Application Effect of Linaclotide Combined with Polyethylene Glycol Dissolved in 1l Pulse Beverage in Bowel Preparation for Colonoscopy

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Abstract: Colorectal cancer is a global health threat, and colonoscopy is crucial for early diagnosis. Traditional 2L or 3L polyethylene glycol (PEG) for bowel preparation has issues with patient tolerance. This randomized, endoscopist - blinded, single - center study compared 1L PEG + 580μg linaclotide (1L PEG + L group) and 2L PEG alone in 993 patients scheduled for colonoscopy. There were no significant differences in Boston Bowel Preparation Scale (BBPS) scores, polyp detection rate, or adenoma detection rate between the two groups (P>0.05). However, the incidence of adverse events was 8.87% in the 1L PEG + L group and 33.88% in the 2L PEG group (P<0.05). The 1L PEG + L group is non - inferior to the 2L PEG group in bowel preparation for colonoscopy, with a lower adverse event rate, suggesting a good application prospect.

Keywords: Linaclotide; Polyethylene Glycol; Bowel Preparation; Colonoscopy; Adverse Events

1. Introduction

Colorectal cancer ranks as the third most prevalent malignant tumor globally, representing a significant threat to human life and health. According to GLOBOCAN 2018 data, colorectal neoplasms account for 12.20% of all malignant tumor incidences in China, while deaths related to colorectal neoplasms constitute 9.53% of all malignancy-related fatalities in the country [1-3]. A majority of patients are diagnosed at an advanced stage of the disease [4]. Given that colonoscopy is regarded as the gold standard for diagnosing intestinal disorders [5], standardized colonoscopy can enhance the detection rate of early-stage colorectal cancer.

Linaclotide is a guanylyl cyclase-C (GC-C) receptor agonist that enhances stool water content and promotes bowel movements [6].Linaclotide has demonstrated good safety profiles during long-term use[7]. In recent years, it has been increasingly utilized for colonoscopy bowel preparation. Reports indicate that the combination of 290ug linaclotide with either 2L or 4L PEG is equivalent in efficacy for colonoscopy bowel preparation while offering improved tolerability [8]. A clinical study revealed that oral administration of 290ug linaclotide one hour prior to colonoscopy yields results comparable to those achieved with oral administration of 2L PEG the night before, regarding the quality of capsule colonoscopy bowel preparation, without any statistically significant differences observed [9]. These findings suggest that linaclotide exhibits both efficacy and safety in bowel preparation; however, it does not eliminate the drawback associated with consuming large volumes of PEG solution. Nevertheless, there are limited reports on the combined use of linaclotide and PEG for pre-colonoscopy bowel preparation, and all studies reviewed have small sample sizes; thus, further data are necessary to validate these findings.

2. Patients and Methods

2.1 Design and Setting

General Information A total of 1000 patients scheduled for colonoscopy at our hospital from August 2023 to August 2023 were selected as study subjects. Three patients met the exclusion criteria and were not included in the study, while four patients declined to participate. Ultimately, 993 patients were enrolled; they were randomly assigned to either the experimental group (497 patients) or the control group (496 patients). One patient in the experimental group withdrew from the

study due to personal reasons, while two patients in the control group withdrew because of adverse reactions to medication during bowel preparation. In conclusion, 496 patients in the experimental group completed the study, whereas 494 patients in the control group finished their participation (Fig. 1). The experimental group received linaclotide combined with a dissolved pulsatile polyethylene glycol electrolyte solution for bowel preparation, while participants in the control group were administered only a dissolved pulsatile polyethylene glycol electrolyte solution for this purpose. There were no significant differences between groups regarding gender, age, smoking history, alcohol consumption history, BMI (kg/m2), education level, etc., indicating comparability between them (P>0.05), as detailed in Table 1. This study was approved by the Ethics Committee of Deyang People's Hospital; all participants provided informed consent voluntarily prior to their involvement in this research.

2.2 Patients

The inclusion criteria: ① Age 18-75 years old, regardless of gender. ② Individuals who needed colonoscopy due to physical examination or clinical symptoms and were willing to participate in this study. The exclusion criteria were as follows: ① Individuals under the age of 18 or over 75 years; ② Pregnant or lactating women; ③ Individuals with an allergy to PEG solution or linagliptin; ④ Those experiencing constipation or who have a history of long-term use of linagliptin; ⑤ Individuals who have used laxatives, anti-diarrheal agents, or intestinal motility medications within the past two weeks; ⑥ Individuals with gastrointestinal bleeding; ⑦ Patients with intestinal obstruction, toxic megacolon, or suspected intestinal obstruction; ⑧ Patients with a history of serious illness, including severe liver disease (Child-Pugh B/C grade), end-stage renal disease (dialysis-dependent), severe coagulation disorders, congestive heart failure, and respiratory failure; ⑨ Patients with a recent history of myocardial infarction or stroke; ⑩ Patients with a history of mental illness that impairs their ability to cooperate; ⑪ Patients who are bedridden and unable to care for themselves; ⑫ Patients currently participating in other studies or those who have recently completed other clinical trials.

2.3 Randomization

Eligibility patients were random distribute(1:1)into either the 1L PEG+L or 2L PEG group according to random number table.Patients in the 1L PEG+L groups recerived one bag of PEG(137.15g,each bag containing 1.46 g of sodium chloride, 5.68 g of anhydrous sodium sulfate, 0.74 g of potassium chloride, 1.68 g of sodium bicarbonate and 59 g of PEGl 4000 Shenzhen Wanhe Pharmaceutical Co Ltd, Shenzhen, China.) and two capsules of linaclotide(290ug/capsule).patients in the 2L PEG group received two bags of PEG.The investigators or endoscopists collecting the primary and secondary outcome data were blinded to participant allocation. To achieve this blinding, subjects were instructed not to disclose their study allocation to the endoscopists or investigators.

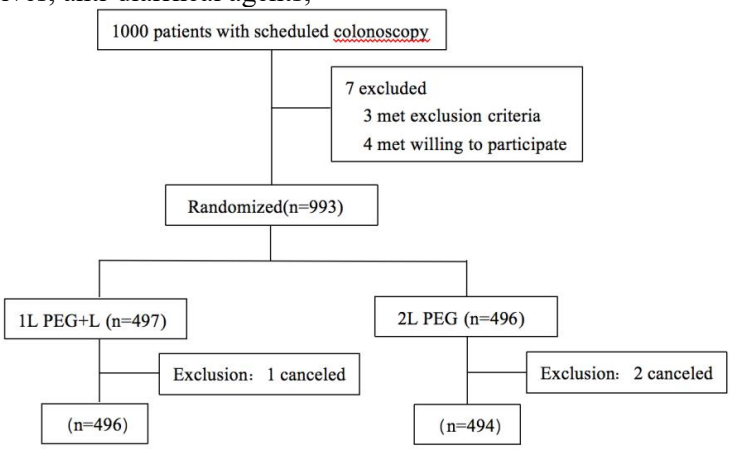

Figure 1. Flow Diagram of Patients Enrolled

Table 1. Comparison of General Data Between the Two Groups

Variable	1L PEG+L	2LPEG	t/χ^2	P value
Age	45.08±11.82	46.34±11.92	-1.635	0.102
Female	229（46.17）	216（43.55）	0.598	0.439
smoking	93（18.75）	91（18.35）	0.018	0.894
drinking	76（15.32）	80（16.13）	0.132	0.717
Education degree			5.626	0.060
Elementary	141（28.43）	167（33.67）		
Middle school	218（43.95）	219（44.15）		
College	137（27.62）	108（21.77）		
BMI	22.52±2.13	22.57±2.09	-0.411	0.681

Bowel preparation protocol

First,all patients were placed on a restircted diet the day before colonoscopy.This was limited in fruits,vegetables and meats,whlie eggs,milk,noodles,porridge and other low-residue foods were allowed.The experimental group was instructed to take 290 μg of linaclotide at 9:00 PM on the night prior to the examination, followed by the consumption of 500 ml of water. Subsequently, they were directed to take another dose of 290 μg of linaclotide at 7:00 AM the following morning and to drink 1L polyethylene glycol (PEG) dissolved in pulse beverage half an hour later. In contrast, the control group was instructed to consume 2L PEG dissolved in 2 liters of pulse beverage within a duration of one hour. All colonoscopies were arranged in the afternoon(from 2:00 p.m. to 6:00 p.m.).Colonoscopies were performed by the chief physicians(Y.S.M.Z.),all of whom have performed at least 1000 colonoscopies per year.The endoscopists were unware of the group allocation.All endoscopists were instructed to take endoscopic images of each colonic segment that were representative of the colonic cleansing level. The final Boston Bowel Preparation Scale(BBPS) scores were evaluated independently by 2 endoscopists.

2.4 Outcome Assessment

The primary outcome was the adequate of bowel preparation.It was assessed by Boston Bowel Preparation Scale (BBPS) [13,14]. The entire colon was divided into three segments: the left colon, transverse colon, and right colon. Each segment was scored from 0 to 3 points. A score of 0 indicating a significant amount of solid residue and invisible mucosa; a score of 1 denoting the presence of solid or liquid residue along with partially visible mucosa; a score of 2 representing brown liquid with semi-fixed or fixed residue that can be mobilized, accompanied by fully visible mucosa; and a score of 3 signifying complete cleansing with fully visible mucosa. The total score for colon cleansing is derived from the sum of scores across all three segments, yielding a possible total range from 0 to 9 points.,where 9 points represent excellent cleansing,whlie 0 point represent bad cleansing.Adequate Bowel cleansing was adequate with a total score ≥6 and each segmental score ≥2.The secondary outcomes included polyp detection rate,adenoma detection rate（ADR） and adeverse events.

2.5 Statistical Analysis

For patients who meet the inclusion criteria and are scheduled for colonoscopy, they are numbered in the order of admission, and the random number table compiled by Fang Ji Qian, editor of Health Statistics, is used. The patients' appointment numbers are also listed, and a random number from the table is selected at random. The starting point of the random number is selected at random from a specific row and column of the table. The random numbers in the table are then matched with the study subjects' sequence numbers, and the random numbers are divided by 2, with the remainder of 0 being assigned to the control group (2L PEG group), and the remainder of 1 being assigned to the experimental group (1L PEG + 580ug linaclotide).

According to our previous experience, about 77% of patients could achieve acceptable bowel cleansing according to the BBPS score in the 2 L PEG group, compared to 87% of patients in the 1L PEG +L group. In our pretest, 100 patients were recruited in the 1L PEG + L group, and the percentage of

acceptable bowel preparation was 90%. Therefore, we assumed that 90% of patients in the 1L PEG + L group could achieve an acceptable cleansing effect, according to the BBPS score. To achieve 90% power for detecting significant differences among two groups, 400 patients with a significance level (alpha) of 0.05 (on two sides) were recruited into each group to assess the noninferiority of the 1L PEG+L group. Considering a drop-out rate of 15% after randomization, 500 patients were planned to be recruited in each group.

Measurement data were reported as mean ± standard deviation, and one-way analysis of variance and least-significant difference analysis were used for comparisons between groups. The enumeration data were described by frequency (percentage) [N (%)], and comparisons between groups were analyzed by independent sample Chi-square test. All data were analyzed by SPSS (version 22.0; IBM, USA), and *P*-value < 0.05 was considered statistically significant.

3. Results

A total of 1000 patients who underwent colonoscopy were enrolled. Three patients met the exclusion criteria and were not included in the study, while four patients declined to participate. Ultimately, 993 patients were enrolled; they were randomly assigned to either the experimental group (497 patients) or the control group (496 patients). One patient in the experimental group withdrew from the study due to personal reasons, while two patients in the control group withdrew because of adverse reactions to medication during bowel preparation. In conclusion, 496 patients in the experimental group completed the study, whereas 494 patients in the control group finished their participation (Fig. 1). The experimental group received linaclotide combined with a dissolved pulsatile polyethylene glycol electrolyte solution for bowel preparation, while participants in the control group were administered only a dissolved pulsatile polyethylene glycol electrolyte solution for this purpose. There were no significant differences between groups regarding gender, age, smoking history, alcohol consumption history, BMI (kg/m2), education level, etc., indicating comparability between them (P>0.05), as detailed in Table 1.

3.1 Quality of Bowel Cleaning

The scores for the right semicolon, transverse colon, left semicolon, and total mean BBPS score were not significantly different between the 2L PEG and 1LPEG+L group,with a mean±standard deviation total score of 7.29±1.05 vs 7.36±1.0 (P=0.288),no significant differences were noted in terms of right,transverse,and left segmental BBPS scores(all,P>0.05), (Table 2,figure 2,3).

Table 2. Comparison of BBPS among the Two Groups (*x*±*s*）

Variable	1L PEG+L	2LPEG	t	P value
Right colon	2.43±0.6	2.43±0.57	-0.201	0.841
Transverse colon	2.6±0.54	2.66±0.47	-1.793	0.073
Left colon	2.26±0.6	2.27±0.52	-0.177	0.907
Total score	7.29±1.05	7.36±1.0	-1.063	0.288

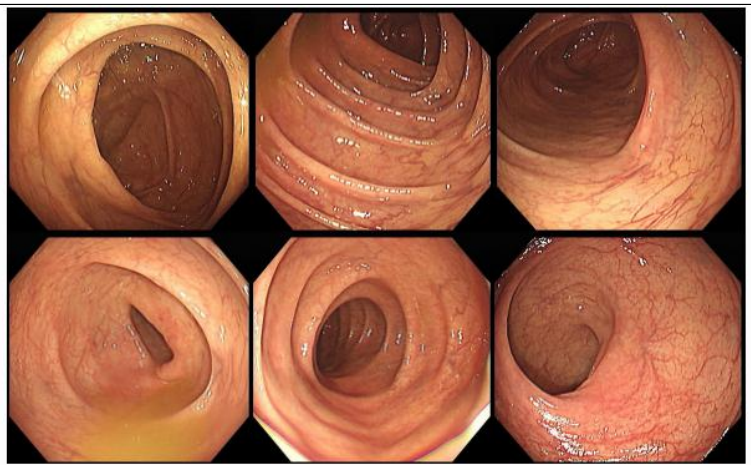

Figure 2. Effect of Intestinal Cleanliness in Control Group

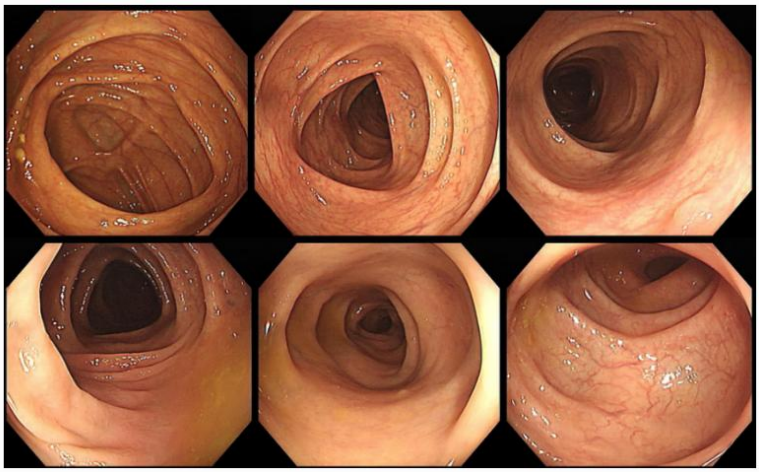

Figure 3. Effect of Intestinal Cleanliness in Test Group

The detection rate of intestinal lesions in the experimental group was comparable to that in the control group, with no statistically significant difference observed between the two groups (P>0.05), (Table 3).

Table 3. Comparison of Intestinal Lesions Between the Two Groups(%)

Variable	1L PEG+L	2LPEG	χ^2	*P value*
Polyp detection rate	155（31.25）	146（29.44）	0.336	0.562
Adenoma detection rate	95（19.15）	88（17.74）	0.295	0.587

3.2 Adeverse Events and Tolerance

Overall, all patients who successfully completed the trial in both groups did not experience any serious adverse reactions. The complications included nausea, vomiting,bloting,abdominal discomfort,dizziness and fatigue.The percentage of complications was higher in the 2LPEG group than in the 1LPEG+L,including nausea(14.52% vs 4.23%,P<0.01),vomiting(8.27% vs 1.41%,P<0.01),abdominal discomfort(9.07 vs 3.23%,P<0.01),dizziness(1.21% vs 0%,P=0.015),fatigue(0.81% vs 0%,P<0.01). (Table 4).

Table 4. comparison of Adeverse Events and Tolerance

Variable	1L PEG+L	2LPEG	χ^2	*P* value
nausea	21（4.23）	72（14.52）	31.095	0.000
vomiting	7（1.41）	41（8.27）	25.455	0.000
Abdominal discomfort	16（3.23）	45（9.07）	14.817	0.000
Dizziness	0（0）	6（1.21）		0.015
Fatigue	0（0）	4（0.81）		0.004

4. Discussion

With the acceleration of modern life and the enhancement of living standards, coupled with environmental and food pollution, increased work and study pressures, as well as various hereditary factors, an increasing number of individuals are experiencing digestive tract symptoms such as diarrhea, abdominal pain, constipation, and bloating. Colonoscopy serves as a vital tool for the early diagnosis of colorectal diseases [17].

The ideal method for complete bowel preparation should possess the following characteristics: ① It effectively empties the colon of feces within a short timeframe; ② It does not induce alterations in the colonic mucosa; ③ It minimizes discomfort for patients and ensures good compliance; ④ It avoids causing electrolyte imbalances; ⑤ It is cost-effective [18]. For many years, bowel preparation methods have included oral medications and enemas [19]. Currently, most hospitals in China adhere to the methods outlined in domestic endoscopic diagnosis and treatment guidelines [20,21], which primarily encompass two strategies: ① Divided oral administration of PEG (polyethylene glycol) at a total volume of 3000 ml (1000 ml taken the night before the examination and an

additional 2000 ml consumed 4-6 hours prior to the examination on the day itself). ② For low-risk patients with inadequate bowel preparation, PEG at a volume of 2000 ml is administered within a timeframe of 4-6 hours before the examination on that same day. PEG serves as an osmotic laxative containing non-absorbable electrolytes. Its primary advantage lies in its ability to enhance intestinal fluid content through hydrogen bonding with water, thereby stimulating intestinal peristalsis and facilitating thorough cleansing by flushing out digestive juices without interfering with intestinal absorption or secretion. This method boasts rapid onset, along with properties that prevent both absorption and decomposition within the intestine, thus mitigating risks associated with electrolyte imbalance [22].

The pulsating drink functions as a solvent for polyethylene glycol (PEG), its most significant attribute is its excellent taste; being colorless allows it to dissolve PEG granules effectively while mitigating the bitter flavor associated with PEG intake, making it more palatable. This study employed a randomized controlled trial design to divide participants into an experimental group and a control group. The control group utilized 2000 ml of Pulsating Drink for dissolving PEG in accordance with current widely accepted practices for intestinal preparation. In contrast, the experimental group incorporated Linagliptin alongside PEG alone; consequently, the total volume of water previously used for dilution was reduced to 1000 ml of Pulsating Drink for intestinal preparation. This approach aimed to explore the application value of Linagliptin in colonoscopy-related intestinal preparations. The findings revealed that regarding cleanliness during intestinal preparation, there was no significant difference between the experimental group and control group ($P>0.05$). Similarly, when assessing detection rates of intestinal lesions, both groups performed comparably without any significant differences noted ($P>0.05$). However, concerning adverse reactions experienced by participants in each group, those in the experimental group reported significantly fewer incidents than those in the control group ($P<0.05$).

This study demonstrates that a bowel cleansing method utilizing 1000ml of PEG dissolved in Gatorade, combined with linagliptin, exhibits

Acknowledgments

This paper is supported by the Xinglin Scholar Discipline Talent Scientific Research Promotion Plan of Chengdu University of Traditional Chinese Medicine (Grant No. YYZX2022066)

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