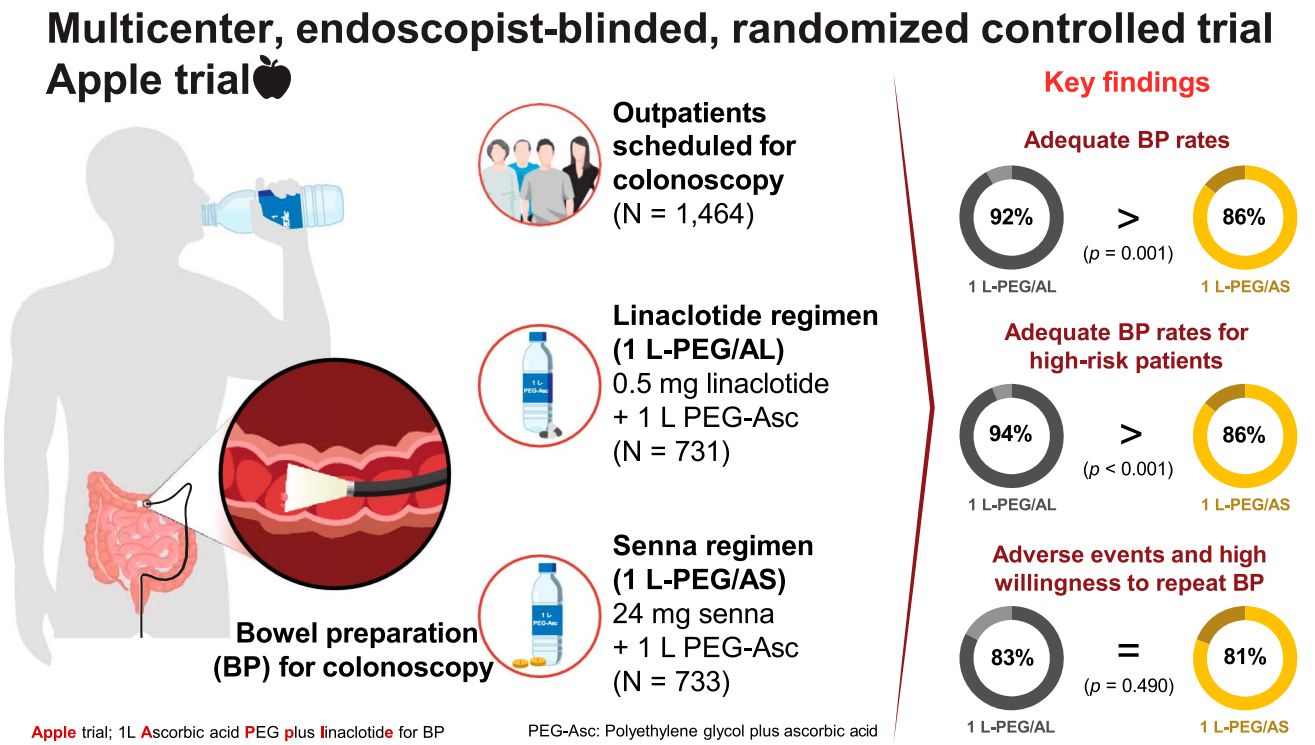
Open

Efficacy of 1 L Polyethylene Glycol Plus Ascorbic Acid With Linaclotide Versus Senna for Bowel Preparation: A Multicenter, Endoscopist-Blinded, Randomized Controlled Trial (Apple Trial)

Natsumi Maeda, MD[1,2], Akira Higashimori, MD, PhD[1,2], Daijiro Kabata, PhD, MPH[3,4], Ikki Yamamoto, MD[2], Tsuyoshi Yanagida, MD[2], Daiyu Kin, MD[2], Yuji Matsumoto, MD, PhD[2], Rieko Nakata, MD, PhD[1], Atsushi Hashimoto, MD, PhD[5], Akinari Sawada, MD, PhD[1], Hirotsugu Maruyama, MD, PhD[1], Junichi Okamoto, MD, PhD[6], Takayuki Katsuno, MD, PhD[7], Yuji Nadatani, MD, PhD[8], Masaki Ominami, MD, PhD[1], Shusei Fukunaga, MD, PhD[1], Kenichi Morimoto, MD, PhD[2], Shuhei Hosomi, MD, PhD[1], Fumio Tanaka, MD, PhD[1], Masami Nakatani, MD, PhD[2], Koichi Taira, MD, PhD[1], Eiji Sasaki, MD, PhD[2], Takashi Fukuda, MD, PhD[2], Keiko Ota, MD[9], Hisako Yoshida, MD[3], Toshio Watanabe, MD, PhD[8] and Yasuhiro Fujiwara, MD, PhD[1]



Maeda et al. *Am J Gastroenterol*. 2025. doi:10.14309/ajg.0000000000003370

[1]Department of Gastroenterology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; [2]Department of Gastroenterology, Minami Osaka Hospital, Osaka, Japan; [3]Department of Medical Statistics, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; [4]Center for Mathematical and Data Science, Kobe University, Kobe, Japan; [5]Department of Gastroenterology, Tsukazaki Hospital, Himeji, Japan; [6]Department of Gastroenterology, Ikuwakai Memorial Hospital, Osaka, Japan; [7]Department of Gastroenterology, Izumiotsu Municipal Hospital, Izumiotsu, Japan; [8]Department of Premier Preventive Medicine, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; [9]Center for Clinical Research and Innovation, Osaka Metropolitan University Hospital, Osaka, Japan. **Correspondence:** Akira Higashimori, MD, PhD. E-mail: higamo@omu.ac.jp.

Received January 10, 2025; accepted February 10, 2025; published online February 25, 2025

COLON

INTRODUCTION: **No bowel preparation (BP) for colonoscopy achieves optimal efficacy and tolerability. Combining polyethylene glycol plus ascorbic acid (PEG-Asc) with adjuvants has been explored to enhance cleansing efficacy and reduce the required volume. The aim of this study was to evaluate whether adding 0.5 mg linaclotide to 1 L PEG-Asc (1 L-PEG/AL) improves superior cleansing compared with adding 24 mg senna (1 L-PEG/AS), which we previously reported to be noninferior to the standard regimen of 2 L PEG-Asc.**

METHODS: **A multicenter, endoscopist-blinded, randomized controlled trial was conducted at 5 centers in Japan with outpatients scheduled for colonoscopy. The primary outcome was adequate BP, evaluated using the Boston Bowel Preparation Scale. Analyses were stratified based on low-risk and high-risk groups for inadequate BP.**

RESULTS: **Between April 2022 and April 2023, 1,464 patients were randomized to the 1L-PEG/AL (n = 731) or 1L-PEG/AS (n = 733). The 1L-PEG/AL demonstrated higher adequate BP rates (92% vs 86%, $P = 0.001$) compared with 1L-PEG/AS. Both groups experienced similar adverse events and expressed high willingness for repeat BP (83% vs 81%, $P = 0.49$). In high-risk patients (n = 892), 1L-PEG/AL had significantly higher adequate BP rates (94% vs 86%, $P < 0.001$), whereas rates were comparably high in low-risk patients (n = 539) (94% vs 94%, $P = 0.66$).**

DISCUSSION: **The linaclotide regimen was superior to the senna regimen reagrding BP efficacy without reducing tolerability. It can be a promising new option for BP, especially in patients at a high risk of inadequate BP.**

KEYWORDS: polyethylene glycol plus ascorbic acid; bowel preparation; linaclotide; senna; Boston Bowel Preparation Scale

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D579

Am J Gastroenterol 2025;120:2679–2686. https://doi.org/10.14309/ajg.0000000000003370

INTRODUCTION

Bowel preparation (BP) is essential for high-quality colonoscopies (1–5). To achieve adequate BP, sufficient volume of BP solution must be administered; however, low tolerance to its volume remains an issue (6). Polyethylene glycol (PEG)-based solutions are commonly used for BP (1,7). Recently, 2 L PEG containing ascorbic acid (PEG-Asc) has been established as an effective alternative to traditional 4 L PEG, improving patient tolerance (8–10). However, the dosage of 2 L still poses a burden. Therefore, several studies have reported the use of adjuvants to reduce the volume of PEG-Asc required to 1 L, thereby improving patient acceptability (11–16). We previously reported that 1 L PEG-Asc combined with senna regimen was noninferior to 2 L PEG-Asc (17). However, the appropriate type and combination of adjunctive agents with 1 L PEG-Asc remain unknown.

Linaclotide, a guanylate cyclase C receptor agonist approved for chronic constipation, can enhance luminal fluid secretion and mediate visceral analgesia, resulting in laxative effects and improved abdominal symptoms (18–21). Recent studies have explored the efficacy of linaclotide as an adjunct to BP before capsule endoscopy and colonoscopy (22–25). We also found that adding linaclotide to 1 L PEG-Asc yielded superior BP results in constipated patients (26) and hypothesized that adding linaclotide to 1 L PEG-Asc would improve cleansing in all patients.

The aim of this study was to evaluate bowel cleansing efficacy, adverse events, and tolerability in the 1 L PEG-Asc with 0.5 mg linaclotide (1 L-PEG/AL) group compared with those in the 1 L PEG-Asc with 24 mg senna (1 L-PEG/AS) group.

METHODS

Study design

This multicenter, endoscopist-blinded, randomized controlled trial was conducted at 5 centers in Japan between April 2022 and April 2023. The study protocol was approved by the Osaka City University Hospital Certified Review Board (OCU0035) and was registered with the Japan Registry of Clinical Trials (jRCTs051210162).

Eligible outpatients (20–85 years) undergoing elective afternoon colonoscopy were enrolled. Exclusion criteria were as follows: (i) severe heart failure (New York Heart Association class III or IV); (ii) severe liver failure (Child-Pugh classification Grade C); (iii) active inflammatory bowel disease; (iv) patients with dementia who had difficulty following instructions; (v) allergy to PEG-Asc, senna, or linaclotide; (vi) suspected bowel obstruction; and (vii) prior colectomy. After screening the patients according to the exclusion criteria, written informed consent was obtained from all patients.

Randomization and masking

Patients were randomly assigned (1:1 ratio) to the 1 L-PEG/AL or 1 L-PEG/AS group through a stratified permuted block design. Random assignment was conducted within the stratified subgroups based on age (<75 years or not), sex (male or female), and institution (5 sites) with a block size of 2 or 4. All randomization procedures were performed using the Research Electronic Data Capture (27,28). The allocated results were confidentially obtained by independent personnel who were not involved in the colonoscopy or data analysis, and all patients were instructed not to disclose their preparation methods to researchers involved.

BP method

All patients received verbal and written instructions from the medical staff regarding BP and were instructed to consume a low-fiber diet and stop taking laxatives other than BP solution the day before the examination. Patients in the 1 L-PEG/AS group received 24 mg senna and those in the 1 L-PEG/AL group received 0.5 mg linaclotide at 8:00 PM the day before colonoscopy, at the prescribed dosage for chronic constipation in Japan. Both groups drank 1 L PEG-Asc solution (Movie Prep; EA Pharma Co., Ltd., Tokyo, Japan) 4–6 hours before the procedure from 9:00 to 11:00 AM, at a rate of 500 mL every 30 minutes, and drank 250 mL of water for every 500 mL of PEG-Asc. Patients were instructed to complete the procedure at least 2 hours before colonoscopy and subsequently drink clear liquids to ensure adequate hydration. Patients who did not defecate before the scheduled colonoscopy were recorded as having insufficient BP, treated with additional PEG-Asc or an enema to allow the colonoscopy to be performed.

Data collection

Demographic and comorbidity data were obtained using questionnaires. Chronic constipation was diagnosed based on evidence-based clinical guidelines for chronic constipation 2023 (29). The severity of constipation was measured using the Constipation Scoring System (range 0–30) (30). Colonoscopy and BP data were obtained through another questionnaire on the day of colonoscopy.

Colonoscopies were performed under sedation by 15 experienced gastroenterologists (experience of >1,000 procedures) using 290 series of high-resolution colonoscopes equipped with a water jet pump (Olympus Optical Corporation, Tokyo, Japan). A complete colonoscopy was defined as arrival at the cecum. Incomplete colonoscopy was attributed to technical difficulty or strictures. Patients who canceled the treatment were asked to inquire about the reasons.

Study data were collected and managed using Research Electronic Data Capture, which is a secure web-based platform that facilitates data capture for research by offering an intuitive interface, audit trails, automated export procedures, and data integration capabilities with external sources.

Study outcomes

The primary outcome was the rate of adequate BP evaluated using the Boston Bowel Preparation Scale (BBPS) (Appendix S1, http://links.lww.com/AJG/D579), defined as a total score of ≥6 and each segmental score of ≥2 (31). An unreached segment and impossible colonoscopy for insufficient BP were defined as scores of 0 (32). All endoscopists completed the BBPS educational module before judging the scores, and disparities in the scores between the 2 endoscopists during the examination were resolved through consensus. In addition, to validate the quality of BP evaluated by the endoscopists, 2 investigators reviewed recorded withdrawal-phase videos.

Secondary outcomes included patient compliance and BP characteristics, adverse events, tolerability, and colonoscopy findings. Compliance with purgative instructions was evaluated based on the adherence to the intake of the prescribed amount of BP solution within the allocated time period. First defecation time was measured as the time from taking senna or linaclotide. The preparation-to-colonoscopy interval was measured from the end of PEG-Asc administration until the start of the examination. The severity of abdominal pain was defined based on the Common Terminology Criteria for Adverse Events version 5.0. The sleep quality on the night before the examination was measured as excellent, good, fair, or bad, and fair and bad quality was defined as sleep disturbance (33). The procedure time was defined as the time required for procedures such as biopsy and polypectomy. Lesion detection rates were assessed based on clinicopathological features (Appendix S2, http://links.lww.com/AJG/D579). Ischemic colitis was diagnosed according to the American College of Gastroenterology guidelines (34). Tolerability was evaluated based on the willingness to repeat BP.

Sample size and statistical analysis

For sample size determination, we assumed the rate of adequate BP as 95% in the 1L-PEG/AL group and 90% in the 1L-PEG/AS group, based on our preliminary study (17). When evaluated using the Pearson χ^2 test with continuity correction, the minimum sample size required to achieve a power of >90% at a 2-sided significance level of 5% was 622 participants per group.

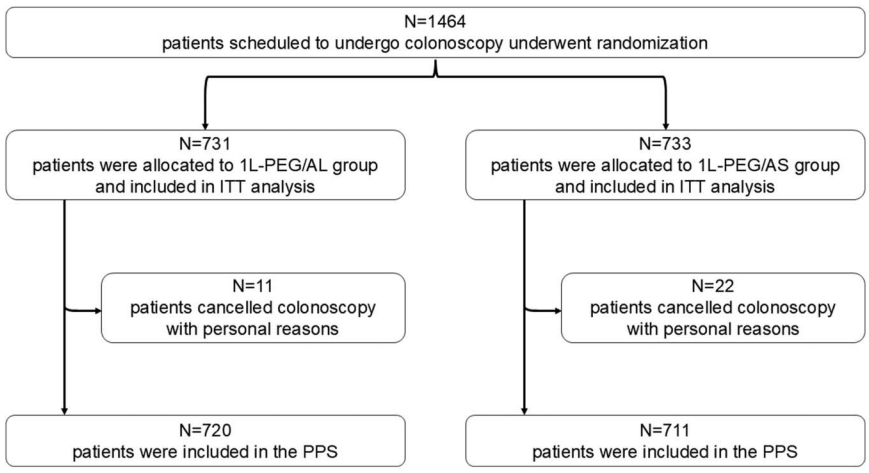


Figure 1. Flow chart of the study. The study flowchart shows the allocation of participants in the study. 1L-PEG/AL, 1 L PEG-Asc plus 0.5 mg linaclotide; 1L-PEG/AS, 1 L PEG-Asc plus 24 mg senna; ITT, intention-to-treat; PEG-Asc, polyethylene glycol plus ascorbic acid; PPS, per-protocol set.

Considering a dropout rate of 15% postrandomization, a final enrollment of 732 participants per group was necessary.

All the randomized patients were included in a full-analysis set, and the patients who did not cancel their colonoscopies were included in a per-protocol set (PPS). All analyses were conducted based on the intention-to-treat (ITT) principle. All missing values were imputed using a multiple imputation approach with 5 iterations, implemented through the *rms::aregImpute* function. Imputations were performed using predictive mean matching—a nonparametric method that selects observed values from other subjects with similar covariate profiles to generate the imputed values.

We compared the odds of the primary end point between the allocated groups using multivariable logistic regression analysis. This analysis simultaneously considered the following stratification factors: enrollment center (5 centers), sex (binary), and age (continuous variable). Furthermore, we conducted similar analyses among the subgroups based on the predictors of inadequate BP and between the low-risk and high-risk groups for inadequate BP. Patients were considered at high risk for inadequate BP if they met at least one of the following criteria: age >75 years, body mass index >25, chronic constipation, diabetes mellitus, stroke, Parkinson disease, or use of tricyclic antidepressants (35–37). In addition, we evaluated whether the effect of treatment differed significantly between the subgroups. To validate the results of the BBPS evaluation by endoscopists, we assessed the agreement between endoscopists and investigators as measured by the κ coefficients.

We used R version 4.4.0 (https://cran.r-project.org/) and SPSS version 22.0 for Windows (IBM Corporation, Armonk, NY) for all analyses with 2-sided significance level.

RESULTS

Study population and patients' baseline characteristics

Figure 1 shows the study flowchart. A total of 1,464 patients scheduled to undergo colonoscopy were randomized to the 1 L-PEG/AL group (n = 731) or the 1 L-PEG/AS group (n = 733). After randomization, 11 patients in the 1 L-PEG/AL group and 22 in the 1 L-PEG/AS group withdrew from the study. Nine patients in the 1 L-PEG/AL group and 22 in the 1 L-PEG/AS group canceled their colonoscopies for personal reasons; 2 patients in the 1 L-PEG/AL group canceled their colonoscopies because they had forgotten to take any of the trial drugs. Ultimately, 720 patients in the 1 L-PEG/AL group and 711 patients from the 1 L-PEG/AS group were included in the PPS. Table 1 presents the baseline patient characteristics.

Table 1. Baseline characteristics

	1L-PEG/AL n = 731	1L-PEG/AS n = 733
Age	68 (57–74)	67 (57–74)
>75 yr	176 (24%)	177 (24%)
≤75 yr	555 (76%)	556 (76%)
Male/Female	370/361	371/362
BMI	23 (21–26)	23 (21–26)
>25 kg/m^2	214 (29%)	224 (31%)
≤25 kg/m^2	517 (71%)	509 (69%)
Low education level	131 (18%)	121 (17%)
Comorbidities		
None	319 (44%)	319 (44%)
Diabetes mellitus	114 (16%)	127 (17%)
Hypertension	264 (36%)	274 (37%)
Coronary artery disease	48 (7%)	43 (6%)
Liver cirrhosis	7 (1%)	6 (1%)
Stroke	7 (1%)	8 (1%)
Insomnia	39 (5%)	35 (5%)
Parkinson disease	2 (0.3%)	0 (0%)
Chronic constipation	121 (17%)	138 (19%)
CSS Score	2 (1–5)	2 (1–5)
Use of medications		
Tricyclic antidepressants	2 (0.3%)	2 (0.3%)
Oral iron supplement	7 (1%)	10 (1%)
Antacid	184 (25%)	185 (25%)
History of colonoscopy	578 (79%)	571 (78%)
Previous abdominal or pelvic surgery	250 (34%)	226 (31%)
Indication for colonoscopy		
Screening	224 (31%)	231 (32%)
Postpolypectomy surveillance	294 (40%)	269 (37%)
Diagnosis	213 (29%)	233 (32%)
Canceling colonoscopy for personal reasons	11 (2%)	22 (3%)

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group. Data are n (%) or median (IQR).
BMI, body mass index; CSS, Constipation Scoring System.

Quality of BP

Table 2 presents BP outcomes. In the ITT analysis using full-analysis set, the 1 L-PEG/AL group showed higher adequate BP rates compared with the 1 L-PEG/AS group (92% vs 86%, adjusted odds ratio [OR]: 1.97, 95% confidence interval [CI]: 1.33–2.85, $P = 0.001$). Similar trends were observed in the PPS (94% vs 89%, adjusted OR: 1.96, 95% CI: 1.33 to 2.86, $P = 0.001$). The overall BBPS was 7.6 ± 1.5 and 7.4 ± 1.6, respectively ($P = 0.002$). In a separate analysis of the mean BBPS scores for each segment, the 1 L-PEG/AL group exhibited significantly higher scores.

The interobserver agreement among endoscopists and investigators was almost perfect (a weighted κ coefficient, 0.975), and validation analyses using BBPS from the evaluators yielded similar results (Supplementary Table 1, http://links.lww.com/AJG/D579).

BP characteristics, adverse events, and tolerability

Table 3 presents BP characteristics. No significant differences were found in compliance with purgatives or dietary instructions between the 2 groups. First defecation time was significantly shorter, and the mean number of defecations before the intake of PEG-Asc was higher in the linaclotide group. No significant differences were found in number of defecations after the intake of PEG-Asc. Both groups underwent colonoscopy within 6 hours of the PEG-Asc solution intake. Amounts of PEG-Asc and additional clear liquid intake were comparable in the 2 groups.

Table 2. Outcomes of bowel preparation

	1L-PEG/AL n = 731	1LPEG/AS n = 733	Adjusted odds ratio (95% CI)	*P* value
Adequate BP				
ITT	675/731 (92%)	632/733 (86%)	1.97 (1.33–2.85)	0.001
PPS	675/720 (94%)	632/711 (89%)	1.96 (1.33–2.86)	0.001
BBPS	7.6 ± 1.5	7.4 ± 1.6	1.35 (1.12–1.63)	0.002
Right colon	2.4 ± 0.6	2.3 ± 0.6	1.45 (1.16–1.75)	0.001
Transverse colon	2.7 ± 0.6	2.6 ± 0.6	1.29 (1.04–1.61)	0.02
Left colon	2.6 ± 0.6	2.5 ± 0.6	1.38 (1.12–1.71)	0.006

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group. Data are n (%) or mean ± SD.
BBPS, Boston Bowel Preparation Scale; BP, bowel preparation; CI, confidence interval; ITT, intention to treat; PPS, per-protocol set.

Table 4 presents adverse events and tolerability. Nausea and vomiting, abdominal pain, and sleep disturbance were comparable between the 2 groups. No patients experienced moderate-to-severe abdominal pain or ischemic colitis. All patients with adverse events recovered without any management. When examined separately before and after the intake of PEG-Asc, no significant difference was found in the frequency of adverse events between the 2 groups (Supplementary Table 2, http://links.lww.com/AJG/D579). The rate of patients willing to undergo a repeat colonoscopy did not differ significantly between the 2 groups. No patients reported return visit within 24 hours after colonoscopy.

Colonoscopy parameters

The rate of complete colonoscopy was 99% in both groups. Incomplete colonoscopy was due to inadequate preparation (1% vs 1%) and technical difficulty or stricture (1% vs 0%). The mean cecal insertion, withdrawal times, and procedure time were comparable between the 2 groups. No significant differences were found between the 2 groups in the parameters related to lesion detection rates, including polyp detection rate, adenoma detection rate, serrated polyp detection rate, and cancer detection rate (Table 5).

Predefined stratified analysis between low-risk and high-risk groups for inadequate BP

In risk-stratified analysis, the rate of adequate BP was significantly higher in the 1L-PEG/AL group of high-risk patients (94% vs 86%, $P < 0.001$), whereas comparably high rates of adequate BP rates were found between 2 regimens in low-risk patients (94% vs 94%, $P = 0.66$). The difference in the treatment effect between the low-risk and high-risk groups was statistically significant (P for interaction = 0.01) (Table 6). Separate exploratory analyses of adequate BP based on each predictor of inadequate BP are shown in Supplementary Figure 1 (http://links.lww.com/AJG/D579).

DISCUSSION

Linaclotide with 1 L PEG-Asc significantly improved BP quality compared with the senna regimen without reducing tolerability. Furthermore, the linaclotide regimen demonstrated efficacy even in the high-risk group with inadequate BP. To the best of our knowledge, this is the first multicenter randomized controlled trial to investigate the efficacy of linaclotide as an adjunct laxative to 1 L PEG-Asc.

The demand for low-volume regimens with high tolerability is increasing (38). Although several low-volume agents (≤1-L) such as sodium picosulfate with magnesium citrate, PEG with a high

Table 3. Patient compliance and bowel preparation characteristics

	1L-PEG/AL n = 731	1L-PEG/AS n = 733	*P* value
Compliance with purgative instructions	701/720 (97%)	679/711 (96%)	0.06
Compliance with dietary instructions	675/720 (94%)	669/711 (94%)	0.83
First defecation time, hr	2.8 (1.5–11)	9.8 (8.5–11)	<0.001
Number of defecations before the intake of PEG-Asc	2 (1–3)	1 (1–2)	<0.001
Number of defecations after the intake of PEG-Asc	7 (5–10)	7 (5–10)	0.10
Preparation-to-colonoscopy interval ≥6h	0/720 (0%)	0/711 (0%)	1.00
PEG-Asc intake, L	1.0 ± 0.1	1.0 ± 0.1	0.68
Additional clear liquid intake, L	0.4 ± 0.3	0.4 ± 0.3	0.56

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group. Data are n (%) or mean ± SD or median (IQR).
PEG-Asc, polyethylene glycol plus ascorbic acid.

Table 4. Adverse events and tolerability

	1L-PEG/AL n = 731	1L-PEG/AS n = 733	*P* value
Nausea and vomiting	33/720 (5%)	29/711 (4%)	0.64
Abdominal pain (mild)	20/720 (3%)	23/711 (3%)	0.66
Abdominal pain (moderate-severe)	0/720 (0%)	0/711 (0%)	1.00
Sleep disturbance	30/720 (4%)	23/711 (3%)	0.40
Ischemic colitis	0/720 (0%)	0/711 (0%)	1.00
Willing to repeat BP	595/720 (83%)	577/711 (81%)	0.49
Return-visit within 24 hr after colonoscopy	0/720 (0%)	0/711 (0%)	1.00

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group. Data are n (%).
BP, bowel preparation.

concentration of ascorbate, sodium phosphate solution, or oral sulfate solution were developed, these regimens except for oral sulfate solution failed to meet the European Society of Gastrointestinal Endoscopy's quality standard of 90% (39). In addition, these hyperosmotic and stimulant agents have been reported to increase risks such as colonic ischemia, renal impairment, and electrolyte disturbance, and the European Society of Gastrointestinal Endoscopy does not recommend the routine use of these agents owing to their safety profile (8). Moreover, most of these low-volume regimens do not eliminate the need for patients to ingest large amounts of fluids along with laxatives to maintain hydration, amounting to 3–4 L of fluids. Therefore, various adjuvants combined with PEG-based solutions have been explored to enhance BP quality and minimize its volume and risks (40). In this study, the 1L-PEG/AL demonstrated higher efficacy with a safety profile similar to that of 1L-PEG/AS, which we previously reported to have noninferior efficacy and greater tolerability compared with the standard 2 L PEG-Asc regimen (17). Although a direct comparison between the linaclotide and standard regimen has not been made, the former may demonstrate noninferiority or even superiority to the standard regimen. In addition, the mean total volume in the 1 L-PEG/AL regimen was <2 L, representing a significant step toward a real reduction of total liquids, potentially enhancing patient acceptability.

Several risk factors have been identified as predictors of inadequate BP (35,36). A few recent studies have demonstrated the efficacy of low-volume regimens for low-risk patients who do not have potential risks for inadequate BP (22,32). However, limited information exists regarding the optimal BP regimen for high-risk patients (8). Our proposed 1L-PEG/AL regimen was highly efficacious, achieving adequate BP greater than the quality standard of 90% in both low-risk and high-risk patients. The use of linaclotide shortened the first defection time and increased the mean number of defecations before starting PEG-Asc without increasing the adverse events compared with the senna regimen. Moreover, these first-acting and strong defecation effects remained robust in high-risk patients with inadequate BP (3.0 [1.5–11] h vs 9.8 [8.5–11] h, $P < 0.01$), which may contribute to adequate BP in the 1 L-PEG/AL group in both low-risk and high-risk patients and may lead to a new promising option of a low-volume regimen for high-risk patients with inadequate BP.

Contrary to expectations for the analgesic effect of linaclotide, the linaclotide regimen did not relieve abdominal symptoms or improve patient tolerance compared with the senna regimen. In a study examining the effects of linaclotide in patients with irritable bowel syndrome with constipation, linaclotide improved spontaneous bowel movements within 24 hours of the first dose, whereas significant improvement in abdominal pain and bowel symptoms required at least 3 months (41). This may explain why high-quality bowel cleansing without improvement in abdominal discomfort was observed in the 1 L-PEG/AL group. Moreover, the amount of senna

Table 5. Parameters associated with the procedure of colonoscopy

	1L-PEG/AL n = 731	1L-PEG/AS n = 733	*P* value
Cecal intubation rate	714/720 (99%)	709/711 (99%)	0.29
Cecal insertion time, min	5.5 ± 3.3	5.5 ± 3.4	0.99
Withdrawal time, min	10 ± 4.9	11 ± 4.9	0.20
Procedure time, min	1.0 ± 0.1	0.9 ± 0.1	0.90
Impossible colonoscopy for insufficient BP	5/720 (1%)	2/711 (0.3%)	0.28
Incomplete colonoscopy for technical difficulty or stricture	1/720 (0.1%)	0/711 (0%)	0.51
Colonoscopy findings			
PDR	425/720 (59%)	422/711 (59%)	0.91
ADR	290/720 (40%)	297/711 (42%)	0.59
SDR	74/720 (10%)	65/711 (9%)	0.48
Early cancer	17/720 (2%)	22/711 (3%)	0.42
Advanced cancer	3/720 (0.4%)	6/711 (0.8%)	0.34
Colonic diverticula	322/720 (45%)	326/711 (46%)	0.67

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group. Data are n (%) or mean ± SD.
ADR, adenoma detection rate; BP, bowel preparation; PDR, polyp detection rate; SDR, serrated polyp detection rate.

Table 6. Predefined stratified analysis between low-risk and high-risk groups for inadequate BP

	1LPEG/AL n = 731	1LPEG/AS n = 733	Adjusted odds ratio (95% CI)	*P* value	*P* for interaction
Risk of inadequate BP					
High risk	412/440 (94%)	389/452 (86%)	2.60 (1.61–4.18)	<0.001	0.01
Low risk	263/280 (94%)	243/259 (94%)	0.99 (0.49–2.01)	0.66	

1 L PEG-Asc plus linaclotide (1L-PEG/AL) or 1 L PEG-Asc plus senna (1L-PEG/AS) group.
BP, bowel preparation; CI, confidence interval.

used in the comparative regimen was already small (24 mg), which has been reported to be the smallest dose for use as an adjunct (16,17,42). In addition, the senna regimen has previously been reported to have high tolerability compared with the standard regimen, 2 L PEG-Asc. The low incidence of abdominal symptoms in the senna group may have influenced the results of this study.

Our results have significant clinical implications. Linaclotide, which is minimally absorbed into the body and acts on the intestinal mucosa, can be administered regardless of renal or liver function. Furthermore, this low-volume linaclotide regimen, which provides high-quality cleansing effects regardless of the patient's risk status for inadequate BP, has the potential to benefit many patients. Moreover, this study used the BBPS, which is the most validated scale with high interobserver agreement for evaluating BP quality. The consistency of the ITT and PPS analyses, along with the analyses using BBPS by the evaluators, further supports the validity of our results.

Our study had several limitations. First, our proposed linaclotide regimen was not directly compared with high-volume standard regimens or other adjuvants. The appropriate type of adjuvant remains unknown, and further studies are required to compare it with other adjuvants and combinations. Furthermore, as linaclotide is more expensive than senna, the choice of regimen may need to consider cost-effectiveness based on the patient's risk of inadequate BP. Second, uniform criteria for low-risk and high-risk populations were lacking. We used predictors related to inadequate BP as risk criteria based on high-quality randomized controlled trials, meta-analyses, and guidelines. Third, several factors might have influenced for this study, including additional patient guidance, strict dietary requirements, and high compliance, and the influence of race also cannot be ruled out (43–45). A high rate of prior experience with BP may have also contributed to the high tolerability. Moreover, patients in this study had a relatively low body mass index, so the results may not be applicable to the Western population. Fourth, we did not assess dehydration or preparation-induced electrolyte imbalance. Previous studies have reported that both PEG-Asc and linaclotide or senna are less likely to elicit biochemical or hematological changes (25,43,46), and no adverse events related to these agents were observed. Fifth, the amount of washing during colonoscopy was not monitored, which might have affected BP quality. Sixth, this linaclotide regimen did not increase the lesion detection rate. However, focusing on lesions ≤5 mm, the 1 L-PEG/AL group showed a higher detection rate than the 1 L-PEG/AS group (Supplementary Table 3, http://links.lww.com/AJG/D579). This result may contribute to the higher detection rate of smaller, harder-to-detect lesions, which may have clinical significance (47).

Linaclotide plus 1 L PEG-Asc significantly increased BP efficacy compared with senna, without reducing tolerability in all patients. It presents a promising option for BP, especially in patients at high risk of inadequate BP.

CONFLICTS OF INTEREST

Guarantor of the article: Akira Higashimori, MD, PhD.

Specific author contributions: N.M., A.H., M.N., T.F., and Y.F. conceived and designed the trial. N.M., A.H., M.N., T.F., and Y.F. contributed to data analysis and interpretation. Data management was performed by N.M., A.H., Y.N., T.W., K.O., and H.Y. Data collection was conducted by N.M., A.H., M.N., I.Y., T.Y., D.K., Y.M., R.N., A.H., A.S., H.M., J.O., T.K., M.O., S.F., K.M., S.H., F.T., K.T., E.S., D.K., K.O., and H.Y. The writing, review, and/or revision of the manuscript was performed by N.M., A.H., and D.K. YF supervised the study. All authors read, revised, and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Financial support: None to report.

Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Two liters of Polyethylene glycol (PEG) containing ascorbic acid (PEG-Asc) is an effective alternative to the traditional 4-L PEG for bowel preparation but still poses a burden.
- ✓ Adjuvants, such as senna, can reduce PEG-Asc volume to 1-L, thereby improving patient tolerability. However, an appropriate adjuvant for PEG-Asc remains unknown.
- ✓ Linaclotide, a guanylate cyclase C receptor agonist, has shown potential as an adjuvant for bowel preparation during capsule endoscopy and colonoscopy.

WHAT IS NEW HERE

- ✓ Adding linaclotide to 1-L of PEG-Asc significantly increased the efficacy of bowel preparation than adding senna without reducing tolerability.
- ✓ This finding remained robust even in high-risk patients for inadequate bowel preparation.

REFERENCES

1. Burke CA, Church JM. Enhancing the quality of colonoscopy: The importance of bowel purgatives. Gastrointest Endosc 2007;66(3):565–73.
2. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Am J Gastroenterol 2015;110(1):72–90.
3. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003;58(1):76–9.
4. Hendry PO, Jenkins JT, Diament RH. The impact of poor bowel preparation on colonoscopy: A prospective single centre study of 10,571 colonoscopies. Colorectal Dis 2007;9:745–8.

5. Gawron AJ, Veerappan A, Keswani RN. High success rate of repeat colonoscopy with standard endoscopes in patients referred for prior incomplete colonoscopy. BMC Gastroenterol 2014;14:56.
6. Johnson DA, Barkun AN, Cohen LB, et al. Optimizing adequacy of bowel cleansing for colonoscopy: Recommendations from the US multi-society task force on colorectal cancer. Gastroenterology 2014;147(4):903–24.
7. Marshall JB, Pineda JJ, Barthel JS, et al. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation. Gastrointest Endosc 1993;39(5):631–4.
8. Hassan C, East J, Radaelli F, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline - Update 2019. Endoscopy 2019;51(8):775–94.
9. Valiante F, Pontone S, Hassan C, et al. A randomized controlled trial evaluating a new 2-L PEG solution plus ascorbic acid vs 4-L PEG for bowel cleansing prior to colonoscopy. Dig Liver Dis 2012;44(3):224–7.
10. Xie Q, Chen L, Zhao F, et al. A meta-analysis of randomized controlled trials of low-volume polyethylene glycol plus ascorbic acid versus standard-volume polyethylene glycol solution as bowel preparations for colonoscopy. PLoS One 2014;9(6):e99092.
11. Kang SH, Jeen YT, Lee JH, et al. Comparison of a split-dose bowel preparation with 2 liters of polyethylene glycol plus ascorbic acid and 1 liter of polyethylene glycol plus ascorbic acid and bisacodyl before colonoscopy. Gastrointest Endosc 2017;86:343–8.
12. Choi SJ, Kim ES, Choi BK, et al. A randomized controlled trial comparing the efficacy of 1-L polyethylene glycol solution with ascorbic acid plus prucalopride versus 2-L polyethylene glycol solution with ascorbic acid for bowel preparation. Scand J Gastroenterol 2018;53(12):1619–24.
13. Kwon JE, Lee JW, Im JP, et al. Comparable efficacy of a 1-L PEG and ascorbic acid solution administered with bisacodyl versus a 2-L PEG and ascorbic acid solution for colonoscopy preparation: A prospective, randomized and investigator-blinded trial. PLoS One 2016;11(9):e0162051.
14. Yamaguchi D, Hidaka H, Matsunaga T, et al. Efficacy of elobixibat as bowel preparation agent for colonoscopy: Prospective, randomized, multi-center study. Dig Endosc 2022;34(1):171–9.
15. Kim SH, Kim ER, Kim K, et al. Combination of bisacodyl suppository and 1 L polyethylene glycol plus ascorbic acid is a non-inferior and comfortable regimen compared to 2 L polyethylene glycol plus ascorbic acid. Dig Endosc 2020;32(4):600–7.
16. Kamei M, Shibuya T, Takahashi M, et al. Efficacy and acceptability of 1 liter of polyethylene glycol with ascorbic acid vs. 2 liters of polyethylene glycol plus mosapride and sennoside for colonoscopy preparation. Med Sci Monit 2018;24:523–30.
17. Maeda N, Higashimori A, Nakatani M, et al. Efficacy and tolerability of 1 L polyethylene glycol plus ascorbic acid with senna versus 2 L polyethylene glycol plus ascorbic acid for colonoscopic bowel preparation: Prospective, randomized, investigator-blinded trial. Dig Endosc 2023;35(6):767–76.
18. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011;365(6):527–36.
19. Fukudo S, Miwa H, Nakajima A, et al. High-dose linaclotide is effective and safe in patients with chronic constipation: A phase III randomized, double-blind, placebo-controlled study with a long-term open-label extension study in Japan. Neurogastroenterol Motil 2019;31(1):e13487.
20. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. Gastroenterology 2013;145(6):1334–46.e11.
21. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012;107(11):1702–12.
22. Zhang C, Chen X, Tang B, et al. A novel ultra-low-volume regimen combining 1 L polyethylene glycol and linaclotide versus 2 L polyethylene glycol for colonoscopy cleansing in low-risk individuals: A randomized controlled trial. Gastrointest Endosc 2023;97(5):952–61.e1.
23. Zhang M, Zou W, Xu C, et al. Polyethylene glycol combined with linaclotide is an effective and well-tolerated bowel preparation regimen for colonoscopy: An endoscopist-blinded, randomized, controlled trial. Eur J Gastroenterol Hepatol 2021;33(1S Suppl 1):e625–33.
24. Stein DJ, Copland A, McDaniel D, et al. Single-dose linaclotide is equal in efficacy to polyethylene glycol for bowel preparation prior to capsule endoscopy. Dig Dis 2019;37(4):297–302.
25. Xu H, He Z, Liu Y, et al. Application of linaclotide in bowel preparation for colonoscopy in patients with constipation: A prospective randomized controlled study. J Gastroenterol Hepatol 2024;39(12):2752–9.
26. Maeda N, Higashimori A, Yamamoto I, et al. Bowel preparation with linaclotide and 1 L polyethylene glycol plus ascorbic acid prior to colonoscopy in chronic constipated patients. Scand J Gastroenterol 2024;59(10):1209–15.
27. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
28. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.
29. Ihara E, Manabe N, Ohkubo H, et al. Evidence-based clinical guidelines for chronic constipation 2023. Digestion 2024;19:1–28.
30. Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum 1996;39(6):681–5.
31. Lai EJ, Calderwood AH, Doros G, et al. The Boston bowel preparation scale: A valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009;69(3 Pt 2):620–5.
32. Kang X, Zhao L, Zhu Z, et al. Same-day single dose of 2 liter polyethylene glycol is not inferior to the standard bowel preparation regimen in low-risk patients: A randomized, controlled trial. Am J Gastroenterol 2018;113(4):601–10.
33. Park SS, Sinn DH, Kim YH, et al. Efficacy and tolerability of split-dose magnesium citrate: Low-volume (2 liters) polyethylene glycol vs. single- or split-dose polyethylene glycol bowel preparation for morning colonoscopy. Am J Gastroenterol 2010;105(6):1319–26.
34. Brandt LJ, Feuerstadt P, Longstreth GF, et al; American College of Gastroenterology. ACG clinical guideline: Epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol 2015;110(1):18–45; quiz 5.
35. Mahmood S, Farooqui SM, Madhoun MF. Predictors of inadequate bowel preparation for colonoscopy: A systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018;30(8):819–26.
36. Gandhi K, Tofani C, Sokach C, et al. Patient characteristics associated with quality of colonoscopy preparation: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16(3):357–69.e10.
37. Higashimori A, Maeda N, Nakatani M, et al. Importance of bowel habits in predicting inadequate bowel preparation: A prospective observational study. Dig Dis Sci 2023;68(11):4148–55.
38. Connor A, Tolan D, Hughes S, et al. Consensus guidelines for the safe prescription and administration of oral bowel-cleansing agents. Gut 2012;61(11):1525–32.
39. van Riswijk MLM, van Keulen KE, Siersema PD. Efficacy of ultra-low volume (≤1 L) bowel preparation fluids: Systematic review and meta-analysis. Dig Endosc 2022;34(1):13–32.
40. Soh JS, Kim KJ. Combination could be another tool for bowel preparation? World J Gastroenterol 2016;22(10):2915–21.
41. Fukudo S, Miwa H, Nakajima A, et al. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. Neurogastroenterol Motil 2018;30(12):e13444.
42. Amato A, Radaelli F, Paggi S, et al. Half doses of PEG-ES and senna vs. high-dose senna for bowel cleansing before colonoscopy: A randomized, investigator-blinded trial. Am J Gastroenterol 2010;105(3):675–81.
43. Ell C, Fischbach W, Bronisch HJ, et al. Randomized trial of low-volume PEG solution versus standard PEG + electrolytes for bowel cleansing before colonoscopy. Am J Gastroenterol 2008;103(4):883–93.
44. Wu KL, Rayner CK, Chuah SK, et al. Impact of low-residue diet on bowel preparation for colonoscopy. Dis Colon Rectum 2011;54(1):107–12.
45. Kang X, Zhao L, Leung F, et al. Delivery of instructions via mobile social media app increases quality of bowel preparation. Clin Gastroenterol Hepatol 2016;14(3):429–35.e3.
46. Radaelli F, Meucci G, Imperiali G, et al. High-dose senna compared with conventional PEG-ES lavage as bowel preparation for elective colonoscopy: A prospective, randomized, investigator-blinded trial. Am J Gastroenterol 2005;100(12):2674–80.
47. Kim J, Choi JM, Lee J, et al. Boston bowel preparation scale score 6 has more missed lesions compared with 7-9. Sci Rep 2024;14(1):1605.