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Effects of Daikenchuto, a Traditional Japanese Herbal Medicine, after Laparoscopic Sacrocolpopexy for Pelvic Organ Prolapse: A Randomized, Single-Center, Open-Label Trial

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Abstract

Background: This study evaluated the efficacy and safety of Daikenchuto (DKT) for Japanese female patients who required Laparoscopic Sacrocolpopexy (LSC) for symptomatic pelvic organ prolapse.

Methods: This prospective, 1-week, two-arm, parallel-group, open-label, single-center randomized trial was conducted between June 2020 and February 2024. The primary endpoint was the time from surgery completion to the first bowel movement. Secondary endpoints were the time from surgery completion to the first flatus, time from surgery completion to solid food toleration, dissatisfaction attributable to constipation, distension, and changes in serum white blood cell counts and C-reactive protein levels.

Results: The time from surgery completion to the first bowel movement of the DKT group (mean, 58.4 h; Standard Error [SE], ± 2.84 h) and that of the control group (66.1 h; SE, ± 2.63 h) were statistically significant (P=0.047). The change in the visual analog scale score for dissatisfaction attributable to constipation of the DKT group (estimated difference, –5.59; SE, ± 2.66; 95% Confidence Interval [CI], 19.5-26.8) and that of the control group (95% CI, 25.0-32.5) were statistically significant (P=0.037). Adverse events attributable to DKT were not observed.

Conclusion: DKT accelerated the onset of intestinal movement and reduced dissatisfaction attributable to constipation.

Keywords: Daikenchuto; Minimally invasive sacrocolpopexy; Bowel movement

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Introduction

Pelvic Organ Prolapse (POP) is characterized by protrusion of the anterior vaginal wall, posterior vaginal wall, uterus, or vaginal apex into the vagina; this descent can involve one or more structures [1]. Laparoscopic surgery offers the benefits of open surgery without a large abdominal incision, abdominal packing, and extensive bowel manipulation, thereby potentially leading to reduced postoperative pain, faster recovery, and a lower risk of bowel obstruction [2]. Sacrocolpopexy is widely acknowledged as the optimal therapeutic approach for managing post-hysterectomy vaginal vault prolapse [3]. Sacrocolpopexy targets apical compartment prolapse encompassing the descent of the uterine vault and vaginal vault and addresses multicompartment pelvic organ prolapse [4,5]. Constipation is a prevalent issue that significantly impacts the quality of life [6]. Furthermore, the prevalence of constipation is higher among women that it is among men [7]. Postoperative restoration of bowel function is a primary concern of women who require pelvic floor reconstruction surgery and their healthcare providers [8]. Typically, the initial Bowel Movement (BM) after surgery may not occur for 2 days, resulting in constipation, discomfort, and abdominal pain [9]. Factors such as preoperative bowel preparation, the persisting effects of anesthesia, opioid use for pain, surgical procedures, and postoperative immobility commonly contribute to constipation in this patient population [7]. Daikenchuto (DKT) extract powder (Tsumura & Co., Tokyo, Japan), which comprises aqueous extracts of Japanese pepper (2.2%), processed ginger (5.6%), ginseng

radix (3.3%), and maltose syrup powder sourced from rice (88.9%) [10], has been used to treat long-term gastrointestinal issues because it provides relief from symptoms such as abdominal pain, bloating, Crohn's disease, irritable bowel syndrome, adhesive ileus, and paralytic ileus [11]. Perioperative administration of DKT accelerates gastrointestinal motility [12-15]. During a study of colon cancer, the first postoperative BM of patients who used DKT after laparoscopic colectomy occurred 17 h earlier than that of patients who did not use DKT [16]. Standardized pharmacological therapies that can alleviate constipation after benign gynecological and urogynecological surgeries are limited [17]. Additionally, adverse effects associated with DKT administration have not been reported. This randomized controlled trial compared the effects of the use of DKT (7.5 g/day) for 7 days with those of the use of MIYA-BM fine granules (3.0 g/day, control treatment; Miyarisan Pharmaceutical Co., Ltd., Tokyo, Japan), which is a viable bacterial preparation, assessed the time to the first BM after Laparoscopic Sacrocolpopexy (LSC), and determined whether DKT could reduce the time to the first postoperative BM.

Materials and Methods

Design

This prospective trial included patients with symptomatic POP who underwent LSC at a single clinic between June 2020 and February 2024. A randomized, open-label, parallel-group trial (Registration number: UMIN000040129) was performed to compare the safety and efficacy of DKT with those of MIYA-BM (control treatment). The total study duration was 7 days. This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of our institute (2020-026). Written informed consent was obtained from all participants.

Participants

One of the treating physicians (H.S.) invited patients to participate in this study between June 2020 and February 2024. The inclusion criteria were age 18 years or older, preoperative Pelvic Organ Prolapse Quantification (POP-Q) stage II or worse [18], and symptomatic apical or multicompartmental prolapse. The exclusion criteria were as follows: History of ulcerative colitis or Crohn's disease; presence of heart disease, kidney disease, or liver disease that could affect postoperative management; history of brain disease accompanied by paralysis; current use of other traditional Oriental medicines or laxatives; contraindications for DKT use; the potential for alterations of the surgical procedure (*e.g.*, change to laparotomy); and ineligibility for this study as determined by the attending physicians.

Randomization

Patients were randomly allocated to the DKT and control groups using a 1:1 ratio. Permuted block randomization, which was performed by an independent investigator who was not involved in the actual treatment, was performed to generate a random number sequence using computer software (R; R Foundation for Statistical Computing, Vienna, Austria), resulting in a block size of four. The investigators and patients were not blinded to the group allocations.

Procedure

During the study period, medications that could potentially affect gastrointestinal motility and function, such as prokinetics and parasympathetic nerve blockers, were prohibited. Additionally, all patients used sennoside (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan) the day before surgery. Patients were randomized to receive either oral DKT (7.5 g) or the control treatment (3.0 g) three times per day from the morning of the day after surgery until discharge. During this 7-day study, observations were performed at baseline (before treatment) and on Postoperative Days (PODs) 1, 3, and 7.

Surgery

All surgeries were conducted by a urologist (H.S.) who was trained in accordance with our operative procedures [19]. Decisions regarding whether to proceed with laparoscopic sacrohysteropexy or laparoscopic supracervical hysterectomy/LSC were based on preoperative consultations with the patients. After thorough counselling regarding the benefits and risks of each procedure, their preferences became pivotal in the decision-making process. Laparoscopic sacrohysteropexy has been suggested for patients with a strong preference for preserving the uterus and those without benign or malignant uterine lesions. The vaginal wall was dissected anterior to the bladder trigone and posterior to the levator ani muscle. Two separate sheets of polypropylene mesh were attached to the anterior and posterior vaginal walls using permanent sutures. The sacral arm of the mesh was attached to the anterior longitudinal ligament of S1-S2 using permanent sutures. For patients who underwent laparoscopic sacrohysteropexy, the right broad ligament was opened and passed through the cephalic anterior mesh. The anterior and posterior mesh pieces were sutured bilaterally to the uterine cervix using permanent sutures. In contrast, laparoscopic supracervical hysterectomy/LSC was performed using the standard method. The peritoneum was sutured over the mesh using absorbable sutures. Prophylactic antibiotics were administered within 60 min before the surgical incision was performed.

Outcomes

The primary endpoint was the time from surgery completion (tracheal tube extubation) to the first postoperative BM. The secondary endpoints were time from surgery completion (tracheal tube extubation) until the first postoperative flatus, time from surgery completion to solid food toleration, Visual Analog Scale (VAS) scores (0-100; 0 = none) for dissatisfaction attributable to constipation, distension, and changes in the serum White Blood Cell (WBC) count and C-Reactive Protein (CRP) level. Adverse events were monitored throughout the perioperative period to determine the safety and side effects of DKT.

Sample size

Sample sizes of 120 and 114 patients in the DKT and control groups, respectively, resulted in a post hoc power of 47.6% to detect differences during a mean of 7.7 h assuming a common standard deviation of 31 based on a type 1 error rate of 5%. A safety analysis of patients in the safety analysis set and an efficacy analysis of the Full Analysis Set (FAS) were performed. The safety analysis set comprised randomized patients who received one dose of the study drug and underwent safety measurements. The FAS included patients in the safety analysis set who underwent at least one efficacy measurement after the initial treatment.

Statistical analysis

To examine the primary endpoint, the effect of medication on BMs was estimated using Student's *t* test. The treatment effect was captured by the 95% Confidence Interval (CI). To allow a more appropriate estimate of the effects of DKT, we performed a Linear Mixed Model (LMM) analysis to estimate the Least Squares (LS) means of the continuous endpoints. The model included the treatment day, POD 1, POD 3, POD 7 (categorical), and baseline values as fixed

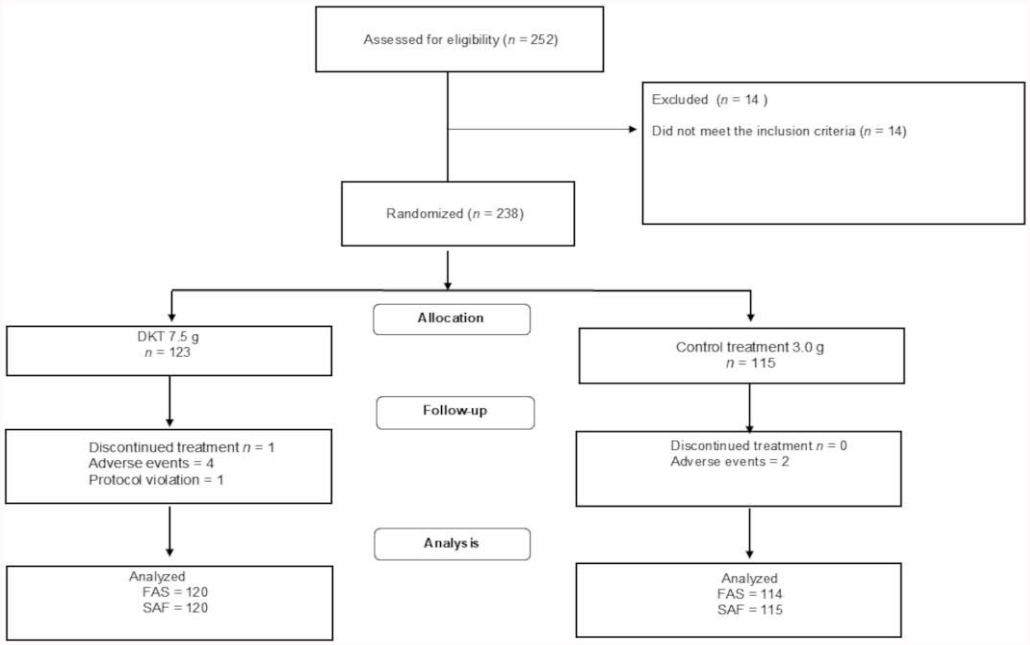

Figure 1: Patient characteristics. FAS: Full Analysis Set; SAF: Safety Analysis Set.

effects. The patient identification number was a random effect used to account for repeated measurements. Imputation of missing data was not applied. Similarly, we performed an LMM analysis of the other secondary endpoints (dissatisfaction attributable to constipation, distension, WBC count, CRP level) and estimated the treatment effects. Additionally, we recorded the 95% CIs, LS means, and Standard Errors (SEs).

All tests were two-sided, and significance was set at P<0.05. All statistical analyses were performed using R (R Foundation for Statistical Computing) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). We performed a sensitivity analysis of the primary endpoint using the Mann-Whitney U test. We also performed a subgroup analysis of age (75 years or older or younger than 75 years), Body Mass Index (BMI; ≥ 30 or <30), and diabetes (yes or no).

Results

A total of 238 patients were randomized to two treatment groups (DKT group: 7.5 g, n=123; control group: 3.0 g, n=115). Four of the 238 patients withdrew from the study during the treatment period (DKT group: n=3; control group: n=1) (Figure 1). The demographic and baseline characteristics of the FAS (n=234) of the two treatment groups were similar (Table 1). Regarding the primary endpoint, the time from surgery completion to the first postoperative BM of the DKT group and that of the control group were statistically significant (mean, 58.4 h; Standard Error [SE], ± 2.84 h; mean, 66.1 h; SE, ± 2.63 h) (Table 2 and Figure 2a). Regarding the secondary endpoints, the time from surgery completion to the first flatus and the time from surgery completion to solid food toleration were not statistically significant (Table 2 and Figure 2b, 2c). The LS mean of the change in the VAS score for dissatisfaction attributable to constipation between baseline and POD 7 of the DKT group and that of the control group were statistically significant (DKT group: Estimated difference, –5.59 points; SE, ± 2.66; LS mean, 23.2; 95% CI, 19.5-26.8; control group: LS mean, 28.8; 95% CI, 25.0-32.5; p=0.037) (Figure 3a). The LS mean of the change in the VAS score for distension between baseline and POD 7 of the DKT group and that of the control groups were not statistically significant (DKT group: Estimated difference, –0.055 points; SE, ± 2.10; LS mean, 21.8; 95% CI, 18.9-24.7; control group: LS mean, 21.8; 95% CI, 18.9-24.8; p=0.98) (Figure 3b). The change in the WBC count between baseline and POD 7 of the DKT group and that of the control group were significantly different (DKT group: Estimated difference, 264.8 mg/L; SE, 129.8; LS mean, 6140; 95% CI, 5961-6318; control group: LS mean, 5875; 95% CI, 5962-6058; p=0.042) (Figure 3c). The change in the CRP level between baseline and POD 7 of the DKT group and that of the control group were not significantly different (estimated difference, 0.26 mg/L; SE, ± 0.19; LS mean, 2.04; 95% CI, 1.77-2.32; LS mean, 1.79; 95% CI, 1.51-2.07; p=0.19) (Figure 3d).

The overall incidence of Treatment-Related Adverse Events (TRAEs) of the DKT group (3.3%) was similar to that of the control group (1.7%) (Table 3). The incidence of diarrhea of the DKT group (2.4%) was similar to that of the control group (1.7%). The incidence of nausea of the DKT group (0.8%) was similar to that of the control group (0%). Serious TRAEs were not observed in the DKT and control groups. However, the study drug was discontinued for one patient in the DKT group because of TRAEs, including diarrhea.

The effectiveness of DKT to shorten the time from surgery completion to the first postoperative BM for patients in subgroups stratified by age (younger than 75 years and 75 years or older) and BMI (<30 and ≥ 30) was evaluated (Table 4). The subgroup of participants younger than 75 years consistently exhibited improvement.

We used the Mann-Whitney U test to perform a sensitivity analysis of the primary endpoint. Regardless of the normality of the data, similar results were observed. Therefore, the normality of the data was robust (p=0.019).

Discussion

The key finding of this study was that oral administration of

Table 1: Baseline patient characteristics of the full analysis set.

Variables	DKT group (n = 120)	Control group (n = 114)
Age, median (IQR), years	72 (67–75)	73 (68–78)
Age, n (%)		
Younger than 65 years	20 (17)	16 (14)
65 years or older	100 (83)	98 (86)
BMI, median (IQR), kg/m^2	24.2 (22.6–26.7)	25.0 (22.3–27.1)
Parity, median (IQR)	2 (2–3)	2 (2–3)
VAS, median (IQR), mm		
Dissatisfaction attributable to constipation	0 (0–16.3)	0 (0–23.0)
Abdominal distension	0 (0–12.0)	0 (0–12.0)
VAS, mean (SD), mm		
Dissatisfaction attributable to constipation	11.8 (20.6)	15.0 (22.3)
Abdominal distension	9.1 (16.9)	10.7 (18.6)
WBC count, median (IQR), /μL	5800 (5000–6525)	5700 (5025–6675)
CRP level, median (IQR), mg/L	0.06 (0.03–0.13)	0.06 (0.04–0.12)
Coexisting conditions at baseline, n (%)		
Hypertension	69 (58)	74 (65)
Diabetes	17 (14)	20 (18)
Pulmonary disease	2 (1.7)	5 (4.4)
Connective tissue disorder	3 (2.5)	2 (1.8)
Tobacco use, n (%)		
Former	9 (7.5)	0
Preoperative POP-Q stage, median (IQR)		
Anterior	3 (3–3)	3 (3–3)
Apical	3 (1–3)	3 (1–3)
Posterior	2 (2–3)	3 (2–3)
Prior abdominal open surgery, n (%)	38 (32)	32 (28)
Prior abdominal laparoscopic surgery, n (%)	7 (5.8)	7 (6.1)
Prior hysterectomy, n (%)	16 (13)	16 (14)
Operative time, min	108 (94–129)	107.5 (92–124)
Estimated blood loss, mL	10 (10–20)	10 (10–20)
Additional procedures		
Posterior repair, n (%)	4 (3.3)	2 (1.8)
LSH, n (%)	17 (14)	19 (17)
BSO, n (%)	19 (16)	18 (16)
Adhesion lysis, n (%)	26 (22)	23 (20)

Data are presented as n (%), median (IQR), or mean (SD).
BMI: Body Mass Index; BSO: Bilateral Salpingo-Oophorectomy; CRP: C-Reactive Protein; DKT: Daikenchuto; IQR: Interquartile Range; LSH: Laparoscopic Sacrohysteropexy; POP-Q: Pelvic Organ Prolapse Quantification; SD: Standard Deviation; VAS: Visual Analog Scale; WBC: White Blood Cell

DKT three times daily for 7 days postoperatively reduced the time to the first postoperative BM by an average of 7 h compared to that associated with the oral administration of the control treatment after LSC. Additionally, we examined the changes in the LS means of the VAS scores for dissatisfaction attributable to constipation of the DKT and control groups and confirmed that the LS mean of the DKT group was lower than that of the control group during the perioperative period, suggesting the potential effectiveness of DKT

Table 2: Efficacy endpoints of the full analysis set.

Endpoint	DKT group (*n*=120)	Control group (*n*=114)
Primary endpoint		
First bowel movement, hours		
Mean ± SE	58.4 ± 2.84	66.1 ± 2.63
P value	0.047	
Secondary endpoints		
First flatus, hours		
Mean ± SE	19.3 ± 1.03	19.0 ± 0.84
P value	0.86	
First solid food, hours		
Mean ± SE	25.0 ± 0.86	25.3 ± 0.84
P value	0.81	
Change in the VAS score for dissatisfaction attributable to constipation between baseline and POD 7, mm		
LS mean	23.2	28.8
95% CI	19.5–26.8	25.0–32.5
Estimated difference ± SE	-5.59 ± 2.66	
P value	0.037	
Change in the VAS score for distension between baseline and POD 7, mm		
LS mean	21.8	21.8
95% CI	18.9–24.7	18.9–24.8
Estimated difference ± SE	-0.055 ± 2.10	
P value	0.98	
Change in the WBC level between baseline and POD 7, /μL		
LS mean	6140	5875
95% CI	5961–6318	5962–6058
Estimated difference ± SE	264.9 ± 129.8	
P value	0.042	
Change in the CRP level between baseline and POD 7, mg/L		
LS mean	2.04	1.79
95% CI	1.77–2.32	1.51–2.07
Estimated difference ± SE	0.26 ± 0.19	
P value	0.19	

CI: Confidence Interval; CRP: C-Reactive Protein; DKT: Daikenchuto; LS: Mean, Least-Squares Mean; POD: Postoperative Day; SE: Standard Error; WBC: White Blood Cell

when managing pain caused by constipation. A meaningful difference in the primary endpoint was observed, and the difference in the VAS score for dissatisfaction attributable to constipation was also clinically meaningful; therefore, further studies of DKT are necessary.

Previous studies have consistently demonstrated a shorter time to the initial BM after laparoscopic colorectal resection [20,21]. Because none of the patients in our study underwent concurrent gastrointestinal resection with LSC, their outcomes were anticipated. The main novel finding of this study was the abbreviated duration to the first BM after LSC.

There was no significant difference in the time to solid food tolerance between groups, and nearly all patients were allowed solid food on the first postoperative day. The typical clinical approach

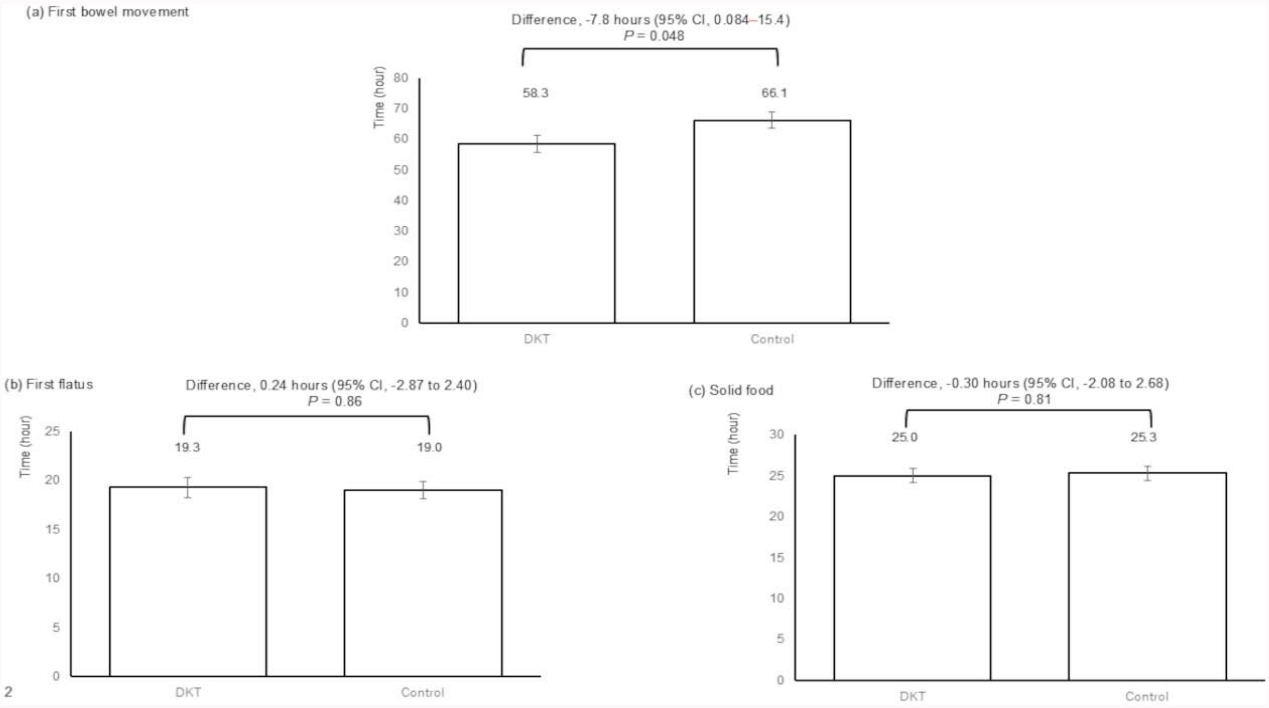

Figure 2: (a) Time to the first postoperative bowel movement of the DKT group and that of the control group. (b) Time to the first postoperative flatus of the DKT group and that of the control group. (c) Time until postoperative solid food intake of the DKT group and that of the control group. CI: Confidence Interval; DKT: Daikenchuto

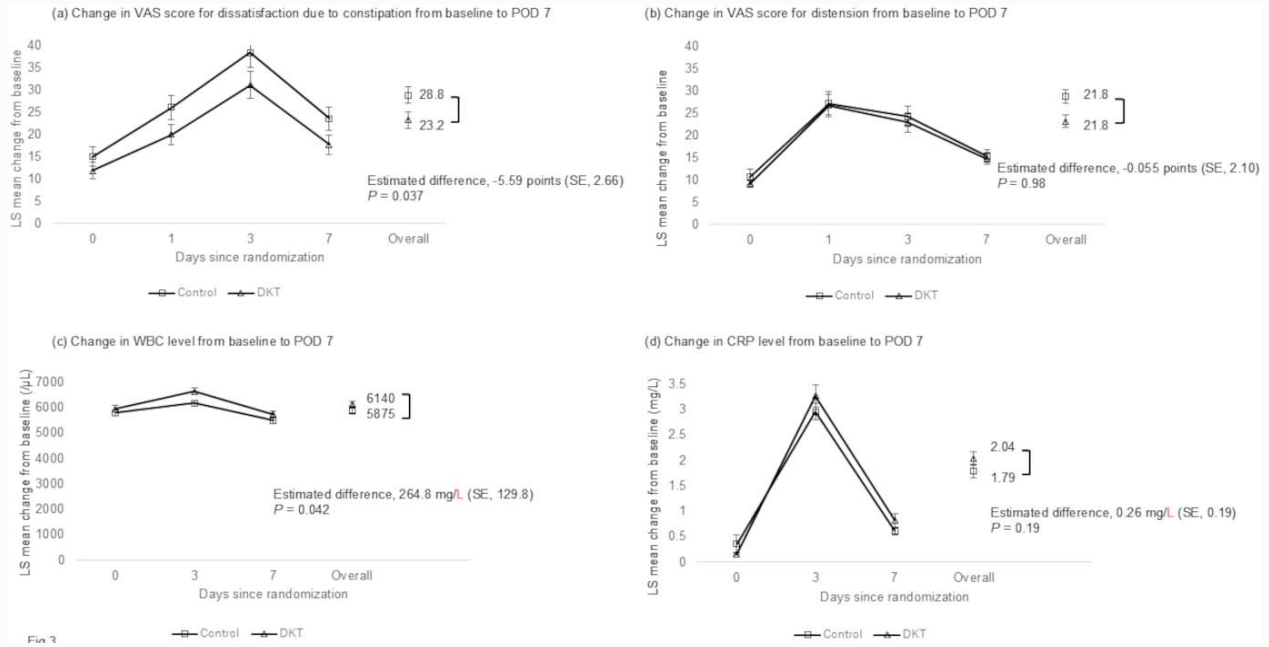

Figure 3: (a) Change in the VAS score for dissatisfaction attributable to constipation between baseline to POD 7 according to LMMs. (b) Change in the VAS score for abdominal distension between baseline and POD 7 according to LMMs. (c) Change in the WBC count between baseline and day 7 according to LMMs. (d) Change in the CRP level between baseline and POD 7 according to LMMs.
CRP: C-Reactive Protein; DKT: Daikenchuto; LMMs: Linear Mixed Models; LS mean: Least-Squares mean; POD: Postoperative Day; SE: Standard Error; VAS: Visual Analog Scale; WBC: White Blood Cell

includes the early intake of solid foods [16]. The time to the first postoperative flatus of the DKT group was not different from that of the control group. However, gas passage was confirmed based on patient reports to the nurses who were not part of this study. Additionally, the patients may not have been aware of any gas passage during sleep.

MIYA-BM, which is a probiotic, can significantly help restore bowel function after surgery [22]. During this study, changes in the VAS scores for abdominal distension of the DKT and control groups were not notably different. However, because of the small size of the

Table 3: Treatment-related adverse events of the safety analysis set.

	DKT group (*n*=123)	Control group (*n*=115)
Patients, *n*	4	2
All treatment-related adverse events, *n* (%)	4 (3.3)	2 (1.7)
Diarrhea, *n*	3	2
Nausea, *n*	1	0

DKT: Daikenchuto

Table 4: Subgroup and sensitivity analyses.

Subgroup *n* of events/total *n*	DKT mean ± SE	Control mean ± SE	95% CI	*P* value
Age				
Younger than 75 years, (152/234)	55.5 ± 3.49	70.0 ± 3.49	4.68–24.4	0.0041
75 years or older (82/234)	65.1 ± 4.85	60.4 ± 3.83	-3.60 to 13.5	0.44
BMI				
<30 kg/m^2 (225/234)	58.6 ± 2.93	65.4 ± 2.62	-0.93 to 14.5	0.085
≥ 30 kg/m^2 (9/234)	53.7 ± 15.7	92.7 ± 23.1	-26.0 to 104.0	0.20
Sensitivity Analysis				
First bowel movement, hours				
Median (IQR)	51.9 (30.8–78.0)	66.8 (44.6–87.6)		0.019

BMI: Body Mass Index; CI: Confidence Interval; DKT: Daikenchuto; IQR: Interquartile Range; SE: Standard Error

study group and the brief study period, further research comprising a larger and more varied group of participants and longer duration of MIYA-BM use are necessary to confirm these results.

DKT has an anti-inflammatory effect that occurs through the release of adrenomedullin and suppression of Prostaglandin E2 (PGE2) [23]. DKT contains processed ginger, which decreases PGE2 production associated with chemotherapy-induced oral mucositis [23]. DKT inhibits cyclooxygenase-2 activity in rats and mice by suppressing inflammation caused by PGE2 [24]. One study confirmed the anti-inflammatory effects of DKT by using a rat intestinal injury model [25]. We expected that such anti-inflammatory effects would result in improvements in the postoperative changes in the WBC count and CRP level attributable to DKT; however, we did not observe these improvements. In particular, although the difference in the CRP level between baseline and POD 7 was statistically significant, it may not have been clinically significant. Based on the amount of bleeding, consistent operative times, and absence of technique-related issues during surgery, the patients who underwent LSC did not notably benefit from the anti-inflammatory effects of DKT.

Subgroup analyses performed during three randomized comparative trials indicated that participants younger than 75 years and those with a BMI <30 who used DKT experienced a significantly improved time to the first postoperative BM compared with that of participants who used the placebo [26].

During this study, the incidence of drug-related adverse events associated with DKT was 3.3%. Serious adverse events were not observed; therefore, DKT is considered safe. Additionally, a systematic review and meta-analysis did not report any TRAEs associated with DKT [27].

This study had several limitations. First, because the extended use of DKT is possible, the 1-week treatment period during this study was too short to accurately assess the efficacy and establish the long-term effectiveness, safety, and tolerability of DKT. Second, a prior sample size calculation was not performed, and multiplicity was not considered. Third, this study was conducted at a single institution. Fourth, this was an open-label trial rather than a placebo-controlled trial; therefore, the risk of observer bias was possible. Assessment tools such as patient questionnaires were not used to evaluate the quality of life, and stool characteristics and daily BM frequency were not assessed. To effectively assess the impact of DKT, the outcomes of DKT plus MIYA-BM treatment and those of DKT treatment alone should be compared. However, we did not perform this comparison.

Conclusion

The perioperative administration of DKT reduced the time to the first postoperative BM and postoperative dissatisfaction attributable to constipation compared with those associated with MIYA-BM administration. The TRAEs associated with DKT were mild, thus indicating its safety.

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References

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29(1):4-20.
2. Higgs PJ, Chua HL, Smith AR. Long term review of laparoscopic sacrocolpopexy. BJOG. 2005;112(8):1134-8.
3. Coolen AWM, van Oudheusden AMJ, Mol BWJ, van Eijndhoven HWF, Roovers JWR, Bongers MY. Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: A randomized controlled trial. Int Urogynecol J. 2017;28(10):1469-79.
4. Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, et al. Abdominal sacrocolpopexy: A comprehensive review. Obstet Gynecol. 2004;104(4):805-23.
5. Parkes IL, Shveiky D. Sacrocolpopexy for treatment of vaginal apical prolapse: Evidence-based surgery. J Minim Invasive Gynecol. 2014;21(4):546-57.
6. Johanson JF, Kralstein J. Chronic constipation: A survey of the patient perspective. Aliment Pharmacol Ther. 2007;25(5):599-608.
7. Werth BL, Christopher SA. Potential risk factors for constipation in the community. World J Gastroenterol. 2021;27(21):2795-817.
8. Patel M, Schimpf MO, O'Sullivan DM, LaSala CA. The use of senna with docusate for postoperative constipation after pelvic reconstructive surgery: A randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2010;202(5):479.
9. Corman ML. Management of postoperative constipation in anorectal surgery. Dis Colon Rectum. 1979;22(3):149-51.
10. Kono T, Kanematsu T, Kitajima M. Exodus of Kampo, traditional Japanese medicine, from the complementary and alternative medicines: is it time yet? Surgery. 2009;146(5):837-40.
11. Tominaga K, Arakawa T. Kampo medicines for gastrointestinal tract disorders: A review of basic science and clinical evidence and their future application. J Gastroenterol. 2013;48(4):452-62.
12. Yamada T, Matsumoto S, Koizumi M, Matsuda A, Shinji S, Yokoyama Y, et al. The effect of *Daikenchuto* on postoperative intestinal motility in patients with right-side colon cancer. Surg Today. 2017;47(7):865-71.
13. Ishizuka M, Shibuya N, Nagata H, Takagi K, Iwasaki Y, Hachiya H, et al. Perioperative administration of traditional Japanese herbal medicine

Daikenchuto relieves postoperative ileus in patients undergoing surgery for gastrointestinal cancer: A systematic review and meta-analysis. Anticancer Res. 2017;37(11):5967-74.

14. Itoh T, Yamakawa J, Mai M, Yamaguchi N, Kanda T. The effect of the herbal medicine dai-kenchu-to on post-operative ileus. J Int Med Res. 2002;30(4):428-32.
15. Oyama F, Futagami M, Shigeto T, Miura R, Osawa Y, Oishi M, et al. Preventive effect of daikenchuto, a traditional Japanese herbal medicine, on onset of ileus after gynecological surgery for malignant tumors. Asia Pac J Clin Oncol. 2020;16(4):254-8.
16. Yaegashi M, Otsuka K, Itabashi T, Kimura T, Kato K, Fujii H, et al. Daikenchuto stimulates colonic motility after laparoscopic-assisted colectomy. Hepatogastroenterology. 2014;61(129):85-9.
17. Woodbury CF, Coughlin AC, Dubois B, Romanova A. Prevention of postoperative constipation in urogynecology patients: a systematic review. Urogynecology. 2023;29(2):175-82.
18. Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996;175(1):10-7.
19. Sato H, Otsuka S, Abe H, Tsukada S. Comparison of outcomes of laparoscopic sacrocolpopexy with concomitant supracervical hysterectomy or uterine preservation. Int Urogynecol J. 2023;34(9):2217-24.
20. Hoshino N, Kawada K, Hida K, Wada T, Takahashi R, Yoshitomi M, et al. Effect of Daikenchuto (TJ-100) on gastrointestinal symptoms following laparoscopic colectomy in patients with colon cancer: study protocol for a randomized controlled trial. Trials. 2017;18(1):553.
21. Wakasugi M, Suzuki Y, Tei M, Ueshima S, Akamatsu H, Nishida T. Effects of Daikenchuto on postoperative gastrointestinal motility in colorectal carcinoma patients with abdominal pain and distension: A prospective, randomized trial. Surg Today. 2020;50(11):1524-9.
22. Wallström A, Frisman GH. Facilitating early recovery of bowel motility after colorectal surgery: A systematic review. J Clin Nurs. 2014;23(1-2):24-44.
23. Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, et al. Multitargeted effects of hangeshashinto for treatment of chemotherapy-induced oral mucositis on inducible prostaglandin E2 production in human oral keratinocytes. Integr Cancer Ther. 2014;13(5):435-45.
24. Hayakawa T, Kase Y, Saito K, Hashimoto K, Ishige A, Komatsu Y, et al. Effects of Dai-kenchu-to on intestinal obstruction following laparotomy. J Smooth Muscle Res. 1999;35(2):47-54.
25. Chikakiyo M, Shimada M, Nakao T, Higashijima J, Yoshikawa K, Nishioka M, et al. Kampo medicine "Dai-kenchu-to" prevents CPT-11-induced small-intestinal injury in rats. Surg Today. 2012;42(1):60-7.
26. Kono T, Shimada M, Nishi M, Morine Y, Yoshikawa K, Katsuno H, et al. Daikenchuto accelerates the recovery from prolonged postoperative ileus after open abdominal surgery: A subgroup analysis of three randomized controlled trials. Surg Today. 2019;49(8):704-11.
27. Hoshino N, Takada T, Hida K, Hasegawa S, Furukawa TA, Sakai Y. Daikenchuto for reducing postoperative ileus in patients undergoing elective abdominal surgery. Cochrane Database Syst Rev. 2020;2020(3):CD012271.