

ORIGINAL ARTICLE

Bowel preparation efficacy and safety of compound polyethylene glycol electrolyte powder combined with linaclotide for colonoscopy: A randomized controlled trial

Jing Yang,[†] Qian Wei,[†] Zhixiong Xiang, Danyan Wu and Zhuoying Lin 

Department of Gastroenterology, Shangrao People's Hospital, Shangrao, Jiangxi, China

Key words

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Correspondence

Dr Zhuoying Lin, Department of Gastroenterology, Shangrao People's Hospital, Shangrao 334000, Jiangxi, China.

Email: zylinzy@qq.com

[†]Jing Yang & Qian Wei are contributed equally to this work.

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Abstract

Background and Aim: Adequate bowel preparation is essential for colonoscopy, which is important for detecting colon polyps and preventing colorectal cancer. Linaclotide is approved for irritable bowel syndrome with predominant constipation (IBS-C) symptoms. The main objective of this study was to explore the quality of bowel preparation by low-volume compound polyethylene glycol (PEG) combined with linaclotide.

Methods: A total of 266 patients who underwent colonoscopy in Shangrao People's Hospital from June 2021 to June 2022 were randomized to 1 of 3 split PEG regimens: 4LPEG, 2LPEG, and 2LPEG + L (linaclotide). The primary end point was adequate bowel preparation (Boston Bowel Preparation Scale [BBPS] total score of ≥ 6 , with each of three colonic segments subscores ≥ 2). Secondary outcomes were polyp detection rates and the incidence of adverse reactions.

Results: Over 12 months, 266 subjects were randomized into 2LPEG ($n = 12$), 4LPEG ($n = 112$), or 2LPEG + L ($n = 142$). There were no significant differences between the 4LPEG and 2LPEG + L groups in achieving adequate bowel preparation ($P > 0.05$). The mean BBPS score of the total colon, left hemi-colon, right hemi-colon, and transverse in the 2LPEG + L group was higher than that in the 2LPEG group ($P < 0.001$). Patient's sleeping quality and the incidence of adverse reactions of 2LPEG + L group were compatible with 2LPEG group, but it was significantly lower than that in 4LPEG group. There was no statistically significant difference in the detection rate of colon polyps between each group.

Conclusion: The quality of bowel preparation of the compound polyethylene glycol electrolyte powder combined with linaclotide is approximately the same as that of 4LPEG, and it can reduce the adverse reactions in the process of bowel preparation, and its intestinal cleansing effect is also better than that of 2LPEG.

Introduction

Colorectal cancer is one of the major cancers that threaten the life and health of Chinese residents. The 2018 China Cancer Statistics Report shows that the incidence and mortality rate of colorectal cancer in China ranked third and fifth among all malignant tumors, respectively.¹ The development of colorectal cancer mostly follows the sequence of "adenoma-cancer," and it generally takes 5–10 years to progress from precancerous lesions to cancer, which provides an important time window for early diagnosis and clinical intervention. Colonoscopy is an important modality for detecting colorectal lesions or cancer, while bowel preparation is an essential part of colonoscopy and a decisive factor of the examination quality. The gold standard regimen for bowel preparation recommended by clinical guidelines and previous studies is a split-dose regimen of 4 L polyethylene glycol (PEG), which provides high-quality bowel cleansing.^{2–4} However, patients often find it difficult to tolerate such a large volume

of fluid, and its adverse reactions such as nausea and vomiting also result in low tolerance and acceptance. Linaclotide, a selective guanylate cyclase-C receptor agonist, was approved by the U.S. Food and Drug Administration in 2012 for the treatment of constipation-predominant irritable bowel syndrome (IBS-C).⁵ However, there are few studies related to linaclotide combined with PEG as a bowel preparation regimen. In the present study, 266 patients who underwent colonoscopy were selected to investigate the effectiveness and tolerability of the compound polyethylene glycol electrolyte powder combined with linaclotide in bowel preparation before colonoscopy.

Methods

Two hundred sixty-six outpatients aged 18–80 years who underwent colonoscopy at Shangrao People's Hospital from June 2021 to June 2022 were selected as study subjects. Exclusion criteria included: (i) history of colorectal surgery; (ii) history of severe

heart, liver, lung, and kidney diseases; (iii) patients who had taken linaclotide within 7 days or were allergic to linaclotide; (iv) long-term chronic constipation or severe constipation; (v) patients with inflammatory bowel disease, intestinal perforation, or ileus; (vi) patients who were pregnant or breastfeeding during the study period. The study protocol was approved by the Ethics Committee of Shangrao People's Hospital.

According to the random number table, all individuals were randomly distributed into three groups: 4LPEG (patients received two bags of PEG), 2LPEG (patients received one bag of PEG), and 2LPEG + L (patients received one bag of PEG and two capsules of linaclotide). There was no statistically significant difference ($P > 0.05$) in the age and sex of the patients among three groups (Table 1). Poor quality of bowel preparation in the 2LPEG group was found in our preliminary study, so we reduced the inclusion of patients in this group, and 112 patients in the 4LPEG group, 142 patients in the 2LPEG + L group, and 12 patients in the 2LPEG group were finally included. All patients were asked for a semiliquid diet the night before colonoscopy, and fasting at breakfast on the day of the examination. Patients in the 2LPEG group were instructed to consume a bag of PEG (II, 137.15 g, Shenzhen Wanhe Pharmaceutical Co., LTD.) solution diluted in 2 L of water 6 h before colonoscopy. Patients in the 4LPEG group consumed the PEG solution from 20:00 h to 22:00 h 1 day before the colonoscopy, and another bag of PEG 6 h before colonoscopy. Patients in the 2LPEG + L group received one capsule of linaclotide (290 µg/capsule) the day before colonoscopy and a bag of PEG solution combined with one capsule of linaclotide 6 h before colonoscopy.

The intestinal cleanness, polyps' detection rate, and the incidence of adverse reactions were compared among the three groups of patients. (i) The quality of bowel preparation was assessed in those groups using the Boston Bowel Preparation Scale (BBPS).^{6,7} The BBPS score divided the colon into three segments: left hemi-colon, right hemi-colon, and transverse. The score for each colon segment was 0, with mucosa not seen due to solid stool that cannot be cleared; 1, with portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool, and/or opaque liquid; 2, with minor amount of residual staining, small fragments of stool, and/or opaque liquid, but mucosa of colon segment seen well; 3, with entire mucosa of colon segment seen well with no residual staining, small fragments of stool, or opaque liquid. The higher the score, the better the degree of intestinal cleanness. (ii) Colorectal polyps detection rate: Make sure that the withdrawal time of each patient is over in 6 min, and the polyps detection rate of each group means the number of polyps detected/total number of cases in the group is $\times 100\%$. (iii) Incidence of adverse reactions: after taking the medicine, ask in detail the adverse

reactions of patients in those three groups, such as sleeping quality (divided into good and poor), nausea, vomiting, bloating, and abdominal pain, and count the incidence.

All data were analyzed in SPSS (version 25.0; IBM, USA) and P -value < 0.05 was considered statistically significant. The continuous variables were described by mean \pm SD ($\bar{X} \pm S$) and comparisons between groups were analyzed by one-way ANOVA test. The categorical variables were described by frequency (percentage) [n (%)] and comparisons between groups were analyzed using the chi-square test and Fisher's exact test.

Results

Comparison of BBPS score among the three groups. All three groups successfully completed colonoscopy, and our findings showed that the mean BBPS score of the total colon, left hemi-colon, right hemi-colon, and transverse in the 2LPEG + L group was higher than that in the 2LPEG group ($P < 0.001$) and showed no significant difference compared with the 4LPEG group ($P > 0.05$) (Fig. 1).

The detection rate of colorectal polyps among the three groups. The detection rate of colorectal polyps was 33.3% in the 2LPEG group, 45.5% in the 4LPEG group, 40.8%

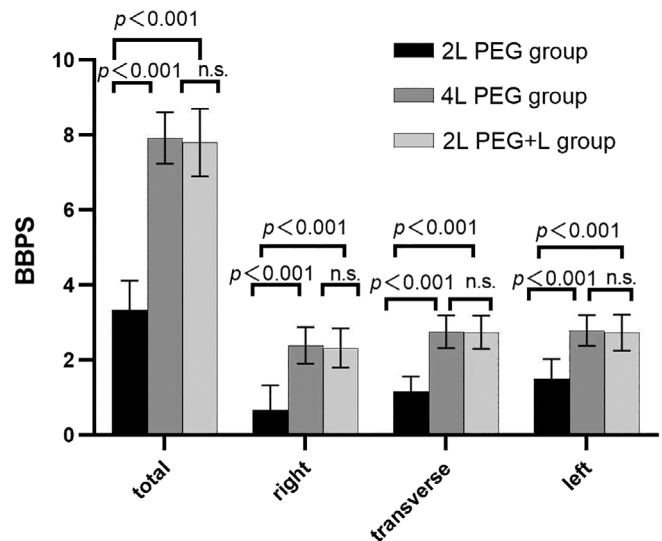


Figure 1 The Boston Bowel Preparation Scale (BBPS) score among three groups. (■), 2L polyethylene glycol (PEG) group; (▒), 2LPEG group; (□), 2LPEG + L group.

Table 1 Comparison of age and sex of patients in the three groups

Group	Number of cases	Age ($\bar{X} \pm S$)	Gender (male/female)
2LPEG	12	50.83 \pm 16.02	4/8
4LPEG	112	49.66 \pm 12.07	50/62
2LPEG + L	142	48.62 \pm 13.27	67/75
P		0.809	0.634

Table 2 Comparison of the incidence of adverse reactions among three groups

Variables	2LPEG	4LPEG	2LPEG + L	<i>P</i> [†]	<i>P</i> [‡]	<i>P</i> [§]
Adverse reactions, <i>n</i> (%)						
Bloating and abdominal pain	1 (8.3)	20 (17.9)	5 (3.5)	0.689	<0.001	0.391
Nausea and vomiting	1 (8.3)	37 (33.0)	17 (12.0)	0.103	<0.001	0.986
Sleeping quality, <i>n</i> (%)				0.184	0.001	0.965
Good	11 (91.7)	81 (72.3)	127 (89.4)			
Worse	1 (8.3)	31 (27.7)	15 (10.6)			

[†]2LPEG *versus* 4LPEG.

[‡]4LPEG *versus* 2LPEG + L.

[§]2LPEG *versus* 2LPEG + L.

in the 2LPEG + L group, and the highest rate in the 4LPEG group, but there was no statistically significant difference among the three groups ($P > 0.05$).

The incidence of adverse reactions among the three groups.

The incidence of adverse reactions included sleeping quality, nausea, vomiting, bloating, and abdominal pain, which are shown in Table 2. The incidence of adverse reactions in the 4LPEG group was higher than that in the other two groups, which include that patients in 2LPEG + L group had better sleeping quality than the 4LPEG group (89.4% *vs* 72.3%, $P = 0.001$), and the incidence of bloating and abdominal pain (3.5% *vs* 17.9%, $P < 0.001$), nausea, and vomiting (12.0% *vs* 33.0%, $P < 0.001$) was lower than that in the 4LPEG group.

Discussion

Colorectal cancer is the third most common cancer, and colonoscopy is the preferred and most widely used modality for colorectal cancer and lesion screening. Studies have shown that colonoscopy can reduce the incidence and mortality of colorectal cancer by detecting and removing precancerous polyps.^{8–11} The quality of bowel preparation is critical to the effectiveness of colonoscopy for colorectal lesion screening. However, studies have shown that up to a quarter of colonoscopies may be performed with inadequate bowel preparation, which not only affects the lesion detection but may also lead to prolonged procedure time, repeat colonoscopy, cecum intubation rates, and increased associated costs. In addition, there is growing evidence that the administration of large doses of laxatives for bowel preparation and the adverse reactions experienced during the administration of the medication lead many people to fear bowel preparation and thus refuse to undergo colonoscopy. Therefore, it is important to choose the bowel preparation medication, which is safe, with rapid onset of action, high-quality bowel cleansing, and few adverse reactions.

The agents currently used for bowel preparation in China include compounded polyethylene glycol electrolyte powder, magnesium sulfate, and sodium pyrosulfate, but all have their advantages and disadvantages, some have poor taste, some have poor stool softening effect, etc. Among them, 4LPEG is now recommended by most clinical guidelines as the “gold standard” for bowel preparation because of its powerful bowel cleansing effect.¹² PEG is the most commonly used oral electrolyte bulk in clinical practice and consists of polyethylene glycol, sodium bicarbonate,

sodium sulfate, potassium chloride, and sodium chloride. Its main component, polyethylene glycol, can stably bind to water molecules in intestinal contents through hydrogen bonding without being absorbed by the colon, thus turning fecal water into isotonic liquid and thus balancing the osmotic pressure inside and outside the intestinal mucosa.¹³ However, the high oral dose of 4LPEG bowel preparation regimen with many adverse effects leads to poor patient compliance and low willingness to repeat the same bowel preparation regimen, so that about 5–15% patients are unable to complete the bowel preparation and abandon colonoscopy.¹⁴ In recent years, there have also been studies on combination regimens, such as compounded polyethylene glycol electrolytes powder combined with other bowel-promoting or bowel-activating agents, such as mosapride,¹⁵ lactulose,¹⁶ and dimethicone oil.¹⁷ However, all of them have their limitations.

Linaclotide is a guanylate cyclase-C (GC-C) agonist that increases intestinal chloride and fluid secretion by activating the guanosine cyclic phosphate (cGMP) cascade.¹⁸ It is mainly used for the treatment of IBS-C and chronic idiopathic constipation (CIC), as it can moisten the stool and relieve the symptoms of constipation.^{19,20} There are few studies on the use of linaclotide as an adjunctive agent to PEG for bowel preparation prior to colonoscopy.

In this study, we investigated the intestinal cleanness, polyps' detection rate, and the incidence of adverse reactions of three different bowel preparation protocols, and the results showed that the total BBPS score, left hemi-colon, right hemi-colon, and transverse were higher in the 2LPEG combined with two capsules of linaclotide (2LPEG + L) group than in the 2LPEG group, and similar to the 4LPEG group. Moreover, the incidence of adverse reactions was lower in the 2LPEG + L group than in the 4LPEG group, and patients had higher tolerability. The results of this study showed that the 2LPEG + L group had good cleansing effect in bowel preparation with less adverse reactions, which could reduce the occurrence of bloating, abdominal pain, nausea, and vomiting, while ensuring intestinal cleanliness and sleeping quality. The protocol was not costly, making it a suitable alternative regimen to 4LPEG with some potential for future application. There was no statistically significant difference in the detection rate of colorectal polyps among the three groups of patients in this study, which may be related to the small sample size of 2LPEG patients.

There are several limitations to our study. First, it was a single-center study, and the experimental results had not been confirmed in other centers, which may limit the generalizability

of these results. Second, there were fewer observation indicators. Third, the study sample was small and more patients in the 2LPEG group with poor bowel preparation should be included. More large-sample, multicenter studies are needed to further explore the value of the combination of the two agents in bowel preparation in the future.

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