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The effects of combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single blind clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2025-099687
Article Type:	Protocol
Date Submitted by the Author:	23-Jan-2025
Complete List of Authors:	Guo, Chunmei; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Wang, Jing; Capital Medical University Affiliated Beijing Shijitan Hospital Li, Li; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Cui, Jianfang; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Liu, Hong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Yang, Guodong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology
Keywords:	Clinical Trial, Endoscopy < GASTROENTEROLOGY, Clinical Protocols

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The effects of combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single blind clinical trail

Abstract

Introduction Chronic constipation is an independent risk factor for inadequate bowel preparation. The objective of this study is to evaluate the effectivity and safety of combined use of linaclotide and oral sulfate solution (OSS)in chronic constipation patients undergoing chronic constipation patients undergoing colonoscopy.

Methods and analysis This is a prospective, randomized, controlled, single-blind (endoscopist) clinical trial which compare three bowel cleansing regimens for in chronic constipation patients undergoing chronic constipation patients undergoing colonoscopy. Regimen A consists of 2d-linaclotide and OSS, Regimen B consists of 3d-linaclotide and OSS, Regimen C consists of OSS. All patients were required to consume a low-fiber diet for three days and clear fluid diet for one day before the colonoscopy. The primary outcome is adequate bowel preparation (defined as each segment Boston Bowel Preparation Scale (BBPS) score≥2 and a total BBPS score≥6). The secondary outcomes include defecation frequency, caecal intubation rate, adenoma detection rate (ADRs), colonoscope insertion time and withdrawal time. The third outcomes include complication of colonoscopy, adverse events (AE) and comfort degree, evaluated by self-design questionnaire of comfort (QSC).

Ethics and dissemination The research will be conducted according to Good Clinical Practice principles. Ethical approval has been obtained from Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (IIT2024-146-003). Study findings will be published in peer-reviewed journals.

Trial registration number ChiCTR2500096394

Introduction

Colorectal cancer (CRC) has become a global major public health concern, with a secondary mortality rate among all cancers and thirdly global prevalence[1]. CRC is largely preventable through screening for colorectal adenomas, which are benign growths but may develop into cancer if not removed[2]. Early detection and removal of colorectal adenomas can effectively block the "adenoma-carcinoma sequence" pathway and prevent the development of CRC ultimately[3]. Because of increased use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), CRC incidence has stabilized or started

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to decrease continuously in USA or other high-income countries over the past two decades[4]. In China, however, the all-age disability-adjusted life years (DALY) rate of CRC has increased by 69.8% since 1990, which may attribute to highly misdiagnosis of colorectal adenomas[5]. Adequate pre-procedural bowel cleansing maximizes the adenomas detection rates (ADRs), thus beneficial to CRC prevention[6].

PEG is widely used for bowel preparation. However, inadequate cleansing was observed in many chronic constipation patients by using 4L PEG. As a common gastrointestinal disorder, constipation affects 12%~17% population, and is considered as one of the risk factors of inadequate bowel cleansing. Improving water intake to 5~6L can improve bowel cleansing comfort, but accompanied to worse tolerability and worse compliance [7]. The main reasons of the poor compliance include low tolerance and acceptance caused by salty taste and large volume liquid[8 9]. Tolerability should be coordinate with cleansing efficacy to improve patients' compliance and willingness to repeat colonoscopy. By improving bowel cleansing, several studies have been conducted by combined use of PEG and additional agents, such as ascorbic acid, lactulose, mosapride, et al[8-10]. However, all of them have their limitations. For colonoscopy preparation, the oral sulfate solution(OSS) is recommended by ESGE (European Society of Gastrointestinal Endoscopy) and ASGE (American Society of Gastrointestinal Endoscopy) guidelines, attributed to noninferiority efficacy, higher safety, and better tolerability[9 11 12].Thus we aimed to explore a OSS based derivative regimen with balanced effectiveness, safety and comfort.

Linaclotide is a selective guanylate cyclase-C (GC-C) receptor agonist and is known to soften dejection and increase the frequency of defecation by accelerated intestinal transit and by stimulating intestinal fluid secrete[13]. Meanwhile, it can reduce celialgia by inhibiting the activity of pain-sensing nerves[14]. Its action occurs mainly in the gastrointestinal tract and the adverse effects are generally mild[14]. Thus combined use of linaclotide and OSS is believed to be a potentially effective bowel cleansing regimen. As far as we know, no research has been conducted to evaluate the effectiveness and safety of linaclotide combined with OSS as a bowel preparation regimen. On the other hand, the administration regimen of linaclotide mixed with OSS, including the optimal dosage of linaclotide, administration time of linaclotide, and duration administration of linaclotide are still in the exploratory phase and require further investigation. We aimed to explore an effectiveness, comfortable and safety bowel preparation administration regimen of linaclotide mixed with OSS in this prospective,

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randomized, controlled, single blind (endoscopist) clinical trial. This study may optimize bowel preparation protocols in clinical practice.

Materials and Methods

Study design and patient population

This is a randomized, controlled, single blind clinical trial comparing three bowel preparation regimens for chronic constipation patients undergoing colonoscopy. The study will be conducted at Capital Medical University affiliated Beijing Shijitan Hospital.

Inclusion criteria for the study include chronic constipation patients undergoing colonoscopy meet the following criteria: (1) age 18-65 years; (2) met the Rome IV criteria of chronic constipation. the Rome IV criterion[15] was the presence of ≥ 2 of the following:① straining for＞25% of defecations, ②lumpy or hard stools (form 1 or 2 on the Bristol Stool Form Scale) for＞25% of defecations, ③sensation of incomplete evacuation for＞25% of defecations, ④sensation of anorectal obstruction/blockage for＞25% of defecations, ⑤ manual maneuvers to facilitate defecation for ＞ 25% of defecations; (3) were able to comprehend the trial, sign a written informed consent, including consent a screening procedure to determine eligibility; (4) can communicate with the investigators well and follow verbal and written instructions; (5) can take oral sulfate solution (OSS) correctly according to the procedure; (6) undergo follow-up in accordance with the protocol.

Exclusion criteria include patients meet one or more following criteria: (1) lack of indications for total colonoscopy; (2) exist general contraindications to colonoscopy bowel cleansing, for instance, acute surgical abdomen including intestinal perforation, acute diverticulitis and appendicitis, gastrointestinal obstruction, toxic megacolon; (3) has one of the following diseases: electrolyte disturbances, severe diseases of the heart, liver or kidney; (4) history of any colonic surgery; (5) is taking or has taken linalotide, or is allergic to linalotide; (6) pregnant women; (7) lactating women; (8) are participating in other clinical trials or participated in other clinical trials within 60 days.

Randomization and blind method

Subjects will be randomized with 1:1:1 ratio to Regimen A, B or C, via a computer-based random number table. The randomization process is performed by clinicians. They prepare study product, provide education on bowel preparation and involved in the day-to-day care of patients. They will not be involved in performing procedures. All endoscopists in this trial and biostatisticians are unaware to allocation. Blinding of the endoscopist will be strictly enforced. They will remain blinded until the main analysis is complete. Because of the

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volume differences and dose differences among the three regimens, blinding of the patients is impossible. Therefore, investigators will ask the subjects to refrain from talking about bowel cleansing with endoscopists, either before or during the colonoscopy.

Selection of bowel preparation regimens

Before bowel preparation, each patient was provided with written instructions on dietary restrictions and bowel cleansing methods. The following strict dietary restrictions will give to all subjects: (1) follow a low-fiber diet for three days before the colonoscopy, (2) follow a clear fluid diet for one day before the colonoscopy, (3) On the day of the colonoscopy, patients had to fast. A low-fiber diet is defined as a diet with the total fiber intake less than 10g/d. Patients will stop intake laxatives or prokinetics seven days before the colonoscopy.

Study participants were equally divided into 3 groups using a random number table. In regimen A, subjects will (1) take 1d-linaclotide at 7AM on the day before the procedure, (2) ingested diluted OSS followed by 1L water on the night before the procedure starting at 7 PM, OSS were dissolved in approximately 500 ml water, (3) take 1d-linaclotide at 5AM on the day of the procedure, and (4) drink 500mL diluted OSS and 1L water on the day of the procedure, starting at 7AM and completed at least 4 hours before the colonoscopy. Previous studies[16 17] found a single dose of linaclotide taken 1 hour before video capsule endoscopy significantly improved bowel preparation quality and visualization, reducing transit time by 20% compared to published standards. Taking into account that this study includes patients with chronic constipation, Regimen A designed as combined use 2d-linaclotide and OSS[14].

In regimen B, subjects will (1) take 1d-linaclotide at 7AM two days before the procedure, (2) 1d-linaclotide at 7AM on the day before the procedure, (3) ingested diluted OSS followed by 1L water on the night before the procedure starting at 7 PM, OSS were dissolved in approximately 500 ml water, (4) take1d-linaclotide at 5AM on the day of the procedure, and (5) drink 500mL diluted OSS and 1L water on the day of the procedure, starting at 7AM and completed at least 4 hours before the colonoscopy. Regimen B was adapted from Wang[18] and Xu[19] who combined use 3L PEG and 3d-linaclotide, and found that this regimen was satisfactory for chronic constipation patients[18].

In regimen C, subjects will (1) ingested diluted OSS followed by 1L water on the night before the procedure starting at 7 PM, OSS were dissolved in approximately 500 ml water, and (2) drink 500mL diluted OSS and 1L water on the day of the procedure, starting at 7AM and completed at least 4 hours before the colonoscopy. All patients received 5ml of

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simethicone solution mixed in the last dose of laxative. Regimen C was control group, consisting of traditional 1L diluted OSS and 2L water.

Rescue regimen for inadequate bowel preparation: clinicians will gauge whether the last excreta is adequate before colonoscopy according to standard pictures (Figure 1). For inadequate cleanings, supplement 500mL diluted OSS and 1L water will be taken. Rescue regimen will be recorded in case report form (CRF). Schedule of enrolment, interventions and assessments is presented in table 1.

Table 1 Schedule of enrolment, interventions and assessments

	Study period				
	Enrolment	Allocation	Postallocation		
Content	Screening and baseline assessment	Randomisation and bowel preparation	Endoscopic screening and polypectomy	Follow-up	Close-out
Timepoint	T_0	T_1 1-3 days	T_2 0 day	T_3 0-14days	T_4 14days
Enrolment					
Eligible screen	×				
Informed consent	×				
Allocation		×			
Interventions					
Regimen A		×			
Regimen B		×			
Regimen C		×			
Endoscopic screening			×		
Assessment					
Baseline data	×				
BBPS score			×		
Safety assessment		×	×	×	×
QSC		×			

BBPS, Boston Bowel Preparation Scale; QSC, questionnaire of comfort

Study procedures

The investigator will perform all observations, investigations and evaluations according to the descriptions provided. Subjects will be given written instructions including diet, dose and timing of experimental drugs in accordance with randomization. Clinicians distribute the study drugs to the participants, provide instructions on the administration and face to face bowel preparation education to ensure that participants will take their drugs correctly. All colonoscopies were performed by designated, professional endoscopists (had accomplished more than 1000 colonoscopies examinations individually) using the Olympus CV-260 or

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CV-290 colonoscope (Olympus Medical Systems, Tokyo, Japan). All participating endoscopists will be standardized trained in the use of the BBPS before participate in the study and evaluate bowel preparation quality based on BBPS. Endoscopists cannot use additional adjuvant devices or adjuvants to improve bowel preparation.

Data collection

The following clinical variables were collected: (1) Demographics of the participants: gender, age, body weight index (BMI), comorbidities, usage of calcium channel blocker, smoking or alcohol consumption, family history and laboratory indexes (routine blood test, liver and kidney function, coagulation function). (2) Bowel preparation: subject's compliance, subject's ability to understand and follow the instructions for bowel preparation; usage of laxatives, interval between the first OSS and the first defecation, and interval between the last OSS and colonoscopy. (3) Colonoscopy: BBPS score (total score and each segment scores), cecal intubation rate, colonoscope insertion time and withdrawal time, adenoma detection rate. (4) Safety: We will assess adverse events and serious adverse events of the agents before, during and after colonoscopy bowel cleansing. (5) Comfort: Results of comfort questionnaire, including discomfort symptom (nausea, vomiting, abdominal pain, abdominal distention, bowel incontinence, dizziness, headache, fatigue, and tiredness), sleep quality (somnipathy, totally sleep duration, frequency of sleep awakenings in the evening before colonoscopy), willingness to duplicate colonoscopy bowel cleansing.

Study outcomes

The primary outcome will be adequate bowel preparation, defined as each segment BBPS scores ≥2 and/or total score ≥6 [20 21]. BBPS was based on three colon segments scores (right sided colon, transverse colon, left sided colon), while each segment score defined by a four-point scoring system (0–3). Right sided colon including the cecum and ascending colon, transverse colon was defined from hepatic flexure to splenic flexure, whereas any more distal colon and rectum was defined as left-sided colon. Each segment score rated between 0 and 3 as follows: 0=an unprepared colon segment with solid stool on the mucosa; 1=portions of the mucosa can be seen, but other areas are covered by staining, residual stool, and/or opaque liquid, thus cannot be seen clearly; 2=minor areas covered by residual staining, small stool fragments, and/or opaque liquid, but the colon segment seen well; 3= the entire mucosa can be adequately seen, with no residual staining, small fragments of stool, or opaque liquid. As an superior trial, the BBPS total score and segment scores in regimen A and B should be superior to regimen C statistically.

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The secondary outcome include defecation frequency, interval between the first OSS and the first defecation, interval between the last OSS and the colonoscopy examination, caecal intubation rate, colonoscope insertion time and withdrawal time, and adenoma detection rate (ADRs).

The third outcome will be comfort degree, evaluated by self-design questionnaire of comfort (QSC). The questionnaire of comfort (QSC) was adapted from previous studies[9 22], composed by complications and sleep quality during bowel preparation, as well as pre-procedure anxiety and willingness to repeat bowel preparation. Complications including abdominalgia, abdominal distension, nausea, vomiting and bowel incontinence during bowel preparation. Sleep quality including somnipathy, sleep duration, number of sleep awakenings during bowel cleansing.

Safety indicators: adverse events (AE) and serious adverse events (SAE), including abdominal pain, abdominal distension, fecal incontinence, allergic reaction and other adverse drug reaction, will be recorded and evaluated. Meanwhile we will record complication of EMR or ESD, such as intraprocedural haemorrhage (any immediate bleeding which require any form of endoscopic hemostasis or oozing last for at least 60s), delayed haemorrhage (any bleeding requiring endoscopy reintervention or hospitalisation within 2 weeks), intraprocedural perforation (any perforation requiring endoscopic clips sealing), and delayed perforation (any perforation occurs within 2 weeks), intestinal infection (bellyache, fever and/or raised C reaction protein needing antibiotic).

Statistical analysis and sample size

Statistical analysis will be executed by SPSS version 20.0 (IBM Corp, Armonk, NY, United States). Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) according to normal/non normal distribution, and will be analyzed with independent samples t-test or Wilcoxon's rank-sum test. Categorical variables are represented as count (percentage), and will be evaluated by $\chi 2$ or Fisher's exact test appropriately. Make $P<0.05$ as the boundary of statistically significant. In the study protocol, the sample size calculation was performed with an alpha of 0.05 and a power of 0.8, assuming a 20% difference in the rate of colonic cleansing and a 10% dropout rate. In our center, the rate of adequate bowel preparation was 70% among chronic constipation patients. A final inclusion of 65 participants in each group was needed. Compare the efficacy, safety and tolerability of bowel preparation based on intention-to-treat approaches or per-protocol analysis.

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Data management

Data will be collected through paper forms directly from investigators. Data from the forms will be extracted and input into a database on a password-protected computer. Data will be supervised by independent data monitoring committee.

Patient and public involvement

Patients and the public were not involved in the development of the protocol.

Ethics and dissemination

The study has been registered with Chinese Clinical Trial Registry and permitted by Ethics Committee of Capital Medical University affiliated Beijing Shijitan Hospital(IIT2024-146-003), and will informed consents from all patients prior to enrollment. The researchers will do their best to protect the information provided by patients from leaking personal privacy and without informed consent.

The findings of this study will be published in peer-reviewed journals for widespread dissemination. Individuals who contribute significantly to the research will be granted for authorship, including research design, implementation, subject recruitment, data collection, statistical analysis and manuscript writing and revision.

Discussion

This study aims to explore an innovative bowel preparation regimen combined-use linaclotide and OSS, which balance the efficacy, safety and comfort in chronic constipation patients undergoing colonoscopy. Bowel cleansing is an essential segment of colonoscopy. OSS and PEG are widely used in clinic practice[23], but are not optimal in patient satisfaction and quality of bowel preparation in chronic constipation. Improving PEG water intake to 5-6L can improve effectiveness, but can weaken the comfort, and influence the compliance of bowel preparation correspondingly[24]. Uncomfortable and low compliance caused by huge volume liquid is the critical factor of inadequate bowel preparation[24].

There were numbers PEG-based derivative regimen, for example combined with ascorbic acid, lactulose, mosapride, et al[8-10]. However, some patients have difficulty in tolerating PEG and all of PEG-based derivative regimen have their limitations. OSS is recommended by ESGE (European Society of Gastrointestinal Endoscopy) and ASGE (American Society of Gastrointestinal Endoscopy) guidelines, attributed to non-inferiority efficacy, higher safety,

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and better tolerability than PEG[9 11 12]. OSS, a newly launched bowel preparation agent in China, is composed of sodium sulfate and functions as an osmotic laxative. It improves the osmotic pressure derived from sulfate ions and replenishes sodium and potassium ions, thereby mitigating the risk of water-electrolyte imbalances. Phase III clinical trials indicated that OSS showed significantly higher BBPS scores compared to the 3-4L PEG split-dose regimen. Additionally, OSS facilitated swift bowel movements and the achievement of clear, watery stools, with a reduced incidence of nocturnal defecation. Hence, we want to explore an innovative OSS-based derivative bowel cleansing scheme which can lead to adequate bowel preparation in chronic constipation patients.

As a selective guanylate cyclase-C (GC-C) receptor agonist, linaclotide proved to be effective and safe for the treatment of chronic constipation (RR=3.26, 95%CI: 2.45-4.33) and irritable bowel syndrome with constipation (RR=2.26, 95%CI: 1.86-2.74), with slightly adverse reaction such as diarrhea[25]. Linaclotide bind to GC-C receptor, results in accelerated gastrointestinal motility, increased fluid in the intestine, and reduced abdominal pain[26]. Based on pharmacological mechanism mentioned above, we believe that linaclotide will be a potential effective, comfortable and safety adjuvant for colonoscopy bowel preparation. Few studies[8 14 18] had used linaclotide as an adjuvant to improve the cleansing efficacy, but the administration regimen is not confirmed and high-grade evidence from clinical trials is also very limited.

To elucidate the administration protocol, we conducted an exhaustive literature review for this trial design. Considering the absence of prior studies on the combined use of linaclotide and OSS, our regimen is modeled on the combination use of linaclotide and PEG. According to Yang[8] et al, the BBPS total score and individual segment score in the 2LPEG+1d-linaclotide group was higher than the 2LPEG group (P<0.001), with a compatible sleeping quality or adverse reaction incidence. 2LPEG +1d-linaclotide showed no significant difference in adequate bowel preparation but better sleeping quality and less adverse reaction than 4LPEG group. Song[14] et al performed a prospective randomized research, and found that the 3LPEG+1d-linaclotide group was comparable to the 4LPEG group in adequate

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bowel preparation with shorter withdrawal time (P<0.05). In a RCT[18] conducted in chronic constipation patients, compared to the 4LPEG group, the 4LPEG+1d-linaclotide group and the 3LPEG+3d-linaclotide group were superior in adequate bowel preparation rates with lower percentage of mild adverse events (P<0.01). In a prospective, single-center RCT[19], the combination of 3-L PEG and 3-d linaclotide demonstrated significantly higher rates of adequate and excellent bowel preparation (P<0.05) with a reduced volume of intake. These suggest that linaclotide could improve the cleansing efficacy without additional adverse events. These PEG-based derivative regimen still displayed poor compliance due to huge volume liquid and unacceptable taste. OSS showed non-inferiority efficacy, higher safety, and better tolerability compared to PEG[3 12]. Hence, based on previous studies and clinical practice, we design this randomized control trail to clarify the administration regimen of combine use of OSS and linaclotide. On the other hand, this trial includes patients who reflected the real clinical situation, which makes the results more valuable for clinical practice. We expect that this study will provide propositions for chronic constipation patients undergoing colonoscopy bowel preparation.

Strengths and limitations of this study

To the best of our knowledge, this is the first prospective study to investigate the efficacy and safety of intake linaclotide in addition to OSS before colonoscopy. Our study has the following strengths: (1) explore an innovative bowel cleansing scheme which can lead to adequate bowel preparation while not improving intake of OSS dose; (2) patients will be asked to discontinue medicines that may affect intestinal motility, such as laxatives or prokinetics. This may reflect the real impact of linaclotide in bowel preparation and makes the trail findings more informative for clinical practice. Nevertheless, our study also has the following limitations: (1) as a single-center study, selective bias is inevitable. (2) The administration regimen of linaclotide and OSS is still uncertainty. The optimal dosage, administration time and administration duration require further investigation.

Author affiliations

Acknowledgements We thank all participants for their voluntary participation in this study and thank all researchers for their hard-working in study procedures.

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Author's Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were GCM, CJF, WJ, LL and LH. The first draft of the manuscript was written by GCM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by Beijing Municipal Administration of Hospitals Incubating Program (PX2021030); The Science and Technology Development Project of China State Railway Group (J2021Z609) and Youth Fund of Beijing Shijitan Hospital, Capital Medical University (2022-q12)

Competing interests The authors declare no competing interests.

Patient and public involvement Patients and the public were not involved in the development of the protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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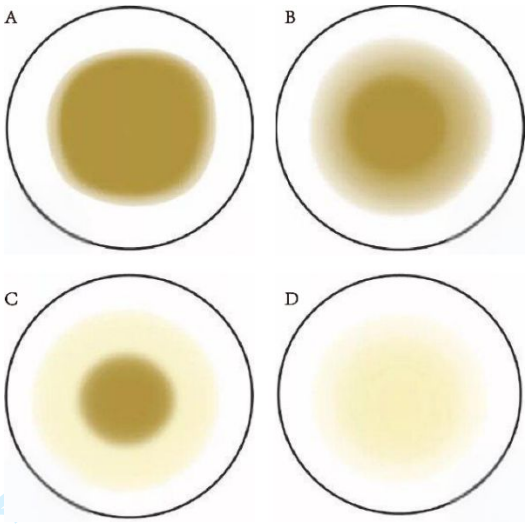

Figure 1 Standard pictures for the last excreta before colonoscopy. A turbid liquid with fecal residue; B opaque liquid without residual stool; C slight-staining and clear liquid; D colorless and clear liquid. For patients with inadequate cleanings (A or B), supplement 500mL diluted OSS and 1L water will be taken.

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BMJ Open

The effects of the combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single-blind clinical trial from a single center in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2025-099687.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Apr-2025
Complete List of Authors:	Guo, Chunmei; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Wang, Jing; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Li, Li; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Cui, Jianfang; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Liu, Hong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Yang, Guodong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Clinical Trial, Endoscopy < GASTROENTEROLOGY, Clinical Protocols

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BMJ Open: first published as 10.1136/bmjopen-2025-099687 on 6 May 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .
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The effects of the combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single-blind clinical trial from a single center in China

Abstract

Introduction Chronic constipation is an independent risk factor for inadequate bowel preparation. The objective of this study is to evaluate the effectiveness and safety of the combined use of linaclotide and oral sulfate solution (OSS)in chronic constipation patients undergoing colonoscopy.

Methods and analysis This is a prospective, randomized, controlled, single-blind (endoscopist) clinical trial that compares three bowel cleansing regimens for chronic constipation patients undergoing colonoscopy. Regimen A consists of 2d-linaclotide and OSS, Regimen B consists of 3d-linaclotide and OSS, and Regimen C consists of OSS. All patients are required to consume a low-fibre diet for three days and then a clear fluid diet for one day before the colonoscopy. The primary outcome is adequate bowel preparation (defined as a Boston Bowel Preparation Scale (BBPS) score ≥2 for each segment and a total BBPS score ≥6). The secondary outcomes include defecation frequency, caecal intubation rate, adenoma detection rate (ADR), and colonoscope insertion time and withdrawal time. The tertiary outcomes include complications of colonoscopy, adverse events (AEs) and degree of comfort, which is evaluated via a self-designed questionnaire of comfort (QSC).

Strengths and limitations of this study

(1) This trial explores an innovative bowel cleansing scheme which can lead to adequate bowel preparation without increasing the OSS dose for chronic constipation patients. (2) This trial discontinues medicines that may affect intestinal motility, which may reflect the real impact of linaclotide in bowel preparation. (3) As a single-centre study, selection bias is inevitable. (4) The administration regimens of linaclotide and OSS, such as the optimal dosage, administration time and duration, are still uncertain and require further investigation.

Ethics and dissemination The research will be conducted according to Good Clinical Practice principles. Ethical approval has been obtained from Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (IIT2024-146-003). Study findings will be published in peer-reviewed journals.

Trial registration number ChiCTR2500096394

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Introduction

Colorectal cancer (CRC) has become a major public health concern worldwide, with the second highest mortality rate among all cancers and the third highest global prevalence[1]. CRC is largely preventable through screening for colorectal adenomas, which are benign growths but may develop into cancer if not removed[2]. Early detection and removal of colorectal adenomas can effectively block the "adenoma-carcinoma sequence" pathway and ultimately prevent the development of CRC[3]. Because of the increased use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), the incidence of CRC has stabilized or started to decrease continuously in the USA and other high-income countries over the past two decades[4]. In China, however, the all-age disability-adjusted life years (DALY) rate of CRC has increased by 69.8% since 1990, which may be attributed to the high misdiagnosis rate of colorectal adenomas[5]. Adequate preprocedural bowel cleansing maximizes adenoma detection rates (ADRs), which is beneficial for CRC prevention[6].

Polyethylene glycol (PEG) is widely used for bowel preparation. However, inadequate cleansing is observed in many chronic constipation patients when 4L of PEG is used. As a common gastrointestinal disorder, constipation affects 12%~17% of the population and is considered one of the risk factors for inadequate bowel cleansing. Improving water intake to 5~6L can improve bowel cleansing comfort but is accompanied by worse tolerability and worse compliance[7]. The main reasons for poor compliance include low tolerance and acceptance caused by a salty taste and large volume of liquid[8 9]. Tolerability should be coordinated with cleansing efficacy to improve patients' compliance and willingness to repeat colonoscopy. To improve bowel cleansing, several studies have been conducted on the combined use of PEG and additional agents, such as ascorbic acid, lactulose, and mosapride[8-10]. However, all of these methods have limitations. For colonoscopy preparation, the oral sulfate solution (OSS) is recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines owing to its noninferiority efficacy, greater safety, and better tolerability[9 11 12]. Thus, we aimed to explore an OSS-based derivative regimen with balanced effectiveness, safety and comfort.

Linaclotide is a selective guanylate cyclase-C (GC-C) receptor agonist that softens dejection and increases the frequency of defecation by accelerating intestinal transit and by stimulating the secretion of intestinal fluid[13]. Moreover, linaclotide can reduce celialgia by

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inhibiting the activity of pain-sensing nerves[14]; its action occurs mainly in the gastrointestinal tract, and the adverse effects are generally mild[14]. Thus, the combined use of linaclotide and OSS is believed to be a potentially effective bowel cleansing regimen. To the best of our knowledge, no research has been conducted to evaluate the effectiveness and safety of linaclotide combined with OSS as a bowel preparation regimen. The administration regimens of linaclotide mixed with OSS, including the optimal dosage of linaclotide, the administration time of linaclotide, and the duration of linaclotide administration, are still in the exploratory phase and require further investigation. We aimed to explore the effectiveness, comfort and safety of a bowel preparation administration regimen of linaclotide mixed with OSS in this prospective, randomized, controlled, single-blind (endoscopist) clinical trial. The results obtained in this study may optimize bowel preparation protocols in clinical practice.

Materials and methods

Study design and patient population

This is a randomized, controlled, single-blind clinical trial comparing three bowel preparation regimens for chronic constipation patients undergoing colonoscopy. The study will be conducted at Beijing Shijitan Hospital, Capital Medical University from March 1st, 2025, to December 31st, 2026.

The inclusion criteria for the study include chronic constipation patients undergoing colonoscopy who meet the following criteria: (1) are aged 18-65 years; (2) meet the Rome IV criteria[15] for chronic constipation which includes the presence of ≥ 2 of the following: ① straining for＞25% of defecations, ② lumpy or hard stools (form 1 or 2 on the Bristol Stool Form Scale) for＞25% of defecations, ③ sensation of incomplete evacuation for＞25% of defecations, ④sensation of anorectal obstruction/blockage for＞25% of defecations, ⑤ manual manoeuvers to facilitate defecation for＞25% of defecations; (3) have the ability to comprehend the trial, sign a written informed consent, including consent for a screening procedure to determine eligibility; (4) have the ability to communicate with the investigators well and follow verbal and written instructions; (5) have the ability to take oral sulfate solution (OSS) correctly according to the procedure; and (6) have the ability to perform follow-up in accordance with the protocol.

The exclusion criteria include patients meeting one or more of the following criteria: (1) having a lack of indications for total colonoscopy; (2) having general contraindications to colonoscopy bowel cleansing, such as acute surgical abdomen, including intestinal

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perforation, acute diverticulitis and appendicitis, gastrointestinal obstruction, toxic megacolon; (3) having one of the following diseases: electrolyte disturbances or severe diseases of the heart, liver or kidney; (4) having a history of any colonic surgery; (5) taking or having taken linalotide or being allergic to linalotide; (6) being pregnant; (7) lactating; or (8) participating in other clinical trials or participating in other clinical trials within 60 days.

Randomization and blinding method

Subjects will be randomized at a 1:1:1 ratio to Regimens A, B or C, via a computer-based random number table. The randomization process will be performed by clinicians. They will prepare study products, provide education on bowel preparation and will be involved in the day-to-day care of patients. They will not be involved in performing the procedures. All endoscopists in this trial and biostatisticians will be unaware of each patient's regimen allocation. Blinding of the endoscopist will be strictly enforced, and they will remain blinded until the main analysis is complete. Due to the volume differences and dose differences among the three regimens, blinding of the patients is impossible. Therefore, investigators will ask the subjects to refrain from talking about bowel cleansing with the endoscopists, either before or during the colonoscopy.

Selection of bowel preparation regimens

Before bowel preparation, each patient will be provided with written instructions on dietary restrictions and bowel cleansing methods. The following strict dietary restrictions will be given to all subjects: (1) follow a low-fibre diet for three days before the colonoscopy, (2) follow a clear fluid diet for one day before the colonoscopy, and (3) fast on the day of the colonoscopy. A low-fibre diet is defined as a diet with a total fibre intake of less than 10g/d. Patients will stop taking laxatives or prokinetics seven days before the colonoscopy.

The study participants will be equally divided into 3 groups via a random number table. In regimen A, the subjects will (1) take 1d-linaclotide at 7AM on the day before the procedure, (2) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L of water on the night before the procedure starting at 7 PM, (3) take 1d-linaclotide at 5AM on the day of the procedure, and (4) drink 500mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy. Previous studies[16 17] revealed that a single dose of linaclotide taken 1 hour before video capsule endoscopy significantly improved bowel preparation quality and visualization, reducing transit time by 20% compared with published standards. Chronic constipation patients would experience their first spontaneous bowel movements within 24

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hours, accompanied by a shortened first defection time and an increased number of defecations after taking linaclotide. Considering that the OSS is taken the day before and the day of the colonoscopy, regimen A was designed with the combined use of 2d-linaclotide and the OSS[14].

In regimen B, the subjects will (1) take 1d-linaclotide at 7AM two days before the procedure, (2) take 1d-linaclotide at 7AM on the day before the procedure, (3) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L water on the night before the procedure starting at 7 PM, (4) take 1d-linaclotide at 5AM on the day of the procedure, and (5) drink 500 mL of a diluted OSS and 1 L water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy. Regimen B was adapted from Wang[18] and Xu[19], who combined 3 L PEG and 3d-linaclotide and reported that this regimen was satisfactory for chronic constipation patients[18].

In regimen C, the subjects will (1) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L of water on the night before the procedure starting at 7 PM, and (2) they will drink 500 mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7 AM and completing at least 4 hours before the colonoscopy. All patients will receive 5 ml of simethicone solution mixed with the last dose of laxative. Regimen C is the control group, consisting of a traditional 1 L diluted OSS and 2 L water.

As a rescue regimen for inadequate bowel preparation, clinicians will gauge whether the last excreta is adequate before colonoscopy according to standard pictures (Figure 1). For inadequate cleanings, 500 mL of diluted OSS and 1 L of water will be taken. The rescue regimen will be recorded on a case report form (CRF). The schedule of enrolment, interventions and assessments is presented in Table 1.

Table 1 Schedule of enrolment, interventions and assessments

	Study period				
	Enrolment	Allocation	Postallocation		
Content	Screening and baseline assessment	Randomisation and bowel preparation	Endoscopic screening and polypectomy	Follow-up	Close-out
Timepoint	T_0	T_1 1-3 days	T_2 0 day	T_3 0-14days	T_4 14days
Enrolment					
Eligible screen	×				
Informed consent	×				
Allocation		×			
Interventions					

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Regimen A		×			
Regimen B		×			
Regimen C		×			
Endoscopic screening			×		
Assessment					
Baseline data	×				
BBPS score			×		
Safety assessment		×	×	×	×
QSC		×			

BBPS, Boston Bowel Preparation Scale; QSC, questionnaire of comfort

Study procedures

The investigator will perform all the observations, investigations and evaluations according to the descriptions provided. The subjects will be given written instructions including the diet, dose and timing of the experimental drugs, in accordance with randomization. Clinicians will distribute the study drugs to the participants, provide instructions on the administration and face-to-face bowel preparation education to ensure that the participants will take their drugs correctly. All colonoscopies will be performed by designated, professional endoscopists (had performed more than 1000 colonoscopies individually) via the Olympus CV-260 or CV-290 colonoscope (Olympus Medical Systems, Tokyo, Japan). All participating endoscopists will be standardized and trained in the use of the BBPS before they participate in the study, and bowel preparation quality will be evaluated based on the BBPS. Endoscopists cannot use additional adjuvant devices or adjuvants to improve bowel preparation.

Data collection

The following clinical variables will be collected: (1) Demographics of the participants: sex, age, body mass index (BMI), comorbidities, use of calcium channel blockers, smoking or alcohol consumption, family history and laboratory indices (routine blood tests, liver and kidney function, coagulation function). (2) Bowel preparation: subject compliance, ability to understand and follow the instructions for bowel preparation, usage of laxatives, interval between the first OSS and the first defecation, and interval between the last OSS and colonoscopy. (3) Colonoscopy: BBPS score (total score and each segment score), caecal intubation rate, colonoscope insertion time and withdrawal time, and adenoma detection rate. (4) Safety: We will assess adverse events and serious adverse events associated with the agents before, during and after colonoscopy bowel cleansing. (5) Comfort: Results of the

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comfort questionnaire, including discomfort symptoms (nausea, vomiting, abdominal pain, abdominal distention, bowel incontinence, dizziness, headache, fatigue, and tiredness), sleep quality (somnipathy, total sleep duration, frequency of sleep awakenings in the evening before colonoscopy), and willingness to duplicate colonoscopy bowel cleansing.

Study outcomes

The primary outcome will be adequate bowel preparation, defined as each segment's BBPS scores being ≥2 and/or having a total score ≥6 [20 21]. The BBPS is based on three colon segment scores (right-sided colon, transverse colon, and left-sided colon), and each segment score is defined by a four-point scoring system (0–3). The right-sided colon included the caecum and ascending colon, and the transverse colon was defined from the hepatic flexure to the splenic flexure, whereas any more distal colon or rectum was defined as the left-sided colon. Each segment score is between 0 and 3 as follows: 0=an unprepared colon segment with solid stool on the mucosa; 1=portions of the mucosa can be seen, but other areas are covered by staining, residual stool, and/or opaque liquid and thus cannot be seen clearly; 2=minor areas covered by residual staining, small stool fragments, and/or opaque liquid, but the colon segment can be seen well; 3= the entire mucosa can be adequately seen, with no residual staining, small fragments of stool, or opaque liquid. As a superior trial, the BBPS total score and segment scores in regimens A and B should be statistically superior to those in regimen C.

The secondary outcomes include defecation frequency, the interval between the first OSS and the first defecation, the interval between the last OSS and the colonoscopy examination, the caecal intubation rate, the colonoscope insertion time and withdrawal time, and the adenoma detection rate (ADR).

The third outcome will be the degree of comfort, which is evaluated via a self-designed questionnaire of comfort (QSC). The questionnaire of comfort (QSC) was adapted from previous studies[9 22] and is composed of complications and sleep quality during bowel preparation, as well as preprocedure anxiety and willingness to repeat bowel preparation. The complications included abdominalgia, abdominal distension, nausea, vomiting and bowel incontinence during bowel preparation. Sleep quality, including somnipathy, sleep duration, and the number of sleep awakenings during bowel cleansing, was also recorded.

Safety indicators, such as adverse events (AEs) and serious adverse events (SAEs), including abdominal pain, abdominal distension, faecal incontinence, allergic reactions and other adverse drug reactions, will be recorded and evaluated. Moreover, we will record

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complications of EMR or ESD, such as intraprocedural haemorrhage (any immediate bleeding that requires any form of endoscopic haemostasis or oozing lasting for at least 60 s), delayed haemorrhage (any bleeding requiring endoscopy reintervention or hospitalisation within 2 weeks), intraprocedural perforation (any perforation requiring endoscopic clip sealing), delayed perforation (any perforation occurring within 2 weeks), and intestinal infection (bellyache, fever and/or increased C-reactive protein requiring antibiotics).

Statistical analysis and sample size

Statistical analysis will be executed by SPSS version 20.0 (IBM Corp, Armonk, NY, United States). Continuous variables are expressed as the mean ± standard deviation (SD) or median (interquartile range, IQR) according to a normal/nonnormal distribution, and will be analysed with independent samples t tests or Wilcoxon's rank-sum tests. Categorical variables are represented as counts (percentages), and will be evaluated by the $\chi 2$ test or Fisher's exact test appropriately. To address the issue of multiple comparisons across the three study arms, we will employ adjustment methods, such as the Bonferroni correction, to ensure the robustness and validity of our statistical inferences. $P<0.05$ will be set as the cut-off for statistically significant.

In the study protocol, the sample size calculation is performed with an alpha of 0.05 and a power of 0.8, assuming a 20% difference in the rate of colonic cleansing and a 10% dropout rate. Over the past year, approximately 500 patients with chronic constipation have undergone bowel preparation using OSS at our centre, resulting in an adequate bowel cleansing rate of approximately 70%. A final inclusion of 65 participants in each group was needed. The efficacy, safety and tolerability of bowel preparation will be compared based on intention-to-treat approaches or per-protocol analysis.

Patient and public involvement

Patients and the public were not involved in the development of the protocol.

Ethics and dissemination

The study has been registered with the Chinese Clinical Trial Registry and permitted by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (IIT2024-146-003), and informed consent will be obtained from all patients prior to enrolment. The researchers will do their best to protect the personal information provided by patients from being leaked or used without informed consent. Data will be collected through paper forms directly from investigators. Data from the forms will be extracted and input into a database

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on a password-protected computer. The data will be supervised by an independent data monitoring committee.

The findings of this study will be published in peer-reviewed journals for widespread dissemination. Individuals who contribute significantly to the research will be granted authorship, including research design, implementation, subject recruitment, data collection, statistical analysis and manuscript writing and revision.

Discussion

The aim of this study is to explore an innovative bowel preparation regimen that combines linaclotide and an OSS, which balances efficacy, safety and comfort in chronic constipation patients undergoing colonoscopy. Bowel cleansing is an essential component of colonoscopy. OSS and PEG are widely used in clinical practice[23], but are not optimal for patient satisfaction or the quality of bowel preparation in patients with chronic constipation. Improving PEG water intake to 5-6 L can improve effectiveness but can lessen comfort and influence compliance with bowel preparation[24]. Discomfort and low compliance caused by a large volume of liquid are critical factors for inadequate bowel preparation[24].

There are several PEG-based derivative regimens, such as those combined with ascorbic acid, lactulose, and mosapride[8-10]. However, some patients have difficulty tolerating PEG and all of PEG-based derivative regimens have limitations. OSS is recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines due to its noninferiority efficacy, greater safety, and better tolerability than PEG[9 11 12]. OSS, a newly developed bowel preparation agent in China, is composed of sodium sulfate and functions as an osmotic laxative; it improves the osmotic pressure derived from sulfate ions and replenishes sodium and potassium ions, thereby mitigating the risk of water-electrolyte imbalances. Phase III clinical trials have indicated that the OSS results in significantly higher BBPS scores than the 3-4 L PEG split-dose regimen does. Additionally, OSS facilitated swift bowel movements and achieved clear, watery stools, with a reduced incidence of nocturnal defecation. Hence, we aimed to explore an innovative OSS-based derivative bowel cleansing scheme that can lead to adequate bowel preparation in chronic constipation patients.

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As a selective guanylate cyclase-C (GC-C) receptor agonist, linaclotide has proven to be effective and safe for the treatment of chronic constipation (RR=3.26, 95% CI: 2.45-4.33) and irritable bowel syndrome with constipation (RR=2.26, 95% CI: 1.86-2.74), with slight adverse reactions such as diarrhoea[25]. Linaclotide binds to the GC-C receptor, resulting in accelerated gastrointestinal motility, increased fluid in the intestine, and reduced abdominal pain[26]. Based on the pharmacological mechanism mentioned above, we believe that linaclotide may be an effective, comfortable and safe adjuvant for colonoscopy bowel preparation. Few studies[8 14 18] have used linaclotide as an adjuvant to improve the cleansing efficacy, especially in patients at high risk of inadequate bowel preparation[27]. However, the appropriate administration regimen has not been confirmed, and high-grade evidence from clinical trials is also very limited.

To elucidate the administration protocol, we have conducted an exhaustive literature review for this trial design. Considering the absence of prior studies on the combined use of linaclotide and OSS, our regimen is modelled on the combined use of linaclotide and PEG. According to Yang[8] et al., the BBPS total score and individual segment score in the 2LPEG+1d-linaclotide group were greater than those in the 2LPEG group (P<0.001), with a compatible sleeping quality or adverse reaction incidence. Compared with the 4LPEG group, the 2LPEG +1d-linaclotide group showed no significant difference in adequate bowel preparation but had better sleep quality and fewer adverse reactions. Song[14] et al. performed a prospective randomized study and reported that the 3LPEG+1d-linaclotide group was comparable to the 4LPEG group in terms of adequate bowel preparation with a shorter withdrawal time (P<0.05). In a prospective, randomized, observer-blinded, multicentre study[28], 2d-linaclotide+PEG were used for bowel cleansing. This regimen shortened the first defecation time after consuming PEG (P<0.01), which may contribute to adequate preparation with minimal side effects. Moreover, nausea and vomiting were less common in this group, which could be interpreted as a reduction in volume. The use of linaclotide shortened the first defecation time and increased the mean number of defecations before starting

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PEG[29]. These findings encouraged us to choose a 2d-linaclotide regimen with greater cleansing efficacy, better tolerability and a more pleasant experience during colonoscopy.

In an RCT[18] conducted in chronic constipation patients, compared with the 4LPEG group, the 4LPEG+1d-linaclotide group and the 3LPEG+3d-linaclotide group were superior in terms of adequate bowel preparation rates, with a lower percentage of mild adverse events ($P<0.01$). In a prospective, single-centre RCT[19], the combination of 3-L PEG and 3-d linaclotide demonstrated significantly higher rates of adequate and excellent bowel preparation ($P<0.05$) with a reduced volume of intake. These findings suggest that linaclotide could improve the cleansing efficacy without additional adverse events. These PEG-based derivative regimens still display poor compliance due to the large volume of liquid and unacceptable taste. OSS has shown noninferiority efficacy, greater safety, and better tolerability than does PEG[3 12]. Based on these previous studies and clinical practice, we hypothesize that the additional use of linaclotide may improve the cleansing efficacy without additional OSS intake. Given that chronic constipation patients first experience spontaneous bowel movements within 24 hours after taking linaclotide[29], the OSS is taken the day before and the day of the colonoscopy. We designed 2-d linaclotide (the day before and the day of the colonoscopy) +OSS and 3-d linaclotide (2 days before, the day before, and the day of the colonoscopy) +OSS. This trial includes patients who reflect the real clinical situation, which makes the results more valuable for clinical practice. We expect that this study will provide propositions for chronic constipation patients undergoing colonoscopy bowel preparation.

Acknowledgements We thank all participants for their voluntary participation in this study and thank all researchers for their hard-working in study procedures.

Author's Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were CMG, JW, LL, JFC, HL and GDY. The first draft of the manuscript was written by CMG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. GDY is the guarantor.

Funding This work was supported by Beijing Municipal Administration of Hospitals Incubating Program (PX2021030); The Science and Technology Development Project of

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China State Railway Group (J2021Z609) and Youth Fund of Beijing Shijitan Hospital, Capital Medical University (2022-q12)

Competing interests CMG received funding from Beijing Shijitan Hospital, Capital Medical University during the conduct of this study. The study sponsor had no role or influence in the study design, in the collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication. The authors declare no competing interests.

Patient and public involvement Patients and the public were not involved in the development of the protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Researchers with legitimate academic or scientific interests may contact the corresponding author at guoguo10086@163.com to request access to the data. Access will be granted only for non-commercial purposes and is subject to appropriate conditions and institutional approval.

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Figure Legend

Figure 1 Standard pictures for the last excreta before colonoscopy. A turbid liquid with fecal residue; B opaque liquid without residual stool; C slight-staining and clear liquid; D colorless and clear liquid. For patients with inadequate cleanings (A or B), supplement 500mL diluted OSS and 1L water will be taken.

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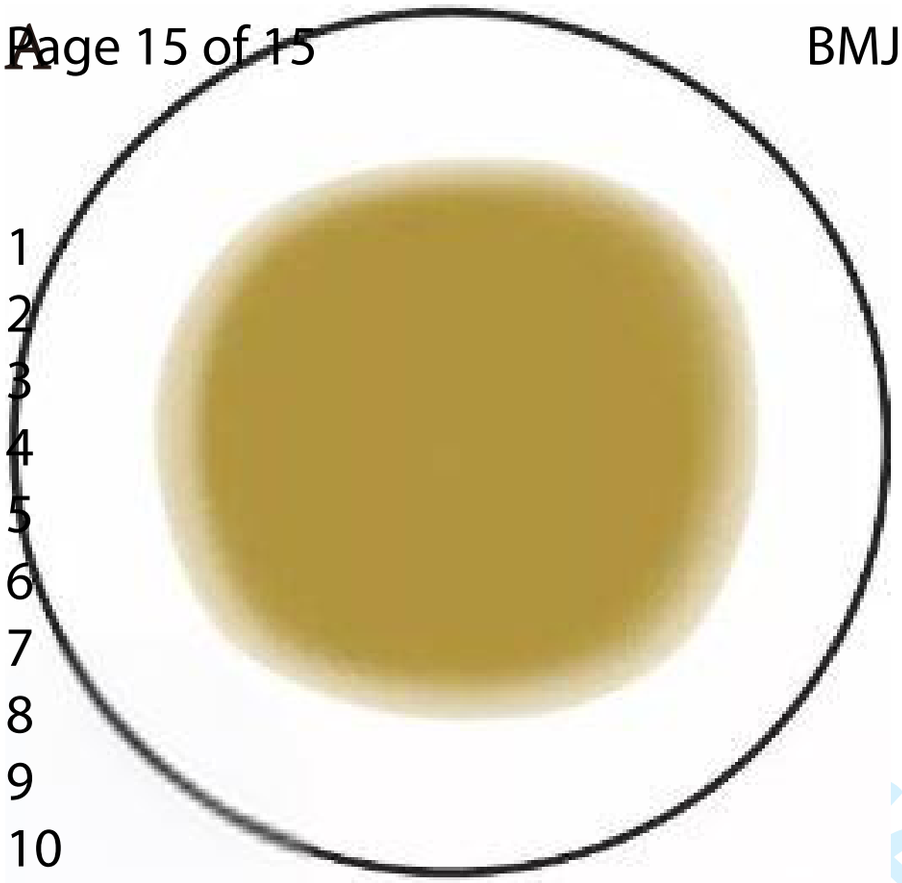

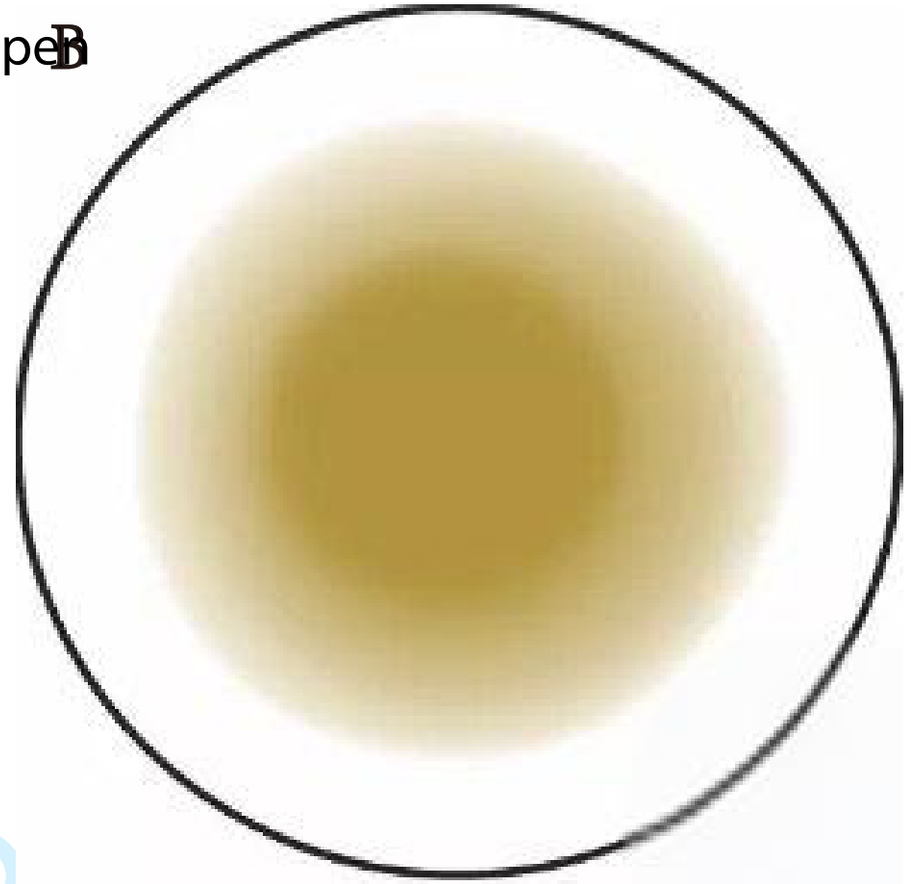

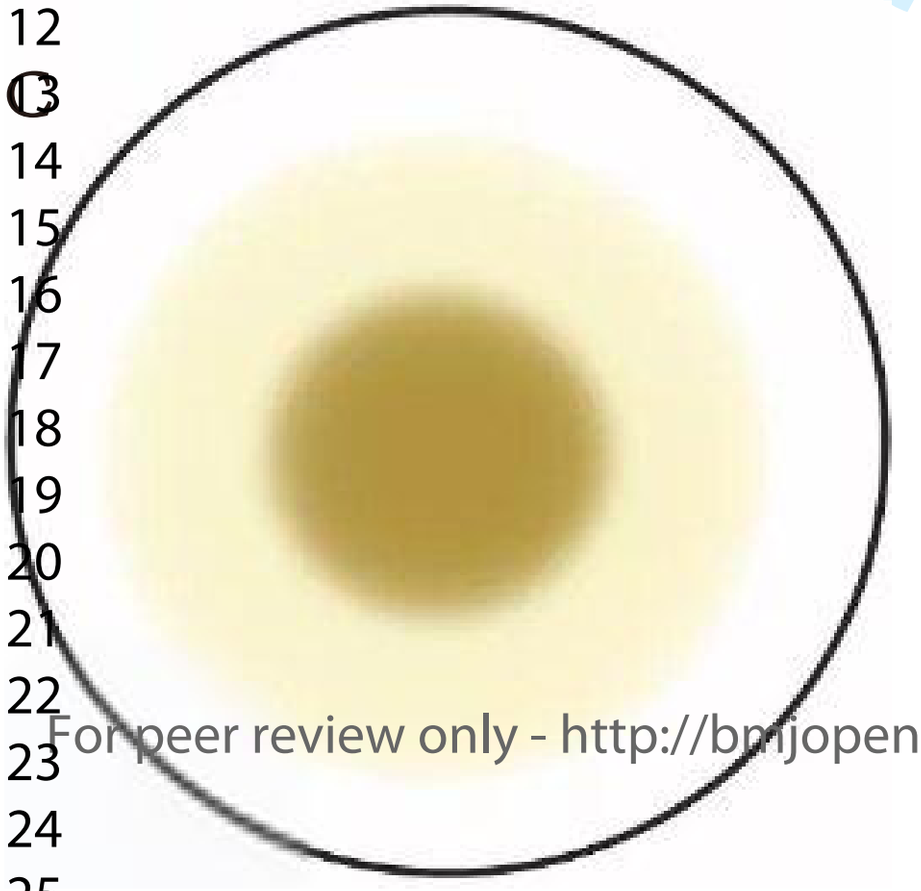

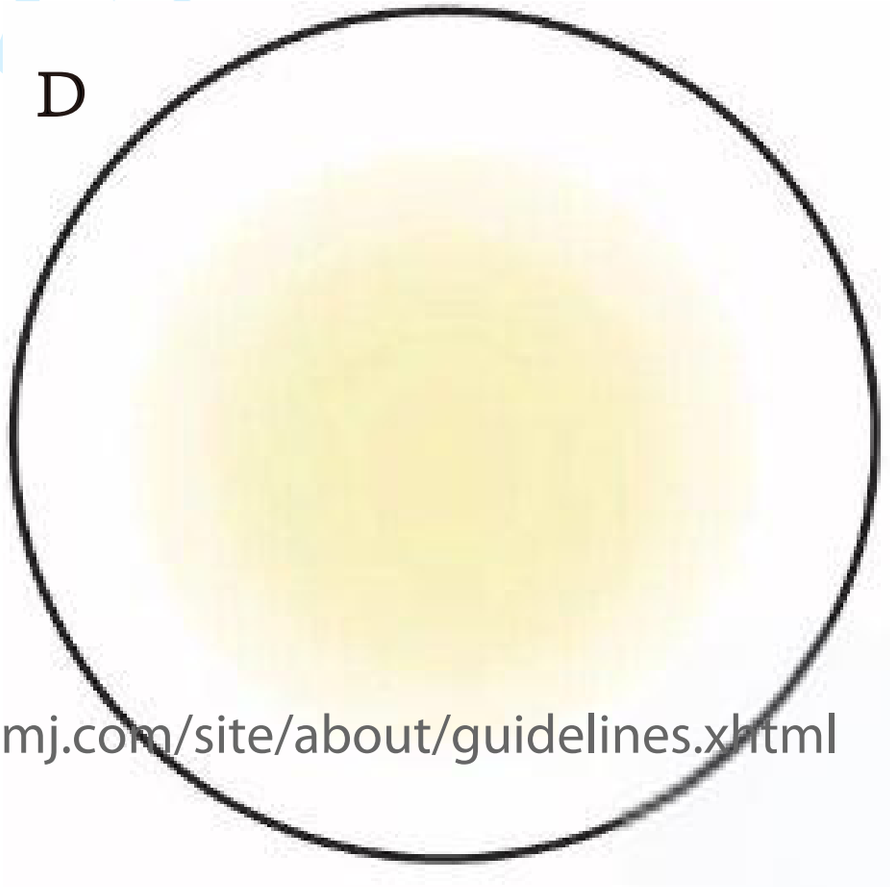

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2025-099687.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2025
Complete List of Authors:	Guo, Chunmei; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Wang, Jing; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Li, Li; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Cui, Jianfang; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Liu, Hong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology Yang, Guodong; Capital Medical University Affiliated Beijing Shijitan Hospital, Department of Gastroenterology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Clinical Trial, Endoscopy < GASTROENTEROLOGY, Clinical Protocols

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BMJ Open: first published as 10.1136/bmjopen-2025-099687 on 6 May 2025. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .
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The effects of the combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single-blind clinical trial from a single center in China

Abstract

Introduction Chronic constipation is an independent risk factor for inadequate bowel preparation. The objective of this study is to evaluate the effectiveness and safety of the combined use of linaclotide and oral sulfate solution (OSS)in chronic constipation patients undergoing colonoscopy.

Methods and analysis This is a prospective, randomized, controlled, single-blind (endoscopist) clinical trial that compares three bowel cleansing regimens for chronic constipation patients undergoing colonoscopy. Regimen A consists of 2d-linaclotide and OSS, Regimen B consists of 3d-linaclotide and OSS, and Regimen C consists of OSS. All patients are required to consume a low-fibre diet for three days and then a clear fluid diet for one day before the colonoscopy. The primary outcome is adequate bowel preparation (defined as a Boston Bowel Preparation Scale (BBPS) score ≥2 for each segment and a total BBPS score ≥6). The secondary outcomes include defecation frequency, caecal intubation rate, adenoma detection rate (ADR), and colonoscope insertion time and withdrawal time. The tertiary outcomes include complications of colonoscopy, adverse events (AEs) and degree of comfort, which is evaluated via a self-designed questionnaire of comfort (QSC).

Strengths and limitations of this study

(1) This will be a prospective, randomized, controlled, single-blind (endoscopist) clinical trial focused on bowel preparation for chronic constipation patients. (2) This trial discontinues laxatives or prokinetics seven days prior to colonoscopy, thereby allowing a more accurate assessment of the true impact of linaclotide on bowel preparation. (3) As a single-centre study, selection bias is inevitable. (4) The administration regimens of linaclotide and OSS, such as the optimal dosage, administration time and duration, are still uncertain and require further investigation.

Ethics and dissemination The research will be conducted according to Good Clinical Practice principles. Ethical approval has been obtained from Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (IIT2024-146-003). Study findings will be published in peer-reviewed journals.

Trial registration number ChiCTR2500096394

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Introduction

Colorectal cancer (CRC) has become a major public health concern worldwide, with the second highest mortality rate among all cancers and the third highest global prevalence[1]. CRC is largely preventable through screening for colorectal adenomas, which are benign growths but may develop into cancer if not removed[2]. Early detection and removal of colorectal adenomas can effectively block the "adenoma-carcinoma sequence" pathway and ultimately prevent the development of CRC[3]. Because of the increased use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), the incidence of CRC has stabilized or started to decrease continuously in the USA and other high-income countries over the past two decades[4]. In China, however, the all-age disability-adjusted life years (DALY) rate of CRC has increased by 69.8% since 1990, which may be attributed to the high misdiagnosis rate of colorectal adenomas[5]. Adequate preprocedural bowel cleansing maximizes adenoma detection rates (ADRs), which is beneficial for CRC prevention[6].

Polyethylene glycol (PEG) is widely used for bowel preparation. However, inadequate cleansing is observed in many chronic constipation patients when 4L of PEG is used. As a common gastrointestinal disorder, constipation affects 12%~17% of the population and is considered one of the risk factors for inadequate bowel cleansing. Improving water intake to 5~6L can improve bowel cleansing comfort but is accompanied by worse tolerability and worse compliance[7]. The main reasons for poor compliance include low tolerance and acceptance caused by a salty taste and large volume of liquid[8 9]. Tolerability should be coordinated with cleansing efficacy to improve patients' compliance and willingness to repeat colonoscopy. To improve bowel cleansing, several studies have been conducted on the combined use of PEG and additional agents, such as ascorbic acid, lactulose, and mosapride[8-10]. However, all of these methods have limitations. For colonoscopy preparation, the oral sulfate solution (OSS) is recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines owing to its noninferiority efficacy, greater safety, and better tolerability[9 11 12]. Thus, we aimed to explore an OSS-based derivative regimen with balanced effectiveness, safety and comfort.

Linaclotide is a selective guanylate cyclase-C (GC-C) receptor agonist that softens dejection and increases the frequency of defecation by accelerating intestinal transit and by stimulating the secretion of intestinal fluid[13]. Moreover, linaclotide can reduce celialgia by inhibiting the activity of pain-sensing nerves[14]; its action occurs mainly in the

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gastrointestinal tract, and the adverse effects are generally mild[14]. Thus, the combined use of linaclotide and OSS is believed to be a potentially effective bowel cleansing regimen. To the best of our knowledge, no research has been conducted to evaluate the effectiveness and safety of linaclotide combined with OSS as a bowel preparation regimen. The administration regimens of linaclotide mixed with OSS, including the optimal dosage of linaclotide, the administration time of linaclotide, and the duration of linaclotide administration, are still in the exploratory phase and require further investigation. We aimed to explore the effectiveness, comfort and safety of a bowel preparation administration regimen of linaclotide mixed with OSS in this prospective, randomized, controlled, single-blind (endoscopist) clinical trial. The results obtained in this study may optimize bowel preparation protocols in clinical practice.

Materials and methods

Study design and patient population

This is a randomized, controlled, single-blind clinical trial comparing three bowel preparation regimens for chronic constipation patients undergoing colonoscopy. The study will be conducted at Beijing Shijitan Hospital, Capital Medical University from March 1st, 2025, to December 31st, 2026.

The inclusion criteria for the study include chronic constipation patients undergoing colonoscopy who meet the following criteria: (1) are aged 18-65 years; (2) meet the Rome IV criteria[15] for chronic constipation which includes the presence of ≥ 2 of the following: ① straining for＞25% of defecations, ② lumpy or hard stools (form 1 or 2 on the Bristol Stool Form Scale) for＞25% of defecations, ③ sensation of incomplete evacuation for＞25% of defecations, ④sensation of anorectal obstruction/blockage for＞25% of defecations, ⑤ manual manoeuvers to facilitate defecation for＞25% of defecations; (3) have the ability to comprehend the trial, sign a written informed consent, including consent for a screening procedure to determine eligibility; (4) have the ability to communicate with the investigators well and follow verbal and written instructions; (5) have the ability to take oral sulfate solution (OSS) correctly according to the procedure; and (6) have the ability to perform follow-up in accordance with the protocol.

The exclusion criteria include patients meeting one or more of the following criteria: (1) having a lack of indications for total colonoscopy; (2) having general contraindications to colonoscopy bowel cleansing, such as acute surgical abdomen, including intestinal perforation, acute diverticulitis and appendicitis, gastrointestinal obstruction, toxic

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megacolon; (3) having one of the following diseases: electrolyte disturbances or severe diseases of the heart, liver or kidney; (4) having a history of any colonic surgery; (5) taking or having taken linalotide or being allergic to linalotide; (6) being pregnant; (7) lactating; or (8) participating in other clinical trials or participating in other clinical trials within 60 days.

Randomization and blinding method

Subjects will be randomized at a 1:1:1 ratio to Regimens A, B or C, via a computer-based random number table. The randomization process will be performed by clinicians. They will prepare study products, provide education on bowel preparation and will be involved in the day-to-day care of patients. They will not be involved in performing the procedures. All endoscopists in this trial and biostatisticians will be unaware of each patient's regimen allocation. Blinding of the endoscopist will be strictly enforced, and they will remain blinded until the main analysis is complete. Due to the volume differences and dose differences among the three regimens, blinding of the patients is impossible. Therefore, investigators will ask the subjects to refrain from talking about bowel cleansing with the endoscopists, either before or during the colonoscopy.

Selection of bowel preparation regimens

Before bowel preparation, each patient will be provided with written instructions on dietary restrictions and bowel cleansing methods. The following strict dietary restrictions will be given to all subjects: (1) follow a low-fibre diet for three days before the colonoscopy, (2) follow a clear fluid diet for one day before the colonoscopy, and (3) fast on the day of the colonoscopy. A low-fibre diet is defined as a diet with a total fibre intake of less than 10g/d. Patients will stop taking laxatives or prokinetics seven days before the colonoscopy.

The study participants will be equally divided into 3 groups via a random number table. In regimen A, the subjects will (1) take 1d-linaclotide at 7AM on the day before the procedure, (2) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L of water on the night before the procedure starting at 7 PM, (3) take 1d-linaclotide at 5AM on the day of the procedure, and (4) drink 500mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy. Previous studies[16 17] revealed that a single dose of linaclotide taken 1 hour before video capsule endoscopy significantly improved bowel preparation quality and visualization, reducing transit time by 20% compared with published standards. Chronic constipation patients would experience their first spontaneous bowel movements within 24 hours, accompanied by a shortened first defection time and an increased number of defecations

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after taking linaclotide. Considering that the OSS is taken the day before and the day of the colonoscopy, regimen A was designed with the combined use of 2d-linaclotide and the OSS[14].

In regimen B, the subjects will (1) take 1d-linaclotide at 7AM two days before the procedure, (2) take 1d-linaclotide at 7AM on the day before the procedure, (3) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L water on the night before the procedure starting at 7 PM, (4) take 1d-linaclotide at 5AM on the day of the procedure, and (5) drink 500 mL of a diluted OSS and 1 L water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy. Regimen B was adapted from Wang[18] and Xu[19], who combined 3 L PEG and 3d-linaclotide and reported that this regimen was satisfactory for chronic constipation patients[18].

In regimen C, the subjects will (1) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L of water on the night before the procedure starting at 7 PM, and (2) they will drink 500 mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7 AM and completing at least 4 hours before the colonoscopy. All patients will receive 5 ml of simethicone solution mixed with the last dose of laxative. Regimen C is the control group, consisting of a traditional 1 L diluted OSS and 2 L water.

As a rescue regimen for inadequate bowel preparation, clinicians will gauge whether the last excreta is adequate before colonoscopy according to standard pictures (Figure 1). For inadequate cleanings, 500 mL of diluted OSS and 1 L of water will be taken. The rescue regimen will be recorded on a case report form (CRF). The schedule of enrolment, interventions and assessments is presented in Table 1.

Table 1 Schedule of enrolment, interventions and assessments

	Study period				
	Enrolment	Allocation	Postallocation		
Content	Screening and baseline assessment	Randomisation and bowel preparation	Endoscopic screening and polypectomy	Follow-up	Close-out
Timepoint	T_0	T_1 1-3 days	T_2 0 day	T_3 0-14days	T_4 14days
Enrolment					
Eligible screen	×				
Informed consent	×				
Allocation		×			
Interventions					
Regimen A		×			
Regimen B		×			

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Regimen C		×			
Endoscopic screening			×		
Assessment					
Baseline data	×				
BBPS score			×		
Safety assessment		×	×	×	×
QSC		×			

BBPS, Boston Bowel Preparation Scale; QSC, questionnaire of comfort

Study procedures

The investigator will perform all the observations, investigations and evaluations according to the descriptions provided. The subjects will be given written instructions including the diet, dose and timing of the experimental drugs, in accordance with randomization. Clinicians will distribute the study drugs to the participants, provide instructions on the administration and face-to-face bowel preparation education to ensure that the participants will take their drugs correctly. All colonoscopies will be performed by designated, professional endoscopists (had performed more than 1000 colonoscopies individually) via the Olympus CV-260 or CV-290 colonoscope (Olympus Medical Systems, Tokyo, Japan). All participating endoscopists will be standardized and trained in the use of the BBPS before they participate in the study, and bowel preparation quality will be evaluated based on the BBPS. Endoscopists cannot use additional adjuvant devices or adjuvants to improve bowel preparation.

Data collection

The following clinical variables will be collected: (1) Demographics of the participants: sex, age, body mass index (BMI), comorbidities, use of calcium channel blockers, smoking or alcohol consumption, family history and laboratory indices (routine blood tests, liver and kidney function, coagulation function). (2) Bowel preparation: subject compliance, ability to understand and follow the instructions for bowel preparation, usage of laxatives, interval between the first OSS and the first defecation, and interval between the last OSS and colonoscopy. (3) Colonoscopy: BBPS score (total score and each segment score), caecal intubation rate, colonoscope insertion time and withdrawal time, and adenoma detection rate. (4) Safety: We will assess adverse events and serious adverse events associated with the agents before, during and after colonoscopy bowel cleansing. (5) Comfort: Results of the comfort questionnaire, including discomfort symptoms (nausea, vomiting, abdominal pain, abdominal distention, bowel incontinence, dizziness, headache, fatigue, and tiredness), sleep

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quality (somnipathy, total sleep duration, frequency of sleep awakenings in the evening before colonoscopy), and willingness to duplicate colonoscopy bowel cleansing.

Study outcomes

The primary outcome will be adequate bowel preparation, defined as each segment's BBPS scores being ≥2 and/or having a total score ≥6 [20 21]. The BBPS is based on three colon segment scores (right-sided colon, transverse colon, and left-sided colon), and each segment score is defined by a four-point scoring system (0–3). The right-sided colon included the caecum and ascending colon, and the transverse colon was defined from the hepatic flexure to the splenic flexure, whereas any more distal colon or rectum was defined as the left-sided colon. Each segment score is between 0 and 3 as follows: 0=an unprepared colon segment with solid stool on the mucosa; 1=portions of the mucosa can be seen, but other areas are covered by staining, residual stool, and/or opaque liquid and thus cannot be seen clearly; 2=minor areas covered by residual staining, small stool fragments, and/or opaque liquid, but the colon segment can be seen well; 3= the entire mucosa can be adequately seen, with no residual staining, small fragments of stool, or opaque liquid. As a superior trial, the BBPS total score and segment scores in regimens A and B should be statistically superior to those in regimen C.

The secondary outcomes include defecation frequency, the interval between the first OSS and the first defecation, the interval between the last OSS and the colonoscopy examination, the caecal intubation rate, the colonoscope insertion time and withdrawal time, and the adenoma detection rate (ADR).

The third outcome will be the degree of comfort, which is evaluated via a self-designed questionnaire of comfort (QSC). The questionnaire of comfort (QSC) was adapted from previous studies[9 22] and is composed of complications and sleep quality during bowel preparation, as well as preprocedure anxiety and willingness to repeat bowel preparation. The complications included abdominalgia, abdominal distension, nausea, vomiting and bowel incontinence during bowel preparation. Sleep quality, including somnipathy, sleep duration, and the number of sleep awakenings during bowel cleansing, was also recorded.

Safety indicators, such as adverse events (AEs) and serious adverse events (SAEs), including abdominal pain, abdominal distension, faecal incontinence, allergic reactions and other adverse drug reactions, will be recorded and evaluated. Moreover, we will record complications of EMR or ESD, such as intraprocedural haemorrhage (any immediate bleeding that requires any form of endoscopic haemostasis or oozing lasting for at least 60

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s), delayed haemorrhage (any bleeding requiring endoscopy reintervention or hospitalisation within 2 weeks), intraprocedural perforation (any perforation requiring endoscopic clip sealing), delayed perforation (any perforation occurring within 2 weeks), and intestinal infection (bellyache, fever and/or increased C-reactive protein requiring antibiotics).

Statistical analysis and sample size

Statistical analysis will be executed by SPSS version 20.0 (IBM Corp, Armonk, NY, United States). Continuous variables are expressed as the mean ± standard deviation (SD) or median (interquartile range, IQR) according to a normal/nonnormal distribution, and will be analysed with independent samples t tests or Wilcoxon's rank-sum tests. Categorical variables are represented as counts (percentages), and will be evaluated by the $\chi 2$ test or Fisher's exact test appropriately. To address the issue of multiple comparisons across the three study arms, we will employ adjustment methods, such as the Bonferroni correction, to ensure the robustness and validity of our statistical inferences. $P<0.05$ will be set as the cut-off for statistically significant.

In the study protocol, the sample size calculation is performed with an alpha of 0.05 and a power of 0.8, assuming a 20% difference in the rate of colonic cleansing and a 10% dropout rate. Over the past year, approximately 500 patients with chronic constipation have undergone bowel preparation using OSS at our centre, resulting in an adequate bowel cleansing rate of approximately 70%. A final inclusion of 65 participants in each group was needed. The efficacy, safety and tolerability of bowel preparation will be compared based on intention-to-treat approaches or per-protocol analysis.

Patient and public involvement

Patients and the public were not involved in the development of the protocol.

Ethics and dissemination

The study has been registered with the Chinese Clinical Trial Registry and permitted by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (IIT2024-146-003), and informed consent will be obtained from all patients prior to enrolment (see online supplemental material 1). The researchers will do their best to protect the personal information provided by patients from being leaked or used without informed consent. Data will be collected through paper forms directly from investigators. Data from the forms will be extracted and input into a database on a password-protected computer. The data will be supervised by an independent data monitoring committee.

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The findings of this study will be published in peer-reviewed journals for widespread dissemination. Individuals who contribute significantly to the research will be granted authorship, including research design, implementation, subject recruitment, data collection, statistical analysis and manuscript writing and revision.

Discussion

The aim of this study is to explore an innovative bowel preparation regimen that combines linaclotide and an OSS, which balances efficacy, safety and comfort in chronic constipation patients undergoing colonoscopy. Bowel cleansing is an essential component of colonoscopy. OSS and PEG are widely used in clinical practice[23], but are not optimal for patient satisfaction or the quality of bowel preparation in patients with chronic constipation. Improving PEG water intake to 5-6 L can improve effectiveness but can lessen comfort and influence compliance with bowel preparation[24]. Discomfort and low compliance caused by a large volume of liquid are critical factors for inadequate bowel preparation[24].

There are several PEG-based derivative regimens, such as those combined with ascorbic acid, lactulose, and mosapride[8-10]. However, some patients have difficulty tolerating PEG and all of PEG-based derivative regimens have limitations. OSS is recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines due to its noninferiority efficacy, greater safety, and better tolerability than PEG[9 11 12]. OSS, a newly developed bowel preparation agent in China, is composed of sodium sulfate and functions as an osmotic laxative; it improves the osmotic pressure derived from sulfate ions and replenishes sodium and potassium ions, thereby mitigating the risk of water-electrolyte imbalances. Phase III clinical trials have indicated that the OSS results in significantly higher BBPS scores than the 3-4 L PEG split-dose regimen does. Additionally, OSS facilitated swift bowel movements and achieved clear, watery stools, with a reduced incidence of nocturnal defecation. Hence, we aimed to explore an innovative OSS-based derivative bowel cleansing scheme that can lead to adequate bowel preparation in chronic constipation patients.

As a selective guanylate cyclase-C (GC-C) receptor agonist, linaclotide has proven to be effective and safe for the treatment of chronic constipation (RR=3.26, 95% CI: 2.45-4.33)

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and irritable bowel syndrome with constipation (RR=2.26, 95% CI: 1.86-2.74), with slight adverse reactions such as diarrhoea[25]. Linaclotide binds to the GC-C receptor, resulting in accelerated gastrointestinal motility, increased fluid in the intestine, and reduced abdominal pain[26]. Based on the pharmacological mechanism mentioned above, we believe that linaclotide may be an effective, comfortable and safe adjuvant for colonoscopy bowel preparation. Few studies[8 14 18] have used linaclotide as an adjuvant to improve the cleansing efficacy, especially in patients at high risk of inadequate bowel preparation[27]. However, the appropriate administration regimen has not been confirmed, and high-grade evidence from clinical trials is also very limited.

To elucidate the administration protocol, we have conducted an exhaustive literature review for this trial design. Considering the absence of prior studies on the combined use of linaclotide and OSS, our regimen is modelled on the combined use of linaclotide and PEG. According to Yang[8] et al., the BBPS total score and individual segment score in the 2LPEG+1d-linaclotide group were greater than those in the 2LPEG group (P<0.001), with a compatible sleeping quality or adverse reaction incidence. Compared with the 4LPEG group, the 2LPEG +1d-linaclotide group showed no significant difference in adequate bowel preparation but had better sleep quality and fewer adverse reactions. Song[14] et al. performed a prospective randomized study and reported that the 3LPEG+1d-linaclotide group was comparable to the 4LPEG group in terms of adequate bowel preparation with a shorter withdrawal time (P<0.05). In a prospective, randomized, observer-blinded, multicentre study[28], 2d-linaclotide+PEG were used for bowel cleansing. This regimen shortened the first defecation time after consuming PEG (P<0.01), which may contribute to adequate preparation with minimal side effects. Moreover, nausea and vomiting were less common in this group, which could be interpreted as a reduction in volume. The use of linaclotide shortened the first defecation time and increased the mean number of defecations before starting PEG[29]. These findings encouraged us to choose a 2d-linaclotide regimen with greater cleansing efficacy, better tolerability and a more pleasant experience during colonoscopy.

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In an RCT[18] conducted in chronic constipation patients, compared with the 4LPEG group, the 4LPEG+1d-linaclotide group and the 3LPEG+3d-linaclotide group were superior in terms of adequate bowel preparation rates, with a lower percentage of mild adverse events (P<0.01). In a prospective, single-centre RCT[19], the combination of 3-L PEG and 3-d linaclotide demonstrated significantly higher rates of adequate and excellent bowel preparation (P<0.05) with a reduced volume of intake. These findings suggest that linaclotide could improve the cleansing efficacy without additional adverse events. These PEG-based derivative regimens still display poor compliance due to the large volume of liquid and unacceptable taste. OSS has shown noninferiority efficacy, greater safety, and better tolerability than does PEG[3 12]. Based on these previous studies and clinical practice, we hypothesize that the additional use of linaclotide may improve the cleansing efficacy without additional OSS intake. Given that chronic constipation patients first experience spontaneous bowel movements within 24 hours after taking linaclotide[29], the OSS is taken the day before and the day of the colonoscopy. We designed 2-d linaclotide (the day before and the day of the colonoscopy) +OSS and 3-d linaclotide (2 days before, the day before, and the day of the colonoscopy) +OSS. This trial includes patients who reflect the real clinical situation, which makes the results more valuable for clinical practice. We expect that this study will provide propositions for chronic constipation patients undergoing colonoscopy bowel preparation.

Acknowledgements We thank all participants for their voluntary participation in this study and thank all researchers for their hard-working in study procedures.

Author's Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were CMG, JW, LL, JFC, HL and GDY. The first draft of the manuscript was written by CMG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. GDY is the guarantor.

Funding This work was supported by Beijing Municipal Administration of Hospitals Incubating Program (PX2021030); The Science and Technology Development Project of China State Railway Group (J2021Z609) and Youth Fund of Beijing Shijitan Hospital, Capital Medical University (2022-q12)

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Competing interests CMG received funding from Beijing Shijitan Hospital, Capital Medical University during the conduct of this study. The study sponsor had no role or influence in the study design, in the collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication. The authors declare no competing interests.

Patient and public involvement Patients and the public were not involved in the development of the protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Researchers with legitimate academic or scientific interests may contact the corresponding author at guoguo10086@163.com to request access to the data. Access will be granted only for non-commercial purposes and is subject to appropriate conditions and institutional approval.

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Figure Legend

Figure 1 Standard pictures for the last excreta before colonoscopy. A turbid liquid with fecal residue; B opaque liquid without residual stool; C slight-staining and clear liquid; D colorless and clear liquid. For patients with inadequate cleanings (A or B), supplement 500mL diluted OSS and 1L water will be taken.

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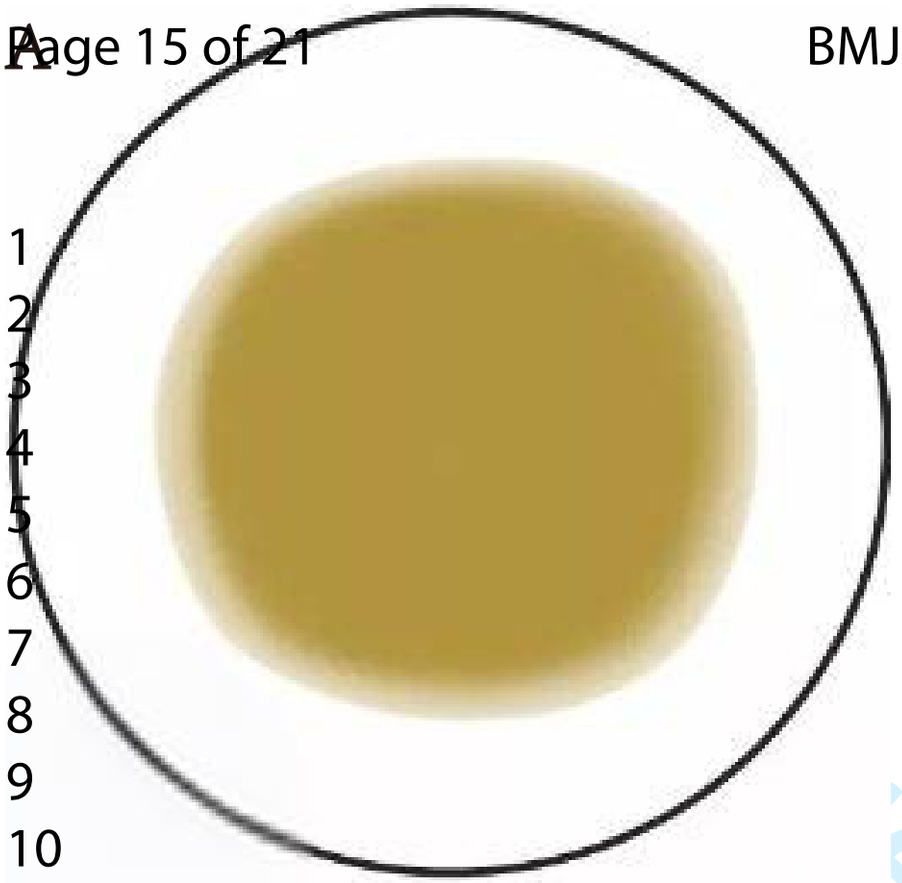

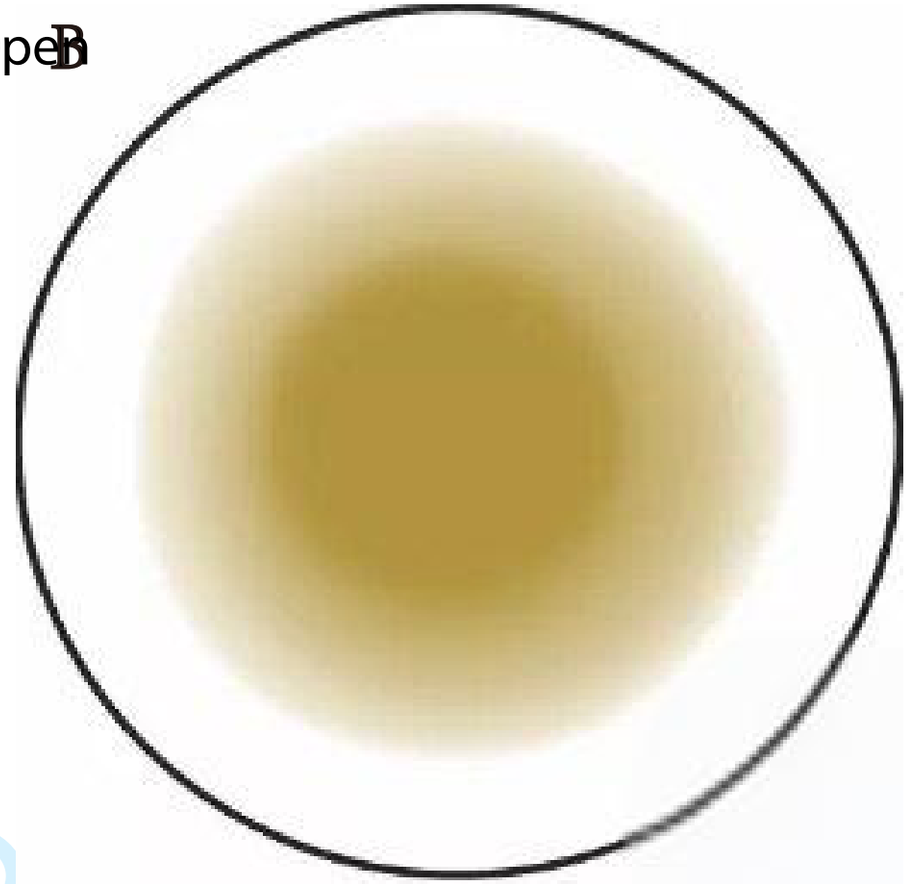

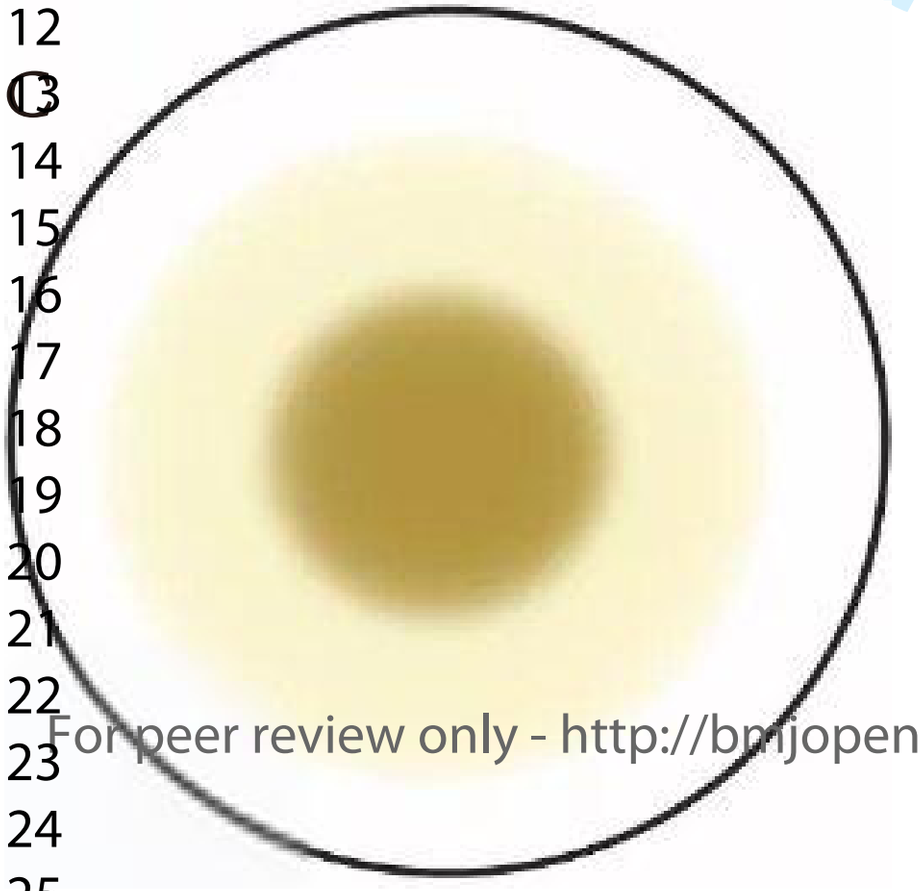

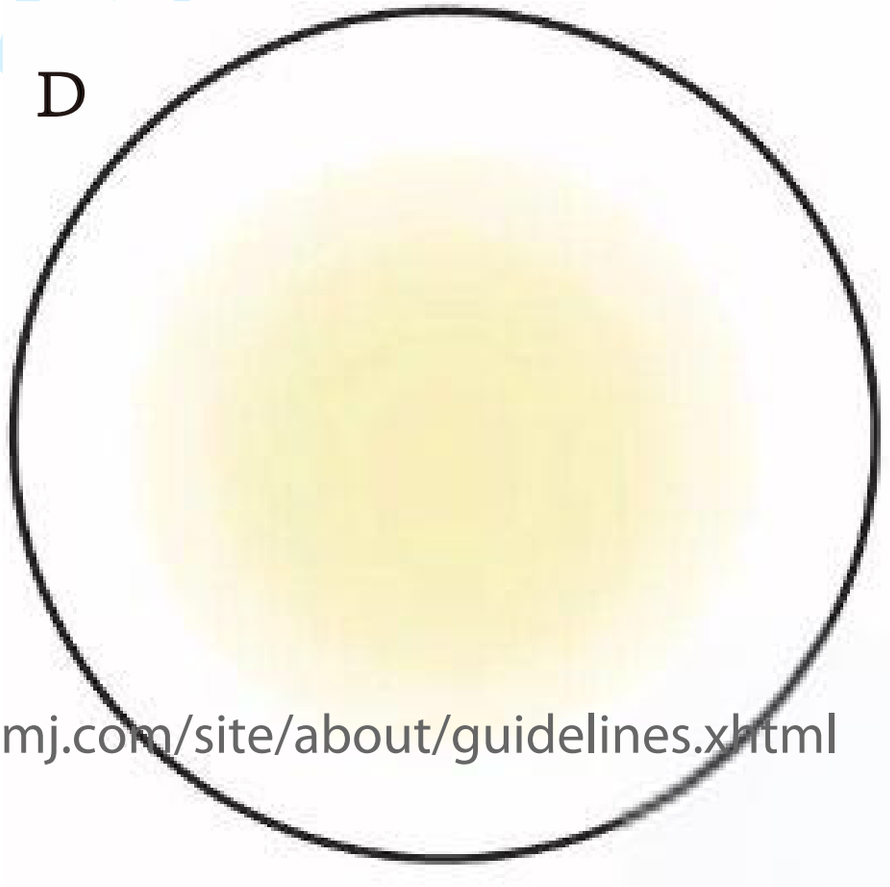

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Informed Consent Form

Beijing Shijitan Hospital, Capital Medical University

Version: 9.0

Version Date: December 19, 2024

Clinical Research Informed Consent Form

Dear Participant/Volunteer,

Greetings!

We invite you to participate in a medical study titled 'The effects of the combined use of linaclotide and oral sulfate solution in bowel preparation for chronic constipation patients undergoing colonoscopy: protocol of a prospective, randomized, controlled, single-blind clinical trial from a single center in China'. The study is led by the Department of Gastroenterology at Beijing Shijitan Hospital, Capital Medical University. Your participation in this study is entirely voluntary. To help you understand this research, this informed consent form will provide you with detailed information about the study's purpose and process and the possible risks and benefits of your participation. If you are interested, please read the following content carefully. The researchers and medical staff will answer any questions you may have. If all your questions are satisfactorily answered and you decide to participate, you may sign this consent form.

1.Study background

Colorectal cancer (CRC) has become a major public health concern worldwide, with the second highest mortality rate among all cancers and the third highest global prevalence. CRC is largely preventable through screening for colorectal adenomas, which are benign growths but may develop into cancer if not removed. Because of the increased use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), the incidence of CRC has stabilized or started to decrease continuously in the USA and other high-income countries over the past two decades. In China, however, the all-age disability-adjusted life years (DALY) rate of CRC has increased by 69.8% since 1990, which may be attributed to the high misdiagnosis rate of colorectal adenomas. Adequate preprocedural bowel cleansing maximizes adenoma detection rates (ADRs), which is beneficial for CRC prevention.

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Polyethylene glycol (PEG) is widely used for bowel preparation. However, inadequate cleansing is observed in many chronic constipation patients when 4L of PEG is used. The main reasons for poor compliance include low tolerance and acceptance caused by a salty taste and large volume of liquid. For colonoscopy preparation, the oral sulfate solution (OSS) is recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines owing to its noninferiority efficacy, greater safety, and better tolerability. Thus, we aimed to explore an OSS-based derivative regimen with balanced effectiveness, safety and comfort.

Linaclotide is a selective guanylate cyclase-C (GC-C) receptor agonist that softens dejection and increases the frequency of defecation by accelerating intestinal transit and by stimulating the secretion of intestinal fluid. Moreover, linaclotide can reduce celialgia by inhibiting the activity of pain-sensing nerves; its action occurs mainly in the gastrointestinal tract, and the adverse effects are generally mild. Thus, the combined use of linaclotide and OSS is believed to be a potentially effective bowel cleansing regimen. We aimed to explore the effectiveness, comfort and safety of a bowel preparation administration regimen of linaclotide mixed with OSS in this prospective, randomized, controlled, single-blind (endoscopist) clinical trial. The results obtained in this study may optimize bowel preparation protocols in clinical practice.

2. Who will be invited to participate in this study?

The inclusion criteria for the study include chronic constipation patients undergoing colonoscopy who meet the following criteria: (1) are aged 18-65 years; (2) meet the Rome IV criteria for chronic constipation which includes the presence of ≥ 2 of the following: ① straining for＞25% of defecations, ② lumpy or hard stools (form 1 or 2 on the Bristol Stool Form Scale) for＞25% of defecations, ③ sensation of incomplete evacuation for＞25% of defecations, ④ sensation of anorectal obstruction/blockage for＞25% of defecations, ⑤ manual manoeuvers to facilitate defecation for＞25% of defecations; (3) have the ability to comprehend the trial, sign a written informed consent, including consent for a screening procedure to determine eligibility; (4) have the ability to communicate with the investigators well and follow verbal and written instructions; (5) have the ability to take OSS correctly according to the procedure; and (6) have the ability to perform follow-up in accordance with the protocol.

The exclusion criteria include patients meeting one or more of the following criteria: (1) having a lack of indications for total colonoscopy; (2) having general contraindications to

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colonoscopy bowel cleansing, such as acute surgical abdomen, including intestinal perforation, acute diverticulitis and appendicitis, gastrointestinal obstruction, toxic megacolon; (3) having one of the following diseases: electrolyte disturbances or severe diseases of the heart, liver or kidney; (4) having a history of any colonic surgery; (5) taking or having taken linalotide or being allergic to linalotide; (6) being pregnant; (7) lactating; or (8) participating in other clinical trials or participating in other clinical trials within 60 days.

3. **How many participants will be involved in this study?**

195 participants will be enrolled in this study,

4. **How is this study conducted?**

This is a prospective, randomized, controlled, single-blind (endoscopist) clinical trial.

The following clinical variables will be collected: (1) Demographics of the participants: sex, age, body mass index (BMI), comorbidities, use of calcium channel blockers, smoking or alcohol consumption, family history and laboratory indices (routine blood tests, liver and kidney function, coagulation function). (2) Bowel preparation: subject compliance, ability to understand and follow the instructions for bowel preparation, usage of laxatives, interval between the first OSS and the first defecation, and interval between the last OSS and colonoscopy. (3) Colonoscopy: BBPS score (total score and each segment score), caecal intubation rate, colonoscope insertion time and withdrawal time, and adenoma detection rate. (4) Safety: We will assess adverse events and serious adverse events associated with the agents before, during and after colonoscopy bowel cleansing. (5) Comfort: Results of the comfort questionnaire, including discomfort symptoms (nausea, vomiting, abdominal pain, abdominal distention, bowel incontinence, dizziness, headache, fatigue, and tiredness), sleep quality (somnipathy, total sleep duration, frequency of sleep awakenings in the evening before colonoscopy), and willingness to duplicate colonoscopy bowel cleansing.

Before bowel preparation, each participant will be provided with written instructions on dietary restrictions and bowel cleansing methods. The following strict dietary restrictions will be given to all subjects: (1) follow a low-fibre diet for three days before the colonoscopy, (2) follow a clear fluid diet for one day before the colonoscopy, and (3) fast on the day of the colonoscopy. A low-fibre diet is defined as a diet with a total fibre intake of less than 10g/d. Patients will stop taking laxatives or prokinetics seven days before the colonoscopy.

The study participants will be equally divided into 3 groups via a random number table. In regimen A, the subjects will (1) take 1d-linaclotide at 7AM on the day before the procedure, (2) ingest a diluted OSS dissolved in approximately 500 ml of water followed by

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1 L of water on the night before the procedure starting at 7 PM, (3) take 1d-linaclotide at 5AM on the day of the procedure, and (4) drink 500mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy.

In regimen B, the subjects will (1) take 1d-linaclotide at 7AM two days before the procedure, (2) take 1d-linaclotide at 7AM on the day before the procedure, (3) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L water on the night before the procedure starting at 7 PM, (4) take 1d-linaclotide at 5AM on the day of the procedure, and (5) drink 500 mL of a diluted OSS and 1 L water on the day of the procedure, starting at 7AM and completing at least 4 hours before the colonoscopy.

In regimen C, the subjects will (1) ingest a diluted OSS dissolved in approximately 500 ml of water followed by 1 L of water on the night before the procedure starting at 7 PM, and (2) they will drink 500 mL of a diluted OSS and 1 L of water on the day of the procedure, starting at 7 AM and completing at least 4 hours before the colonoscopy. All patients will receive 5 ml of simethicone solution mixed with the last dose of laxative.

As a rescue regimen for inadequate bowel preparation, clinicians will gauge whether the last excreta is adequate before colonoscopy according to standard pictures. For inadequate cleanings, 500 mL of diluted OSS and 1 L of water will be taken.

5. Potential risks and discomforts

By participating in this study, you may experience the following discomforts: bloating, belching, abdominal pain, flatulence, nausea, vomiting, intestinal perforation, fecal incontinence, dizziness, headache, orthostatic hypotension, shock, electrolyte disturbances and allergic reactions. This study involves questionnaires that may cause you psychological discomfort. You have the right to refuse to answer any questions that make you feel uneasy.

The research team will closely monitor each participant for any adverse effects during the study. However, not all potential side effects are known, and these may range from mild to severe. Your physician may prescribe medication to alleviate any adverse reactions, and all treatment-related side effects will be addressed with free medical care.

6. Possible benefits

As a participant, you will receive professional follow-up assessments. If any abnormalities are discovered during the research, we will inform you and arrange for more detailed tests or treatment. You may benefit from enhanced bowel preparation quality, which could lead to a more effective colonoscopy.

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7. Costs

If you agree to participate in this study, the OSS and linalotide in this study are free of charge. By Beijing Shijitan Hospital, Capital Medical University.

8. Confidentiality of information

In China, relevant legislation safeguards privacy, data protection, and controlled access. We will rigorously follow these legal standards when gathering and processing your research data to maintain your confidentiality. Your personal information, including your name, ID number, address, and phone number, will only be disclosed to the research team and not shared externally unless legally mandated. Any information will be anonymized with a coding system to shield your identity. This coded data will be securely stored at the Department of Gastroenterology in Beijing Shijitan Hospital, Capital Medical University. Your identity will remain confidential in all research outputs, whether presented at scientific conferences or published in journals. That said, your records may still be subjected to review by relevant authorities, including the ethical review committee at the Beijing Shijitan Hospital, Capital Medical University, as required by law.

9. Withdrawal from the study

Your participation in this study is completely voluntary. You have the right to refuse or withdraw from the study at any time, without needing to provide a reason, and you will not face any discrimination or retaliation. Your rights and medical treatment will remain unchanged. However, you must return any unused research medications. If you experience severe side effects, or if your doctor believes that it is not in your best interest to continue, you may be withdrawn from the study. In such instances, we will inform you immediately, and your study doctor will discuss alternative options with you. After you withdraw, no further data regarding you will be collected. Regardless of the withdrawal reason, we will still attempt to gather effectiveness and safety data for participants who have withdrawn. The reason will be documented in your original medical records.

10. Related inquiries

If you have any questions about this study, please contact Dr. Guo at 13426471832.

If you have any concerns regarding your rights or would like to express dissatisfaction or concerns about the process of participating in this study, please contact the Ethics Committee Office at 010-63926341.

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Participant's Statement and Signature:

I have thoroughly reviewed this informed consent form and had the chance to ask questions. The researchers have given clear explanations and answered my questions. I recognize that participating in this study is completely voluntary, and I can withdraw at any time without needing to explain, with no impact on my medical or legal rights. I permit the sponsor, researchers, and health monitoring authorities to access my medical records, and I am aware that reasonable precautions will be taken to safeguard my privacy. I consent to participate in this study and will receive a signed copy of this consent form.

Participant's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Legal Guardian's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Primary Investigator's Statement and Signature:

I and my research team have thoroughly explained the purpose, process, and possible risks and benefits of this clinical trial to the participant and answered all related questions.

Principal Investigator's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Designated Contact Person's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

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