

Original Article

Clinical efficacy of Daikenchuto for gastrointestinal dysfunction following colon surgery: a randomized, double-blind, multicenter, placebo-controlled study (JFMC39-0902)

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Abstract

Objective: This exploratory trial was performed to determine whether Daikenchuto accelerates recovery of gastrointestinal function in patients undergoing open colectomy for colon cancer.

Methods: A total of 386 patients undergoing colectomy at 1 of the 51 clinical trial sites in Japan from January 2009 to June 2011 were registered for the study (JFMC39-0902). Patients received either placebo or Daikenchuto (15.0 g/day, t.i.d) between post-operative day 2 and post-operative day 8. Primary end-points included time to first bowel movement, frequency of bowel movement and stool form. The incidence of intestinal obstruction was evaluated post-operatively. The safety profile of Daikenchuto until post-operative day 8 was also evaluated.

Results: The results for 336 patients (Daikenchuto, $n = 174$; placebo, $n = 162$) were available for statistical analysis. The time to first bowel movement did not differ significantly between the two groups. All patients reported having diarrhea or soft stools immediately after surgery, and the time until stool normalization (50th percentile) in the Daikenchuto and placebo groups was 6 days and 7 days, respectively. The placebo group had a significantly greater number of hard stools at post-operative day 8 ($P = 0.016$), and bowel movement frequency continued to increase until post-operative day 8 as well. In contrast, bowel movement frequency in the Daikenchuto group increased until post-operative day 6, however decreased from post-operative day 7 and was significantly lower at post-operative day 8 compared with the placebo group ($P = 0.024$).

Conclusion: The moderate effects of Daikenchuto were observed ~1 week after the operation. Although Daikenchuto had an effect on gastrointestinal function after open surgery in patients with colon cancer, this study did not show its clinical benefits adequately.

Key words: Daikenchuto, bowel movement, colon cancer, herbal medicine

Introduction

Post-operative ileus (POI) is an uncomplicated ileus that occurs after major abdominal surgery, often considered inevitable, resolving spontaneously within 2–3 days (1). Paralytic POI, defined as POI lasting for longer than 3 days (2), aggravates nutritional conditions and post-operative morbidity. POI can last for a long time despite the use of the enhanced recovery after surgery (ERAS) protocol that is supposed to stimulate and enhance gut motility (3).

Daikenchuto (DKT) is the most frequently prescribed herbal medicine in Japan. It consists of a powder extracted from dried Sichuan pepper, processed ginger, ginseng and maltose and has been used for the treatment of paralytic ileus and radiation-induced enteritis because of the possibly of its prokinetic effect (4–6). Kampo extract formulations meet with strict specifications for coverage under the Japanese National Health Insurance plan, which are comparable with their western counterparts regarding quality and therapeutic effects. Moreover, DKT has been approved as an investigational drug by the US Food and Drug Administration (7), and several placebo-controlled double-blind trials have been completed in the USA to investigate its efficacy in cases of constipation, irritable bowel syndrome and Crohn's disease.

In animal experiments, intraduodenal and intrajejunal administration of DKT (a modern herbal product of DKT manufactured in the granule form) dose dependently increased the motility of the duodenum, proximal jejunum and distal jejunum in conscious dogs (8). *In vivo* and *in vitro* experiments have shown that the prokinetic effect of DKT after intestinal dysmotility, induced laparoscopically or chemically, was inhibited by atropine or a 5-HT₄ antagonist, suggesting that DKT modulates cholinergic and serotonergic mechanisms (9–11). DKT also stimulated acetylcholine release in porcine ileal smooth muscle (12). In healthy adult humans, DKT appears to be safe and well tolerated, demonstrating prokinetic effects on ascending colon emptying (13).

A recent multicenter, placebo-controlled study of 209 patients (DKT, *n* = 108; placebo, *n* = 101) undergoing hepatectomy (7) suggested that DKT accelerated the time to first bowel movement (BM), significantly compared with placebo [Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) 40-1001].

Here we performed a study to determine whether DKT accelerates recovery of gastrointestinal (GI) function in patients undergoing open colectomy for colon cancer as a multicenter, Phase III trial in Japan.

Patients and methods

Data management

This trial was conducted in accordance with the World Medical Association Declaration of Helsinki. The protocol was approved by the institutional review board of each participating hospital, and the study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 00001592). Written informed consent was obtained from all patients before study enrollment.

All members of the steering committee designed the study protocol. Eligibility criteria checking report forms were sent to the JFMC 39-0902 data center. Patients were allocated randomly and registered into two arms. Collection of data was performed by the JFMC 39-0902 data center.

The data were analyzed by an independent data and safety monitoring committee. All academic members of the steering committee confirmed the validity and completeness of the data and analyses. All authors reviewed and approved the final version of the manuscript before submission.

Patient selection

Subjects were considered eligible for the study if they met the following criteria: (i) qualified for curative colonic open resection for colon cancer (including cancer of the rectosigmoid) that had been diagnosed pre-operatively according to the disease staging (I, II, IIIa, IIIb, TNM category distribution: T = 1–3, N = 0–2, M = 0); (ii) diagnosed with a performance status (PS) of 0–1; (iii) able to tolerate oral administration of DKT; (iv) aged 20 years or older; (v) man or woman; (vi) able to stay in hospital during the entire length of study period; and (vii) able to provide written informed consent.

The following subjects were excluded from the study: (i) those scheduled for endoscopic or laparoscopic surgery; (ii) those having complicated inflammatory bowel disease (ulcerative colitis and Crohn's disease); (iii) those requiring emergency surgery; (iv) those diagnosed with double cancer, serious liver disorder or serious renal disorder; (v) those with a history of laparotomy and peritonitis (excluding surgery for appendicitis); (vi) those taking other Kampo medicines; (vii) those who were pregnant, possibly pregnant, lactating or considering pregnancy; and (viii) those unfit for the study as determined by the attending physician.

Study design and treatment

This multicenter, placebo-controlled, double-blind, randomized, exploratory trial on the effect of DKT in patients undergoing colectomy for colon cancer was conducted at 51 institutions in Japan. DKT and a matching placebo were manufactured by Tsumura & Co. (Tokyo, Japan). Patients who met all the eligibility criteria were randomly allocated to receive either oral doses of 15 g/day (5 g t.i.d) of DKT or placebo from post-operative day (POD) 2 to POD8.

The primary efficacy end-points included the time from the end of surgery (tracheal tube extubation) until first BM, frequency of BM per day and change in the Bristol Stool Scale (BSS) scores after surgery. The secondary efficacy end-points were evaluation of quality of life (QOL) according to the Gastrointestinal Symptom Rating Scale (GSRS, Japanese version) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scale, serum C-reactive protein (CRP) levels and the incidence of intestinal obstruction. Adverse events (AEs) were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0).

Statistical analysis

We determined the difference between the DKT group and placebo group in terms of the time from tracheal tube removal until first BM. We assumed the mean time from extubation until first BM in the placebo group to be 3.5 ± 3.3 days and that DKT would shorten this time by 1 day (30%). Based on these assumptions, we required 200 patients per group (400 patients in total) to provide 81% power to detect a difference at the 5% level of significance in a two-sided test. To meet with any possible dropouts and the considerable

uncertainty in the assumption for sample size calculation, the sample size was set to 200 patients per treatment arm (400 patients in total).

Primary efficacy analyses were performed using the per-protocol population that included patients who met the protocol-specified criteria and had at least one on-treatment primary efficacy evaluation (BM, frequency of BM per day and BSS scores).

Baseline characteristics were compared between the two groups using the χ^2 test, Wilcoxon's rank-sum test or Fisher's exact test. The time from end of surgery until first BM was analyzed using the Cox proportional hazard model. BM frequency and changes in BSS scores were analyzed using Wilcoxon's rank-sum test. Serum CRP levels were compared between the two groups using the *t*-test. The incidence of intestinal obstruction was compared between the two groups using Fisher's exact test. Subset analysis regarding the frequency of hard stool voidance between the 2 groups was compared using the unpaired *t*-test. If an event did not occur during the study observation period (maximum 8 days post-operatively), the patient was assigned a censored time for the event. Differences in the frequency of AEs between the two groups were assessed with Fisher's exact test.

Calculated parameters were presented as means \pm standard deviations (SDs). Probability (*P*) values of <0.05 were considered to indicate statistical significance. All statistical analysis was performed using the SAS Release 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 386 patients scheduled to undergo colectomy for colon cancer at 51 Japanese hospital centers from January 2009 to June 2011 were enrolled in the study. Patients were randomly assigned to the DKT group or the placebo group. After randomization, 32 patients were considered ineligible for the study because of the following

reasons: 8 set up stoma; 7 had stage IV cancer; 5 had a history of laparotomy; 4 had complications, including ileus or hepatic disease; 3 were not diagnosed with colon cancer; 1 underwent laparoscopic surgery; 1 declined informed consent; 1 was diagnosed with double cancer; and 2 were dismissed for other reasons. Furthermore, 18 patients were not treated for the following reasons: 7 could not be treated because of their circumstances, 5 suffered complications, 2 were intolerant to drug administration, 2 refused drug administration, 1 declined treatment after initiation of the study and 1 could not receive treatment because of his conditions. As a result, data on 336 patients (DKT group, $n = 174$; placebo group, $n = 162$) were included and evaluated in statistical analysis (Fig. 1).

No significant difference was observed between the two groups in terms of baseline characteristics (clinical factors, surgical factors and pathological factors), as given in Table 1.

Primary end-points

The time of first BM in both groups was compared using the Cox proportional hazards model and no significant difference was observed between the two groups (Fig. 2).

Post-operative change in BSS scores

On POD2, the mean BSS scores for the DKT and placebo groups indicated soft stools for both groups (6.68 and 6.17, respectively) (Fig. 3). The mean BSS scores for the DKT and placebo groups changed on POD8 to 4.81 and 4.89, respectively, indicating a change in stool form from soft to moderately hard. There was no significant difference in stool forms between the two groups during POD2 to POD8.

Post-operative BM frequency

The average number of BMs for the DKT and placebo groups on POD2 was 0.8 and 0.6, respectively (Fig. 4). The number of BMs

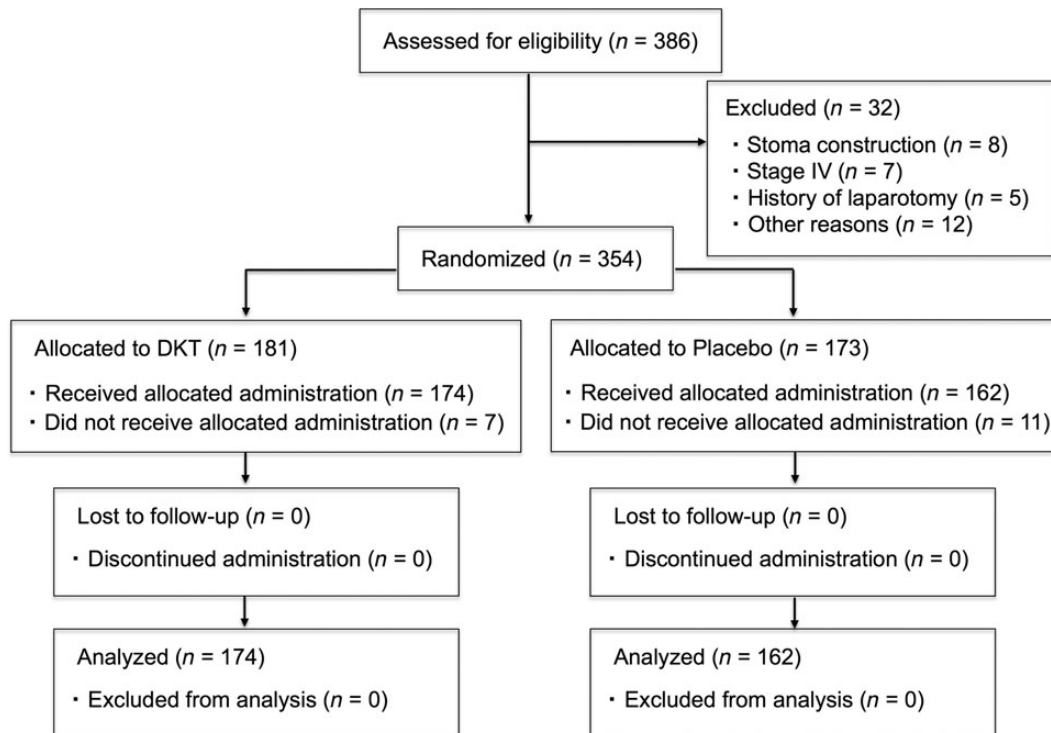


Figure 1. Flow diagram showing study design.

Table 1. Patient characteristics (clinical, surgical and pathological factors)

	DKT (n = 174)	Placebo (n = 162)	P value
Gender			
Male	98	99	0.378
Female	76	63	
Age (years)	68 (28–88)	69 (35–91)	0.238
Height (cm)	159.04 ± 8.76	159.39 ± 9.34	0.716
Body weight (kg)	57.52 ± 11.34	56.90 ± 11.37	0.658
Performance status (ECOG)			
0	158	147	1.000
1	16	15	
Past history			
(–)	120	100	0.170
(+)	54	62	
Bowel preparation			
(+)	150	140	1.000
(–)	24	22	
Anesthetic time (h)	3.95 ± 1.07	4.06 ± 1.21	0.473
Epidural anesthesia			
(+)	150	139	1.000
(–)	2	2	
N/A	22	21	
Operative time (h)	2.91 ± 0.89	3.00 ± 1.00	0.446
Estimated blood loss (ml)	202.5 ± 226.9	222.9 ± 265.5	0.774
Type of operation			
Ileocecal resection	13	11	0.064
Right hemicolectomy	41	34	
Left hemicolectomy	12	8	
Sigmoidectomy	36	15	
Anterior resection	58	37	
Partial resection	10	13	
Adhesion preventive sheet			
(+)	90	81	0.827
(–)	84	81	
Tumor size (mm)	54.9 ± 21.5	52.3 ± 22.4	0.098
T			
T1	3	10	0.218
T2	10	13	
T3	153	130	
T4	8	7	
N			
N0	86	83	0.820
N1	63	55	
N2	17	19	
N3	8	5	
M			
M0	173	161	1.000
M1	1	1	
Curability			
R0	170	157	0.918
R1	3	3	
R2	1	1	

DKT, Daikenchuto; N/A: not applicable.

for the DKT group on POD6 increased to 2.2, decreasing however to 1.9 on POD8. In the placebo group, the number of BMs increased up to 2.4 on POD8. The frequency of BM in the DKT group at POD8 was significantly lower than that in the placebo group (Wilcoxon’s rank-sum test, $P = 0.024$).

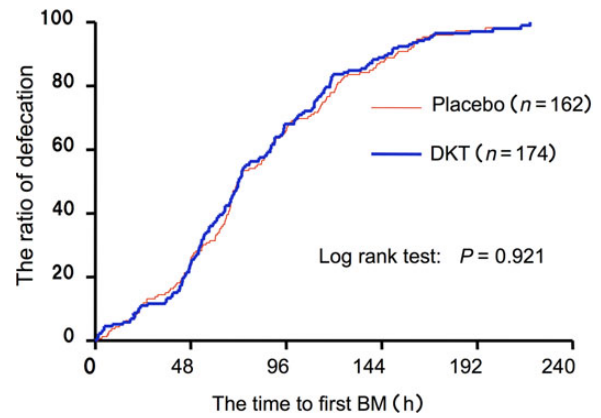


Figure 2. Time to first bowel movement (BM) after endotracheal tube removal.

Subset analysis

The day when the stools of at least 50% of the study individuals in each of the two groups could be scored as 3, 4 or 5 on the BSS after surgery was compared between the two groups. The DKT group reached the 50th percentile on POD6, whereas the placebo group reached the 50th percentile only on POD7, indicating that stool normalization occurred 1 day earlier in the DKT group (Fig. 5).

BSS scores 1 and 2 indicated hard stool, whereas scores 6 and 7 indicated soft stool. Using this classification, the frequency of BM between POD2 and POD8 for each stool form was compared for the two groups. The frequency of BM for hard stools on POD8 was significantly higher in the placebo group than in the DKT group (unpaired *t*-test, $P = 0.016$) (Fig. 6).

Secondary end-points

The mean serum CRP levels on POD 1 and POD 3 were 7.8 and 9.0 mg/dl, respectively, in the placebo group and 7.5 and 8.0 mg/dl, respectively, in the DKT group. The rate of increase of mean serum CRP levels in the placebo group tended to be steeper than that in DKT group without reaching statistical significance ($P = 0.133$). The incidence of intestinal obstruction over the 1- and 3-year post-operative periods was 7.5 and 11.5%, respectively, in the DKT group and 9.9 and 15.4%, respectively, in the placebo group, showing non-significant differences.

Furthermore, there was no significant difference in the evaluation of QOL by the GSRS (Japanese version) and FACT-C scale.

Safety assessment

AEs were classified according to the CTCAE (version 3.0). In each group, 7 patients had AEs over Grade 3, although there was no difference in the frequency rate between the two groups (Table 2). Grade 4 AEs were not identified in any of the two groups.

Discussion

DKT is the most widely prescribed Kampo medicine in Japan and is used mainly for prophylactic and therapeutic measures in patients with post-operative ileus (4,5). In order to clarify the clinical benefits of DKT, a large-scale randomized control trial was performed.

In the present study, the time of the first BM after colon surgery did not differ significantly between the DKT and placebo groups, although

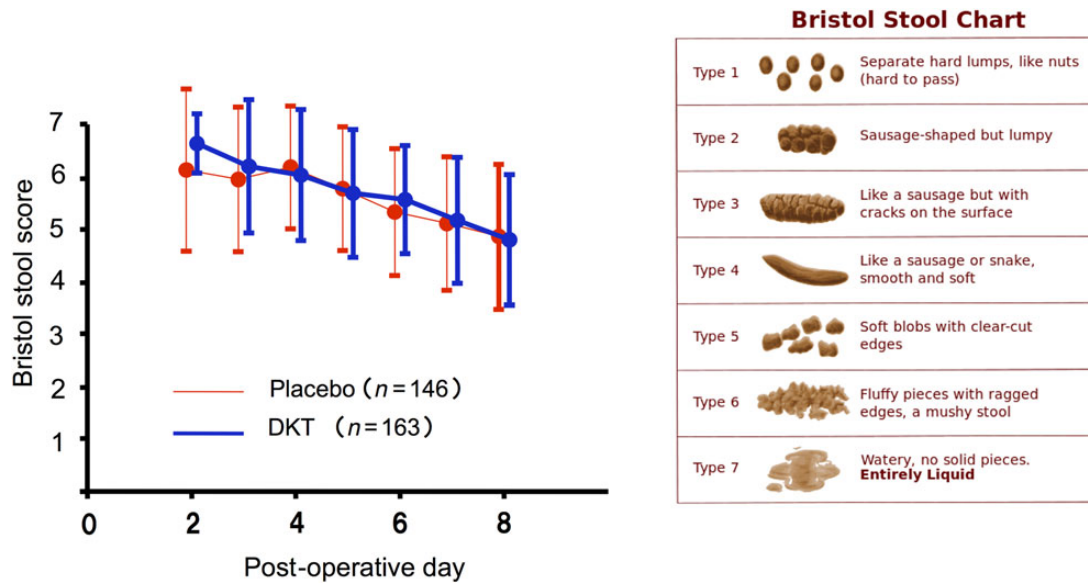


Figure 3. Changes in Bristol stool scale (BSS) scores over time post-operatively.

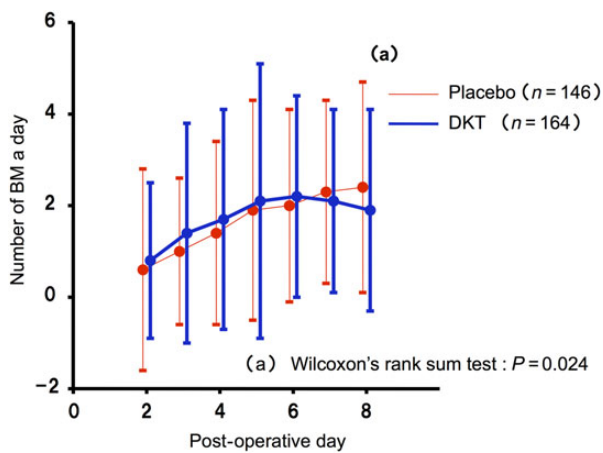


Figure 4. Changes in the frequency of bowel movement (BM) over time post-operatively.

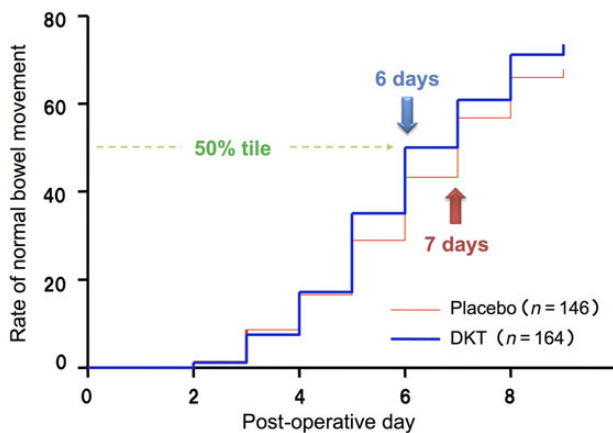


Figure 5. Time to normalization of stool evacuation post-operatively (BSS score 3-5).

Shimada et al. (7) demonstrated that DKT administration accelerated the time of first BM after hepatic resection in patients with liver cancer (JFMC40-1001 study). Major differences between the two studies regarding surgical procedures could be the degree of bowel manipulation and requirement for restoring bowel continuity. DKT may have offered its advantages in accelerating BM more markedly in the JFMC40-1001 study than in the present study presumably because of the difference in the surgical stress derived from bowel manipulation. Based on a randomized control trial, Yoshikawa et al. (14) reported that post-operative DKT administration significantly shortened the time until first flatus following laparoscopic colorectal resection. Results of the present study indicate that DKT may fail to prove effective under the considerable surgical manipulation characterizing open colon surgery. Furthermore, Manabe et al. (13) demonstrated in a randomized, double-blind, placebo-controlled study that DKT administration significantly accelerated colonic transit validated by scintigraphy in healthy human volunteers. Based on the above results, laparotomy, intestinal manipulation and exposure to air may cause deterioration of gastrointestinal motility to a greater extent than expected. Further considerations are required for future clinical studies with respect to the dose and method of DKT administration in open colon surgery.

DKT administration may have had a profound impact on first BM after surgery. In the JFMC40-1001 study, DKT was administered more intensively from 3 days before surgery to POD 10. The main reason why the JFMC40-1001 study opted for perioperative DKT administration was that DKT increases portal blood flow, which affects liver regeneration through increased intensity of wall shear stress without any significant change in blood pressure or heart rate in healthy individuals, cirrhotic patients and post-liver transplant patients as reported by Ogasawara et al. (15). Several clinical studies, including the present trial and animal experiments, have been performed using post-operative DKT administration. For example, Suehiro et al. (16) reported that DKT administration improves bowel motility and shortens hospital stay after colorectal surgery. In addition, Fukuda et al. (17) reported that DKT administration accelerates delayed gastrointestinal transit induced by bowel manipulation in rats. Various effects of

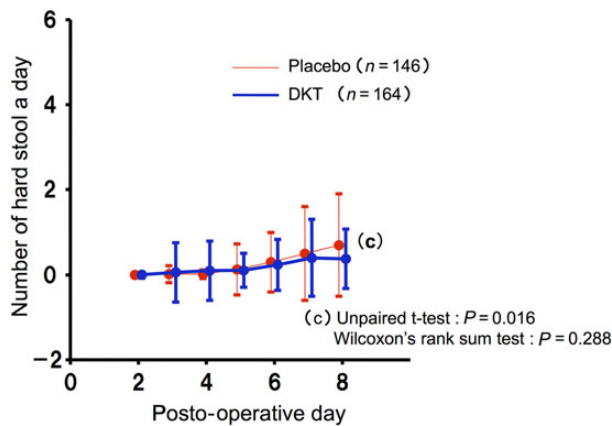


Figure 6. Frequency of hard stools (BSS score 1–2) per day post-operatively.

Table 2. Incidence of adverse events

Grade 3			
Placebo			
Diarrhea	(4)	4.3%	NS
Atelectasis	(1)		
Pneumonitis	(1)		
Pleural effusion	(1)		
DKT			
Diarrhea	(5)	4.0%	
Vomiting	(1)		
Abdominal pain	(1)		

NS, not significant.

DKT administration have been stipulated in previous reports, such as promotion of acetylcholine secretion by stimulation of the smooth muscle (18) and increased plasma levels of calcitonin gene-related peptide (CGRP) (19,20), motilin (21,22) and VIP (23). Recent studies on the pharmacokinetics of DKT (24,25) have revealed that the agents inducing the above reactions had rapidly been absorbed. Several common characteristics of Kampo medicine affecting multiple targets by multiple ingredients have been elucidated (26). However, no clinical study has been implemented that directly had compared bowel motility between the post-operative and perioperative administration of DKT. Therefore, it is evident that the method of administration cannot be adequately discussed here, and this issue needs to be addressed in the future.

As observed in the present study, the frequency of BM in the DKT group at POD8 was significantly lower than that in the placebo group, indicating that DKT not only accelerates bowel motility but also regulates its function. Moreover, DKT normalized BSS scores (3–5) a day earlier than placebo in the subset analysis. DKT may be effective in reducing the duration of hospitalization and eventually saving costs. The bowel regulations observed by DKT administration were presumably primarily attributable to improvement of bowel blood flow, leading to amelioration of water absorption and minimization of mucosal damage. Kono et al. (19) demonstrated that DKT increased colonic vascular conductance, which was mainly mediated by CGRP and its receptor components. Second, bowel regulations could be attributed to the effect of adrenomedullin (ADM) (27). DKT was recently reported to alleviate microvascular dysfunction by upregulating endogenous ADM in a rat model of Crohn's disease (28).

The rate of increase of mean serum CRP levels in the placebo group tended to be steeper than that in the DKT group in the study, even if it

did not differ significantly between the groups. One of the various effects of DKT is the anti-inflammatory effect caused by the release of ADM and suppression of prostaglandin E2 (PGE2) (29). DKT contains processed ginger, which is also found in Hangeshashinto (a Kampo medicine) and which reduces the production of PGE2 in the treatment of chemotherapy-induced oral mucositis (29). Hayakawa et al. (30) reported that DKT inhibited COX-2 activity in rats and mice. Yoshikawa et al. (31) provided the first evidence that DKT has the potential to prevent bacterial translocation through suppression of inflammatory cytokines such as interferon- γ , maintaining the integrity of intestinal epithelium in a fasted and anti-tumor agent-treated rat model. We assume that these anti-inflammatory effects may promote the recovery of bowel function after surgery.

Although the incidence of bowel obstruction in the DKT group tended to be lower than that in the placebo group, it did not differ significantly either 1 year or 3 years after surgery. DKT appears to be safe and well tolerated, with no evidence of increased morbidity.

Conclusion

The moderate effects of DKT were observed ~1 week after the operation at the time of considering the hospital discharge. The efficacy of DKT administration after open surgery in patients with colon cancer was limited despite maintaining a good safety and tolerance profile. Although DKT had an effect on post-operative gastrointestinal function, this study did not show its clinical benefits adequately.

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Conflict of interest statement

None declared.

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Appendix

The members of the multicenter, Phase III trial (JFMC39-0902) group were as follows:

Steering Committee: Masahiko Watanabe, Junichi Sakamoto, Toru Kono, Hiroto Hasegawa, Satoshi Morita, Yoshiyuki Furukawa and Yoshihiro Imazu.

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Independent Data and Safety Monitoring Committee: Hiromi Sarashina, Yasutsuna Sasaki and Chikuma Hamada.

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