

Bowel preparation efficacy and discomfort of 2 L polyethylene glycol combined with linaclotide versus 3 L polyethylene glycol: a noninferiority, prospective, multicenter, randomized controlled trial

Jiandi Wu , Song Liu, Shuyu Li, Gangping Li, Erchuan Wang, Tao Bai, Xiaohua Hou and Jun Song 

Abstract

Background: Three liters of polyethylene glycol administered in a split dose is a commonly recommended regimen for bowel preparation before colonoscopy.

Objectives: The aim of this study was to compare the quality and tolerability of low-dose (2 L) polyethylene glycol combined with linaclotide (2 L+L) versus the 3 L polyethylene glycol (PEG) bowel preparation regimen.

Design: A noninferiority, prospective, multicenter, randomized controlled trial.

Methods: In this noninferiority, prospective, multicenter, randomized controlled study, patients scheduled for colonoscopy were enrolled and randomized to receive a 3 L PEG or 2L PEG+L regimen. The quality of bowel preparation and patients' discomfort was assessed.

Results: Over 12 months, 458 patients were randomized into 3 L PEG and 2 L+L groups. The primary endpoints showed that the 2 L+L regimen was superior to the 3L PEG regimen in overall bowel cleansing scores (Ottawa Bowel Preparation Scale: 3.3 ± 2.1 vs 3.7 ± 2.1 , $p=0.021$), but no significant difference in adequate bowel preparation rate between the two groups according to the OBPS score (97% vs 97.4%, $p=0.791$). Before colonoscopy, patients in the 2 L+L regimen group had lower bloating scores (0.5 [0, 2] vs 1 [0, 3], $p=0.013$), discomfort scores (1 [0, 2] vs 1 [0, 3], $p=0.006$), and intolerability scores (1 [0, 3] vs 2 [0, 4], $p=0.016$) than did those in the 3L PEG group.

Conclusion: Two liters of polyethylene glycol combined with linaclotide may be an alternative regimen to 3 L of PEG taken in split doses for bowel preparation before colonoscopy.

Trial registration: ChiCTR2100041992.

Ther Adv Gastroenterol

2024, Vol. 17: 1–10

DOI: 10.1177/
17562848241299739

© The Author(s), 2024.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Xiaohua Hou
Jun Song

Department of
Gastroenterology, Union
Hospital, Tongji Medical
College, Huazhong
University of Science and
Technology, 1277 Jiefang
Road, Wuhan 430022,
China

houxh@hust.edu.cn
song111jun@126.com

Jiandi Wu
Gangping Li
Erchuan Wang
Tao Bai

Department of
Gastroenterology, Union
Hospital, Tongji Medical
College, Huazhong
University of Science and
Technology, Wuhan, China

Song Liu
Department of
Gastroenterology, Wuhan
No. 1 Hospital, Wuhan
Hospital of Traditional
Chinese and Western
Medicine, Wuhan, Hubei,
China

Shuyu Li
Department of
Gastroenterology, Hubei
No. 3 People's Hospital of
Jiangnan University,
Wuhan, China

Plain language summary

Improvement in bowel preparation efficacy and patients' discomfort after polyethylene glycol (2 L) combined with linaclotide.

The commonly recommended intestinal cleanser regimen is 3 L of polyethylene glycol, which achieves cleansing of the intestinal segments but may give discomfort to the patients. We have conducted a noninferiority, prospective, multicenter, randomized controlled trial to compare 2 L polyethylene glycol+ linaclotide and 3 L polyethylene glycol. The results showed that similar patients' percentage had adequate bowel preparation rate in two groups according to the OBPS score. However, the 2 L+L regimen was superior to the 3 L PEG regimen in overall bowel cleansing scores and patients' discomfort. Trial registration number: ChiCTR2100041992.

Keywords: bowel preparation, colonoscopy, linaclotide, polyethylene glycol

Received: 18 July 2024; revised manuscript accepted: 28 October 2024.

Introduction

Colorectal cancer is one of the most common malignant tumors worldwide,¹ endangering human health and life. Colonoscopy has proven to be the most effective method for detecting, screening, and diagnosing colorectal cancer. Detecting and removing colorectal polyps as soon as possible can help prevent tumors. However, colonoscopy efficacy is influenced by the quality of bowel preparation. It has been found that 18%–35% of patients have inadequate bowel preparation.² This leads to missed polyps, extended operating times, and unsuccessful cecal intubation. A modified split-dose regimen of 3 L of PEG is used in China to provide high-quality bowel preparation, while a 4 L polyethylene glycol (PEG) split-dose regimen is recommended for bowel cleaning preparation in Europe and America.^{3,4} However, ingesting a large volume of unpleasant-tasting liquid can lead to unpleasant side effects such as nausea and vomiting, which could lower patient compliance and tolerance and lead to an undesirable bowel preparation.⁵ Since the quality of bowel preparation is closely related to patient tolerance, clinicians must consider improved bowel preparation protocols to enhance patient tolerance and compliance.

Linaclotide is a selective guanylate cyclase-C (GC-C) receptor agonist with visceral analgesic and pro-secretory effects⁶ that can alleviate abdominal pain and constipation symptoms caused by irritable bowel syndrome.⁷ Binding of linaclotide to GC-C increases intracellular cyclic guanosine monophosphate (cGMP), resulting in increased fluid secretion and an inhibited visceral nociceptive response.⁸ The bowel preparation process causes unpleasant symptoms such as bloating, and linaclotide in combination with low-dose PEG may be a good bowel preparation regimen for improving patient tolerance. Compared with 4 L of PEG, linaclotide combined with low-dose (2 L) PEG is reported in some studies to be an effective and well-tolerated bowel preparation regimen.^{9,10} However, few studies have explored the quality and tolerability of low-dose (2 L) polyethylene glycol combined with linaclotide (2L+L) versus 3 L of PEG in

China. Therefore, prospective, multicenter randomized controlled studies are needed to confirm the feasibility of low-dose (2 L) + linaclotide as an alternative to 3 L PEG. Considering patient compliance, 580 µg linaclotide (290 µg/day for 2 days) combined with a 2L PEG split dose was compared with a 3L PEG split dose in this study.

The primary objective of this study was to compare the bowel preparation quality of linaclotide combined with a low-dose (2 L) PEG split-dose regimen with that of the 3L PEG regimen.

Methods

Study design and participants

This multicenter prospective, randomized controlled study was conducted from February 1, 2021, to February 1, 2022, at Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, the First Hospital of Wuhan, the Third People's Hospital of Hubei Province, and the People's Hospital of Liupanshui City. The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (ethics number: 2020-0559-01) and was registered in the Chinese Clinical Trial Registry (ChiCTR2100041992), and in accordance with the Helsinki Declaration of 1975 as revised in 2013. The randomized trial in this study followed the CONSORT statement.¹¹ Patients were consecutively and randomly included in the study and signed an informed consent form before examination. Subsequently, all patient details were de-identified.

The study inclusion criteria were as follows: (1) age of 18–65 years; (2) scheduled for colonoscopy; (3) signed and dated informed consent form; and (4) commitment to comply with the study procedures and to cooperate with the implementation of the study. The exclusion criteria were as follows: (1) severe heart failure (New York Class III or IV); (2) recent acute myocardial infarction or unstable angina; (3) uncontrolled hypertension; (4) chronic kidney disease; (5)

suspected intestinal obstruction or perforation; (6) scheduled for intestinal resection; (7) gastroparesis; (8) diarrhea more than three times per day; (9) cirrhosis of the liver or ascites; (10) pregnancy or nursing; (11) mental illness with an inability to cooperate with the examination; and (12) allergies to bowel preparation drugs.

Randomization and blinding

Computer-generated random numbers were sealed in envelopes, with odd numbers representing the 2L+L group and even numbers representing the 3L PEG. Eligibility screening for all patients was completed by a specialized internist and followed the principles of randomization and continuity. After eligibility screening, consent, and assessment, each patient was randomly assigned (1:1) to either the 2L+L group or the 3L PEG group by a dedicated nurse according to numerical numbers in envelopes. The examiners were unaware of the patient's bowel preparation regimens. The investigators or endoscopists collecting data on the primary and secondary outcomes were unaware of the subject assignment.

Bowel preparation protocol and colonoscopy

Patients were randomized into a conventional bowel preparation group or a linaclotide-modified preparation group. For the conventional bowel preparation group, PEG (Beaufour Ipsen Pharma, Boulogne-Billancourt-France) was used as the bowel preparation agent (1 L of PEG bowel preparation solution ingested at 8:00pm the day before the examination and 2 L of PEG bowel preparation solution ingested 4–6h before the examination). For the linaclotide-modified group, on the day before the examination, 290 µg of linaclotide (AstraZeneca Pharmaceuticals Limited, Wuxi, China) was taken before the first meal, and 1 L of the PEG bowel preparation solution was ingested at 8:00pm; subsequently, 290 µg of linaclotide and 1 L of the PEG bowel preparation solution were used 4–6h before the examination. The linaclotide was dispensed directly to the patients by the investigator, and the patients did not make an additional payment. All patients were counseled on how to properly prepare their bowels and were placed on a low/no residue diet (i.e., no vegetables or fruits) for 3 days prior to the exam. A colonoscopy would be done when the bowel movements become watery, clear, and

yellowish (checked by endoscopists). If the patient's bowel preparation was poor, a colonoscopy would be performed without imposing an intervention. In this case, OBPS scoring and recording of polyp detection (without rinsing) were performed first, followed by rinsing through colonoscopy and repeat examination. Based on the quality of the patient's final examination, a decision was made regarding the need for a short-term follow-up examination. All patients underwent colonoscopy while awake and filled out a questionnaire (including baseline information and feelings scores) before colonoscopy, then described the corresponding feeling scores during the colonoscopy procedure (recorded by nurses).

All the examinations were performed by experienced endoscopists using a high-resolution colonoscopy instrument (CF-HQ290I, Olympus, Tokyo, Japan); these endoscopists had performed at least 1000 colonoscopies. The examiners were trained on the Ottawa Bowel Preparation Scale (OBPS) prior to the examination and were asked to take high-quality pictures representing the level of bowel preparedness during colonoscopy.¹² The assessment was completed at the time of initial endoscopic passes. The OBPS was scored uniformly by two endoscopists for all subjects, and disagreements were confirmed by a third endoscopist after a comprehensive evaluation.

Outcome assessment

The primary outcome was to assess the quality of bowel preparation based on the total OBPS score. A total score of ≤ 7 was considered adequate bowel preparation.

The secondary outcomes were each site's bowel score, patients' comfort level before and during the bowel examination; willingness to repeat the preparation in the future; and rates of cecal intubation, polyp detection, and adenoma detection. Each patient's comfort level was measured on a 10-point scale for each of the following symptoms: abdominal pain, bloating, discomfort, and intolerability.

Statistical analysis

Sample size calculations were based on previously published data with a performance goal for optimal bowel preparation defined as $\geq 85\%$ of outpatients according to the Colonoscopy Quality

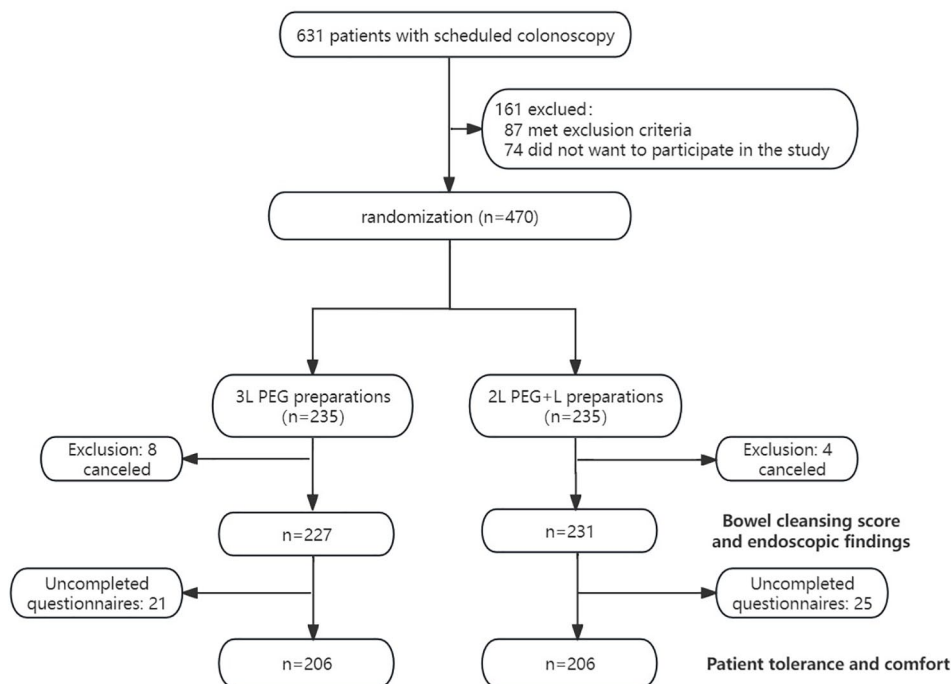


Figure 1. The flowchart of the research.

Index.¹³ Assuming an overall cleansing success rate of 85% in the linaclotide group, 85% in the 3L PEG group, a noninferiority margin of 12%, and an alpha level of 2.5%, a sample size of at least 374 patients (187 patients in each group) would be required to provide at least 90% efficacy to demonstrate noninferiority in each group. Considering a 10% dropout rate, a minimum of 410 patients needed to be included in this study. Continuous variables are described herein as the mean \pm standard deviation or median (interquartile spacing) and were analyzed using Student's *t* test or the Mann–Whitney *U* test. Categorical variables are expressed as frequencies and percentages and were analyzed using the Pearson χ^2 test or Fisher's exact test, as appropriate. Statistical analysis was performed using the SPSS 25.0 software package (IBM Corp., Armonk, NY, USA), and two-sided $p < 0.05$ was considered to indicate statistical significance.

Results

A total of 631 patients were screened for eligibility; 470 patients met the inclusion criteria and were randomly assigned to receive 3 L of PEG or

2L+L. Following the withdrawal of 12 patients (8 patients from the 3L group and 4 from the 2L+L group), 227 and 231 patients were included in the 3L PEG and 2L+L groups, respectively (Figure 1). Overall, the 2L+L group had a greater percentage of men than did the 3L PEG group (170 (73.6%) vs 146 (64.3%), $p = 0.034$), but there were no appreciable differences in age (42.0 ± 12.5 vs 42.0 ± 12.2 , $p = 0.103$) or body mass index (23.0 ± 3.3 vs 23.5 ± 3.2 , $p = 0.511$; Table 1). Other basic information such as hypertension (18 (7.8%) vs 22 (9.7%), $p = 0.034$), diabetes mellitus (2 (0.9%) vs 2 (0.9%), $p > 0.999$), medication history (42 (18.2%) vs 47 (20.7%), $p = 0.555$), history of abdominal surgery (34 (14.7%) vs 38 (16.7%), $p = 0.608$) and constipation (20 (8.7%) vs 28 (12.3%), $p = 0.223$) were not significantly different between the two groups.

Primary outcome

The results showed that similar patients' percentages had adequate bowel preparation in two groups according to the OBPS score (97% vs 97.4%, $p = 0.791$). However, the 2L+L regimen was superior to the 3L PEG regimen in overall

Table 1. Baseline characteristics.

Variables	3 L PEG <i>n</i> = 227	2 L PEG + L <i>n</i> = 231	<i>p</i> Value
Male sex, <i>n</i> (%)	146 (64.3%)	170 (73.6%)	0.034
Age, years, mean \pm SD	42.0 \pm 12.2	42.0 \pm 12.5	0.969
BMI, mean \pm SD, kg/m ²	23.5 \pm 3.2	23.0 \pm 3.3	0.103
Hypertension, <i>n</i> (%)	22 (9.7%)	18 (7.8%)	0.511
Diabetes mellitus, <i>n</i> (%)	2 (0.9%)	2 (0.9%)	>0.999
Medicines, <i>n</i> (%)	47 (20.7%)	42 (18.2%)	0.555
History of abdominal surgery, <i>n</i> (%)	38 (16.7%)	34 (14.7%)	0.608
Constipation, <i>n</i> (%)	28 (12.3%)	20 (8.7%)	0.223

BMI, body mass index; PEG, polyethylene glycol.

Table 2. Bowel preparation outcome scores and colonic intubation rate.

Variables	3L PEG <i>n</i> = 227	2L PEG + L <i>n</i> = 231	<i>p</i> Value
OBPS—A score LC, mean \pm SD	1.1 \pm 0.7	0.9 \pm 0.7	0.016
OBPS—A score TC, mean \pm SD	1.0 \pm 0.7	0.8 \pm 0.7	0.018
OBPS—A score RC, mean \pm SD	1.1 \pm 0.7	1.0 \pm 0.7	0.159
OBPS-B, mean \pm SD	0.5 \pm 0.5	0.5 \pm 0.5	0.485
OBPS overall score, mean \pm SD	3.7 \pm 2.1	3.3 \pm 2.1	0.021
Adequate bowel preparation, <i>n</i> (%)	222 (97.4%)	223 (97.0%)	0.791
Cecal intubation rate, <i>n</i> (%)	223 (98.2%)	229 (99.1%)	0.446

OBPS, Ottawa Bowel Preparation Scale; PEG, polyethylene glycol; LC, left colon; RC, right colon; TC, transverse colon.

bowel cleansing results (3.3 ± 2.1 vs 3.7 ± 2.1 , $p = 0.021$).

Secondary outcomes

As for segment scoring, the left colon and transverse colon in the 2L+L regimen outperformed the 3L PEG regimen (left colon: 0.9 ± 0.7 vs 1.1 ± 0.7 , $p = 0.016$; transverse colon: 0.8 ± 0.7 vs 1.0 ± 0.7 , $p = 0.018$) (Table 2 and Figure 2). The cecal intubation rate of the 2L PEG+L group was not inferior to that of the 3L PEG group (99.1% vs 98.2%, $p = 0.446$).

There were 206 patients who completed the questionnaires on tolerance and comfort scores in the two groups (Table 3). Before colonoscopy, patients in the 2L+L regimen group had lower bloating scores ($0.5(0, 2)$ vs $1(0, 3)$, $p = 0.013$), discomfort scores ($1(0, 2)$ vs $1(0, 3)$, $p = 0.006$), and intolerability scores ($1(0, 3)$ vs $2(0, 4)$, $p = 0.016$) than did those in the 3L PEG group (Figure 3), but the willingness to undergo the same cleaning regimen in the future was similar (85.4% vs 83.0%, $p = 0.589$). Interestingly, patients who received the 2L+L regimen were more willing during the colonoscopy to repeat

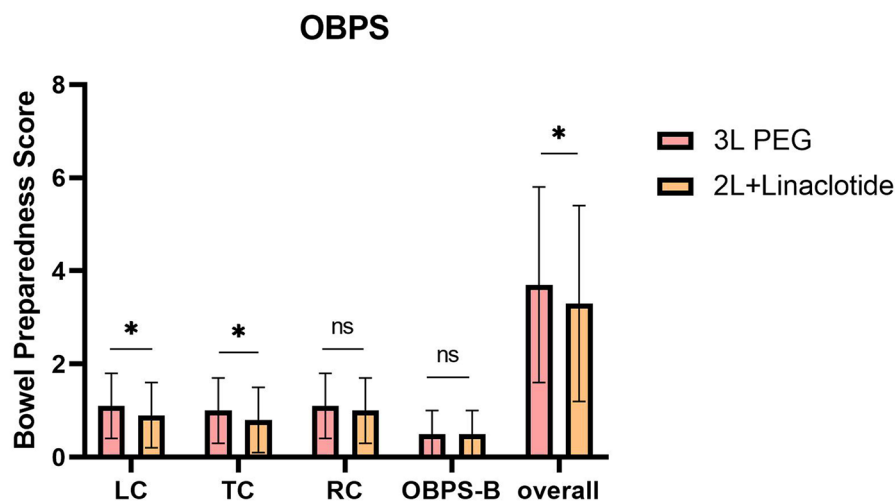


Figure 2. Bowel-preparation outcome scores for the two groups.

the bowel preparation regimen than those were in the 3 L PEG group (86.4% vs 74.8%, $p=0.004$). Additionally, patients in the 2L+L group scored lower than those in the 3 L PEG group on abdominal pain, abdominal distension, and discomfort scores, although there was no statistically significant difference (abdominal pain score: 2.8 ± 2.4 vs 3.1 ± 2.3 , $p=0.324$; abdominal bloating score: 3.6 ± 2.4 vs 3.8 ± 2.5 , $p=0.557$; abdominal discomfort score: 3.3 ± 2.3 vs 3.6 ± 2.5 , $p=0.557$).

Endoscopic findings in two bowel cleaning regimens

The results showed that endoscopic findings in the 2L+L group were not inferior to those in the 3L PEG group (Table 4). There was no significant difference in the overall polyp detection rate, adenoma detection rate, or advanced adenoma detection rate between the two groups, but the number of polyps per person in the 2L+L regimen group was greater than that in the 3L PEG group (0.7 vs 0.6 , $p=0.003$). The polyp detection rate and adenoma detection rate of each bowel segment were also similar in the two bowel preparation protocols.

Adverse events

In total, 303 (73.5%) patients presented with mild adverse events that were mostly associated with bowel preparation, including slight bloating, abdominal pain, discomfort, intolerability,

without the most frequent treatment-emergent adverse events (Table 2). Interestingly, the 2L+L group had a lower adverse event rate than the 3L PEG group (68.9% vs 78.2%, $p=0.044$).

Discussion

We performed a prospective, multicenter, randomized controlled trial in China that compared bowel cleansing efficacy and preexamination and intra-examination tolerability between a 2L+L group and a 3L PEG group. The results showed that the 2L+L group was superior to the 3L PEG group in colon cleansing scores. The degree of bowel cleansing is critical to the quality of colonoscopy. Small-volume detergents in combination with other medications may improve patient compliance and achieve similar bowel cleansing results relative to high-dose detergents. Two studies demonstrated that 2L+L provided an intestinal cleansing efficacy similar to that of 4 L of PEG,^{9,10} and 2L+L was also suggested as an intestinal cleansing regimen that could be used instead of 4 L of PEG. However, there is no direct comparison between 2L+L and 3 L of PEG bowel-cleansing regimens, and the feasibility of introducing 2L+L in China is uncertain. This multicenter prospective, randomized controlled study demonstrated that 2L+L was superior to 3 L of PEG for overall bowel cleansing scores. Meanwhile, the adequate bowel cleansing rates and cecum intubation rates were not significantly different between the two groups. A previous

Table 3. Comparison of patient adverse events and tolerance between the two groups.

Variables	3 L PEG <i>n</i> = 206	2 L PEG + L <i>n</i> = 206	<i>p</i> Value
Adverse events	161 (78.2%)	142 (68.9%)	0.044
Abdominal pain, <i>n</i> (%)	93 (45.2%)	79 (38.4%)	0.194
Bloating, <i>n</i> (%)	118 (57.3%)	103 (50.0%)	0.167
Discomfort, <i>n</i> (%)	125 (60.7%)	108 (50.2%)	0.112
Intolerability, <i>n</i> (%)	133 (64.6%)	113 (54.9%)	0.056
Before the colonoscopy			
Abdominal pain score (0–10), median (IQR)	0 (0, 2)	0 (0, 2)	0.056
Bloating score (0–10), median (IQR)	1 (0, 3)	0.5 (0, 2)	0.013
Discomfort score (0–10), median (IQR)	1 (0, 3)	1 (0, 2)	0.006
Intolerability score (0–10), median (IQR)	2 (0, 4)	1 (0, 3)	0.016
Willingness to repeat the same bowel prep program, <i>n</i> (%)	171 (83.0%)	176 (85.4%)	0.589
During colonoscopy			
Abdominal pain score (0–10), mean \pm SD	3.1 \pm 2.3	2.8 \pm 2.4	0.324
Bloating score (0–10), mean \pm SD	3.8 \pm 2.5	3.6 \pm 2.4	0.557
Discomfort score (0–10), mean \pm SD	3.6 \pm 2.5	3.3 \pm 2.3	0.143
Willingness to repeat the same bowel prep program, <i>n</i> (%)	154 (74.8%)	178 (86.4%)	0.004
PEG, polyethylene glycol.			

study also showed that the adequate bowel cleansing rate and cecum intubation rate of 2L+L were comparable to those of 4L PEG or other drugs combined with 2L PEG.⁹

Relative to 3L PEG, the 2L+L regimen improved patients' pre-examination discomfort. Polyethylene glycol, a macromolecular polymer that is rarely absorbed in the intestinal tract, reduces exogenous water absorption, thereby increasing the water content of the feces, softening the feces, and facilitating elimination, and generally does not affect the balance of water and electrolyte exchange.¹⁴ However, high doses of polyethylene glycol are poorly tolerated in patients, which influences the effectiveness of cleansing. In patients in poor physical condition, short-term and large doses of laxatives may cause water-electrolyte disorders. Therefore, a bowel-cleansing regimen that reduces patient discomfort at a low dose of PEG without compromising the cleansing effect should be

explored by clinicians. Previous studies have indicated that 2L+L or 2L PEG combined with other drugs (e.g., citrates and simethicone) can reduce patient discomfort and increase their willingness to repeat bowel-cleansing regimens relative to 4L PEG.^{9,15,16} On this basis, the present study divided tolerance into two time points, before and during colonoscopy, confirming that 2L+L improved patients' discomfort mainly before colonoscopy, while there was no significant difference from the 3L regimen during the examination. The present results suggest that medication improves symptoms mainly during bowel preparation, and it is difficult to have an impact on the sensation experienced during colonoscopy, which may need more research for future improvement.

Linaclotide, a guanylate cyclase-C (GC-C) agonist that increases intestinal chloride and fluid secretion by activating the guanosine cyclic phosphate (cGMP) cascade reaction¹⁷ for the

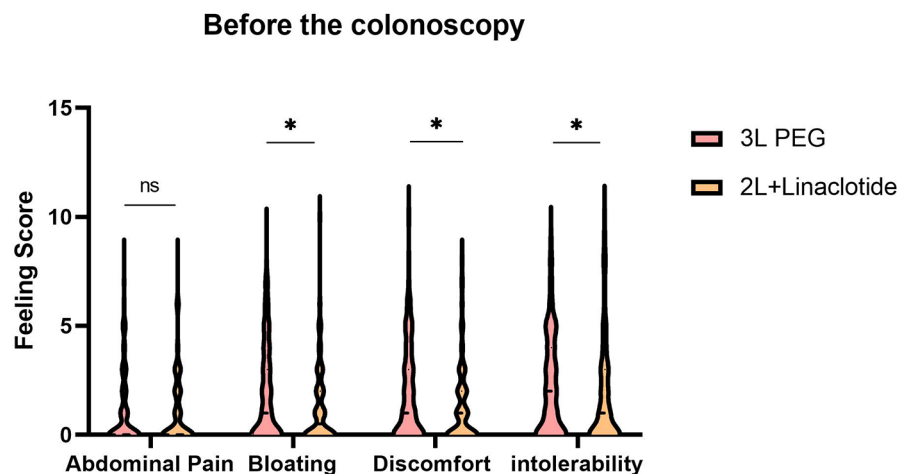


Figure 3. Precolonoscopy tolerance scores for the two groups.

Table 4. Comparison of polyp detection between the two groups.

Variables	3L PEG <i>n</i> = 227	2L PEG + L <i>n</i> = 231	<i>p</i> Value
Size, mm, median (IQR)	3 (3, 5)	3 (3, 4)	0.298
Polyp per person, <i>n</i> / <i>N</i>	0.6	0.7	0.003
Overall PDR, <i>n</i> (%)	66 (29.1%)	68 (29.4%)	0.967
Overall ADR, <i>n</i> (%)	42 (18.5%)	54 (23.8%)	0.184
Advanced ADR, <i>n</i> (%)	5 (2.2%)	3 (1.3%)	0.468
LC PDR, <i>n</i> (%)	51 (22.5%)	57 (24.7%)	0.618
LC ADR, <i>n</i> (%)	34 (15.0%)	43 (18.6%)	0.287
TC PDR, <i>n</i> (%)	14 (6.2%)	15 (6.5%)	0.867
TC ADR, <i>n</i> (%)	10 (4.4%)	14 (6.1%)	0.530
RC PDR, <i>n</i> (%)	13 (5.7%)	11 (4.8%)	0.659
RC ADR, <i>n</i> (%)	19 (8.4%)	10 (4.4%)	0.087

ADR, adenoma detection rate; LC, left colon; PDR, polyp detection rate; RC, right colon; TC, transverse colon.

treatment of irritable bowel syndrome (IBS) and visceral pain,⁷ has proven to be safe in clinical trials.^{3,18} A study noted that linaclotide combined with PEG was superior to PEG alone in patients with chronic constipation in terms of both an adequate bowel preparation rate and the Boston Bowel Preparation Scale (BBPS) score.¹⁹ Linaclotide also exerted a positive effect on intestinal cleansing regimen in low-risk individuals that without the following associated risk factors: constipation, age older than 70 years, body mass

index (BMI) over 25 kg/m², diabetes, Parkinson's disease, prior surgery of gastrectomy or colorectal resection, history of stroke or spinal cord injury, and use of narcotics or tricyclic antidepressants. In the low-risk population, the ultralow-volume regimen (1 L of PEG+L) was not inferior to the low-dose regimen (2 L of PEG) and resulted in better tolerability in patients, as well as their willingness to repeat the bowel preparation.²⁰ In brief, linaclotide has promising applications in bowel-cleansing regimens.

The endoscopic findings in the 2L+L group were comparable to those in the 3 L PEG group. The adenoma detection rate (ADR) is strongly correlated with postcolonoscopy colorectal cancer incidence, CRC-related deaths, and serrated lesion detection, and it has been shown to be the gold standard for colonoscopy quality.²¹ Few studies have further examined the changes in the adenoma detection rate and polyp detection rate with the 2L+L regimen, and our study confirmed that this regimen was not inferior to the high-dose cleansing regimen in terms of overall adenoma detection, polyp detection, advanced-adenoma detection, and adenomas detected in various parts of the bowel segments. Therefore, 2L+L achieved a similarly adequate bowel preparation rate but was superior to the 3L PEG regimen in overall bowel cleansing results and improved patient tolerance, and this cleansing regimen could be applicable not only in Europe and the United States but also in China.

Limitations

Nonetheless, our study has limitations. First, there were not enough indicators to evaluate patient tolerance, and more symptoms (e.g., nausea, vomiting, and sleep quality) could have been included. Second, other baseline information such as specific drug classifications (like TCA, laxative, and opioids), bowel habits and colorectal diverticula were missing and may have had a biased effect on the results. Third, we did not add an additional group undergoing the 4 L PEG cleansing regimen but instead used the 3L PEG regimen alone, which is commonly used in China. Finally, although the multicenter bowel-cleansing regimen research was conducted, the total number of people included in the present study was still relatively small, and more studies may be needed in the future to investigate the effects of the combination of two drugs on bowel preparation.

Conclusion

In conclusion, 2 L PEG combined with 580 µg linaclotide (290 µg/day for 2 days) yielded better intestinal cleanliness and patient tolerability than the 3 L PEG regimen, and the adenoma detection rate and polyp detection rate were not inferior to those with the 3 L PEG regimen. The addition of linaclotide to low-volume (2 L) PEG may be an alternative to 3 L PEG taken in split doses.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (location: Wuhan; ethics number: 2020-0559-01; ratification date: 2020-12-08) and was registered in the Chinese Clinical Trial Registry (ChiCTR2100041992). The patient/guardian/participant agreed to participate in the study.

Consent for publication

All patients/guardians/participants agreed to publication.

Author contributions

Jiandi Wu: Data curation; Formal analysis; Investigation; Resources; Software; Writing – original draft; Writing – review & editing.

Song Liu: Data curation; Investigation; Methodology; Resources.

Shuyu Li: Data curation; Investigation; Methodology; Resources; Supervision.

Gangping Li: Conceptualization; Data curation; Investigation; Supervision.

Erchuan Wang: Data curation; Investigation; Methodology; Supervision.

Tao Bai: Data curation; Methodology; Resources; Supervision.

Xiaohua Hou: Conceptualization; Data curation; Methodology; Project administration; Resources; Supervision; Validation.

Jun Song: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

Acknowledgements

All the authors thank the patients for their participation and the staff of the endoscopy center for their assistance.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data supporting these results will not be made available to the public due to privacy and ethical constraints. Interested scholars can contact the corresponding author for access.

ORCID iDs

Jiandi Wu  <https://orcid.org/0000-0002-5239-3286>

Jun Song  <https://orcid.org/0000-0002-0255-4547>

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; 74: 229–263.
2. Mahmood S, Farooqui SM and Madhoun MF. Predictors of inadequate bowel preparation for colonoscopy: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2018; 30: 819–826.
3. 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: 903–924.
4. Hassan C, East J, Radaelli F, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2019. *Endoscopy* 2019; 51: 775–794.
5. Huang L, Li C, Jiang Y-Z, et al. Vitamin drinks improve palatability and reduce adverse events associated to polyethylene glycol electrolyte solutions. *Helvion* 2024; 10: e37590.
6. Braga Emidio N, Tran HNT, Andersson A, et al. Improving the gastrointestinal stability of linaclotide. *J Med Chem* 2021; 64: 8384–8390.
7. Chang L, Lacy BE, Moshiree B, et al. Efficacy of linaclotide in reducing abdominal symptoms of bloating, discomfort, and pain: a phase 3B trial using a novel abdominal scoring system. *Am J Gastroenterol* 2021; 116: 1929–1937.
8. Keto Y and Kosako M. [Pharmacological and clinical profile of linaclotide (Linzess®), a novel therapeutic agent for irritable bowel syndrome with constipation and chronic constipation]. *Nihon Yakurigaku Zasshi* 2019; 153: 289–298.
9. 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: e625–e633.
10. Yang J, Wei Q, Xiang Z, et al. Bowel preparation efficacy and safety of compound polyethylene glycol electrolyte powder combined with linaclotide for colonoscopy: a randomized controlled trial. *JGH Open* 2023; 7: 636–639.
11. Schulz KF, Altman DG and Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c332.
12. Rostom A and Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. *Gastrointest Endosc* 2004; 59: 482–486.
13. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Am J Gastroenterol* 2015; 110: 72–90.
14. Jouët P, Sabate JM, Flourie B, et al. Effects of therapeutic doses of lactulose vs. Polyethylene glycol on isotopic colonic transit. *Aliment Pharmacol Ther* 2008; 27: 988–993.
15. Spada C, Cesaro P, Bazzoli F, et al. Evaluation of Clensia®, a new low-volume PEG bowel preparation in colonoscopy: multicentre randomized controlled trial versus 4L PEG. *Dig Liver Dis* 2017; 49: 651–656.
16. Kim ES, Kim KO, Jang BI, et al. Comparison of 4-L Polyethylene Glycol and 2-L polyethylene glycol plus ascorbic acid in patients with inactive ulcerative colitis. *Dig Dis Sci* 2017; 62: 2489–2497.
17. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol* 2010; 649: 328–335.
18. Hassan C, Bretthauer M, Kaminski MF, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2013; 45: 142–150.
19. Wang L, Zhang Y, Li J, et al. Efficacy of polyethylene glycol electrolyte powder combined with linaclotide for colon cleansing in patients with chronic constipation undergoing colonoscopy: a multi-centre, single-blinded, randomized-controlled trial. *Clin Transl Gastroenterol* 2024; 15.
20. 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: 952–961.e1.
21. Dawwas MF. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; 370: 2539–2540.