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Original Article

Efficacy and safety of oral sulfate solution for bowel preparation in Japanese patients undergoing colonoscopy: Noninferiority-based, randomized, controlled study

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Objectives: To compare the efficacy and safety of oral sulfate solution administered using the same-day dose and the split-dose regimens with those of polyethylene glycol plus ascorbate solution, used for bowel preparation in Japanese patients undergoing colonoscopy.

Methods: This multicenter (n = 13), randomized, active-controlled, colonoscopist- and image evaluator-blinded, noninferiority study with parallel-group comparison recruited 632 patients from December 2018 to June 2019. Of these, 602 patients were divided into the oral sulfate solution same-day dose group (n = 200); oral sulfate solution split-dose group (n = 202); and polyethylene glycol plus ascorbate same-day dose group (n = 200). Differences in the efficacy rates between the polyethylene glycol plus ascorbate group and each oral sulfate solution group were calculated using the asymptotic method. The safety of the oral sulfate solution was evaluated, based on the occurrence of adverse events and reactions.

Results: Both oral sulfate solution protocols were confirmed as noninferior to the polyethylene glycol plus ascorbate protocol for bowel-cleansing. The occurrence of adverse reactions was significantly lower in the oral sulfate solution same-day dose group than in the polyethylene glycol plus ascorbate group (P = 0.010). The occurrence of adverse reactions was not significantly different between the oral sulfate solution split-dose and the polyethylene glycol plus ascorbate group.

Conclusions: Oral sulfate solution is not only safe and efficacious but also not inferior to polyethylene glycol plus ascorbate solution (active control). It could be used for bowel preparation in Japanese patients scheduled for colonoscopy (Clinical trial registration number: NCT03794310).

Key words: colonoscopy, human, oral sulfate solution, polyethylene glycol, sulfate

INTRODUCTION

THE DEMAND FOR colonoscopy is increasing owing to the increasing number of colorectal cancer cases. Sufficient bowel preparation to remove intestinal contents is an essential pretreatment before colonoscopy for finding

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flat and depressed tumors. Insufficient bowel preparation increases the difficulty and time needed for examination,[1] lowers the detection rate of adenomas,[2] and can cause adverse events.[3] Bowel preparation is also important for endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR); the Japanese guidelines for colon ESD/EMR include recommendations on bowel preparation.[4]

Polyethylene glycol-electrolyte lavage solution (PEG-ELS) has been used widely for decades, has a good bowel-cleansing effect, and is safe to use.[5,6] However, bowel preparation with PEG-ELS requires the administration of a large amount of the solution of up to 4 L; this decreases the rate of patient acceptance. Polyethylene glycol plus ascorbate solution (PEG-ASC), a hypertonic agent, was developed later to improve patient acceptance; ingesting 2 L of the drug solution and 1 L of water had the same efficacy as PEG-ELS.[7] PEG-ASC is the most widely used agent for bowel preparation in Japan.

The oral sulfate solution (OSS), developed in the United States in 2010, contains sulfate salts of sodium, magnesium, and potassium as active ingredients. This formulation is advantageous because the dose of the drug solution required for bowel preparation is smaller than those of conventional bowel preparation agents; approximately 960 mL of the drug solution and twice that amount of water are required. The efficacy and safety of OSS have been reported.[8,9] In the United States, the split-dose dosage regimen is approved (i.e., taking the drug the evening before and the morning of colonoscopy). The split-dose regimen has a higher patient acceptance because of the lower fluid intake required each day. A phase III trial conducted in the United States[10] and some South Korean studies[11,12] confirmed the noninferiority of OSS to PEG-ASC. OSS has also been used in Europe and certain Latin American territories. However, it has not yet been approved in Japan. A pilot study on OSS[13] on Japanese people demonstrated no major safety issues and good bowel-cleansing effect with a split-dose of OSS. Therefore, we believe that OSS can elicit an excellent bowel-cleansing effect on Japanese people.

This study is the first phase III comparative study performed to confirm the efficacy and safety of OSS in Japanese patients undergoing colonoscopy. The results were compared with those of PEG-ASC. Same-day dose (taken on the day of colonoscopy) is the mainstream regimen in Japan; therefore, this study examined the efficacy and safety of OSS administered in both split-dose and same-day dose regimens.

METHODS

Study design

THIS WAS A multicenter, randomized, active-controlled, colonoscopist-/image evaluator-blinded, noninferiority study with parallel-group comparison. It was conducted—based on the tenets of the Declaration of Helsinki and Japanese GCP standards—in 13 medical institutions in Japan with colonoscopy specialists. The protocol and informed consent form were approved by the Institutional Review Board of each medical institution. The trial was registered with Clinical Trial.gov (http://www.clinicaltrials.gov/NCT03794310).

The participants were recruited from December 2018 to June 2019. Patients who satisfied the following inclusion criteria were included: (i) Japanese and aged ≥20 years at the time of providing consent, (ii) required colonoscopy (excluding emergency cases), and (iii) were able to fill in the informed consent form for participation. The main exclusion criteria were patients with: (i) current or suspected gastrointestinal tract obstruction, (ii) current or suspected intestinal perforation, (iii) current or suspected toxic megacolon, (iv) current or suspected delayed gastric emptying (e.g., gastroparesis), and (v) intestinal stricture or severe constipation (e.g., bowel movements less than twice weekly or require regular laxative use).

Study drugs

Oral sulfate solution (480 mL) containing anhydrous sodium sulfate (17.51 g), potassium sulfate (3.13 g), and magnesium sulfate hydrate (3.276 g) was procured from Nihon Pharmaceutical Co., Ltd., Tokyo, Japan; a maximum of 960 mL was required to complete the bowel preparation. PEG-ASC solution (EA Pharma Co., Ltd., Tokyo, Japan), a commercially available bowel preparation reagent approved by the Ministry of Health, Labour and Welfare (Tokyo, Japan), was used as the control; a maximum of 2000 mL was required to complete the bowel preparation.

Procedures

After the patients provided written informed consent, they underwent screening tests. Eligible patients were enrolled using a central registration method. The patients were randomly allocated, using a dynamic allocation method, in a 1:1:1 ratio to the OSS same-day dose group, OSS split-dose group, or PEG-ASC same-day dose group. Age, sex, and body weight were the factors determining allocation. The

allocated patients were not permitted to use laxatives, enema agents, antidiarrheal drugs, or bowel-cleansing agents other than those used in the study, from two days before, to the end of the colonoscopic examination.

In the OSS same-day dose group, 480 mL of OSS and 960 mL of water were administered on the day of colonoscopy. If the stools did not become clear, 240 mL of OSS and 480 mL of water were administered once or twice until the stools became clear. OSS administration was initiated at least 3 h before the start of colonoscopy.

In the OSS split-dose group, 480 mL of OSS and 960 mL of water were administered once on the day before and once on the day of colonoscopy. If the stools became clear during administration on the day of colonoscopy, the administration was stopped, and the patient was instructed to drink twice the amount of water as that of the administered OSS. On the day of colonoscopy, OSS administration was initiated at least 2 h before the start of colonoscopy.

In the PEG-ASC same-day dose group, 1000 mL of PEG-ASC and 500 mL of water were administered once or twice on the day of colonoscopy until the stools became clear. PEG-ASC administration was initiated at least 3 h before the start of colonoscopy.

Patients whose bowels were prepared with the study drug evaluated their acceptance levels of preparation and underwent colonoscopy. The colonoscopists captured images of the five segments of the large intestine (i.e., cecum/ascending, transverse, descending, and sigmoid colons, and the rectum) after cleaning the observation site (i.e., through normal suction, aeration, or water, washing) under blinded conditions. OSS and PEG-ASC have different dosage forms and dosing methods. Therefore, at the medical institution, only the colonoscopists were blinded.

The images were then submitted to the Image Evaluation Committee (IEC), which is a third-party evaluation committee. The IEC-evaluated images were randomized to hide the medical institution, subject, administration group, and imaged site. Randomized codes were computer-generated by an independent staff and were not disclosed to the colonoscopists or image reviewers until the end of the study.

Blood and urine samples were tested at the time of screening and one week after colonoscopy. Electrocardiograms were performed at the time of screening, after administration of the study drug, and one week after colonoscopy.

Outcome measures

The primary endpoint was achieving an effective rate of overall bowel-cleansing, as evaluated by the IEC using the bowel preparation evaluation scale (Table 1). Cases with ratings of 1 or 2 on the scale for the five large intestine segments were considered to have had effective bowel-cleansing.

The secondary endpoints were the evaluation of the efficacy rate of the overall bowel-cleansing effect by the colonoscopist—using the bowel preparation evaluation scale and on the Ottawa Scale, the time required to complete bowel preparation on the day of colonoscopy, the doses of the study drug and water, and the patient's acceptance of the procedure. The occurrence of adverse events and reactions was investigated as safety evaluation items. Additionally, the required doses of OSS, PEG-ASC, and water were aggregated after conducting the procedures.

Statistical analysis

The primary endpoints were the number of cases and efficacy (%) in each group, based on the scores determined by IEC evaluation with two-sided 95% confidence intervals (CIs) and calculated using the exact Clopper–Pearson method. In addition, the differences in efficacy rates between the OSS same-day dose and split-dose groups compared to the PEG-ASC group and the 95% CIs on both sides thereof were calculated with the asymptotic method. Noninferiority was demonstrated if the lower limits of the 95% CIs for the differences in efficacy rates between the PEG-ASC and each OSS group exceeded the noninferiority margin of −10%.

A closed testing procedure was performed to verify the noninferiority of the OSS split-dose and PEG-ASC groups only when the noninferiority of the OSS same-day dose and PEG-ASC groups was verified. Furthermore, when noninferiority was verified for each group, superiority was verified with the closed testing procedure using the same order as above. Superiority was demonstrated if the lower limits of the 95% CIs for the differences in efficacy rates between the PEG-ASC and each OSS group exceeded the equivalence limit of 0%.

Based on the results of clinical trials in the United States and assuming a 90% efficacy rate for OSS and PEG-ASC, a one-sided significance level of 0.025, a noninferiority

Table 1 Bowel preparation evaluation scale

1	Almost no residual stool in the colon; this enables good observation
2	Some residual stool but it does not impede observation
3	Observation impeded because of residual stool
4	Observation impossible because of the large amount of residual stool
5	Undeterminable

equivalence limit $\Delta = 0.10$, and a power of 90%, the required number of patients was 190 per group. Taking into consideration the withdrawals before the administration of the study drug, the target sample size was set at 200 per group (i.e., 600 patients for the three groups).

RESULTS

FIGURE 1 SHOWS the flow chart of this study. A total of 618 subjects were enrolled. The study drug was administered to 602 (OSS same-day dose group, $n = 200$ patients; OSS split-dose group, $n = 202$ patients; PEG-ASC group, $n = 200$ patients), and was set as the largest analysis set and safety analysis set. The characteristics of the patients enrolled in this study are shown in Table 2.

Efficacy evaluation

The overall efficacy rate of the bowel-cleansing effect (95% CI) was 97.0% (93.6–98.9) in the OSS same-day dose group, 92.1% (87.5–95.4) in the OSS split-dose group, and 95.0% (91.0–97.6) in the PEG-ASC group. The differences in efficacy rates of the OSS same-day dose and split-dose groups, relative to the PEG-ASC group, and the respective two-sided 95% CIs were 2.0% (−1.8 to 5.8) and −2.9% (−7.7 to 1.9). In the OSS same-day dose and split-dose groups, the lower limit of the 95% CI for the difference in efficacy rate compared to the PEG-ASC group exceeded the noninferiority margin of −10%, thereby demonstrating noninferiority relative to the PEG-ASC group (Table 3). Then, when we tried to verify superiority, we were unable to demonstrate the superiority of the OSS same-day dose group over the PEG-ASC group. Therefore, superiority was not verified for the OSS split-dose group.

Table 4 shows the results of the secondary endpoints. The time taken to complete the bowel preparation on the day of colonoscopy was significantly shorter in the OSS split-dose group ($P < 0.001$) than the PEG-ASC group. No notable differences were observed for the remaining secondary endpoints between the three groups.

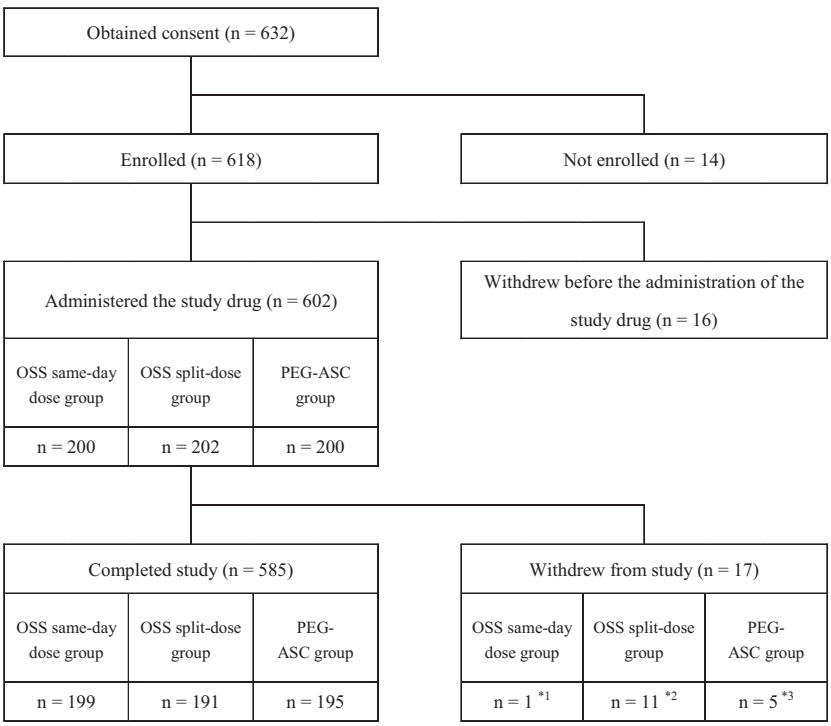

Figure 1 Flow chart of this study. *[1] Discontinued from the study because the patient was using or had used a prohibited concomitant drug ($n = 1$). *[2] Discontinued from the study because the patient was using or had used a prohibited concomitant drug ($n = 4$), faced an adverse event ($n = 3$), had difficulty continuing with the clinical study ($n = 1$), or withdrew consent ($n = 3$). *[3] Discontinued from the study because the patient was using or had used a prohibited concomitant drug ($n = 1$), faced an adverse event ($n = 2$), or had difficulty continuing with the clinical study ($n = 2$).

Table 2 Characteristics of the patients enrolled in this study

Characteristic	OSS same-day dose group (*n* = 200)	OSS split-dose group (*n* = 202)	PEG-ASC group (*n* = 200)	*P*-value	
Sex, *n* (%)					
Male	115 (57.5)	115 (56.9)	119 (59.5)	0.684*	0.601**
Female	85 (42.5)	87 (43.1)	81 (40.5)		
Age (years)					
Mean (SD)	53.5 (13.6)	53.7 (13.5)	53.3 (13.3)	0.890***	0.780****
Range	20–81	21–82	20–82		
Weight (kg)					
Mean (SD)	63.8 (12.7)	64.5 (13.3)	65.0 (13.3)	0.366***	0.705****
Height (cm)					
Mean (SD)	164.7 (8.8)	164.8 (8.7)	164.9 (9.5)	0.877***	0.895****
Reason for having colonoscopy, *n* (%)					
Positive fecal occult blood test	48 (24.0)	38 (18.8)	47 (23.5)	0.664*	0.668**
Medical checkup or colorectal cancer screening	63 (31.5)	73 (36.1)	70 (35.0)		
Routine follow-up	48 (24.0)	53 (26.2)	51 (25.5)		
Other	41 (20.5)	38 (18.8)	32 (16.0)		
Number of bowel movements in the week before taking the study drug, *n* (%)					
<7 times	39 (19.5)	49 (24.3)	46 (23.0)	0.392*	0.766**
≥7 times	161 (80.5)	153 (75.7)	154 (77.0)		
Previous colonoscopy, *n* (%)					
No	89 (44.5)	85 (42.1)	91 (45.5)	0.840*	0.489**
Yes	111 (55.5)	117 (57.9)	109 (54.5)		
Comorbidities, *n* (%)					
No	31 (15.5)	29 (14.4)	31 (15.5)	1.000*	0.747**
Yes	169 (84.5)	173 (85.6)	169 (84.5)		
Diabetes, *n* (%)					
No	188 (94.0)	192 (95.0)	189 (94.5)	0.829*	0.804**
Yes	12 (6.0)	10 (5.0)	11 (5.5)		
<Time for colonoscopy>					
Observation time (min)					
Mean (SD)	9.5 (6.2)	9.3 (5.2)	10.0 (5.6)	0.712***	0.405****
Overall procedure time (min)					
Mean (SD)	14.8 (7.9)	15.0 (7.0)	15.7 (7.2)	0.775***	0.209****

OSS, oral sulfate solution; PEG-ASC, polyethylene glycol plus ascorbate solution.
*Based on the χ^2 test (OSS same-day dose group vs. PEG-ASC group).
**Based on the χ^2 test (OSS split-dose group vs. PEG-ASC group).
***Based on the *t*-test (OSS same-day dose group vs. PEG-ASC group).
****Based on the *t*-test (OSS split-dose group vs. PEG-ASC group).

Adverse events

Table 5 shows the incidence of adverse events and reactions. No deaths or serious adverse events occurred. The incidence of adverse events was 4.0% (8/200) for the OSS same-day dose group, 9.4% (19/202) for the OSS split-dose group, and 7.5% (15/200) for the PEG-ASC group. There were no significant differences between the PEG-ASC and the two OSS groups (taken individually). The incidence of adverse reactions was 0.5% (1/200) in the OSS same-day dose group, 6.4% (13/202) in the OSS split-dose group, and 4.5% in the PEG-ASC group (9/200). Comparing the incidence of adverse reactions in the PEG-ASC group with each OSS group separately, we found that the incidence in the OSS same-day dose group was significantly lower than that in the PEG-ASC group ($P = 0.010$). The incidence did not vary significantly between the OSS split-dose group and the PEG-ASC group. Follow-up studies were conducted only when an adverse event occurred or when they were deemed necessary.

Table 3 Overall efficacy rate of the bowel-cleansing effect, as evaluated by the Image Evaluation Committee, based on the bowel preparation evaluation scale

	OSS same-day dose group (n = 200)	OSS split-dose group (n = 202)	PEG-ASC group (n = 200)	P-value (noninferior)		P-value (superior)
Efficacy rate, % (n)	97.0 (194)	92.1 (186)	95.0 (190)			
Difference in efficacy rate (95% CI)†	2.0 (−1.8, 5.8)	−2.9 (−7.7, 1.9)		<0.001*	<0.001**	>0.05***

OSS, oral sulfate solution; PEG-ASC, polyethylene glycol plus ascorbate solution.
*The hypothesis test is that the lower limit of the 95% CI of the difference in the efficacy rate does not fall below the noninferiority margin (OSS same-day dose group vs. PEG- ASC group; noninferiority margin is −10%).
**The hypothesis test is that the lower limit of the 95% CI of the difference in the efficacy rate does not fall below the noninferiority margin (OSS split-dose group vs. PEG- ASC group; noninferiority margin is −10%).
***The hypothesis test is that the lower limit of the 95% CI of the difference in the efficacy rate does not exceed the equivalence limit (OSS same-day dose group vs. PEG- ASC group; equivalence limit is 0%).
†Difference in relation to the PEG-ASC group.

Table 4 Results of the secondary endpoints

	OSS same-day dose group	OSS split-dose group	PEG-ASC group	P-value	
Efficacy rate of the overall bowel-cleansing effect (endoscopists)					
Efficacy rate, % (n)	89.0 (178)	86.1 (174)	86.5 (173)		
Difference in the efficacy rate (95% CI)†	2.5 (−3.9, 8.9)	−0.4 (−7.1, 6.4)			
Ottawa Scale score					
Mean (SD)	4.2 (3.2)	4.2 (3.7)	4.6 (3.4)	0.354*	0.126**
Time to complete the bowel preparation (min)					
Mean (SD)	170.2 (57.4)	119.0 (45.0)	165.2 (51.3)	0.362***	<0.001****
Study drug and water dose (mL)					
Mean (SD)	2384.3 (545.2)	2866.9 (86.5)	2485.3 (571.8)		
Study drug dose (mL)					
Mean (SD)	794.8 (181.8)	956.4 (26.5)	1656.8 (381.2)		
Water dose (mL)					
Mean (SD)	1589.5 (363.5)	1910.5 (66.6)	828.4 (190.6)		
Subject acceptability evaluation, mean (SD)					
Taste of study drug	5.3 (2.4)	4.9 (2.4)	6.4 (2.4)		
Amount of study drug	6.1 (2.2)	5.7 (1.8)	5.9 (2.1)		
Amount of water taken after the study drug	7.2 (2.1)	6.7 (2.3)	7.6 (1.9)		
Acceptability (overall evaluation)	7.3 (2.3)	6.6 (2.6)	7.0 (2.4)		

OSS, oral sulfate solution; PEG-ASC, polyethylene glycol plus ascorbate solution.
*Based on the Wilcoxon rank-sum test (OSS same-day dose group vs. PEG-ASC group).
**Based on the Wilcoxon rank-sum test (OSS split-dose group vs. PEG-ASC group).
***Based on the t-test (OSS same-day dose group vs. PEG-ASC group).
****Based on the t-test (OSS split-dose group vs. PEG-ASC group).
†Difference in relation to the PEG-ASC group.

DISCUSSION

HEREIN, WE COMPARED the efficacy and safety of OSS with those of PEG-ASC in Japanese patients undergoing colonoscopy. Our study was the first phase III study conducted in Japan comparing the properties and performance of OSS with those of PEG-ASC. In addition, the study was a novel attempt to investigate the same-day OSS regimen (not approved in the United States at the time of writing this paper).

The bowel preparation evaluation scale is a modification of the Boston bowel preparation scale, which is an

Table 5 Summary of adverse events and adverse reactions

	OSS same-day dose group (*n* = 200)	OSS split-dose group (*n* = 202)	PEG-ASC group (*n* = 200)
Number of cases with adverse events, *n* (%)	8 (4.0)[†]	19 (9.4)[‡]	15 (7.5)
Adverse events experienced by ≥2 patients in any group, *n* (%)			
Nausea	1 (0.5)	4 (2.0)	1 (0.5)
Vomiting	1 (0.5)	4 (2.0)	1 (0.5)
Nasopharyngitis	1 (0.5)	1 (0.5)	3 (1.5)
Protein in urine	0 (0.0)	1 (0.5)	2 (1.0)
Number of cases with adverse reactions, *n* (%)	1 (0.5)[§]	13 (6.4)[¶]	9 (4.5)
Adverse reactions seen in two or more subjects in any group, *n* (%)			
Nausea	0 (0.0)	4 (2.0)	1 (0.5)
Vomiting	0 (0.0)	4 (2.0)	1 (0.5)
Protein in urine	0 (0.0)	1 (0.5)	2 (1.0)

OSS, oral sulfate solution; PEG-ASC, polyethylene glycol plus ascorbate solution.
[†]No significant difference in incidence ($P = 0.132$, based on the χ^2 test [OSS same-day dose vs. PEG-ASC group]).
[‡]No significant difference in incidence ($P = 0.492$, based on the χ^2 test [OSS split-dose group vs. PEG-ASC group]).
[§]Significant difference in incidence ($P = 0.010$, χ^2 test [OSS same-day dose group vs. PEG-ASC group]).
[¶]No significant difference in incidence ($P = 0.393$, based on the χ^2 test [OSS split-dose group vs. PEG-ASC group]).

internationally established evaluation index.[14] The bowel-cleansing effects of the OSS same-day dose and split-dose groups were confirmed to be noninferior to that of the PEG-ASC group. However, the superiority of OSS over PEG-ASC was not demonstrated. Our results were similar to those obtained for an OSS split-dose regimen in a phase III trial in the United States. Moreover, no notable differences that undermined generalizability in efficacy rates or patient demographic data were observed between the study groups. The efficacy was higher with the same-day dose regimen than that with the split-dose regimen because patients received the entire dose of the study drug in one shot on the day of colonoscopy in the same-day dose regimen. Results of the patient acceptability evaluation were nearly the same in the three groups. The efficacy rate evaluated by the IEC was higher than the rate evaluated by colonoscopists by approximately 10% in each group; this may be because the committee used only the colonoscopy images to evaluate the efficacy while the colonoscopists evaluated the entire bowel. The efficacies of the OSS-based bowel preparations and the PEG-ASC-based bowel preparation were not significantly different when evaluated by the IEC or colonoscopists.

The OSS used in this study is a formulation containing three types of sulfate salts as active ingredients and no PEG. The three sulfate salts have laxative effects. However, bowel preparations containing only sulfates are not approved in Japan. Besides, in Japan, the bowel preparation regimen for colonoscopies is usually administered entirely on the day of the examination. This situation is different in the United States. The 2015 American Society for Gastrointestinal Endoscopy guidelines recommended using the split-dose regimen for bowel preparation in all colonoscopy patients.[15] However, recent reports on the same-day dose regimen indicate a superior cleansing effect with this regimen than with the split-dose regimen. Besides, it improves patients' quality of life because it allows them to sleep well the night before the examination.[16–19] Based on these results, the American Society for Gastrointestinal Endoscopy also recommended the same-day dose regimen, solely for afternoon colonoscopy. Therefore, the split-dose regimen is still the only approved regimen for OSS in the United States.

Concerning safety, no new clinically adverse events of interest occurred. There were no deaths and other serious adverse events in any of the three groups. Overall, OSS is safe for use in Japanese patients.

There were some limitations in our study. First, the concomitant use of laxatives was prohibited. However, laxatives are commonly used in combination with bowel preparation formulations for pretreatment before colonoscopies in Japan. Therefore, in clinical practice, the doses of the drugs used and the time required to complete the bowel preparation may differ from those considered in this study. The combined use of laxatives may reduce the dose and time required for bowel preparation; however, this hypothesis requires further verification. Second, the mean age of patients in this study was lower than that of patients who typically undergo colonoscopies in real-world settings in Japan. A future study including older patients undergoing colonoscopy is necessary to confirm the generalizability of the efficacy and safety data determined in this study.

In conclusion, the same-day dose and split-dose OSS regimens were not inferior to the same-day dose PEG-ASC regimen for bowel-cleansing in Japanese patients. There were no new safety concerns or clinically relevant events in any of the treatment groups. OSS may be widely used for bowel preparation for colonoscopy in Japan, as in the United States and other countries.

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CONFLICT OF INTEREST

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