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審査学位論文
(博士)

Daikenchuto stimulates colonic motility after laparoscopic-assisted colectomy

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Running head: Effects of daikenchuto after laparoscopic colectomy

Abstract

Background. Paralytic ileus after laparoscopic-assisted surgery often occurs. We investigated whether daikenchuto (DKT), a traditional Japanese herbal medicine, improves intestinal motility in patients undergoing laparoscopic-assisted colectomy for colon cancer.

Methods. Fifty-four patients who underwent colectomy at Iwate Medical University Hospital between October 2010 and March 2012 were randomized to either the DKT group (7.5g/day, p.o.) or the control group (lactobacillus preparation, 3g/day, p.o.). Primary endpoints included time to first flatus, bowel movement, and tolerance of diet after extubation. Secondary endpoints were WBC count, C-reactive protein (CRP) level, length of hospital stay, and postoperative ileus. Colonic transit time was measured using radiopaque markers and abdominal radiographs.

Results. Fifty-one patients (DKT, 26 vs. control, 25) were included in the per-protocol analysis. The DKT group had significantly faster time until first flatus ($67.5 \pm 13.6\text{h}$ vs. $77.9 \pm 11.8\text{h}$, $P < 0.01$) and bowel movement ($82.9 \pm 17.8\text{h}$ vs. $99.5 \pm 18.9\text{h}$, $P < 0.01$) and colonic transit time ($91.9 \pm 19.8\text{h}$ vs. $115.2 \pm 12.8\text{h}$, $P < 0.05$). There were no significant intergroup differences in secondary endpoints and adverse events.

Conclusions. DKT accelerates colonic motility in patients undergoing laparoscopic-assisted

colectomy for colon cancer.

Keywords: daikenchuto, traditional Japanese herbal medicine, laparoscopic-assisted colectomy,
intestinal motility, colon cancer

INTRODUCTION

Laparoscopic-assisted surgery for colorectal cancer is a minimally invasive procedure that allows rapid recovery and early discharge from the hospital. Nevertheless, concerns remain about postoperative paralytic ileus as it can delay resumption of oral intake and passage of flatus and stool.

Daikenchuto (DKT), a traditional Japanese herbal medicine, is known to accelerate gastrointestinal (GI) motility (1-6) and improve intestinal mucosal blood flow (7,8). Clinically, DKT has been reported to shorten hospital stay and decrease time to first flatus after laparotomy for colorectal cancer (9-12). The purported mechanisms underlying the stimulatory effect on GI motility include serotonin receptor-mediated acetylcholine release as well as stimulation of motilin secretion and vanilloid receptor-mediated activity in the intestinal epithelium (2-5,8,9). Thus, we hypothesized that DKT may improve or prevent paralytic ileus after laparoscopic-assisted surgery by facilitating GI motility.

The objective of this randomized controlled trial was to determine whether DKT could shorten the time until start of flatus, bowel movement, and tolerance of oral diet in patients who underwent laparoscopic-assisted colectomy for colon cancer. As an additional study, we

measured the colonic transit time with radiopaque markers (SITZMARKS[®]) and abdominal radiographs to objectively assess whether DKT facilitates postoperative colonic motility.

MATERIALS AND METHODS

The protocol of this open-label randomized controlled trial was approved in December 2009 by the Ethics Committee of Iwate Medical University Hospital.

Two groups of patients, i.e., a group treated with oral DKT (DKT group) and another given oral lactobacillus preparation (control group) were compared. For randomization, 3 surgical sites (right colon, transverse colon, and left colon) were used as stratification factors to minimize confounding. The permuted block method with envelope technique was used to assign patients to the DKT group or control group.

Patients were randomized (1:1) to each group based on the surgical procedure. The following fixed block sizes were used: 4 for the right colon, 4 for the transverse colon, and 6 for the left colon. Randomization was performed according to a computer-generated schedule and researchers were not informed of the block sizes. The sealed envelope was kept by a third person and was opened after the subjects were

assigned. The study investigators and medical staff performed all aspects of data collection and evaluation.

Study subjects were colon cancer patients referred to the Department of Surgery at Iwate Medical University Hospital from other departments of the same hospital or related facilities between October 2010 and March 2012. Of the 62 eligible patients, 8 met the exclusion criteria resulting in 54 randomized patients. Patients were at least 20 years old and their preoperative TNM classification were T=1–3, N=0–2, and M=0.

Performance status (PS) was 0 or 1 as determined by ECOG Performance Status Scale, and patients had colon cancer that included Rs amenable to elective surgery.

Preoperative diagnostic imaging techniques comprised lower GI endoscopy, lower GI series, and CT. Exclusion criteria were i) History of laparotomy or peritonitis; ii)

Complication of inflammatory disease such as ulcerative colitis; iii) Emergency surgery; iv) Presence of serious disease in the heart, kidney, or liver that may affect postoperative management; v) History of brain disease accompanied by paralysis; vi) Multiple cancers; vii) Current use of other Oriental medicines or laxatives; viii) Pregnancy, breast-feeding, or attempting to become pregnant; ix) Possibility of altering the surgical

procedure, such as change to laparotomy; x) Other conditions judged inappropriate by the presiding physician.

In all patients, lymph node dissection was carried out by a medial approach using 5 ports, intestines were subsequently mobilized, and a small longitudinal incision of 4cm was made in the umbilicus. The abdominal air pressure was set at 8mmHg/H₂O. The energy devices used were harmonic scalpel *II (Ethicon Endo-Surgery, Cincinnati, OH) and ENDOPATH Bipolar Cord (Ethicon Endo-Surgery, Cincinnati, OH). The technique of intestinal anastomosis was functional end-to-end anastomosis (FEEA) for the cecum to the descending colon, and the double stapling technique (DST) for the sigmoid colon to rectum (RS). All operations were carried out by surgeons whose skills were accredited by the Japan Society for Endoscopic Surgery. General anesthesia was used in all patients.

The nasogastric tube was removed from all patients within 1 hour after the surgery. Fluid intake, which included enteral nutrition and liquid diet, was commenced on postoperative (POD) day 1 or 2 as nearly all patients in the past have shown tolerance to early fluid intake at our institution. Medical therapy was offered and mobilization encouraged from POD 1 as well. Solid food intake was resumed on POD 3 because the reported mean time to tolerance of solid food on

POD 1 or 2 has been traditionally low at around 20% to 30% (13,14). Solid foods at our institution typically consists of rice porridge in half degree (“gobu-gayu” = rice-to-water ratio of 1:10 or 50g rice cooked in 500ml water) plus side dishes without special preparations. The patients were monitored for symptoms of ileus such as bloating, pain, nausea, and vomiting, and the time to pass first flatus and stool. The order for hospital discharge was written on or after POD 6 for all patients. White blood cell (WBC) count and C-reactive protein (CRP) level were determined immediately after surgery and at 6:00 AM on POD 1, 3, and 5.

Patients in the DKT group took the medication (2.5g per sachet) orally 3 times a day from two days prior to surgery until the morning of surgery, and then from the morning after the surgery until discharge. In the control group, patients were given a lactobacillus preparation (1.0g per packet) orally 3 times a day in a similar manner as DKT. Oral administration was continued in both groups for the duration of hospitalization.

Statistical analysis

Primary endpoints were time to first flatus, time to first bowel movement, and time to tolerance of oral diet after extubation following surgery. Secondary endpoints were WBC count,

CRP level, length of hospital stay, and the occurrence of postoperative ileus. Ileus was defined as the presence of a grade 3 or worse bowel obstruction or paralysis as determined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Other complications and adverse events were also evaluated throughout the study. If DKT or placebo was discontinued for whatever reasons, the patient was excluded from analysis.

On the basis of a report by Kabeshima et al. (12), which showed that DKT administration reduced the time to first flatus after surgery by 12 hours in patients who underwent laparotomy for colon cancer, we predicted that 24 patients in each group would be required to detect the difference in mean time to first flatus between the two groups with 80% statistical power while maintaining a significance level of 5% in a two-sided *t*-test. Further, by taking into account the possibility of unanalyzable patients, we set the target number at 25 patients for each group (total 50).

Results are reported as mean±SD. We used the *t* test to compare two independent groups. The normality of distribution was tested by *F* test prior to *t* test. The chi-square test was used for comparison of quantitative data. The unpaired *t* test was used to determine the difference in mean values. Differences were considered statistically significant when $P < 0.05$. JMP for Macintosh

(Ver. 10.0 JMP, SAS Institute Inc., Japan) was used.

Additional study

An additional study using the radiopaque marker SITZMARKS[®] (Konsyl Pharmaceuticals, Inc., Fort Worth, TX, USA) was conducted to evaluate gut motility in patients who underwent surgery in the left colon. SITZMARKS[®] capsules were administered orally with about 100mL of water at 9:00 AM on POD 1. Abdominal radiography was performed at 3:00 PM on POD 1 and at 9:00 AM from POD 2 to 5.

SITZMARKS[®] capsules are 20 ring-shaped markers filled with plant-derived gelatin. The time required for 10 of the 20 markers to pass through each boundary of the GI tract was defined as half-clearance time (T_{10}). This transit time was calculated using the following formula

(15,16):

$$T_{10} = \frac{\frac{N_{i+1}-N_i}{T_{i+1}-T_i} - \frac{N_{i+1}-10}{T_{i+1}-T_{10}}}{N_{i+1}-N_i} \cdot \frac{(10-N_i)T_{i+1} + (N_{i+1}-10)T_i}{N_{i+1}-N_i}$$

where T_{i+1} =time taken by the first 10 radiopaque markers to reach the target segment,

T_i =time taken by the first 10 markers that did not reach the target segment, N_{i+1} =total number

of markers present on a given film sector at T_{i+1} , and N_i =total number of markers present on a given film sector at T_i . In this analysis, a proportional calculation formula was obtained as an approximation formula.

RESULTS

A total of 54 patients (27 in each group) participated in the study between October 2010 and March 2012. Patients with postoperative complications and those who discontinued the study or were excluded from the analysis are described in Table 1. The per-protocol analysis included 26 patients in the DKT group and 25 patients in the control group (Figure 1). Background factors of the patients included in the analysis are summarized in Table 2. There was no significant difference between the groups with regard to any of the background factors.

The mean time and the *P* value for each primary endpoint are shown in Table 3. The mean times to pass first flatus and bowel movement after extubation following surgery were both significantly faster in the DKT group than in the control group. There was no significant difference in time to tolerance of solid food and length of hospital stay between the groups.

Figures 2 and 3 show the time course of WBC count and CRP value obtained immediately after surgery and on POD 1, 3, and 5 as well as a comparison of these values between the groups. Both followed a similar trajectory of changes in both WBC count and CRP value and no statistically significant intergroup differences were found.

With regard to postoperative complications, one patient in the DKT group developed fever

and abdominal distention on POD 5 and discontinued treatment. One patient in the control group discontinued treatment due to fever and malaise that developed on POD 3, while another developed a surgical site infection requiring wound care on POD 4 and was excluded from the analysis. The overall incidence of adverse events was similar between the two groups, and our data did not reveal a clear association between treatment and postoperative complications (Table 1).

The mean half-clearance time and *P* value in the additional study for evaluation of postoperative colonic motility are shown in Table 4. The study included 17 of the 29 patients who underwent surgery in the left colon (10 from the DKT group and 7 from the control group) and gave consent to ingestion of SITZMARKS[®] (Figure 1). The colonic transit time was significantly faster in the DKT group than in the control group.

DISCUSSION

We found that DKT significantly reduced time to first flatus by about 10 hours and time to first bowel movement after extubation by about 17 hours, and our data from the additional study using SITZMARKS provided the mechanical underpinnings of decreased colonic transit time by DKT. Although the differences in time to first solid food was not significant between the groups, almost all patients, despite their advanced age, were able to resume oral nutrition on POD 3, which is in line with the standard clinical pathway favoring early solid foods. Plain rice porridge is traditionally used in Japan as the first postoperative solid diet because of its ease of digestibility. At our institution, we offered gobu-gayu (approximately 1200kcal) as part of the standard postoperative diet with the same side dishes that were prepared for full meals. With respect to the lack of difference in length of hospital stay between the DKT and control groups, hospital discharge was often dictated by domestic circumstances and particularly so for the elderly, regardless of the readiness of the patient. Thus, while the significant clinical effect of DKT on reducing the length of stay observed in previous trials was not reproduced, our findings nevertheless indicate that DKT restores colonic function soon after laparoscopic-assisted colectomy, and its potential benefits in hastening the start of the solid food, preventing

postoperative ileus, and reducing the length of stay are worthy of further investigation.

According to a study by Kabeshima et al. (12), DKT (7.5g/day) decreases time to first flatus after laparotomy for colorectal cancer by about 1 day compared to that of no medication.

However, in the latter study (12,17), there was no difference in time to first flatus and length of hospital stay after laparoscopic-assisted surgery for colorectal cancer. Patients on DKT also had a significantly lower CRP value on POD 3, but the WBC count did not differ significantly between the two groups (17).

Although there have been occasional reports on early improvement of postoperative intestinal paralysis in patients who underwent laparotomy and received DKT, the effect of DKT has not been sufficiently investigated in patients undergoing laparoscopic-assisted surgery. In our study, DKT (7.5g/day) administration resulted in a significant decrease in time until first flatus and bowel movement after laparoscopic-assisted surgery, although the extent of reduction was not as significant as that observed in patients after laparotomy. It should be borne in mind that this study differed from other studies with respect to various study conditions, dosage, timing of administration, surgical technique, surgical site, and method of anesthesia, and therefore, simple comparisons of our results with other findings may not be feasible. However, objective evidence

obtained through the use of SITZMARKS[®] in our additional study and reduced time to first flatus and bowel movement demonstrated that DKT does indeed have a colonic motility-stimulating effect in patients who underwent laparoscopic-assisted surgery. In our study, we administered DKT from POD 1 on the basis of data indicating intestinal paralysis persisting for 48–72 hours after surgery (18) and DKT contributing to early improvement in intestinal paralysis when it is given within 1–2 days after laparotomy for colorectal cancer instead of 3 or more days after surgery (12). Thus, we surmised that our protocol for DKT administration from POD 1 might have contributed to achieving favorable results.

Several studies have investigated the molecular mechanisms by which DKT exerts its vasodilatory and anti-inflammatory effects in the gut (7,19-23) properties which are thought to be conducive in accelerating early recovery from postoperative ileus. DKT has been shown to promote the release of calcitonin gene-related peptide (CGRP) from the nerve terminal and adrenomedullin (ADM) from the intestinal epithelium (7,20,22) In that process, the receptor activity-modifying membrane proteins (RAMP) are also upregulated by DKT. RAMPs exist in 3 forms, namely, RAMP1, RAMP2 and RAMP3. When these proteins bind with the promiscuous calcitonin receptor-like receptor (CRLR), the latter can function as either a receptor for CGRP or

ADM. RAMP1 and CRLR association confers a CGRP receptor, a potent vasodilator peptide, whereas in the presence of RAMP2 and RAMP3, CRLR becomes an ADM receptor, a potent anti-inflammatory peptide that attenuates the production of IFN- γ and TNF- α . In our study, we started DKT administration before surgery to leverage its purported anti-inflammatory effect, yet we found no differences in postoperative changes in WBC count, CRP value, or in incidence of postoperative complications between the two groups. Considering the extent of bleeding, consistent operating time, and lack of technique-related problems during surgery, patients were not particularly benefited by the anti-inflammatory effect of DKT during minimally invasive laparoscopic-assisted surgery. However, we conjectured that improved intestinal blood flow and bowel motility by preoperative administration of DKT might have contributed to early recovery of colonic function soon after surgery.

Our study had some limitations. The DKT and control groups were not adequately matched with regard to sex, age and cancer stage, although this did not affect the results. In addition, the standard DKT dose administered to all patients may not have been the most accurate method of dose determination given that DKT has a dose-dependent activity and body weight varied among patients.

In conclusion, DKT (7.5g/day) started 2 days prior to surgery and restarted on POD 1 accelerates colonic motility in patients undergoing laparoscopic colectomy for colon cancer, without increased risk, as measured by comparable incidences of adverse drug reactions between the active treatment and placebo groups. DKT is an inexpensive, easy-to-use drug with minimal side effects and has a long track record of safe use in Japan. Our clinical data is the first to show that DKT can enhance the safety of and dovetail with the less invasive nature of laparoscopic-assisted surgery through its ability to promote colonic motility. Further clinical studies with a well-matched control group, a larger sample size, and administration of different doses are needed to confirm our present findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

FIGURE LEGENDS

Figure 1. Flow diagram of study participants.

Figure 2. Time course of changes in white blood cell count

*Comparisons by unpaired *t* test. Mean and standard deviations of WBC count.

Figure 3. Time course of changes in C-reactive protein level

*Comparisons by unpaired *t* test. Mean and standard deviations of C-reactive protein level.

Fig 1 Flow diagram of study participants

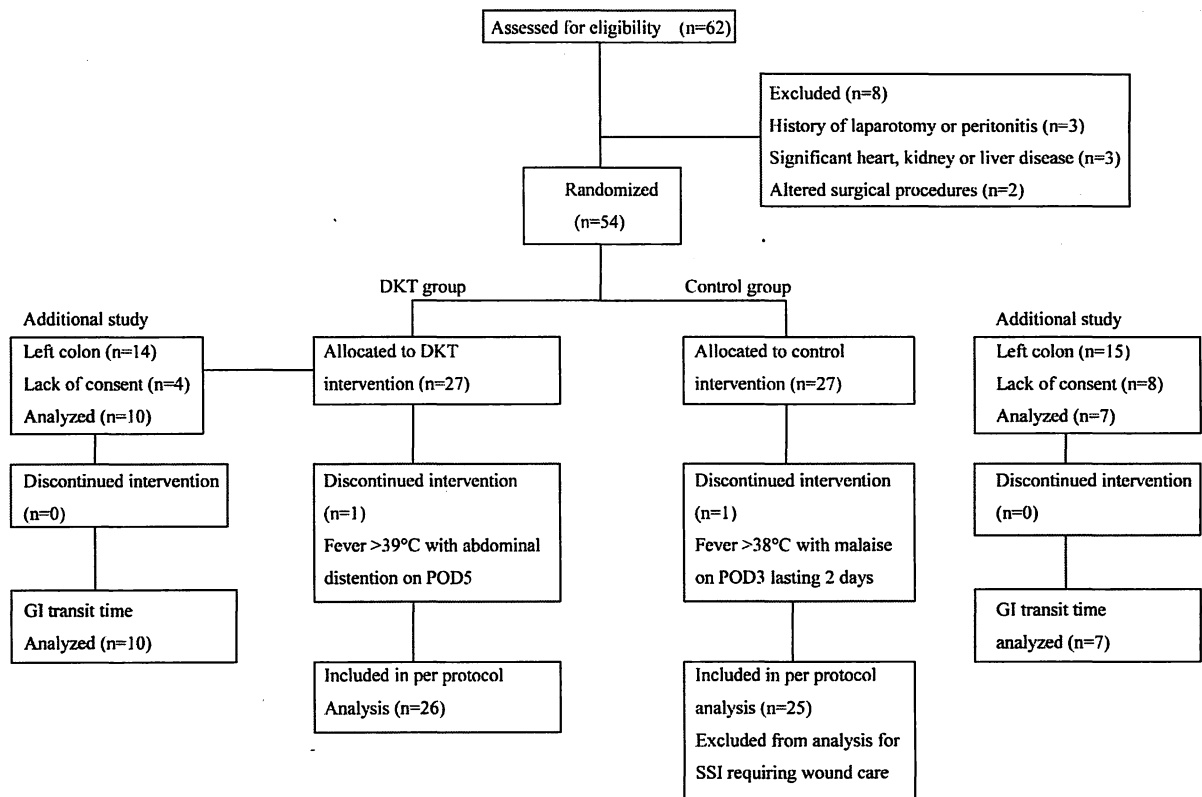


Fig. 2 Changes in WBC count over time

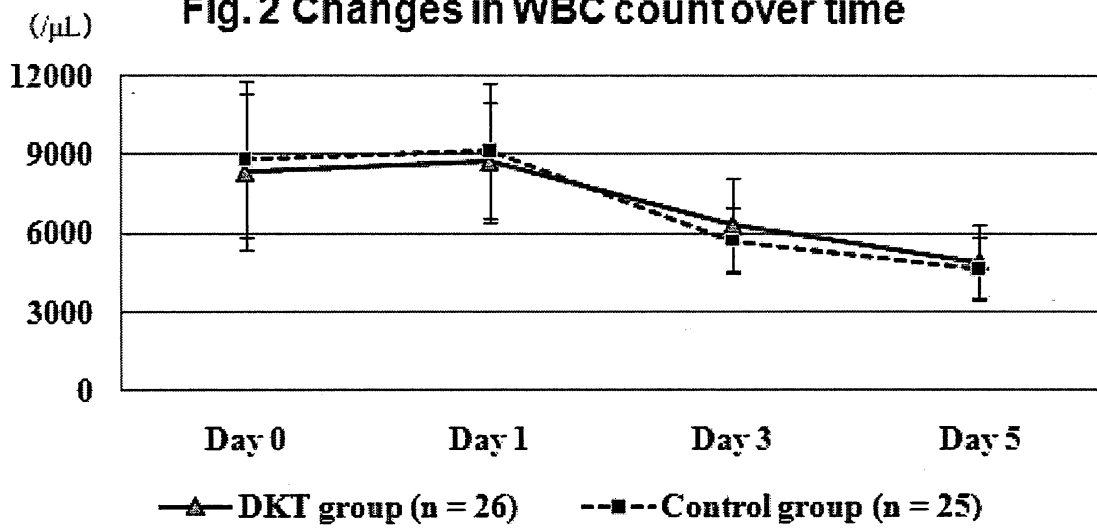


Fig. 3 Changes in C-reactive protein level over time

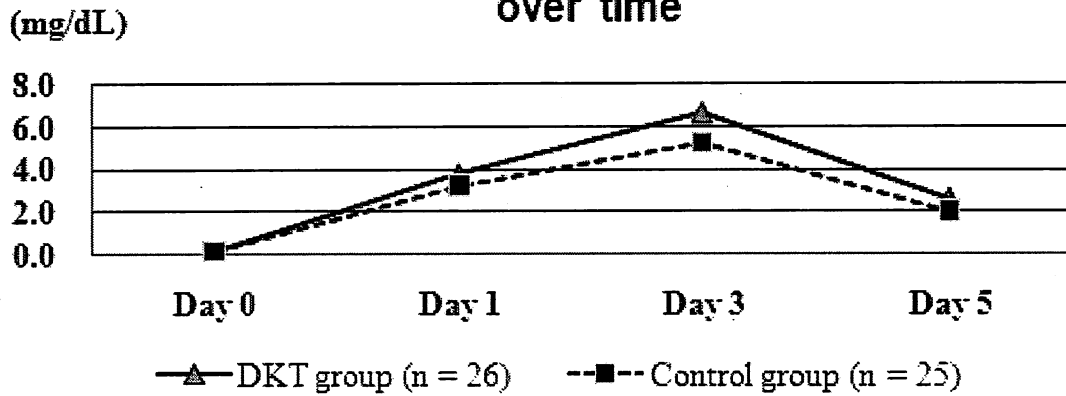


Table 1. Postoperative complications and reasons for discontinuing intervention and analysis

DKT group: 1 case (3.7%, n = 27)	a) Fever (exceeding 39°C) and abdominal distention on the 5th postoperative day.
Control group: 2 cases (7.4%, n = 27)	b) Fever (exceeding 38°C) and malaise occurred on the 5th postoperative day and persisted for 2 days. c) SSI occurred on the 4th postoperative day and required wound treatment.
	a)b) Temporary fasting and antibiotic therapy to improve symptoms.
	c) Hospital stay due to SSI was prolonged, and the case deviated from the clinical pathway.

Table 2. Patient characteristics

	DKT group (n = 26)	Control group (n = 25)	P
Sex (M:F)	15:11	10:15	0.206*
Site			
Right colon	8	7	
Transverse colon	4	3	
Left colon	14	15	
Age, yrs (range)	69(51-83)	68(43-89)	0.869†
Operation time, min (range)	187(147-225)	176(130-300)	0.274†
Bleeding, mL (range)	12(2-36)	15(1-65)	0.341†

*Comparison by χ^2 test.

†Comparisons by unpaired t test

Table 3. Summary of Endpoints

	DKT group (n = 26)	Control group (n = 25)	<i>P</i>
First flatus, h (SD)	67.54(13.61)	77.88(11.84)	<0.006*
First bowel movement, h (SD)	82.88(17.76)	99.48(18.93)	0.002*
First solid food, h (SD)	81.35(17.29)	87.8(9.94)	0.108*
Length of hospital stay, day(SD)	7.46(0.99)	7.92(1.58)	0.153*

*Comparisons by unpaired t test

Table 4. Half-clearance time with SITZMARKS

	DKT group (n = 10)	Control group (n = 7)	<i>P</i>
Colonic transit time, h (SD)	91.9(19.8)	115.2(12.87)	0.016*

*Comparisons by unpaired t test