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Efficacy of Oral Sulfate Tablet and 2 L-Polyethylene Glycol With Ascorbic Acid for Bowel Preparation: A Prospective Randomized KASID Multicenter Trial

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ABSTRACT

Background: Oral sulfate tablets (OSTs) are bowel preparation agents that combine oral sulfate solution and simethicone. This study compared the efficacy, tolerability, and safety of OST compared to 2 L-polyethylene glycol plus ascorbic acid (2 L-PEG/ASC).
Methods: This prospective, randomized, controlled, single-blinded, multicenter, noninferiority trial enrolled 211 healthy adults who underwent colonoscopy between May 2020 and September 2022 at 13 university hospitals. The bowel cleansing rate was assessed using the Boston Bowel Preparation Scale (BBPS) and Harefield Cleansing Scale (HCS), and the preparation agents were administered in split regimens.
Results: The total BBPS score (8.2 ± 1.5 vs. 7.8 ± 1.4, $p = 0.040$) and the high-quality bowel cleansing rates in the right colon (73.2% vs. 50.5), transverse colon (80.6% vs. 68.0%), and left colon (81.5% vs. 67.0%) on the BBPS were significantly higher in the OST group than in the 2 L-PEG/ASC group. However, the rates of successful cleansing according to BBPS (90.7% vs. 91.2%) and HCS (96.3% vs. 94.2%) did not significantly differ between the two groups. The taste, ease, and amount of consumption of the preparation agent; and willingness to repeat colonoscopy with the same agent (89.8% vs. 78.6%, $P = 0.026$) were significantly better in the OST group compared to the 2 L-PEG/ASC group. Adverse events and clinically

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Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Jung Y, Kang HW, Park JJ, Kim HG. Data curation: Jung Y, Yang DH, Baek DH, Chun J, Gweon TG, Goong HJ, Kwak MS, Lee HJ, Park SK, Lee JH, Kim HG. Formal analysis: Jung Y. Funding acquisition: Jung Y, Kim HG. Investigation: Jung Y, Yang DH, Kang HW, Park JJ, Baek DH, Chun J, Gweon TG, Goong HJ, Kwak MS, Lee HJ, Park SK, Lee JH. Methodology: Jung Y, Yang DH, Kang HW, Park JJ, Baek DH, Chun J, Gweon TG, Goong HJ, Kwak MS, Lee HJ, Park SK, Lee JH, Kim HG. Resources: Kim HG. Supervision: Kim HG. Validation: Kim HG. Visualization: Jung Y, Kim HG. Writing - original draft: Jung Y. Writing - review & editing: Kim HG.

significant laboratory changes were not significantly different between the two groups. **Conclusion:** The OST was not inferior to 2 L-PEG/ASC in terms of bowel cleansing efficacy and showed better tolerability when used for bowel preparation for colonoscopy.

Trial Registration
Clinical Research Information Service Identifier: KCT0005017

Keywords: Colonoscopy; Bowel Preparation; Polyethylene Glycol; Sulfate

INTRODUCTION

Adequate bowel preparation is essential for high-quality colonoscopy, both for the endoscopic diagnosis and treatment of colorectal neoplasms, as well as for post-polypectomy surveillance.[1-4] Therefore, selection of an effective agent is important. Novel agents have been developed with the aim of improving both bowel cleansing and patient compliance. Use of polyethylene glycol (PEG)-based solutions began in the 1980s.[5] These are widely used worldwide, because they are non-absorbable iso-osmotic solutions with excellent bowel cleaning effects and no significant fluid or electrolyte shifts. The 4 L-PEG solution is one such agent. However, despite its excellent efficacy and safety, it is not currently widely used because of the large volume ingested and its unpleasant taste. Indeed, it has been estimated that 15% to 20% of patients have difficulty taking the agent.[6,7] To improve patient tolerability, agents with smaller required volumes (such as 2 L-[8] and 1 L-PEG solution[9]) and improved taste (such as sulfate-free PEG solution) have been developed.[6] However, patient compliance with bowel preparation regimes is still an issue, and about one-third of patients do not wish to again undergo colonoscopy using the same agents.[10]

Oral sulfate solution (OSS), also called trisulfate, consists of magnesium sulfate, sodium sulfate, and potassium sulfate. Adequate bowel preparation has reportedly been achieved by 98.0% of patients who use it, noninferior to the 96% for 4 L-PEG. Although the rates of acceptance, compliance, and satisfaction are significantly higher for OSS than for 4 L-PEG, gastrointestinal (GI) adverse symptoms may not be significantly improved. Furthermore, abdominal pain may be more frequent with OSS than with 4 L-PEG.[11] In a meta-analysis of OSS and 2 L-PEG with ascorbic acid (2 L-PEG/ASC), the rates of successful bowel cleansing and adverse GI events (such as nausea, abdominal distension, and abdominal discomfort) were not significantly different between the two preparation agents. However, the excellent bowel preparation rate was significantly higher with OSS than with 2 L-PEG/ASC, whereas the mean intensity of vomiting was higher with OSS.[12]

Oral sulfate tablets (OSTs) (Orafang; Pharmbio Korea Co., Seoul, Korea) were recently developed to enhance GI comfort and tolerability. Orafang is composed of 28 tablets, each containing a blend of three sulfates—sodium sulfate, potassium sulfate, and magnesium sulfate—acting as osmotic laxatives, similar to OSS. Additionally, simethicone is included as a defoaming agent to reduce bubble formation. A phase 3 study showed that the bowel cleansing rate of OST was noninferior to that of OSS and its tolerability was superior.[13] However, comparisons of OST with other bowel preparation agents are lacking. Thus, we compared the efficacy, tolerability, and safety of OST and 2 L-PEG/ASC.

METHODS

Study design

This was a prospective, randomized, controlled, colonoscopist-blinded, multicenter, noninferiority trial that enrolled 211 healthy adults who underwent colonoscopy between May 2020 and September 2022 at 13 university hospitals.

Study population

Eligible patients were consecutive men and women aged 19 to 75 years with a body mass index (BMI) ≥ 19 to < 30 kg/m^2 who underwent scheduled colonoscopy. The exclusion criteria were as follows: acute myocardial infarction within 1 year; advanced congestive heart failure (NYHA III or IV); inflammatory bowel disease; previous significant GI surgery; known or suspected ileus, gastric retention, bowel perforation, or obstruction in the previous 12 months; history of significant constipation (< 3 bowel movements per week regardless of regular laxatives); regular use of laxatives or colon motility-altering drugs; and severe renal insufficiency (serum creatinine > 3 mg/dL).

Bowel preparation protocol

Following written consent, patients were randomly allocated in a 1:1 ratio to either the OST group (Orafang tablets, Pharmbio Korea; composition per tablet: anhydrous sodium sulfate 1,125 mg, potassium sulfate 201.07 mg, anhydrous magnesium sulfate 102.86 mg, simethicone 11.43 mg) or the 2 L-PEG/ASC group (Haprep powder, Pharmbio Korea; composition per liter: sodium chloride 2.89 g, potassium chloride 1.015 g, anhydrous sodium sulfate 7.5 g, PEG 3350 100 g, ascorbic acid 4.7 g, sodium ascorbate 5.9 g). Assignment was based on computer-generated random numbers issued to consecutive patients at the time of scheduling their colonoscopies, which were all conducted between 9 a.m. and 1 p.m.

On the day of randomization, participants were given detailed instructions on bowel preparation methods and dietary restrictions through a leaflet provided by the primary study hospital. They were instructed to follow a low-residue diet starting 3 days before their colonoscopy and to transition to a clear liquid diet beginning the afternoon before the procedure. Compliance with these dietary guidelines was assessed using a Yes/No survey. Both groups followed a split-dose regimen for bowel preparation. Patients in the OST group took a total of 14 tablets of Orafang with 425 mL water and drank the same amount of free water for the next hours in the evening (6–8 p.m.) of the day before the colonoscopy. Patients in the 2 L-PEG/ASC group drank 1 L Haprep solution with a further 500 mL free water in the evening of the day before the colonoscopy. The same procedures were repeated with the same agents early in the morning of the next day for colonoscopy in both groups. All preparations were completed at least two hours before the examination, ensuring that the colonoscopies were performed within 5 hours of the last dose of agent.

Assessments and endpoints

The principal investigator, colonoscopists, and endoscopy assistant nurses were blinded to the agent assignments until the completion of the study. High-definition colonoscopes (260 and 290 series; Olympus America, Center Valley, PA, USA) were used to measure the efficacy of bowel cleansing in all colon segments.

The primary outcome was the efficacy of bowel cleansing using the 5-point (0–4) Harefield Cleansing Scale (HCS), which assigns scores to five segments (cecum [CE], ascending

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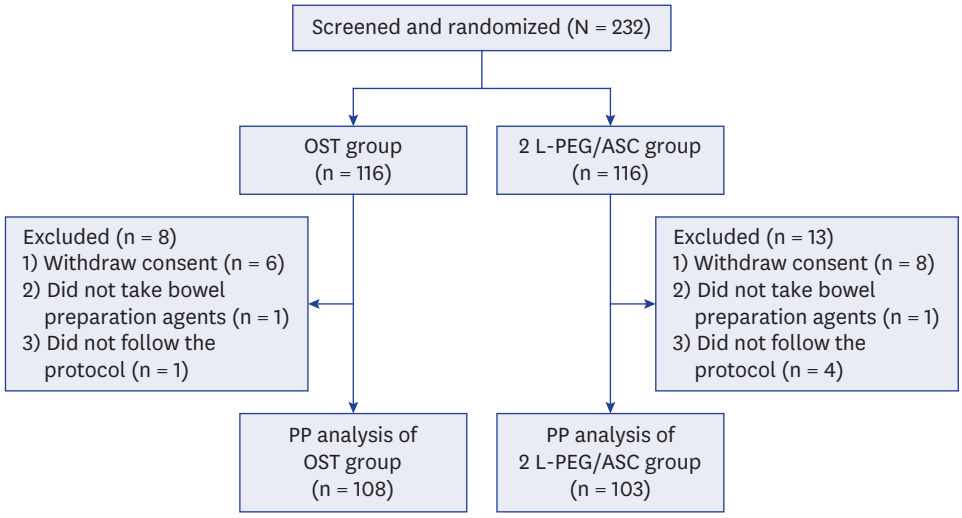

Fig. 1. Study flowchart (OST, oral sulfate tablet; PEG, polyethylene glycol).
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid.

colon [AC], transverse colon [TC], descending colon [DC], sigmoid colon [SC], and rectum [RC]).[14] Overall HCS grade was categorized as: A (all segments scored 3 or 4), B (≥ 1 segment scored 2 but no segment scored < 2), C (≥ 1 segment scored 1 but no segment scored < 1), and D (≥ 1 segment scored 0). We also used the 4-point (0–3) Boston Bowel Preparation Scale (BBPS), which assigns scores to three segments (right colon [CE and AC], TC, and left colon [DC, SC, and RC]).[15] The HCS and BBPS scores were measured simultaneously during colonoscopies. Successful overall bowel preparation was defined as an overall HCS grade of A or B and ≥ 2 scores for all segments on the BBPS. High-quality overall preparation was defined as an overall HCS grade of A. High-quality preparation as determined in segmental evaluations was defined as grade A (score 3 or 4) on the HCS and a score of 3 on the BBPS. To reduce interobserver variation in the assessment of preparation quality using the BBPS and HCS, we provided educational materials for use during each procedure (**Supplementary Fig. 1**). Additionally, before starting the study, we held in-person meetings to discuss and coordinate the training and standardization efforts.

The secondary endpoints were the polyp detection rate (PDR) and adenoma detection rate (ADR) calculated as the percentage of patients with at least one polyp (PDR) or adenoma (ADR) in the analyzed population. The mean number of adenoma detections per colonoscopy and the cancer detection rate were also evaluated.

Evaluation of tolerability and safety

Tolerability and safety were evaluated using a questionnaire. Tolerability was evaluated in terms of 'degree of difficulty with bowel preparation protocol,' 'taste of the preparation agent,' 'ease and amount of consumption of the preparation agent,' and 'willingness to repeat colonoscopy with the same agent.' The first was evaluated using a 3-point scale (1 = easy, 2 = tolerable, and 3 = difficult), the second two were evaluated using a 10-point scale of 1 (worst) to 10 (best), and the final item was evaluated using Yes/No questions inquiring about patient satisfaction. Safety was assessed through adverse events reporting, clinical and laboratory evaluations, vital signs, and physical examinations. Adverse events related to bowel preparation were nausea, vomiting, abdominal pain, thirst, dehydration, headache, dizziness, lethargy, and

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others. The participants underwent blood tests for levels of blood urea nitrogen, creatinine, and electrolytes such as sodium, potassium, chloride, calcium, phosphate, and magnesium on the day of the colonoscopy, prior to the procedure.

Statistical analysis

The primary outcome was inferiority/noninferiority of OST compared to 2 L-PEG/ASC in terms of bowel cleansing efficacy. The upper limit of noninferiority was set at 10%, the standard acceptable level for noninferiority in previous bowel preparation studies.[16-21] Assuming an overall bowel cleansing success rate of 94.8% for the 2 L-PEG/ASC group,[22] and with a noninferiority margin of 10% and a one-sided significance threshold of $P < 0.025$, a sample of 104 patients per group provided a statistical power of at least 90% to demonstrate noninferiority. Ultimately, 232 patients per group were analyzed after applying a dropout rate of 10%. For secondary outcomes, continuous variables are presented as means ± SDs and were analyzed using Student's *t*-test or Wilcoxon rank-sum test. Categorical variables are described as frequencies and proportions and were analyzed using the χ^2 test or Fisher's exact test. Two-sided values of $P < 0.05$ were considered indicative of statistical significance. Summary and descriptive statistics were calculated where appropriate. Statistical analysis was conducted using SAS software (v. 9.4; SAS Institute, Cary, NC, USA).

Ethics statement

This study was approved by the Ethics Committees of the participating institutions and is registered at the Clinical Research Information Service (KCT0005017; https://cris.nih.go.kr/cris/en/index.jsp). Informed consent was obtained from all patients before their enrollment. The study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Boards of Soonchunhyang University Hospital Seoul [Soonchunhyang Universtiy Hospital (SCHUH) 2020–03–015].

RESULTS

In all, 232 patients were randomized to the OST group (n = 116) and 2 L-PEG/ASC group (n = 116). Of them, 21 patients were excluded, among which 14 patients withdrew consent and 2 did not take the bowel preparation agents due to personal circumstances related to work. In addition, five patients did not comply with the study protocol, such as not submitting a questionnaire and not having a blood test performed. All were excluded from the per-protocol (PP) analysis. The PP population (n = 211) consisted of 108 patients in the OST group and 103 patients in 2 L-PEG/ASC group (**Fig. 1**).

Baseline characteristics were balanced between the groups (**Table 1**). The mean age, sex, BMI, and indication for colonoscopy were not significantly different between the groups. The interval from the last dose of bowel purgative intake to colonoscopy and comorbidities such as hypertension and diabetes mellitus were also not significantly different between the groups. Complete colonoscopy with cecal intubation was achieved in all patients.

Efficacy of bowel cleansing

OST was noninferior to 2 L-PEG/ASC for the primary efficacy endpoint. The overall successful bowel cleansing rates based on the HCS grade (A or B) (OST: 96.3% [104/108] vs. 2 L-PEG/ASC: 94.2% [97/103], $\Delta = 2.1\%$; one-sided lower 97.5% confidence limit, -3.6%; test for superiority, $P = 0.531$) and BBPS score (each segment ≥ 2) (OST 90.7% [98/108] vs. 2 L-PEG/

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Table 1. Baseline characteristics of the patients

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Age, yr	54.5 ± 12.1	52.0 ± 13.0	0.162
Sex			0.015
Male	49 (45.4)	64 (62.1)	
Female	59 (54.6)	39 (37.9)	
HTN	35 (32.4)	24 (23.3)	0.141
DM	9 (8.3)	10 (9.7)	0.727
BMI	24.3 ± 3.0	24.2 ± 2.8	0.900
Indication for colonoscopy			
Screening	58 (53.7)	58 (56.3)	
Surveillance	50 (46.3)	45 (43.7)	
Number of bowel movements after preparation			0.254
≤ 5	1 (0.9)	3 (2.9)	
6–9	32 (29.6)	30 (29.1)	
10–12	41 (38.8)	48 (46.6)	
≥ 13	34 (31.5)	22 (21.4)	
Time interval from the last dose of bowel purgative intake to colonoscopy, hr			0.186
3–5	96 (88.9)	85 (82.5)	
5–7	12 (11.1)	18 (17.5)	
Diet control	106 (98.2)	98 (95.2)	0.145

Values are presented as number (%) or mean ± standard deviation.
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid, HTN = hypertension, DM = diabetes mellitus, BMI = body mass index.

ASC 91.2% [94/103], Δ = -0.5%; one-sided lower 97.5% confidence limit, -8.2%; test for superiority, $P = 0.895$) were noninferior in the OST group compared to the 2 L-PEG/ASC group.

The mean overall BBPS scores (8.2 ± 1.5 vs. 7.8 ± 1.4, $P = 0.040$) and high-quality bowel cleansing rates based on the BBPS score (score 3) in the right colon (73.2% vs. 50.5%, $P = 0.002$), transverse colon (80.6% vs. 68.0%, $P = 0.016$), and left colon (81.5% vs. 67.0%, $P = 0.004$) were significantly higher in the OST group than in the 2 L-PEG/ASC group (**Fig. 2A**). However, the high-quality rate based on the HCS (grade A) was not significantly different between the two groups overall (77.8% vs. 70.9%, $P = 0.251$) or in the right colon, descending colon, sigmoid colon, or rectum, but there was a significant difference in the transverse colon (93.5% vs. 84.5%, $P = 0.035$) (**Fig. 2B**). There were significantly fewer intraluminal bubbles in the OST group than the 2 L-PEG/ASC group ($P < 0.001$) (**Table 2**).

The endoscopic outcomes such as PDR (51% vs. 49.5%, $P = 0838$), ADR (30.6% vs. 36.9%, $P = 0.330$), mean adenoma detection per colonoscopy (0.6 ± 1.3 vs. 0.8 ± 1.7, $P = 0.341$), and cancer detection were not significantly differ between the groups (**Table 3**).

Tolerability

The rate of protocol completion (100% of OST vs. 98.1% of 2 L-PEG/ASC, $P = 0.237$) and the degree of difficulty with preparation protocol were not significantly different between the two groups. Taste (7.9 ± 2.7 vs. 6.5 ± 2.3, $P < 0.001$), ease of consumption (7.8 ± 2.5 vs. 6.5 ± 2.3, $P < 0.001$), and amount of consumption (6.9 ± 2.6 vs. 6.1 ± 2.5, $P = 0.024$) were significantly better in the OST group. The rate of willingness to repeat colonoscopy with the same agent (89.8% vs. 78.6%, $P = 0.026$) was significantly higher in the OST group (**Fig. 3** and **Table 4**).

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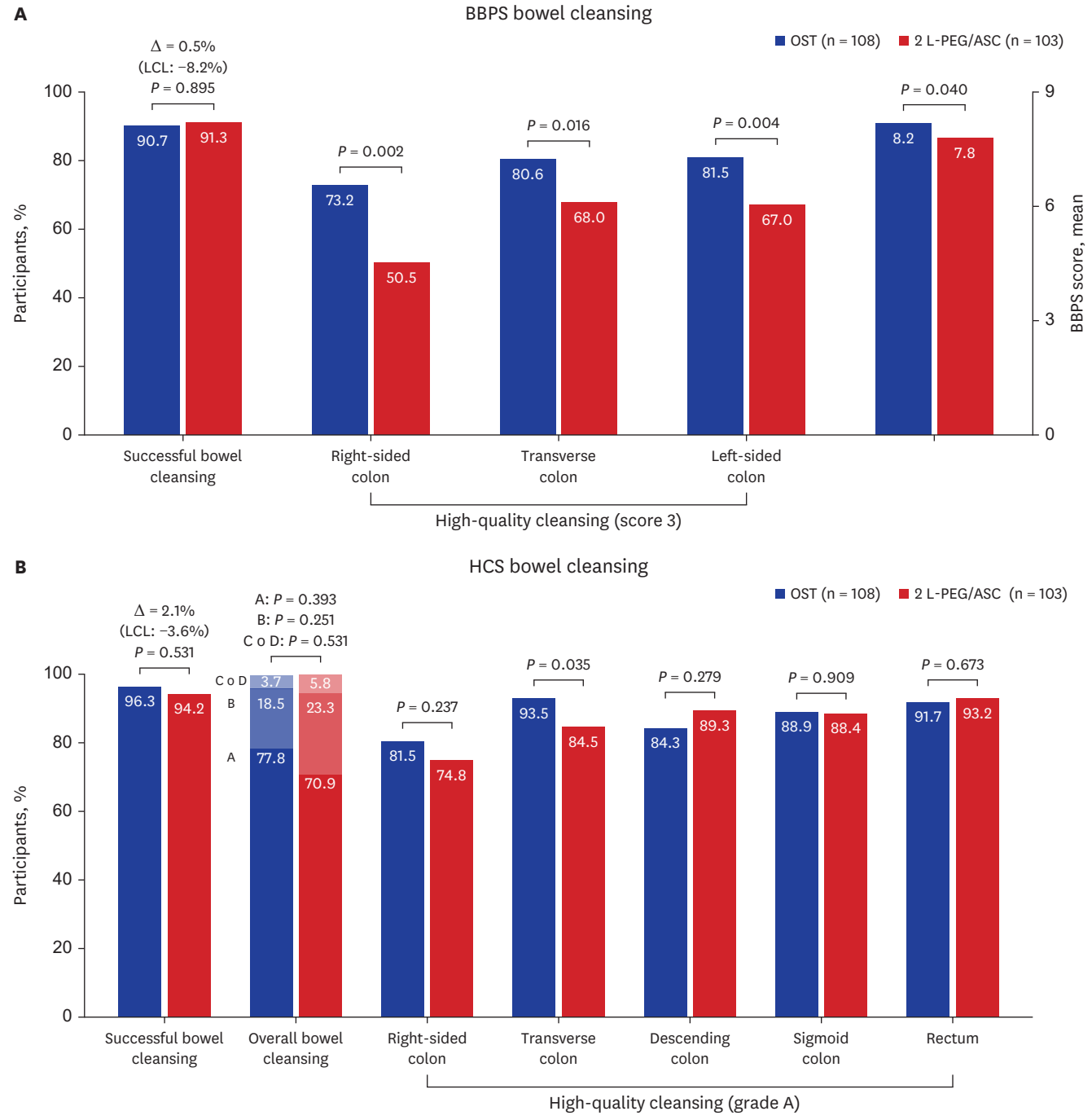

Fig. 2. Efficacy of bowel cleansing as evaluated by (**A**) BBPS and (**B**) HCS.
BBPS = Boston Bowel Preparation Scale, HCS = Harefield Cleansing Scale, LCL = lower confidence limit, OSS = oral sulfate solution, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid, Δ = difference in rates of successful bowel cleansing.

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Table 2. Bowel preparation efficacy

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Boston Bowel Preparation Scale			
Total score	8.2 ± 1.5	7.8 ± 1.4	0.040
Successful cleansing (each segment ≥ 2)	98 (90.7)	94 (91.3)	0.895
High-quality cleansing (score 3 of each segment)			
Right-sided colon	79 (73.2)	52 (50.5)	0.002
Transverse colon	87 (80.6)	70 (68.0)	0.016
Left-sided colon	88 (81.5)	69 (67.0)	0.004
Harefield Cleansing Scale			
Colon cleansing grade			
Grade A	84 (77.8)	73 (70.9)	0.251
Grade B	20 (18.5)	24 (23.3)	0.393
Grade C o D	4 (3.7)	6 (5.8)	0.531
Successful cleansing (grade A/B)	104 (96.3)	97 (94.2)	0.531
High-quality cleansing (grade A)			
Right-sided colon	88 (81.5)	77 (74.8)	0.237
Transverse colon	101 (93.5)	87 (84.5)	0.035
Descending colon	91 (84.3)	92 (89.3)	0.279
Sigmoid colon	96 (88.9)	91 (88.4)	0.909
Rectum	99 (91.7)	96 (93.2)	0.673
Bubble score			< 0.001
1 (no or minimal)	105 (97.2)	62 (60.2)	
2 (moderate, limited to detecting 5 mm. polyps)	3 (2.8)	29 (28.2)	
3 (severe, limited to detecting 10 mm. polyps)	0	12 (11.6)	

Values are presented as number (%) or mean ± standard deviation.
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid.

Table 3. Outcomes of colonoscopy

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Cecal intubation rate	108 (100)	103 (100)	1.000
Polyp detection rate	55 (51.0)	51 (49.5)	0.838
Adenoma detection rate	33 (30.6)	38 (36.9)	0.330
Mean number of adenoma detection per colonoscopy	0.6 ± 1.3	0.8 ± 1.7	0.341
Cancer detection rate	1 (0.9)	0	1.000
Colonoscopy withdrawal time, min	9.7 ± 5.9	10.4 ± 6.6	0.380

Values are presented as number (%) or mean ± standard deviation.
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid.

Safety

There were no serious adverse events in either group. Any adverse events and any GI adverse events including nausea (28.7% vs. 20.4%, $P = 0.161$) vomiting (5.6% vs. 1.0%, $P = 0.120$), abdominal pain (12.0% vs. 15.5%, $P = 0.461$), and bloating (34.3% vs. 32.0%, $P = 0.732$) were not significantly different between the groups. The proportions of patients with clinically abnormal electrolytes (8.3% vs. 4.9%, $P = 3.100$) as well as the estimated glomerular filtration rate (1.9% vs. 2.9%, $P = 0.677$) were not significantly different between the two groups (**Tables 5** and **6**).

DISCUSSION

There have been various attempts to improve patient compliance with bowel cleansing such as reducing the total intake volume,[8,9] removing sulfate from PEG,[6] reducing the content of ascorbic acid in PEG solution,[10] and using bowel preparation tablets.[23] The oral sodium

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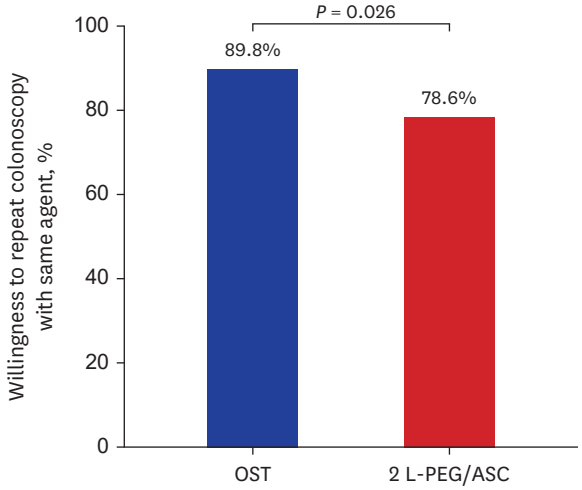

Fig. 3. Percentage of participants who responded "yes" to the question "Willingness to repeat colonoscopy with the same agent."
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid.

Table 4. Bowel preparation tolerability

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Completeness of bowel preparation protocol	108 (100)	101 (98.1)	0.237
Degree of difficulty in bowel preparation protocol			0.213
Easy	71 (65.7)	56 (54.4)	
Tolerable	33 (30.6)	43 (41.8)	
Difficult	4 (3.7)	4 (3.88)	
Taste of the preparation agent (0–10)[a]	7.9 ± 2.7	6.5 ± 2.3	< 0.001
Ease of consumption of the preparation agent (0–10)[a]	7.8 ± 2.5	6.5 ± 2.3	< 0.001
Amount of consumption of the preparation agent (0–10)[a]	6.9 ± 2.6	6.1 ± 2.5	0.024
Willingness to repeat colonoscopy with the same agent	97 (89.8)	81 (78.6)	0.026

Values are presented as number (%) or mean ± standard deviation.
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid.
[a]0 (bad), 10 (good).

Table 5. Safety of bowel preparation

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Serious adverse events or death	0	0	NA
Any of adverse events	67 (62.0)	55 (53.4)	0.204
Any of GI adverse events	60 (55.6)	47 (45.6)	0.150
Mild adverse events			
Nausea	31 (28.7)	21 (20.4)	0.161
Vomiting	6 (5.6)	1 (1.0)	0.120
Abdominal pain	13 (12.0)	16 (15.5)	0.461
Bloating	37 (34.3)	33 (32.0)	0.732
Thirst, dry mouth	14 (13.0)	16 (15.5)	0.593
Headache	3 (2.8)	5 (4.9)	0.491
Dizziness	15 (13.9)	10 (9.7)	0.348
Lethargy	3 (2.8)	8 (7.8)	0.103
Confusion	0	0	NA
Seizure	0	0	NA
Numbness in hands or feet	2 (1.9)	1 (1.0)	1.000
Colon mucosal changes	2 (1.9)	3 (2.9)	0.677

Values are presented as number (%).
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid, NA = not applicable, GI = gastrointestinal.

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Table 6. Clinically abnormal laboratory findings after bowel preparation

Variables	OST group (n = 108)	2 L-PEG/ASC group (n = 103)	*P* value
Patients with clinically abnormal electrolytes	9 (8.3)	5 (4.9)	0.310
Sodium	7 (6.5)	0	0.014
Potassium	0	4 (3.9)	0.055
Chloride	2 (1.9)	1 (1.0)	1.000
Calcium	1 (0.9)	0	1.000
Magnesium	17 (15.7)	18 (17.5)	0.735
Phosphorus	20 (18.5)	12 (11.7)	0.164
Blood urea nitrogen	14 (13.0)	7 (6.8)	0.135
Creatinine	3 (2.8)	3 (2.9)	1.000
eGFR	2 (1.9)	3 (2.9)	0.677

Values are presented as number (%).
OST = oral sulfate tablet, 2 L-PEG/ASC = 2 L-polyethylene glycol plus ascorbic acid, eGFR = estimated glomerular filtration rate.

phosphate (OSP) tablet was developed to avoid poor taste and the ingestion of a very large volume of liquid of the existing preparations.[23] The tablets showed better patient compliance and acceptability rates than PEG-based solutions.[24,25] However, the guidelines of the European Society of Gastrointestinal Endoscopy do not recommend the routine use of OSP due side effects including kidney injury.[26]

OSS is a hyperosmolar laxative that does not cause significant fluid or electrolyte shifts because it is a sulfate, a poorly absorbed anion, and was developed to reduce the amount of total intake compared to previous agents.[27,28] A randomized controlled trial (RCT) reported that successful bowel preparation was significantly more frequent in an OSS group than in a 4 L sulfate-free PEG group [21] and the adequate bowel preparation rate of the OSS group was not significantly different from that of the low-volume PEG group (93.3% vs. 90.6%, $P = 0.16$) in a meta-analysis of RCTs involving 2,049 subjects.[12] OSS showed a satisfactory bowel cleansing efficacy that was noninferior to high- or low-volume PEG but did not significantly improve patient compliance compared to PEG. This is probably because the total amount of intake of OSS is not less than that of low-volume PEG, and nausea and vomiting are more frequent with OSS than with low-volume PEG. To maintain the bowel cleansing effect of OSS and improve patient compliance, OST, a tablet form of the preparation agent, was developed in 2020.[13] In a phase 3 noninferiority trial, the successful bowel cleansing rate of an OST group (95.5%) was noninferior to that of an OSS group (98.2%). In addition, the OST group had fewer intraluminal bubbles (0.9% vs. 81.3%, $P < 0.001$) and lower incidences of nausea and vomiting, with better tolerability and willingness to repeat the regimen (76.8% vs. 41.6%, $P < 0.001$), than the OSS group. A RCT has compared OST and 2 L-PEG/ASC[29]; however, that work was based on a scale not typically used to assess bowel cleansing efficacy, and studies comparing these two bowel preparation agents are notably scarce. Therefore, we evaluated the bowel preparation efficacy of OST compared to 2 L-PEG/ASC using the validated BBPS[15] and HCS[14] and assessed tolerability and adverse events in a prospective multicenter RCT. The overall successful bowel cleansing rate of the OST group was noninferior to that of the 2 L-PEG/ASC group (BPPS; 90.7% vs. 91.3%, $P = 0.895$, HCS: 96.3% vs. 94.2%, $P = 0.531$), as reported previously (OST: 92.4% vs. 2 L-PEG:89.3%, $P = 0.217$).[29] Based on the BBPS, OST was superior to 2 L-PEG/ASC in the right colon, as reported previously. However, the high-quality cleansing rate in the transverse colon and left colon based on the BBPS was superior in the OST group compared to the 2 L-PEG/ASC group. However, the high-quality cleansing rate evaluated using the HCS did not show a significant difference between the two groups. The discrepancy in the higher high-quality cleansing rates between the BBPS and HCS may have occurred because unlike

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the HCS, the BBPS evaluates cleansing after all retained fluid and foam have been flushed and suctioned. Because OST contains simethicone,[13] the rate of intraluminal bubble formation was significantly lower in the OST group than in the 2 L-PEG/ASC group. A recent large-scale retrospective study showed that the ADR (34.5% vs. 30.7%, $P < 0.001$) and PDR (56.0% vs. 50.8%, $P < 0.001$) were higher with OST than with 2 L-PEG.[30] By contrast, we did not find any significant differences in ADR and PDR between our two groups. In actual clinical practice, because simethicone is commonly prescribed and used together with 2 L-PEG/ASC, the rate of intraluminal bubble formation might not show a significant difference between the two bowel cleansing agents. Therefore, there could be a discrepancy between our study results and real-world clinical situations.

Compliance is important for successful bowel preparation. According to an RCT, experience consuming the preparation, overall experience, comparison with previous experience, and willingness to repeat colonoscopy with the same agent are significantly higher with OST than with 2 L-PEG.[29] In our study, the scores for taste, ease, and amount of consumption of the preparation agent, and willingness to repeat colonoscopy with the same agent (89.8% vs. 78.6%, $P = 0.026$), were significantly higher with OST than with 2 L-PEG/ASC.

The OST group was expected to have fewer symptoms such as nausea and vomiting compared to the 2 L-PEG/ASC group due to its better tolerability. However, in a previous RCT comparing OST and 2 L-PEG/ASC, nausea (OST, 17.1% [48/281] vs. 2 L-PEG/ASC, 9.6% [26/271], $P < 0.001$) and vomiting (OST, 8.2% [23/281] vs. 2 L-PEG/ASC, 2.2% [6/271], $P < 0.001$) were less common in the 2 L-PEG/ASC group. Despite this, severe symptoms were rare, with only one case of severe nausea reported in the OST group (0.4%) and no cases of severe vomiting in either group.[29]

In our study, although the differences were not statistically significant, nausea and vomiting were slightly more frequently reported in the OST group compared to the 2 L-PEG/ASC group: nausea (28.7% vs. 20.4%, $P = 0.161$) and vomiting (5.6% vs. 1.0%, $P = 0.120$). Unfortunately, we did not assess the severity of these symptoms, and the limitation of using a yes/no questionnaire did not allow for a more detailed analysis. However, under the same conditions, there was no statistically significant difference between the two cleansing agents. Additionally, no cases of severe nausea or vomiting were observed that would have prevented the completion of the colonoscopy or required discontinuation of the bowel preparation.

Hyponatremia (Na < 135 mEq/L) is a relatively common condition with an incidence and prevalence of approximately 5% in adults. It can sometimes occur due to excessive water intake during bowel preparation. Symptoms such as apathy/agitation, fatigue, anorexia, nausea, headache, muscle cramps, tachycardia, oliguria/anuria, and confusion typically appear when sodium levels fall below 120 to 125 mmol/L.[31] In our study, all 7 patients in the OST group with abnormal sodium levels had mild hyponatremia (130–134 mmol/L), specifically between 132 and 134 mEq/L, with no significant clinical symptoms. Additionally, there were no significant serious adverse events or changes in laboratory parameters in the OST group compared to the 2 L-PEG/ASC group. Therefore, we considered OST to be clinically safe.

With an aging society, the safety and effectiveness of bowel preparation in the elderly are increasingly important. In a previous study, among individuals aged ≥ 65 years, the BBPS score and satisfaction were significantly higher in OST group than in 2L-PEG group, but there were no significant differences in the rate of adverse events between the two groups.[32]

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In our study, among patients ≥ 65 years of age, the BBPS scores, adverse event rates, and tolerability were not significantly different between OST and 2 L-PEG/ASC (**Supplementary Table 1**). However, most of the tolerability indicators—such as taste, ease of consumption, amount of the preparation agent consumed, and willingness to undergo repeat colonoscopy with the same agent—were better in the OST group than in the 2 L-PEG/ASC group. However, these results were not statistically significant, likely because of the small sample size. Hyponatremia was observed only in the OST group, affecting 3 (11.1%) patients (133 mEq/L in 2 patients and 134 mEq/L in 1 patient). All these sodium levels corresponded to mild hyponatremia, and no clinically significant symptoms were observed. In a recent RCT involving 254 patients aged ≥ 70 years, overall satisfaction and tolerability were significantly higher in the OST group than in the 2 L-PEG/ASC group. Additionally, no clinically significant differences in serum laboratory results, including sodium levels, were found between the 2 preparation agents. Additionally, most laboratory parameters outside the normal range remained within normal limits at the third and fourth visits.[33]

This study was not specifically designed for patients aged ≥ 65 years, and the subgroup analysis conducted for this age group is limited by the small sample size, which restricts the robustness of the comparison. Although the results were not statistically significant, the taste, ease, and amount of consumption of the preparation agent, as well as the willingness to repeat colonoscopy with the same agent, were better in the OST group compared to the 2 L-PEG/ASC group. In a larger RCT involving 254 patients aged ≥ 70 years, overall satisfaction and tolerability were significantly higher in the OST group compared to the 2 L-PEG/ASC group.

Further research with a larger population is needed to confirm these trends. There were no significant differences in the successful bowel cleansing rate between patients who had 6 to 9 bowel movements compared to those who had > 10 bowel movements (**Supplementary Table 2**).

This study had several limitations. The participation of multiple institutions introduces the potential for interobserver variability. In addition, we did not conduct gastric endoscopies, which prevented confirmation of an association between gastric mucosal damage and use of bowel preparation agents. Not comparing the laboratory test results before and after the administration of the bowel cleansing agents, and thus being unable to measure any significant changes from baseline or determine whether abnormal results returned to normal, is a limitation in assessing safety. However, no serious adverse effects were observed with either of the two bowel cleansing agents, and we instructed the patients to contact the hospital if any symptoms persisted. No patients needed to return to the hospital after the procedure.

However, this was a multicenter, prospective study that compared OST with 2 L-PEG/ASC using validated bowel preparation quality scales (the BBPS and the HCS). Our findings should help clinicians select the most effective and safe bowel preparation regimen.

In conclusion, OST was noninferior to 2 L-PEG/ASC in terms of bowel cleansing efficacy and showed better tolerability.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Bowel preparation efficacy, tolerability, and safety among patients ≥ 65 years of age

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Supplementary Table 2

Relationship between the number of bowel movements after preparation and clinical significance

Supplementary Fig. 1

Reference material for the assessment of bowel preparation quality.

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