heart disease, lung disease, hematologic disease, and malignant tumor) and a history of hormone therapy or Kampo therapy within 4 weeks prior to treatment initiation were excluded. The depression status of all patients was assessed using the Zung's self-rating depression scale (SDS), and those who scored <62 points were finally considered eligible for this study.

5. Intervention

Arm 1: TSUMURA Kamishoyosan (加味逍遙散) Extract Granules 2.5 g t.i.d., oral administration, 8 weeks, n=101.

Arm 2: Placebo having a similar appearance, smell, and taste to kamishoyosan (provided by Tsumura & Co.) 2.5 g t.i.d., oral administration, 8 weeks, n=104.

6. Main outcome measures

The change in the number of hot flashes (investigated using data from self-report diaries and shown by the mixed effect model for repeated measures), depression scores (SDS), anxiety (State-Trait Anxiety Inventory [STAI]), quality of life (SF-36), and menopausal symptoms (Japan Society of Obstetrics and Gynecology [JSOG] menopausal index) before and 4/8 weeks after initiation of the treatment.

7. Main results

The efficacy was assessed in 194 patients (93 patients in Arm 1 and 101 patients in Arm 2; 11 patients discontinued the treatment). After 8 weeks, the number of hot flushes and SDS decreased in both Arms, but there was no significant difference between the two Arms. No significant differences were observed in the STAI, SF-36, and JSOG menopausal index between the two Arms.

8. Conclusions

Kamishoyosan is safe and may have some effects on climacteric symptoms, but the efficacy is not superior to that of placebo.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Adverse events were noted in 15 patients (18 events) in the kamishoyosan group and 7 patients (8 events) in the placebo group; 14 events (11 patients) in the kamishoyosan group and 3 events (2 patients) in the placebo group had an undeniable causal link to the treatment. In the kamishoyosan group, a serious adverse event was observed in 1 patient (anxiety); other adverse events were not serious (7 gastrointestinal complaints, 2 vertigo, 2 articular pain, 1 palpitation, and 1 common cold). In the placebo group, adverse events (eruption, constipation, and gastric discomfort) were not serious. No patient dropped out because of adverse events.

11. Abstractor's comments

Kampo medicine is frequently used along with hormone replacement therapy for the treatment of menopausal symptoms. Kamishoyosan, one of the three major Kampo formulas in the gynecological field, is often prescribed to patients with menopausal symptoms mainly consisting of *chi-no-michi* syndrome. Given that this article reports on a large-scale study involving 194 patients, the lack of efficacy may have to be objectively acknowledged. However, the study is not based on *sho* (証, pattern/syndrome), and it is hoped that a detailed analysis of cases will be conducted with consideration given to *sho* in the future.

12. Abstractor and date

Kato Y. 9 Feb, 2022.

21. Others

Reference

Hakamatsuka T, Kamakura H, Watanabe J, et al. Bioequivalence test between Kakkonto Extract Granules and Tablets in healthy volunteers. *Shoyakugaku Zasshi* (*The Japanese Journal of Pharmacognosy*) 2020; 74(2): 89-97. Ichushi Web ID: 2021070100, ClinicalTrial Registration No: UMIN000030188, MOL, MOL-Lib

1. Objectives

To evaluate whether it is possible to determine the bioequivalence of kakkonto (葛根湯) extract granules and tablets with ephedrine and pseudoephedrine as markers.

2. Design

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

3. Setting

Single facility (clinic) specializing in clinical trials, Japan.

4. Participants

Healthy adult Japanese men aged between 20 and 44 years. Candidates with a drug allergy or a history of surgery or disease that may influence drug metabolism and excretion were excluded (n=20).

5. Intervention

Arm 1: Kakkonto (葛根湯) extract tablets (manufactured using the same extract lot as standard formulation TSUMURA Kakkonto (葛根湯) Extract Granules [medicinal use]), 8 tablets (containing 1.25 g kakkonto extract) in a single dose. Then 14 days later, TSUMURA kakkonto extract granules (medicinal use) (n=10).

Arm 2: TSUMURA Kakkonto Extract Granules (medicinal use), 1 sachet (containing 1.25 g kakkonto extract). Then 14 days later, kakkonto extract tablets (n=10).

6. Main outcome measures

Area under the plasma concentration time curve (AUC) and maximum plasma concentration (C_{max}) of ephedrine and pseudoephedrine up to 24 hours after administration. If the 90% confidence interval for the logarithmic difference between AUC and C_{max} for both formulations was in the range log (0.80) to log (1.25), they were evaluated as having bioequivalence.

7. Main results

There were no dropouts, the results for all 20 participants were analyzed.

The mean (90% confidence interval) differences in plasma concentrations of ephedrine and pseudoephedrine between the standard formulation and test formulation were 0.98 (0.94 – 1.03) and 0.99 (0.94 – 1.04), respectively, for AUC, and 0.84 (0.77 – 0.91) and 0.83 (0.76 – 0.91), respectively, for C_{max}, showing similar parameter values between formulations for both ingredients. The values for AUC fell within the criteria for bioequivalence for both ingredients, while those for C_{max} did not, and thus bioequivalence in terms of C_{max} was not shown.

8. Conclusions

Kakkonto (葛根湯) extract tablets and TSUMURA Kakkonto (葛根湯) Extract Granules (medicinal use) are not biologically equivalent. It is possible to evaluate equivalence between formulations with ephedrine and pseudoephedrine as markers.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Myalgia was observed in one participant administered the trial drugs, however, no causal relationship with the trial drugs existed (there is no mention of the intervention arm in which the case occurred). Clinical and physiological examinations found no clinically problematic change.

11. Abstractor's comments

This article, which reported on the evaluation of bioequivalence between different formulations of a Kampo medicine (kakkonto) through observation of the time-course of blood concentrations of its principal active components in humans, is meaningful from the perspective of manufacturing control and quality control. It is admirable that the authors presented highly reliable data by employing an RCT-crossover design for healthy people. The nature of Kampo medicines as combination medicines interferes with their specification establishment and efficacy evaluation. As this study offered a strategy for natural medicines evaluation that takes into consideration their characteristics despite the present difficulty in bioavailability evaluation, future development is awaited.

12. Abstractor and date

Kogure T. 22 Feb, 2022

21. Others

Reference

Horii C, Okonogi A, Takahashi R, et al. Studies on bioequivalence of Hachimijiogan decoction and its extract preparation. *Shoyakugaku Zasshi* (*The Japanese Journal of Pharmacognosy*) 2020; 74(1): 46-57. Ichushi Web ID: 2020210640, MOL, MOL-Lib

1. Objectives

To evaluate the equivalence and changes in plasma concentration of hachimijiogan (八味地黄丸) decoction and extract preparation (medicinal use) when administered to humans.

2. Design

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

3. Setting

Not mentioned (the authors belong to the Kampo Research Laboratories, Kracie Pharma, Ltd. and the National Institute of Health Sciences, Japan).

4. Participants

Six healthy males aged 20 to 65 who gave consent to participate in the trial.

5. Intervention

Arm 1: A single oral dose of Kracie Hachimijiogan (八味地黄丸) Extract Granules 6.0 g with 220 mL of water, then 2-week washout, followed by a single oral dose of 220 mL of hachimijiogan (八味地黄丸) decoction (n=3).

Arm 2: A single dose of 220 mL of hachimijiogan (八味地黄丸) decoction, then 2-week washout, followed by a single dose of Kracie Hachimijiogan (八味地黄丸) Extract Granules 6.0 g with 220 mL of water (n=3).

6. Main outcome measures

Plasma concentration changes and pharmacokinetic parameters of benzoylmesaconine, benzoylhypaconine, 14-anisoylaconine, alisol A, alisol A monoacetate, alisol B, alisol B monoacetate, loganin, morroniside, and paeoniflorin after administration.

7. Main results

Results for six participants were analyzed. The signal-to-noise (SN) ratio was insufficient for quantification of alisol B and alisol B monoacetate. A significant difference in plasma concentration between the decoction and the extract preparation was found for the plasma concentration of benzoylhypaconine at 240 minutes after administration ($P<0.01$), plasma concentration of alisol A monoacetate at 60 minutes after administration ($P<0.05$), and plasma concentration of loganin at 60 minutes after administration ($P<0.05$). A significant difference was found in the subject variable for the AUC of benzoylmesaconine ($P<0.05$). There was insufficient statistical power for the C_{max} and $AUC_{0\text{-}8}$ of the 8 components, excluding alisol B and alisol B monoacetate, it was found that the sufficient number of subjects to obtain statistical power for benzoylmesaconine and alisol A was at least 24 per arm and at least 25 per arm for 14-anisoylaconine while it was found that sufficient statistical power could not be obtained for the other components even with at least 61 subjects per arm.

8. Conclusions

Because alisol components are converted by metabolism, etc., alisol A cannot be used as a marker for determining equivalence. Accordingly, benzoylmesaconine and 14-anisoylaconine may be appropriate markers for this prescription.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Although in clinical practice, Kampo medicine is commonly prescribed based on the premise that the extract preparation and decoction of Kampo medicines are almost identical, this premise is in fact an assumption that needs to be validated. This research attempted to identify potential postdose markers for determining equivalence in humans for hachimijiogan extract, which is listed in the Japanese Pharmacopoeia, and each of its component crude medicines, by measuring the time-course of blood concentrations of potential marker compounds after hachimijiogan administration to humans. Although this information does not directly benefit clinical practice, it is notable that such markers are available.

12. Abstractor and date

Koike H. 22 Feb, 2022

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

References

Okada K, Kawai M, Hirono S, et al. Evaluation of the efficacy of daikenchuto (TJ-100) for the prevention of paralytic ileus after pancreaticoduodenectomy: a multicenter, double-blind, randomized, placebo-controlled trial. *Surgery* 2016; 159: 1333-41. CENTRAL ID: CN-01153778, Pubmed ID: 26747224, Clinical Trials Registry: UMIN000007975

Maeda H, Okada KI, Fujii T, et al. Transition of serum cytokines following pancreaticoduodenectomy: A subsidiary study of JAPAN-PD. *Oncol Lett* 2018; 16: 6847-53. CENTRAL ID: CN-01651625, Pubmed ID: 30333892, Clinical Trials Registry: UMIN000007975

Maeda H, Okada K, Fujii T, et al. No significant effect of daikenchuto (TJ-100) on peritoneal IL-9 and IFN-γ levels after pancreaticoduodenectomy. *Clin Exp Gastroenterol* 2020; 13: 461-6. CENTRAL ID: CN-02204519, Pubmed ID: 33116743, Clinical Trials Registry: UMIN000007975

1. Objectives

To assess the efficacy of daikenchuto (大建中湯) for prevention of paralytic ileus after pancreaticoduodenectomy.

2. Design

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

3. Setting

Nine hospitals, Japan.

4. Participants

Patients who underwent pancreaticoduodenectomy for periampullary tumor or tumor of the head of the pancreas (n=224).

5. Intervention

Arm 1: TSUMURA Daikenchuto (大建中湯) Extract Granules (5 g t.i.d. for 17 days taken orally as a solution) (n=112).

Arm 2: Placebo granules (5 g t.i.d. for 17 days taken orally as a solution) (n=112).

On the day of surgery and the first day after surgery (included in the abovementioned 17 days), the daikenchuto (大建中湯) or placebo was injected via tube retained in the duodenum.

6. Main outcome measures

Primary endpoints: Frequency of postoperative paralytic ileus lasting more than 72 hours after surgery, time to occurrence of postoperative paralytic ileus.

Secondary endpoints: QOL assessment (GSRS score), assessment of abdominal pain and distension (VAS), 27 serum cytokine values on the first day (POD1) and third day (POD3) after surgery, etc.

7. Main results

No significant differences were observed between arms for any of the primary or secondary endpoints. Of the 27 cytokines, POD3/POD1 ratios for IL-4, IL-9, IL-10, PFGF-BB, and TNF-α were significantly higher in the daikenchuto (大建中湯) arm compared to the placebo arm (P<0.05).

8. Conclusions

Daikenchuto (大建中湯) does not decrease the frequency of paralytic ileus after surgery.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

The rate of grade 3 or higher adverse events was 11.5% in the daikenchuto (大建中湯) arm and 7.8% in the placebo arm, however, most cases were diarrhea and abnormal clinical laboratory values (no significant difference test).

11. Abstractor's comments

This is a valuable study of the efficacy of daikenchuto (大建中湯) for the prevention of paralytic ileus in a limited population of pancreaticoduodenectomy (PD) patients in a double-blind RCT. It is a rigorous RCT that considered bias risk as far as possible. Although the number of cases was small, subgroup analysis of the 23 patients who underwent pylorus ring-preserving PD found that time to first flatus was shorter in the daikenchuto arm compared to the placebo arm (P=0.034). Furthermore, in the additional paper it was found that the POD3/POD1 ratios for a number of cytokines were significantly higher in the daikenchuto arm compared to the placebo arm, although they did not state the significance. The authors consider that complex factors are involved in post-operative course for PD patients, therefore this study did not set out the efficacy of daikenchuto that has thus far been reported in basic and clinical studies. In focusing on a patient group undergoing the surgical technique of PD and rigorously assessing it, the authors present major implications for the direction of future clinical research into Kampo in Japan.

12. Abstractor and date

Motoo Y, 18 May 2020, 14 February 2021, 8 February 2022

List of Excluded References (Appendix 2021)

Abbreviations: C, The Cochrane Library (CENTRAL); I, Igaku Chuo Zasshi (Japana Centra Revuo Medicana, Ichushi); N, Hand searching 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
B34.9	To evaluate the effect of kakkonto and shosaikotoka-kikyosekko in relieving symptoms and preventing the onset of severe infection in COVID-19 patients	kakkonto (葛根湯), shosaikotoka-kikyosekko (小柴胡湯加桔梗石膏)	Takayama S, Namiki N, Ito T, et al. A multi-center, randomized controlled trial by the Integrative Management in Japan for Epidemic Disease (IMJEDI study-RCT) on the use of Kampo medicine, kakkonto with shosaikotokakikyosekko, in mild-to-moderate COVID-19 patients for symptomatic relief and prevention of severe stage: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020; 21(1): 827.	5) Reference had only a protocol	C
B34.9	To evaluate the preventive effect of Kampo medicines on COVID-19 symptoms	hochuekkito (補中益気湯)	Namiki T, Takayama S, Arita R, et al. A structured summary of a study protocol for a multi-center, randomized controlled trial (RCT) of COVID-19 prevention with Kampo medicines (Integrative Management in Japan for Epidemic Disease by prophylactic study: IMJEDI P1 study). *Trials* 2021; 22(1): 23.	5) Reference had only a protocol	C
C15.9 R19.8	To evaluate the efficacy and safety of bukuryoingo-hangekobokuto as treatment for anxiety and postoperative water brash in esophageal cancer patients	bukuryoingo-hangekobokuto (茯苓飲合半夏厚朴湯)	Arita R, Takayama S, Okamoto H, et al. Exploratory study of clinical effectiveness and safety of TJ-116 bukuryoingohangekobokuto for anxiety and postoperative water brash in esophageal cancer patients (TJ116E). *Medicine* 2020; 99(22): e20317.	5) Reference had only a protocol	C

ICD-10	Research Question	Kampo Formula	References	Reason for exclusion	Source
C80.0	To evaluate the efficacy of ginseng-containing Chinese medicine as treatment for anthracycline-induced cardiotoxicity	ginseng-containing Chinese medicines (朝鮮人参含有漢方薬)	Li Jiali, Takagi C, Okamoto C, Efficacy of Ginseng-Content Chinese Medicine for Anthracycline-Induced Cardiotoxicity (A Meta-Analysis Compatible with PRISMA). *Ōyō yakuri* (*Pharmacometrics*) 2019; 97(3/4): 67-73.	2)	I
G30.9	To evaluate the efficacy and safety of hachimijiogan as treatment for mild Alzheimer disease	hachimijiogan (八味地黄丸)	Kainuma M, Funakoshi K, Ouma S, et al. The efficacy and safety of hachimijiogan for mild Alzheimer disease in an exploratory, open standard treatment controlled, randomized allocation, multicenter trial: A study protocol. *Medicine* 2020; 99(38): e22370.	5) Reference had only a protocol	C
G47.0	To evaluate the effect of saikokaryukotsu-boreito as treatment for insomnia disorder with hypertension	saikokaryukotsu-boreito (柴胡加竜骨牡蛎湯)	Boram Lee, Yeong-Eun Jeong, Hyo-Ju Park, et al. Effects of Sihogayonggolmoryeo-tang (Saikokaryukotsuboreito or Chai-Hu-Jia-Long-Gu-Mu-Li-Tang) for insomnia disorder with prehypertension or stage 1 hypertension: A study protocol for a randomized controlled trial. *Medicine* 2020; 99(29): e20980.	5) Reference had only a protocol	C
J10.1	To compare gingyogedokusan versus oseltamivir as treatment for influenza	gingyogedokusan (銀翹解毒散)	Iwata K, Nishimoto T, Higasa K, et al. Gingyogedokusan versus oseltamivir for the treatment of influenza: Bayesian inference using the Markov chain Monte Carlo method with prior pilot study data. *Traditional & Kampo Medicine* 2019; 6(3): 134-8.	2)	I
K14.6	To evaluate the effect of goreisan as treatment for pain in glossodynia	goreisan (五苓散)	Ayuse T, Okayasu I, Tachi-Yoshida M, et al. Examination of pain relief effect of Goreisan for glossodynia. *Medicine* 2020; 99(33): e21536.	5) Reference had only a protocol	C
R68.8	To evaluate the effect of coix-seed reactive derivatives on the cold sensitivity of female hands and feet	coix-seed reactive derivatives (ハトムギ全粒熱水抽出エキス)	Suzuki N, Kyo H, Okuwa-Hayashi H, et al. Effect of Coix-seed Reactive Derivatives (CRD) on Cold Sensitivity of Female Hands and Feet: A Randomized Controlled Trial. *Nihon Hokan Daitai Iryo Gakkaishi* (*Japanese Journal of Complementary and Alternative Medicine*) 2020; 17(1): 33-6. (in Japanese with English abstract)	2)	I