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Effect of Coadministration of Polyethylene Glycol and Dai-Kenchu-To on Image Definition and Complete Small Bowel Examination Rate in Capsule Endoscopy

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Abstract ***Background and Aim:*** Image definition and complete small bowel examination rate are possible factors contributing to missed lesions during capsule endoscopy. This study aimed to determine the effect of coadministration of polyethylene glycol (PEG) and dai-kenchu-to (DKT) on these factors using PEG and DKT as pretreatment before capsule endoscopy.
Methods: Patients who underwent capsule endoscopy at our hospital between November 2007 and August 2012 were included in the study. Patients were divided into the following three groups: those receiving no pretreatment (control, n=133), those orally administered PEG (PEG, n=20), and those orally administered PEG and DKT (15g) (PEG + DKT, n=25). Image definition and complete small bowel examination rate were examined retrospectively between the three groups.
Results: Image definition in the PEG + DKT group was significantly higher than that in the control group ($p<0.05$), but there was no significant differences between the PEG and control groups. The complete small bowel examination rate was significantly lower in the PEG group than in the control and PEG + DKT groups ($p<0.05$).
Conclusions: Coadministration of PEG and DKT improved image definition and prevented a reduction of the complete small bowel examination rate due to PEG in capsule endoscopy.

Key words: capsule endoscopy, dai-kenchu-to, polyethylene glycol

Introduction

Capsule endoscopy enables direct and non-invasive assessment of the small intestinal mucosa and has been used worldwide since its application was first reported in *Nature* in 2000[1]. Capsule endoscopy is useful for the detection of obscure gastrointestinal bleeding, suspected Crohn's disease, and other diseases[2-5] and has become an essential tool for the diagnosis and treatment of these diseases. Currently, the most important challenge in performing this procedure is to reduce the frequency of missed lesions. Factors contributing to the missing of lesions include a decrease in image definition due to the presence of air bubbles and residues, limited examination time with conventional capsule endoscopy, limited angle of view, and dead angles behind plicae. A previous study reported that

the frequency of missed lesions was 10%[6]. Moreover, previous studies have shown that a complete small bowel examination cannot be achieved within 8 hours in 20-30% of all patients undergoing the procedure [7-9]. Recently, battery performance has been improved and the angle of view has been increased, thereby reducing the frequency of missed lesions. However, no effective measure has been proposed to resolve the decrease in image definition due to the presence of residues.

Many studies of polyethylene glycol (PEG) as premedication for capsule endoscopy have been conducted in which the PEG was often orally administered about 12 to 16 hours before capsule endoscopy, and thus, defecation at night raises concern about disorder of the patient's sleep, leading to the likelihood of a stressful endoscopic procedure[10-12].

Dai-kenchu-to (DKT) is prepared by mixing *Ginseng radix*, *Zanthoxyli fructus*, and *Zingiber siccatum* in the ratio of 3:2:5, extracting the essence, and adding *Saccharum granorum* to it. A beneficial effect of DKT is its prokinetic effect on the gastrointestinal tract. DKT is widely used in clinical practice in Japan and is particularly effective in the treatment of ileus[13]. However, only one study has examined the effect of this agent as a pretreatment before small bowel capsule endoscopy[14]. The objective of this study, therefore, was to determine the combination effect of PEG and DKT pretreatment on image definition and gastrointestinal transit time in capsule endoscopy.

Methods

Patients

This study included 178 patients who underwent capsule endoscopy at our hospital between November 2007 and August 2012, excluding those who underwent resection of the small intestine or endoscopic placement or pre-administration of PEG through the naso-jejunal tube, those who used other prokinetics, and those diagnosed as having massive small intestinal bleeding by capsule endoscopy. All patients were given an explanation of the complications associated with capsule endoscopy, such as an undescended or retained capsule, and on the possible need for surgery in the case of a retained capsule, depending on the situation. The use of orally administered DKT as a pretreatment before capsule endoscopy was approved by the ethics committee of our hospital.

Capsule endoscopy

The PillCam SB capsule endoscopy system (Given Imaging Ltd., Yokneam, Israel) was used. Image interpretation was performed using Rapid Reader (Version 5) software (Given Imaging). Each patient was instructed to fast for 12 hours before the examination and was then asked to swallow the capsule. Patients were divided into the following groups: those who received no pretreatment before examination (control group); those who were orally administered PEG over a 3-hour period before the examination (PEG group); and those who were orally administered DTK (5g) dissolved in a small amount of lukewarm water at 12 hours, 3 hours, and 20 minutes before the examination (total 15g) and orally administered PEG over a 3-hour period before the examination (PEG + DKT group). The oral dose of PEG was adjusted between 1 to 1.8L according to each patient's physique.

All patients in all groups were orally administered dimethicone syrup (40mg) with a small amount of water before the examination to reduce air bubbles. After the examination was started, patients were allowed to drink water after 2 hours and to eat light meals after 4 hours or until it was confirmed that the capsule had arrived at the small intestine as indicated on the real-time viewer. Video recorders were collected after 8 hours or until it was confirmed that the capsule had arrived at the large intestine on the real-time viewer and the data were transferred to a workstation for analysis. Videos were analyzed by two experienced capsule endoscopy readers, (K. S. and S. H.).

Evaluation

Image definition was evaluated on the basis of the data reported by Niv et al.[15] and was classified into three grades according to the ratio of time during which residues were observed relative to total enteroscopy time: ≤20% as grade 2 (good), 21-35% as grade 1 (moderate), and ≥36% as grade 0 (poor). Gas-

trointestinal transit time in capsule endoscopy was measured as gastric transit time (GTT), defined as the transit time from the stomach to the bulbus, and small bowel transit time (SBTT), defined as the transit time from the bulbus to the cecum. A complete examination was considered successful when the capsule was excreted from the ileocecal valve within 8 hours. We evaluated SBTT only in the patients in whom a complete examination was achieved. Completion rate was defined as the rate of patients who achieved a complete examination in each group.

Statistical analysis

Image definition and sex were compared using the Mann-Whitney U-test. GTT, SBTT and age were compared using the t-test. Completion rate was analyzed by the $\chi 2$ test. A value of $p<0.05$ was considered to indicate statistically significance. Statistical analysis was performed with StatView 5 (Abacus Concepts, Berkeley, CA).

Results

Adverse events

All patients excreted the capsule within 2 weeks, and no patient developed complications such as an undescended capsule. No apparent adverse events were found in the PEG group and PEG + DKT group.

Patient characteristics by group

The 178 patients were divided into three groups: 133 in the control group, 20 in the PEG group, and 25 in the PEG + DKT group. Patient characteristics and indications for capsule endoscopy in the study groups are shown in Table 1. The most common indication for capsule endoscopy in the three groups was obscure gastrointestinal bleeding. No significant differences were observed between the groups with respect to age or sex.

Table 1. Patient characteristics and indications for capsule endoscopy.

Indication	Control (n=133)	PEG (n=20)	PEG + DKT (n=25)
Age (y) (mean±SD)	64.2±18.2	65.4±15.4	58.6±14.7
Sex (male/female)	71/62	9/11	15/10
OGIB	96	15	12
Suspected Crohn's disease	8	3	5
Suspected small bowel tumor	8	0	7
Suspected protein-losing enteropathy	21	2	1

OGIB, obscure gastrointestinal bleeding

Image definition

The capsule endoscope did not reach the bulbus in 5 of 133 patients in the control group, and these patients were excluded from examination. Image definition in the PEG + DKT group was not significantly different from that in the PEG group, but it was significantly better than that in the control group (Figure 1).

Completion rate

A complete small bowel examination was achieved in 101 of 133 patients (75.9%) in the control group, 10 of 20 patients (50.0%) in the PEG group, and 20 of 25 patients (80.0%) in the PEG + DKT group. Completion rate in the PEG group was significantly lower than that in the control and PEG + DKT groups (Figure 2).

Gastric transit time and small bowel transit time

No significant difference was observed in GTT between the three groups (Figure 3). SBTT was compared between the patients who achieved a complete examination in each

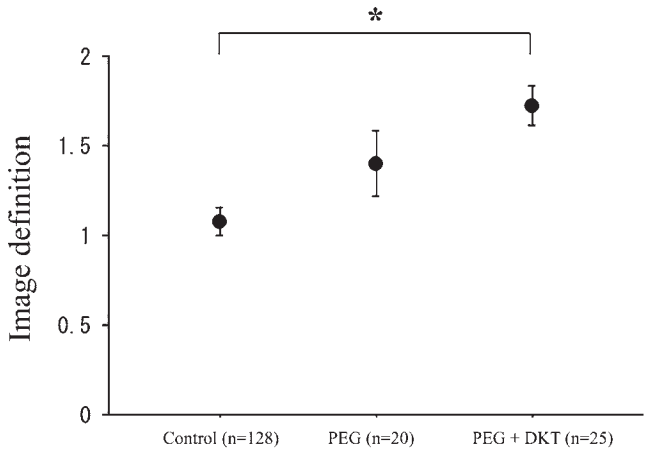

Figure 1. IImage definition in the pretreatment subgroups: Image definition in the polyethylene glycol (PEG) + dai-kenchu-to (DKT) group was not significantly different from that in the PEG group, but it was significantly better than that in the control group. Data represent mean values ± SE; *p<0.05.

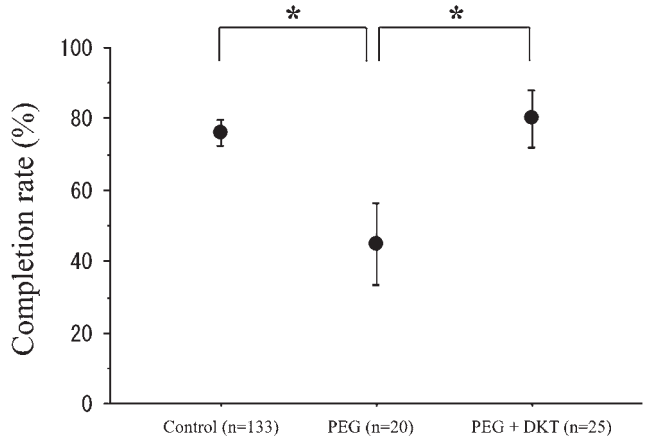

Figure 2. Completion rate in the pretreatment subgroups: A completed small bowel examination was achieved in 101 of 133 patients (75.9%) in the control group, 10 of 20 patients (50.0%) in the polyethylene glycol (PEG) group, and 20 of 25 patients (80.0%) in the PEG + dai-kenchu-to (DKT) group. Completion rate in the PEG group was significantly lower than that in the control and PEG + DKT groups. Values are mean ± SE. *p<0.05.

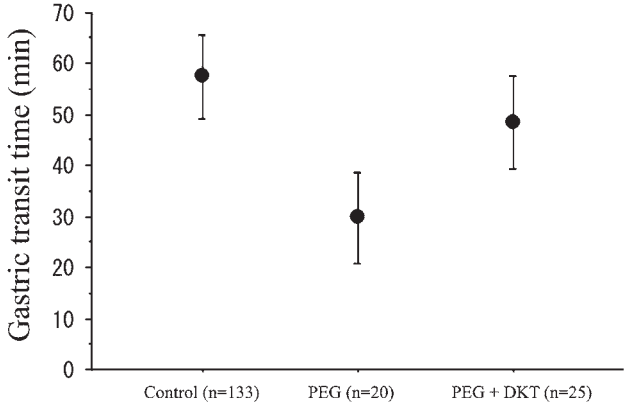

Figure 3. Gastric transit time (GTT) in the pretreatment subgroups: There was no significant difference in GTT between the three groups. Data represent mean values ± SE.

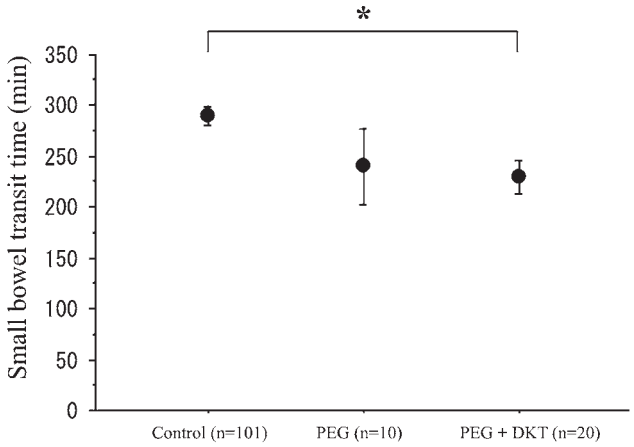

Figure 4. Small bowel transit time (SBTT) in the pretreatment subgroups: SBTT was compared between the patients who achieved a complete examination in each group. SBTT in the polyethylene glycol (PEG) + dai-kenchu-to (DKT) group was not significantly different from that in the PEG group, but it was significantly shorter than that in the control group. Data represent mean values ± SE; *$p<0.05$.

group. SBTT in the PEG + DKT group was not significantly different from that in the PEG group, but it was significantly shorter than that in the control group (Figure 4).

Discussion

The objective of this study was to determine the combination effect of PEG and DKT pretreatment on image definition and gastrointestinal transit time in capsule endoscopy. The results demonstrated that the coadministration of PEG and DKT significantly improved image definition and prevented a reduction of the complete small bowel examination rate due to PEG in capsule endoscopy.

Most previous studies have reported that oral administration of PEG improves image definition in the small bowel and has no effect on completion rate[16]. This study, however, showed that although the PEG group had a trend toward better image definition than that in the control group, there was no significant difference between the 2 groups. Furthermore, completion rate was lower in the PEG group than the other two groups.

A possible cause of the decrease in complete small bowel examination rate without significant improvement in image definition in the PEG group was considered to be the influence of PEG residues in the intestinal tract because PEG was orally administered about 3 hours before the capsule endoscopy, whereas in most previous reports, it was orally administered about 12 to 16 hours before or at midnight before the test[10-12,16]. Because there were no significant differences in GTT between the control, PEG, and PEG+DKT groups, this suggested that oral administration of PEG immediately before the test could adversely affect capsule transit in the small bowel. However, when compared with the control group, the PEG+DKT group showed significant improvement of image definition without a decrease in the completion rate along with shortened SBTT.

These results lead us to conjecture that the administration of DKT facilitates the removal of residues from the small intestine into the large intestine, consequently enhancing the bowel cleansing effect of PEG. Oral administration of PEG 12 to 16 hours before the test or before the previous night's sleep could probably disturb the patient's sleep, and it was thought that if oral administration of PEG 3 hours before the test could obtain sufficient bowel cleansing effect, this premedication would allow for tests with less patient distress.

The suggested mechanisms for the prokinetic effect of DKT include promotion of acetylcholine release via serotonin type 3/4 receptors[17,18], promotion of motilin secretion, a gastrointestinal motility-stimulating hormone[19]. Most studies using DKT have involved animals, and only a few clinical studies have used DKT[13,17-21]. Other studies have examined the benefits of erythromycin[22], metoclopramide[23], and mosapride[24] for improving the completion rate in capsule endoscopy but have failed to establish any standard pretreatment regimen. Given that DKT caused no adverse events in the present study and that no contraindications exist, DKT may be a candidate as a standard pretreatment for capsule endoscopy.

Although the present study examined the coadministration of PEG and DKT, future studies will need to use DKT alone to precisely evaluate its effect. Nakaji et al. reported that administration of DKT prior to capsule endoscopy could improve the speed of capsule endoscopy and the completion rate, but image definition was not examined[14].

No matter how greatly improved the performance of capsule endoscopy might be, the presence of large amounts of residue in the intestinal tract will result in a poorer quality test, and thus, to acquire higher quality in capsule endoscopy, improvement of image definition is essential, which will require further consecutive studies. Meanwhile, capsules with longer battery life have helped to achieve a higher completion rate of small bowel capsule endoscopy. If examination time is limited, such as in examinations of outpatients, the attempt to complete whole small bowel observation within a defined period of time is considered an important issue.

In conclusion, we demonstrated that coadministration of PEG and DKT significantly improved image definition. This is the first study to demonstrate the usefulness of coadministration of PEG and DKT in small bowel capsule endoscopy. In the future, multicenter, randomized, comparative studies should be conducted based on the results of this study.

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Conflict of Interest

The authors state no conflict of interest.

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