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Effectiveness of Daikenchuto, a Traditional Japanese Herbal Medicine, in Accelerating Capsule Endoscopy Transit Time- A Prospective Pilot Study

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1. Introduction

Capsule endoscopy (CE) is an effective and non-invasive method to exam lesions in the small intestine [1][2]. The battery life is a limiting factor for CE examinations. In approximately 20% of the cases, parts of the small intestine cannot be observed due to the delayed passage of the capsule through the small intestine, and thus it is necessary to shorten the passage time [3][4]. Currently, there is no consensus on the preparation of patients to improve the passage of CEs through their digestive tract, and the establishment of a standardized preparatory treatment is necessary. The purpose of this study was to investigate whether the pre-exam administration of Daikenchuto shortens the time during which a CE remains in the small intestine, and to improve the speed at which the capsules reach the large intestine.

2. Patients and methods

Patients: All outpatients who underwent CE at our hospital between May 2009 and April 2010 were included in this study. All patients who were enrolled before December 14, 2009 were in the control group, and all patients after that date were in the DKT group. The purpose of the capsule endoscopy was explained to all patients, and informed consent was obtained from all patients. The inclusion criteria for this study were patients with confirmed or suspected intestinal diseases and patients without suspected organic narrowing of the lumen of the small intestine. The exclusion criteria were patients with a narrowed lumen of the small intestines that could delay CE passage, patients with implanted electronic devices (e.g. cardiac pacemakers), and patients with confirmed or suspected pregnancy.

This study included 135 patients, with 83 males and 52 females, and their age varied from 14 to 85 years.

Methods: The recommended daily dose of Daikenchuto is 15.0 g, and contains 1.25 g of a dried mixture of herbs (50% ginger root, 30% ginseng, and 20% sansho) and 10.0 g of a dried sugary substance. Thirty patients who received 7.5 g per day of DKT (TJ-100, manufactured by Tsumura, Tokyo) between lunch and dinner on the day before the exam and at 7:00 a.m. on the day of the exam (DKT group) were compared to 105 patients who did not receive any DKT (control group). A PillCamSB (Given Imaging, Israel) was used for both DKT and control groups. The PillCamSB1 and PillCamSB2 are the same size (11 x 26 mm) and shape.

The patients were instructed to consume special food according to the modified Brown's method [5] for lunch and dinner (Sanwa Kagaku Kenkyusho, Nagoya) on the day before the exam, and nothing by mouth on the morning of the exam. Upon arrival, the patients took 40 minutes to ingest 900 mL of a magnesium citrate solution along with 10 mL of a simethicone solution before swallowing the capsule endoscope. The patients were allowed to drink water 2 hours later, and to eat either noodles or special food 4 hours later. The data recorders were disconnected 8 hours later.

The location of the capsule was confirmed by a real-time viewer (Given Imaging) one hour later in the first 16 patients of the DKT group. If the capsule was still in the stomach, then the patients received 10 mg of metoclopramide intravenously [6]. A Rapid Reader 4 was initially used for the image analyses, and a Rapid Reader 5 (both manufactured by Given Imaging) was used from October 14, 2009 onwards. The image data for the stomach, duodenum, and appendix were entered, and the time during when the capsule remained in the stomach and small intestine was calculated [13]. Two physicians specialized in endoscopic exams interpreted the radiograms independently from each other.

We defined the overall CE observation time as the time from when the CE was orally ingested until the time when the CE reached the ileocecal junction. The time during when the CE remained in the small intestines was defined as the time from when the CE exited and entered the duodenum until the time the CE reached the ileocecal junction in this study.

3. Statistical analyses

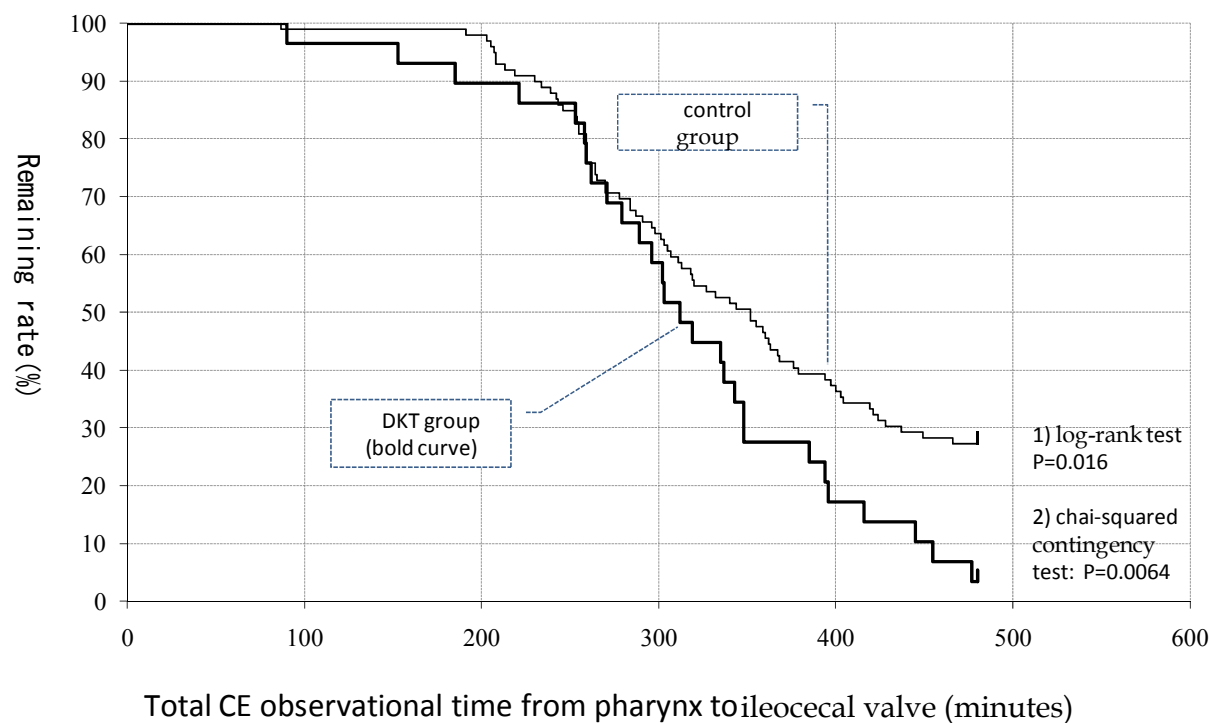
Modified Kaplan-Meier curves were used to investigate the time during when the CE remained in the small intestine. Therefore, the event in the Kaplan-Meier curve was defined as the arrival of the CE at the large intestine. The difference in time during when the CEs remained in the small intestines between the DKT and control groups was investigated using a log-rank test. Chi-square analysis was used to calculate the difference in the CE completion rates between the two groups. Our focus in the Cox proportional hazard model was from the time when the CE entered the duodenum to the time when the CE exited the small intestine, from the point of DKT pharmacological effectiveness.

In order to detect observations with an extremely short time during when the CE remained in the small intestines (CEs inappropriate for accurate visual information to be included in this exam), all patients who completed the exam were plotted using histograms, and the distribution characteristics of the two groups were compared. An alpha level of 0.05 (one-sided test for Chi-square tests and two-sided tests for all others) was used in all statistical tests.

4. Results

The patient background for both groups was as follows: 1) the male to female ratio was 18:11 in the DKT group and 59:40 in the control group ($p=0.36$ Chi-square test); 2) the mean age was 60.7 ± 16.3 years in the DKT group and 59.6 ± 17.9 years in the control group ($p=0.58$ Student t-test); 3) underlying diabetes mellitus was found in 1 patient in the DKT group and 2 patients in the control group; 4) a history of abdominal surgery was found in 5 patients in the DKT group and 6 patients in the control group; and 6) metoclopramide was administered to 12 patients in the DKT group and 4 patients in the control group. There were no statistically significant differences in background between the two groups; therefore, the control group was determined to be appropriate for this study. Three patients with missing data, 2 patients who were unable to swallow the capsule, and 1 patient with pharyngeal obstruction [7] in the control group as well as 1 patient in the DKT group whose narrowing of the intestinal lumen was confirmed during CE were excluded from the analyses.

The remaining curves from both groups during the first three hours were not parallel or even crossing-over between the groups, suggesting DKT not equally affecting to all patients. However, more effectively it seems to accelerating the patients with slower peristalsis (log-rank $P=0.016$) (Fig. 1). The proportion of patients with a successful CE observation was significantly higher in the DKT group than in the control group ($P=0.0064$) (Table 1).



CE: capsule endoscopy

Fig. 1. CE Remaining Curve

	DKT group	non-DKT group	Total (N)
Proportion of success cases (N)	96.5% (28)	72.7% (72)	100.0% (100)
Proportion of failure cases (N)	3.4% (1) *	27.2% (27)	100.0 (28)
Total (N)	100.0% (29)	100.0 % (99)	100% (128)

*Chi-squared contingency test:
P=0.0064

DKT: Tumura Daikennchuto

Table 1. Comparative study between DKT and non-DKT group in CE successful proportion

The Cox proportional model for the time during when the CEs remained in the small intestines revealed that the crude successful ratio between the control group and the DKT group was 1:2.2 (P=0.0008), and the adjusted successful ratio was 1:2.0 (P = 0.0078) after adjusting for age, gender, and metoclopramide use. In other words, we observed a two-fold in the successful intestinal passage using the current CE system (Table 2). A comparison of the distribution characteristics of the time during when the capsules remained in the small intestine between the DKT and control groups showed that they were almost identical to patients in the control group with successful exam completion, and there were no patients with poor observation conditions due to diarrhea (Fig. 2). No patients experienced adverse effects such as liver dysfunction, jaundice or stomach ache caused by the DKT.

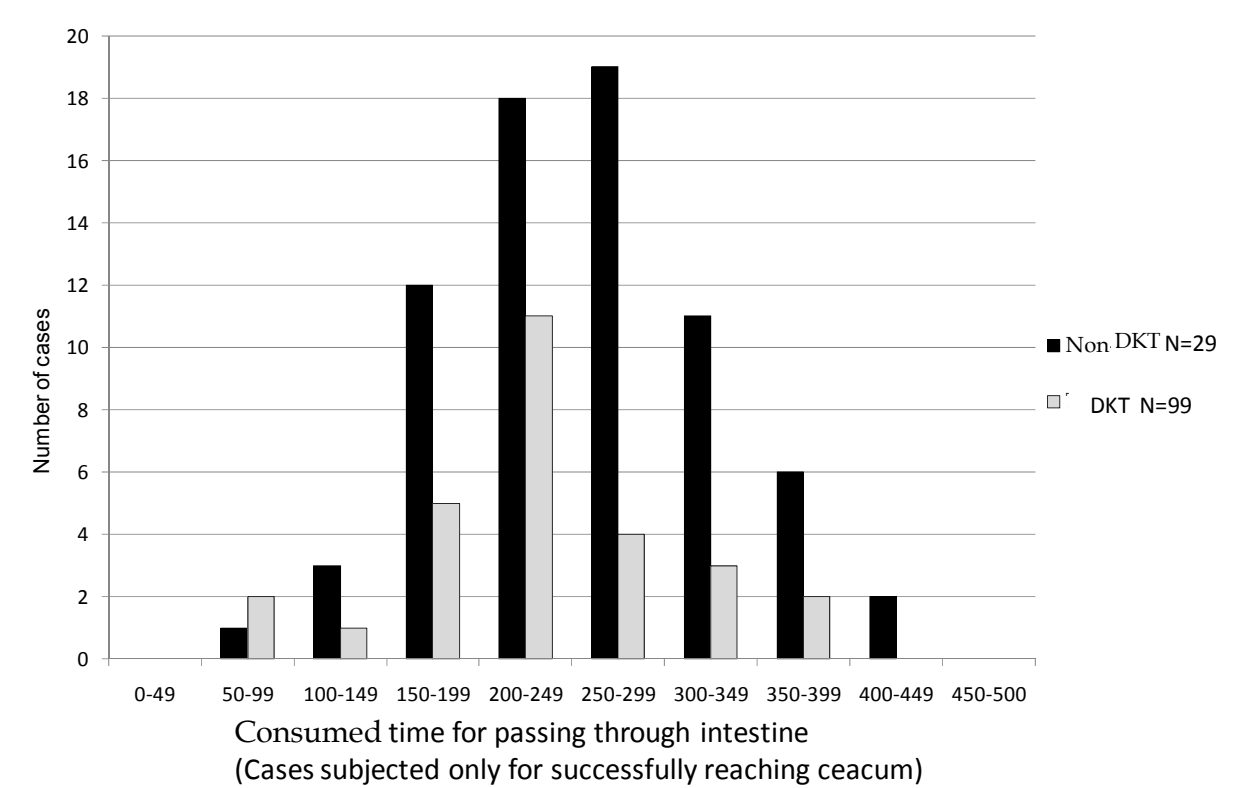
	Variable	Risk Ratio * (RR)	(95% CI)	P value
Crude RR	DKT	2.20	(1.39–3.49)	0.0008
Adjusted RR**	DKT	2.00	(1.20–3.35)	0.0078

*protective factor for CE successful completion

**adjusted with Metoclopramide, aging(+1) and sex

DKT: Tsumura Daikenchuto

Table 2. Evaluation of DKT for CE successful completion analyzed using Cox proportional model



DKT: Tsumura Daikenchuto

Fig. 2. Comparative study for the trasit time distribution between DKT and non-DKT group

5. Discussion

In order to improve the CE successful complete rate, some GI prokinetic agents such as metoclopramide [8][9], mosapride [10], erythromycin [11][12], and chewing gum [13] have been used to prepare patients. Our study is the first of its kind to report the relationship between DKT use as a prokinetic agent and a reduced time that the capsules remained in the small intestine, as well as a better CE successful completion rate.

DKT has been known in Japan to be effective in treating patients with lowered GI peristalsis, such as post-operative ileus [14][15]. The mechanisms for promoting bowel motility remain largely unknown. However, basic research has shown that one of the ingredients in DKT, sansho (*Zanthoxylum piperitum*), promotes acetylcholine release from the ends of the parasympathetic nerves at the neuromuscular junction in the digestive tract, and hence the distal part of intestine as well as the large intestine are affected [16][17][18] . In addition, it also works directly on vanilloid receptors (a type of capsaicin receptor) in the intestinal mucosa, and increases peristalsis by releasing substance P [19]. DKT has also been reported to increase the release of motilin, which increases the peristalsis of the digestive tract [20]. Metoclopramide use did not contribute to a significantly shortened time during when the CE remained in the small intestine that led to successful completion of the exam (data not shown). Previous studies did not provide any evidence that metoclopramide use contributed to a more successful CE or a shortened time during when the CEs remained in the lower half of the small intestines [8].

In this study, we performed: (1) a comparison of the simple successful exam completion rates, (2) an investigation of the temporal properties of the CE survival curves throughout the exam using modified Kaplan-Meier curves (the difference starts to appear after the first three hours), and (3) a determination of the effectiveness of DKT in successfully completing CEs with a battery life of 8 hours.

There were no significant differences in the CE remaining curves between the DKT and control groups during the first 3 hours of the exam, suggesting no clinical effect on patients with originally active peristalsis. Significant differences in the rate of arrival at the large intestine appeared between the 4th and 5th hours, suggesting affecting patients with slower peristalsis. Interestingly, there was no significant difference in the passage from the oral swallowing till stomach exiting between the DKT and control groups ($P=0.884$). This fits with the basic pharmacological studies mentioned above which reported that DKT acts on the distal part of the small intestines and the large intestine.

There are some limitations to this study. Since the number of patients in the study is not large, the results may be equivocal enough due to low statistical power. There may also be a possible information bias since the patients were not blinded, and knew that they took DKT. Although this prospective study did not use convenience sampling and adjusted for gender, age, and metoclopramide use, the presence of possible potential confounders still cannot be ignored because of the non-randomized controlled assignment. However, in a general hospital, it is difficult to conduct randomized studies for various reasons, and this represents the satisfactory clinical research that was ethically and logistically feasible, and acceptable as an exploratory study. Further randomized controlled trial study should be warranted in any case.

CE is a non-invasive and effective procedure to evaluate lesions in the small intestine. To avoid adverse effects from preparation, DKT should be given in the smallest amounts at the time closest to the exam. The recommended daily dose of DKT is 15.0 g, but the 7.5 g / day dose used in our study showed satisfactory effects. If the CE passed through the small intestines too quickly, then the exam quality could have possibly been compromised. However, we did not observe excessive peristalsis such as diarrhea induced by our preparation method. The capsule technology was upgraded during the study. This was solely to improve the quality of the images taken, and we do not believe that it affected the study results since the size and shape of the capsules did not differ. The PillCam SB2 had longer than 8 hours of image recording time. Thus, it was possible to extend the exam time if the real time viewer showed that the CE had not reached the large intestine by the end of the 8 hour exam period. However, we suspected that the time during when the CE remains in the small intestines beyond 8 hours varies greatly, and decided to end the exam at 8 hours for convenience. We did not encounter any problems with discovering minute lesions that may have been adversely affected by the granules of DKT. We are currently dissolving the DKT in hot water before administering it to patients.

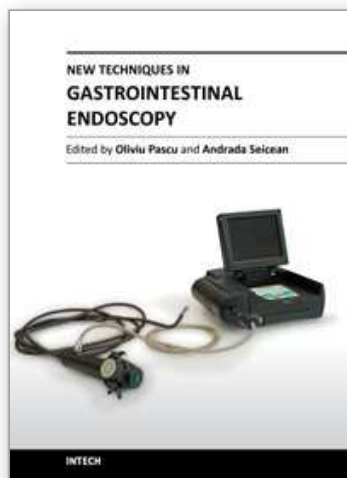
6. Conclusion

The pre-CE administration of DKT may become a standardized method to prepare patients for capsule endoscopy, and multi-site randomized studies should be conducted in the future. These study results suggested that DKT can improve the speed at which the CE reaches the large intestine without compromising exam accuracy by promoting peristalsis of the small intestine.

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