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Split-dose low-volume polyethylene glycol is non-inferior but less preferred compared with same-day bowel preparation for afternoon colonoscopy

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ABSTRACT

Currently, the same-day polyethylene glycol-electrolyte lavage solution (PEG-ELS) regimen is particularly recommended for afternoon colonoscopy as an alternative to the split-dose regimen in western countries. However, in Japan, the split-dose regimen has never been used as a standard colonoscopy preparation regimen. The aim of this study was to compare the efficacy and tolerability of split-dose PEG containing ascorbic acid (ASC) with same-day single dose PEG-ASC in Japan.This was a single-blinded, non-inferiority, two-center, randomized, controlled study. In-hospital patients were randomized to the same-day regimen or the split regimen using a web-based registry system. The same-day group was instructed to take 5 mL of sodium picosulfate in the evening, and on the day of the colonoscopy, they took 1.5 L of PEG-ASC. The split group was instructed to take 1 L of PEG-ASC before the day of colonoscopy, followed by another 1 L of PEG-ASC on the day of colonoscopy. Bowel cleansing was evaluated by the Boston Bowel Preparation Scale.A total of 153 patients were randomized to either the same-day group (n=78, males 60.0%, mean age 62.7 years) or the split group (n=75, 61.3%, 61.9 years). The rates of successful bowel cleansing were 83.3% in the same-day group vs. 92.0% (83.4%–97.0%) in the split group, P=0.10). No serious adverse events occurred in the study population. However, more patients in the same-day group were willing to repeat the same preparation regimen (P<0.001). The split-dose regimen was not inferior to the same-day regimen with respect to the efficacy of bowel preparation, but the patients preferred the same-day regimen.

Keywords: afternoon colonoscopy, bowel preparation, split-dose

Abbreviations:
PEG-ELS: polyethylene glycol-electrolyte lavage solution
ASC: ascorbic acid

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PEG-ASC: polyethylene glycol-electrolyte lavage solution containing ascorbic acid
PICO: picosulfate solution

INTRODUCTION

Appropriate bowel preparation is essential for precise detection of colorectal neoplasms.[1,2] Inadequate bowel preparation is related to a lower adenoma detection rate, longer procedure time, patient discomfort, and increased costs because of the need for repeat procedures.[3-6] An appropriate purgative type, volume, and timing of administration are needed to achieve sufficient bowel cleansing and patient tolerability.[7-9] Split-dose regimens, defined as drinking about half of the cleansing solution over two days, regardless of purgative type or volume, have been shown to improve colonic cleanliness, the adenoma detection rate, and patient tolerability compared with day-before regimens, and they have thus been recommended as a standard bowel preparation regimen in western countries.[10-13] Recently, especially for patients with an afternoon colonoscopy, same-day regimens are also recommended as an effective alternative to split-dose regimens.[12,13]

On the other hand, in Japan, same-day bowel preparation is commonly used for colonoscopy. The Japan Gastroenterological Endoscopy Technicians Society conducted a questionnaire survey in Japan, from August 2015 to February 2016, to investigate the bowel preparation practices for colonoscopy in 1,814 Japanese institutions [unpublished data]. All institutions contacted in this survey performed same-day preparation, with the most preferred bowel preparation regimen being PEG-ELS (45.1%), followed by PEG + ascorbic acid (ASC) (35.8%), magnesium citrate (17.8%), and 86.5% of them took an adjunctive agent such as sodium picosulfate solution (PICO) in the evening of the day before colonoscopy.

PEG-ASC, (Moviprep®, EA Pharma Co., Ltd., Tokyo, Japan) has been available in Japan since June 2013. A phase III trial evaluated the efficacy, tolerability, and safety of PEG-ASC compared with standard PEG-ELS without dietary restriction or laxatives.[14] In this study, the optimal colonoscopy preparation required 1.63 ± 0.38 L PEG-ASC. The addition of ASC reduced the volume of lavage solution with comparable efficacy and better tolerability than standard PEG-ELS. We demonstrated that the 1.5-L PEG-ASC regimen was better accepted by patients than the 2-L PEG-ELS,[15] with similar tolerability, bowel cleansing, and safety between regimens. Based on these results, same-day 1.5 L PEG-ASC and PICO the previous evening have become the standard colonoscopy preparation regimen in our hospital, and it is one of the most preferred regimens in Japan. However, in our subsequent study comparing how to take PEG-ASC, the rates of successful cleansing and patient acceptability of the same-day 1.5 L PEG-ASC regimen were 71.1% and 77.5%, respectively, which were not satisfactory.[16] A more effective colonoscopy preparation regimen is needed to improve efficacy and patient tolerability.

Although same-day regimens and split regimens showed similar bowel cleansing efficacy and overall tolerability, only for trials using the purgative type of PEG-ELS or PEG-ASC, the cleansing efficacy of split-regimens was better, though not significantly, than of same-day regimens.[17-19] Furthermore, for patient tolerance, one study showed less nausea and vomiting in split-regimens.[19] Despite the lower volume (1.5 L) of PEG-ASC, the necessity to drink such a large amount of liquid with an unacceptable taste followed by 0.75 L of clear liquid within about 2 hours has a negative impact on patient compliance. If the pretreatment were divided into two days, the impact may decrease. Therefore, we decided to compare the Western standard regimen, the split-dose regimen, with the Japanese standard regimen. We hypothesized that the split-dose regimen is as effective as the same-day regimen in cleansing efficacy, and, furthermore, that the

split-dose regimen has better patient tolerability in Japanese patients. The purpose of this study was to compare the efficacy and tolerability of split-dose 2 L PEG-ASC with same-day single dose 1.5 L PEG-ASC and 5 mL of PICO.

PATIENTS AND METHODS

The study was conducted at Aichi Cancer Center Hospital, Nagoya, and Aichi Hospital, Aichi Cancer Center Hospital, Okazaki from September 2016 to March 2018. This was a prospective, investigator-blinded, two-center, non-inferiority, randomized comparison of the same-day regimen of 1.5 L PEG-ASC + 5 mL PICO the day prior and the split-dose regimen of 2 L PEG-ASC in patients scheduled for colonoscopy. All included patients provided written, informed consent for inclusion. The ethics committees of both participating hospitals approved the study, which was registered with an international clinical trial registry (UMIN000023895).

All consecutive patients aged 20 years old and over scheduled for treatment colonoscopies such as polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection at each hospital were eligible to participate. The exclusion criteria were: patients with severe comorbidities (cardiac, renal, hepatic, or metabolic disease, ascites, etc.), patients with severe constipation (<2 bowel movements per week), patients with an allergy to PEG-ELS, patients with a history of gastric stapling or bypass procedure, or patients with a history of colorectal surgery.

METHODS

Randomization and blinding

The Pocock and Simon minimization method was used to perform the randomization to balance sex, age (<70 years or ≥70 years), and institution between the two groups.[20] A computer-generated, random-number list allocated patients to receive one of the two alternative bowel preparation regimens. Allocation concealment was ensured by an independent research assistant using a reputable web-based registry system managed by the Data Center of Nagoya University Hospital, Nagoya, Japan. Patients were randomized on the day when hospitalization was decided, and the independent research assistant entered each chosen regimen, which was then registered in the clinical pathway using an electronic medical record. Only the research assistant and the nurses in the ward could know how they were assigned.

Everyone who participated in this study, including endoscopists and endoscopy nurses, were blinded to treatment group. Patients were instructed not to discuss their bowel preparation with anyone other than the research assistant by a ward nurse. Comparisons between the same-day group and the split-dose group were made in an investigator-blinded fashion.

Bowel preparation methods (Fig. 1)

All patients were admitted to each hospital the day before colonoscopy. When patients were hospitalized, their ward nurses gave them an orientation talk about the assigned regimen. The ward nurse carefully explained how the product should be taken, emphasizing the importance of complete intake of the solution for a safe and reliable procedure, using easy-to-understand instructions. They were also instructed to eat a low-residue diet served in each hospital. The same-day group was asked to drink more than 1 L of clear liquid the day before colonoscopy, and instructed to take 5 mL of PICO 0.75%; (Laxoberon®: Teijin Pharma, Ltd., Tokyo, Japan) in the evening (at 9–10 pm). On the day of the colonoscopy, they received 1.5 L of PEG-ASC

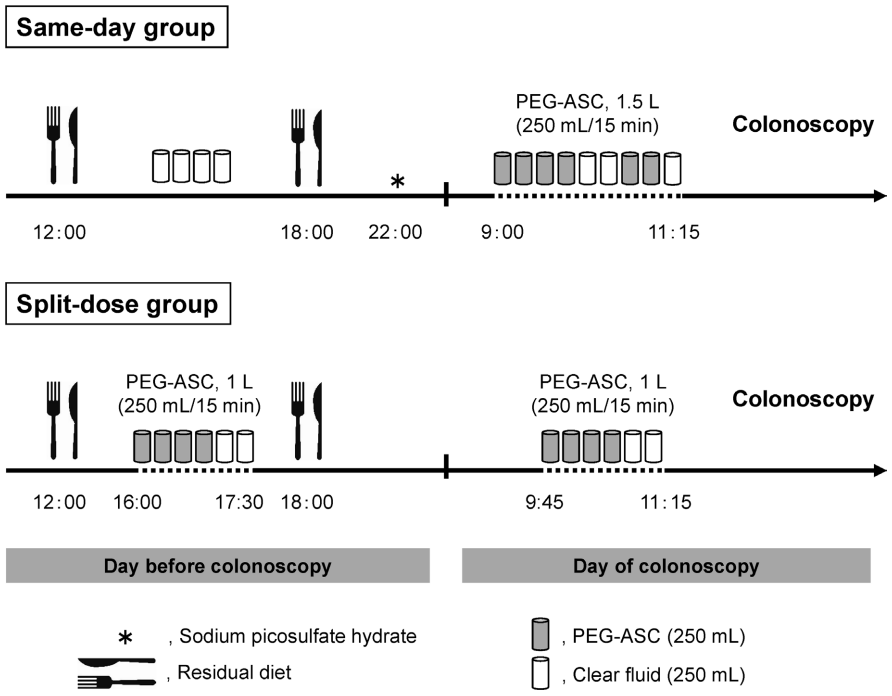

Fig. 1 The study schedule
PEG-ASC: polyethylene glycol electrolyte lavage solution containing ascorbic acid

consisting of 100.0 g macrogol 4000, 7.5 g sodium sulfate, 2.7 g sodium chloride, 1.0 g potassium chloride, 4.7 g ascorbic acid, 5.9 g sodium ascorbate, and lemon flavoring per each liter. They were instructed to drink the first 1 L of cleansing solution followed by 0.5 L of clear fluids at a rate of 0.25 L every 15 min from 9 am. After that, they were instructed to drink the remaining 0.5 L of cleansing solution followed by 0.25 L of clear fluids at the same rate by 11:15 am. The split-dose group was instructed to take 1 L of PEG-ASC followed by 0.5 L of clear liquids at a rate of 0.25 L every 15 min between 4 pm and 5.30 pm the day before colonoscopy, followed by another 1 L of PEG-ASC followed by 0.5 L of clear liquids at a rate of 0.25 L every 15 min between 9.45 am and 11:15 am on the day of colonoscopy. All colonoscopies were scheduled to be performed after 2 pm.

Evaluation of bowel preparation

Efficacy of bowel preparation was assessed by an endoscopist blinded to patient allocation using the Boston Bowel Preparation Scale (BBPS), on a 4-point scale (0–3) per colonic segment (right, transverse, and left colon).[21] Segment scores were summed to calculate the scores of each of the three segments, ranging from 0–9. 'Successful' bowel preparation was defined as total score of 6 or more, and all segment scores were 2 or more; others were considered 'failed' bowel preparation. The ward nurses checked patients' excretions within 1 hour after finishing the preparation on the day of colonoscopy. If solid stool with muddy excretions or no excretion was seen at that time, the patient was given an additional preparation, such as an additional 0.5 L of PEG-ELS or an enema.[16] In Japan, in cases of poor preparation, an enema is often given to promote defecation. Patients who received additional preparation were also

considered to have 'failed' bowel preparation. In this study, all of the procedures were performed by experienced endoscopists, all of whom had performed more than 1,000 colonoscopies. As described in a previous study,[16] each endoscopist performed calibration exercises involving more than 20 colonoscopies before the start of the study, based on their interpretation of the agreed upon scale anchors, to ensure concordance.

As one of the indicators of bowel cleansing effect, the disappearance of the mucus-surrounded gas bubbles in the colonic lumen was evaluated using the optimal visibility grade.[22] The overall mucosal visibility was graded using the following 3-grade scale: optimal was clear imaging with no or minimal amount of bubbles or foams that could be easily removed (grade 0); adequate was a modest amount of bubbles and foams that could be cleared within a minimal amount of time (grade 1); and insufficient was the presence of foam and bubbles that significantly reduced clear visualization of the mucosa (grade 2). Mucosal visibility was assessed in a pre-washing procedure before evaluation of BBPS.

Patient measurements

All patients were asked by ward nurses or the research assistant to complete a questionnaire immediately before the procedure to evaluate preparation completion, tolerability, adverse events, sleep quality, and willingness to repeat the same regimen. They were also asked to record the time and number of bowel movements from the start of ingestion to the appearance of clear excretion. Patient tolerability was measured by the patient's perceived ease or difficulty in taking the preparation on a 4-grade scale. Sleep quality was evaluated using a 4-grade scale according to sleep comfort and sleep disturbances due to the preparation during the night before colonoscopy compared to a usual day. Adverse events were defined by the degree of gastrointestinal symptoms such as nausea, vomiting, abdominal distension, and pain. These symptoms were scored on a 4-grade scale. Willingness to repeat the same regimen was also scored on a 4-grade scale.

Outcome measures

The primary end point of this study was demonstrating the non-inferiority of the split-dose regimen compared to the same-day regimen for successful bowel cleansing. The secondary end points were preparation completion, tolerability, adverse events, sleep quality, willingness to repeat the same regimen, and the rate of optimal mucosal visibility (score 0).

Statistical analysis

On the basis of data from a previous study,[16] the successful bowel cleansing rate with the same-day regimen was estimated to be 71.0%. It was expected that about 81.0% of the split-dose group would show adequate successful bowel cleansing, and the non-inferiority margin was set at –10%. This study was designed to have 80% power to establish non-inferiority (using a one-sided test with alpha of 0.025 and a target sample size of 72 per group). It was decided to enroll more than 150 patients to allow for an approximate drop-out rate of 5%. The primary analysis for non-inferiority was performed on the intention-to-treat population. Per-protocol analysis was performed in patients who did not receive additional treatment.

Descriptive statistics are presented as means ± standard deviation (SD) or as the number of patients (%). The two-sided *t*-test was used to compare the means of continuous variables; the likelihood ratio chi-squared test was used to compare categorical measures. The Mantel extension test adjusted for age and sex was applied to compare clinical outcomes between the two groups.

Categorical variables were compared using the Mantel extension test. P values < 0.05 were considered significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) at the Data Center of Nagoya University Hospital, Nagoya, Japan.

RESULTS

Patients' characteristics

From September 2016 to March 2018, 155 patients were screened for study inclusion, and all patients were randomized into two groups. Two patients in the split-dose group were excluded due to other disease or an accident (Fig. 2). Table 1 shows the baseline characteristics of the patients. There were no significant differences between the two groups.

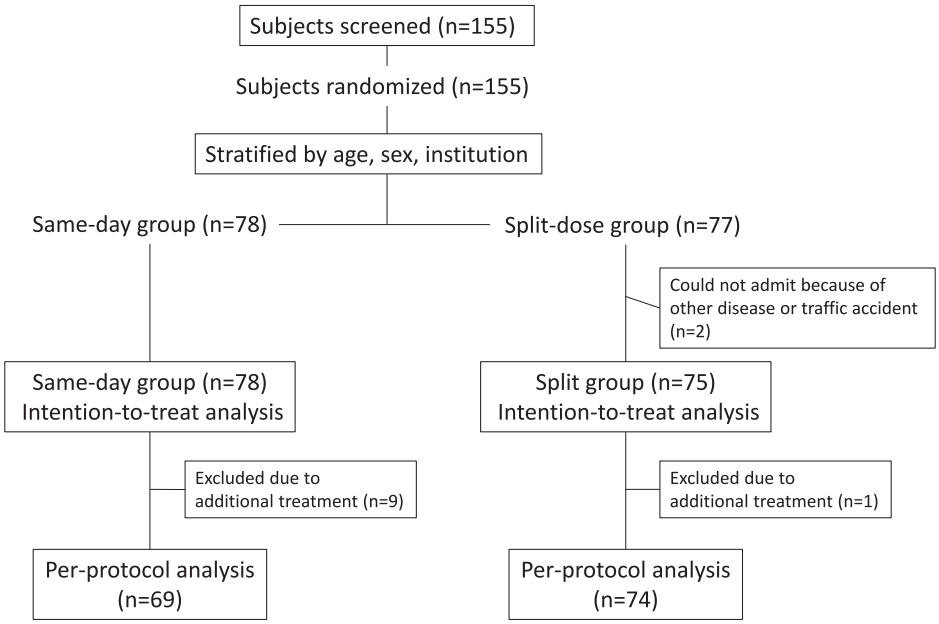

Fig. 2 Patient flow

Table 1 Patients' characteristics

Variable	Standard group	Split group	P value
No. of patients	78	75	
Age (y), mean±SD	62.7 ± 9.9	61.9 ± 11.1	0.63
Male/female	47/31	46/29	0.89
Height (cm)	162.8 ± 9.9	162.8 ± 9.1	0.98
Weight (kg)	62.4 ± 13.7	62.7 ± 13.2	0.87
Body mass index (kg/m^2)	23.4 ± 3.7	23.5 ± 3.1	0.81
Average sleeping time (h)	6.69 ± 1.14	6.49 ± 1.08	0.27
Bowel habit (daily) (n, %)	62 (79.5)	57 (74.0)	0.49

Bowel cleansing efficacy and endoscopic findings (Table 2)

Time to first defecation after the start of ingestion of bowel preparation was shorter in the same-day group compared with Day 1 in the split-dose group (P<0.001). In the split-dose group, the time to first defecation was shorter on Day 2 than on Day 1 (P<0.001) (Fig. 3). The frequency of defecation was lower on Day 2 in the split-dose group compared with the same-day group (P<0.01). Time to preparation was not significantly different between the same-day group and Day 2 of the split-dose group. The average time to last defecation before going to bed after the start of ingestion (4 pm) of bowel preparation was 281.7 minutes (around 9 pm; 95% confidence interval [CI] 262.4–300.9 minutes) (Fig. 4).

Table 2 Results of preparation and endoscopic findings

	Standard	Split group		
Variable		Day 1	Day 2	P value
No. of patients	78	77		
Time to take the solution (min)	115.3 ± 56.7	56.2 ± 23.1	59.1 ± 27.6	<0.001*
Time to first defecation (min, mean±SD)	54.8 ± 34.2	91.1 ± 56.3	47.1 ± 26.2**	0.12*
Frequency of defecation (times, mean±SD)	12.4 ± 4.3	6.8 ± 4.0	10.1 ± 4.7**	<0.01*
Time to preparation (min, mean±SD)	198.1 ± 93.8		175.9 ± 82.9	0.12*
Time to last defecation before going to bed		281.7 ± 83.5		
Preparation scale of last defecation (day 1) (watery clear/clear/muddy/soft stool/normal)		(18/40/14/1/1)		
Elapsed time from last fluid intake to colonoscopy (min, mean+SD)	229 ± 115		233 ± 118	0.82*
Cecal intubation rate (n,%)	78 (100)	77 (100)		
Insertion time (min, mean±SD)	8.8 ± 6.0	9.6 ± 5.5		0.41
Feeling of peristalsis (n, %)	15 (19.2)	12 (16.0)		0.60
Optimal visibility grade (0/1/2)	45/24/9	39/19/17		0.17
BBPS (PP)				
Right colon (mean±SD)	2.1 ± 1.0	2.1 ± 0.7		0.67
Transverse colon (mean±SD)	2.3 ± 1.0	2.5 ± 0.6		0.12
Left colon (mean±SD)	2.4 ± 1.0	2.6 ± 0.6		0.04
Successful bowel cleansing (n, %)***	65 (83.3)	69 (92.0)		0.10
No. with additional PEG intake or enema (n, %)	9 (11.5)	1 (1.3)		0.01

BBPS: Boston bowel preparation scale
PP: per-protocol analysis
* Same-day group vs. split-dose group (Day 2).
** P<0.001, split-dose group (Day 1) vs. split-dose group (Day 2).
*** Difference and 95% confidence interval in the successful bowel preparation rate between the same-day group and the split-dose group was 8.7% (–1.6% to 19.0%).

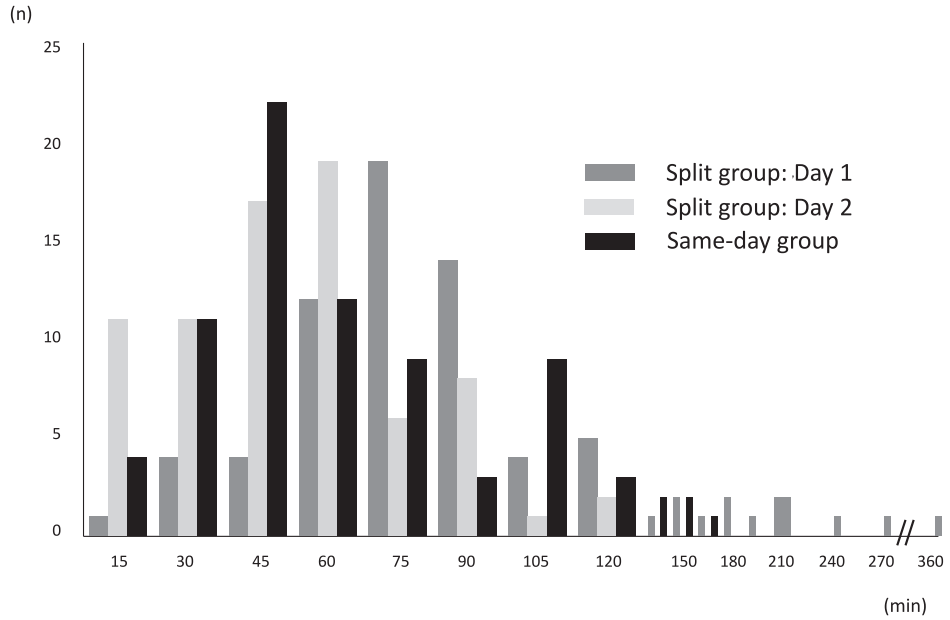

Fig. 3 Distribution of time to first bowel movement
The time to first defecation after the start of ingestion of bowel preparation was shorter in the same-day group compared with Day 1 of the split-dose group (P<0.001). In the split group, the time to first defecation was shorter on Day 2 compared with Day 1 (P<0.001).

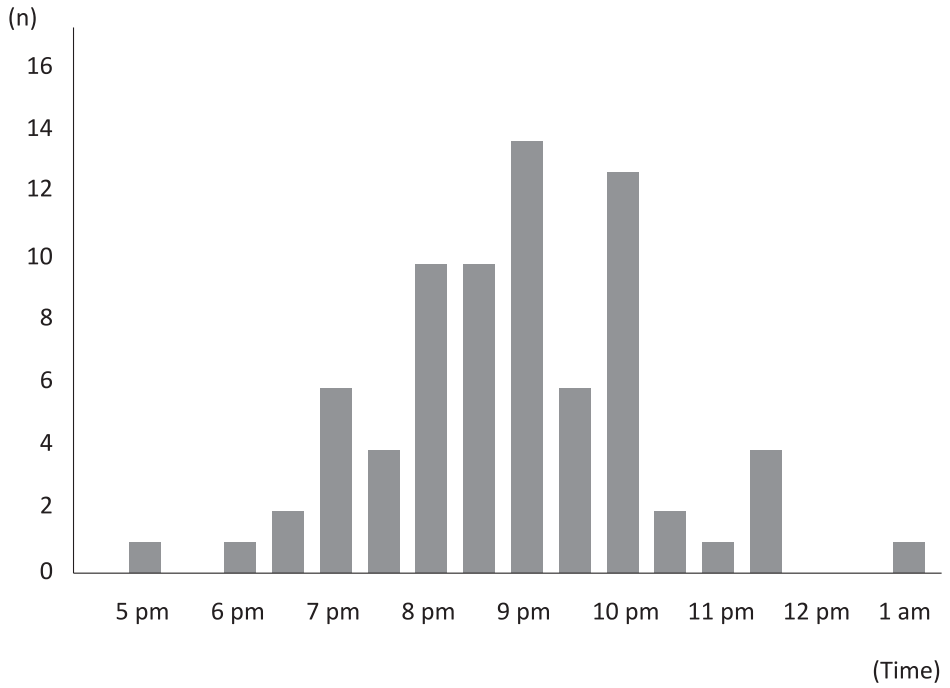

Fig. 4 Time to last bowel movement before sleep (split-dose group only)
The average time to last defecation before going to bed after the start of ingestion (4 pm) of bowel preparation was 281.7 minutes.

There was no significant difference between the same-day group (83.3%; 73.2%–90.8%) and the split-dose group (92.0%; 83.4%–97.0%) in the successful bowel preparation rate. The lower limit of the 95%CI of the difference in proportions between two groups was –1.6%, which was higher than the non-inferiority margin of –10%. In other words, the split-dose regimen was not inferior to the same-day regimen. The rate of patients who required additional preparation was higher in the same-day group (11.5%) than in the split-dose group (1.3%) (P=0.01).

There were no significant differences in the mean total BBPS score between the two groups. However, in the left colon, the mean BBPS score was significantly higher in the split-dose group (2.4 vs. 2.6; P=0.04).

Patient questionnaire

There was no difference in complete intake of the bowel cleansing solution between the two groups (Table 3). In terms of sleep quality of the day before colonoscopy, there were no differences between the two groups in average time, sleep disturbances, number of times waking up for evacuation, and degree of sleeping. Although no serious adverse events occurred, the rate of vomiting tended to be higher in the same-day group and the rate of toilet accidents tended to be higher in the split-dose group (P=0.05, respectively).

With respect to patient preference, the rate of willingness to repeat the same regimen was higher for the same-day group than for the split-dose group (77% vs. 47%; P<0.001).

Table 3 Patient tolerance and acceptance

Variable	Standard	Split group		P value
		Day 1	Day 2	
No. of patients	78	75		
100% intake of solution (n,%)	72 (92.3)	66 (88.0)	72 (96.0)	0.75*
Average sleeping time of Day 1 (h)	6.6 ± 1.6	6.5 ± 1.4		0.80
Did the evacuation disturb your sleep? Yes (n,%)	20 (26.0)	19 (26.4)		0.95
No. of times got up for evacuation	1.9 ± 0.91	2.4 ± 1.6		0.27
Could you sleep well compared to usual day? (well/fair/difficult/very difficult) (%)	(18/44/30/8)	(14/47/36/3)		0.95
Did you feel hungry in the night time of day 1? (none/mild/moderate/severe) (%)	(34/37/25/4)	(34/41/21/4)		0.76
How easy/difficult to take preparation? (easy/fair/difficult/very difficult) (%)	(41/43/8/8)	(37/40/15/8)		0.47
Any symptoms (%)				
Nausea (none/mild/moderate/severe)	(87/6/6/1)	(88/7/4/1)		0.74
Vomiting (no/yes)	(75/5)	(100/0)		0.05
Distension (none/mild/moderate/severe)	(31/36/26/7)	(36/36/20/8)		0.67
Abdominal pain (none/mild/moderate/severe)	(87/10/3/0)	(87/8/5/0)		0.66

Toilet accident (eg, wet one's pants etc.) (no/attempt/yes) (%)	(87/9/4)	(77/13/10)	0.05
Willingness to repeat the same preparation regimen (%) (yes/yes, if anything/no, if anything/no)	(32/45/15/8)	(20/27/30/23)	P<0.001

* Same-day group vs. split-dose group (Day 2).

DISCUSSION

In Japan, the same-day PEG-ELS regimen with some laxatives such as PICO the previous evening has traditionally been used for colonoscopy preparation. This is the first study to evaluate the efficacy and tolerability of the split-dose regimen compared to the same-day regimen in Japan. The present results showed that the split-dose regimen was non-inferior to the same-day regimen in terms of bowel cleansing. Although patient tolerance was similar between the two groups, patients were more willing to repeat the same-day regimen.

Recently, two large meta-analyses compared the efficacy and tolerability of split-dose and same-day regimens.[23,24] In the first report,[23] 484 studies were retrieved, with 14 trials meeting inclusion criteria. The results showed that the rate of patients receiving same-day regimens and split-dose regimens with adequate preparation in the pooled analysis were 79.4% and 81.7%, respectively, with no significant differences in 11 trials (OR 0.92, 95%CI 0.62–1.36). In terms of patient tolerance, willingness to repeat the regimen, plus completion of bowel preparation fluid intake, did not differ significantly between regimens (OR 1.08, 0.45–2.61; OR 0.89, 0.45–1.78, respectively). In another report,[24] 1216 studies were retrieved with 15 trials meeting inclusion criteria. The results showed that the categorical outcome of high-quality bowel preparation for any same-day regimen versus any split-dose regimen did not differ, with adequate preparation in the pooled analysis of 76.2% and 80.2%, respectively, and no significant differences in 11 trials. Willingness to repeat and tolerability/compliance were similar (RR 1.14, 0.96–1.36; RR 1.00, 0.96–1.04, respectively) between regimens. Adverse events were similar except for bloating, which was less frequent in the same-day group. However, both studies included heterogeneity in study design of component trials. In addition to the difference of purgatives, including PEG, PEG-ASC, sodium phosphate, and magnesium citrate, etc., with various dosages in both regimens, there were different methods of preparation, such as diet during preparation, the length of time for diet restriction, and use of laxatives. In this study, split-dose 2-L PEG-ASC was compared with same-day single-dose 1.5-L PEG-ASC with 5 mL of PICO. The difference of 0.5 L of PEG-ASC, regardless of the additional use of PICO in the same-day group, may have led to better outcomes for cleansing efficacy in the left colon and the low rate of additional preparation in the split-dose group; however, time to first defecation after the start of ingestion of bowel preparation was significantly shorter on Day 2 compared with Day 1 in the split-dose group, and the total frequency of defecation during two days was significantly higher in the split-dose group. Day 1 intake of PEG-ASC may boost defecation on Day 2. Although patients with severe constipation were excluded in this study, the booster effect of PEG-ASC the day before colonoscopy may lead to successful bowel preparation for these patients. Furthermore, the cleansing efficacy of the same-day regimen in this study improved from 71.1% to 83.3% compared to a previous study.[16] We think that one of the reasons was the difference between outpatients and inpatients. Although the cleansing efficacy did not differ between the two groups, the split-dose regimen may become an option for patients with poor defecation who required

additional preparation on previous examinations.

As for patient tolerance, there were no significant differences between the two groups. However, the number with vomiting was higher in the same-day group, and the number with toilet accidents such as fecal incontinence was higher in the split-dose group. In the same-day group, patients must ingest 2.25 L (1.5 L PEG-ASC + 0.75 L clear liquid) within 135 minutes. In the split-dose group, the total dose each day was 1.5 L (1 L PEG-ASC + 0.5 L clear liquid). The difference in the amount of liquid may lead to vomiting in the same-day group. Toilet accidents may be related to the shorter time to first defecation on Day 2.

In planning this study, when patients in the split-dose group should start taking PEG-ASC to avoid sleep disturbance on Day 1 was considered. Previous studies reported that patients using same-day regimens had better sleep quality compared with those using split-dose regimens[17,18]; therefore, it was decided that patients should start taking PEG-ASC from 4 pm (before a meal) to decrease sleep disturbances, nausea, and vomiting. It was found that early intake of PEG-ASC succeeded in making no significant difference in sleep quality between the two groups. In a meta-analysis,[23] same-day regimens had better sleep quality than split-dose regimens. One of the reasons why split-dose regimens interfered with sleep may be that the time to start taking purgatives was late, from 6 pm to 9 pm. In the present study, with respect to the time to last defecation before sleep, 80% of patients completed the last defecation by 10 pm. Thus, it may be possible that the time to start taking PEG-ASC could be delayed 2 or 3 hours (to 6 to 7 pm). Furthermore, we served a low-residue diet after Day 1 of PEG-ASC intake. There was also concern about eating a diet after taking PEG-ASC in planning this study, which did not affect the efficacy of bowel cleansing or patient tolerance. Although various ways to improve patient tolerability in split-dose regimens were tried, the willingness to repeat the same regimen was significantly lower in the split-dose group. One of the reasons may be that all patients in this study underwent the same-day regimen on previous occasions before this study, so they were reluctant to take PEG-ASC over 2 days. From the perspective of patient tolerability, split-dose regimens may be appropriate for patients who have vomited with previous preparations or patients who think that they cannot drink more than 1.5 L of cleansing solution and about 1 L of water in several hours. Furthermore, since the time to first defecation and time to preparation on the day of the colonoscopy was shorter in the split-dose regimen, a split-dose regimen may be useful for morning colonoscopy in the future.

There are some limitations in this study. First, this study was conducted in an inpatient setting to ensure patient safety and to maximize compliance, because it was the first trial of a split-dose regimen in Japan. However, this approach minimized bias and provided high rates of good bowel preparation in both groups. Second, in the same-day group, an adjunctive agent such as PICO was given the day before colonoscopy. Strictly speaking, it was not a same-day regimen. However, it was common to give laxatives the day before colonoscopy in Japan, so this study was conducted in a form suitable for practice. Third, this study included only Japanese patients. Body composition and size of Asian populations are different from those of Western populations. Therefore, the result of the current study may not be applicable to Western countries' populations. Fourth, the adenoma detection rate was not evaluated, because endoscopic treatment was planned for the inpatients in this study.

CONCLUSION

The split-dose regimen of 2-L PEG-ASC was not inferior to the same-day regimen of 1.5 L PEG-ASC + 5 mL PICO the day prior in terms of the efficacy of bowel preparation for afternoon

colonoscopy. However, the same-day regimen was preferred by patients. The 2-L PEG-ASC split-dose regimen is feasible for Japanese patients and may be an option for patients with poor defecation who required additional preparation on previous examinations or patients who had vomited during previous preparations.

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CONFLICTS OF INTEREST

Masahiro Tajika received honoraria from EA Pharma Co., Ltd.
All other authors have no conflicts of interest to declare for this work.

AUTHOR CONTRIBUTIONS

MT contributed to study concept and design, data collection, and writing of the draft manuscript; TT, MI, YH, SO, NM, TK, NO, SM, KT, MO, YK, and SK contributed to study design and data collection; MA contributed to analysis and interpretation of data. VB, HK, and YN contributed to study design and revised the manuscript. All authors read and approved the final manuscript.

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