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A prospective, single-blinded, non-inferiority, randomized controlled study comparing the effectiveness and safety of oral lactulose combined with carbohydrate-containing clear liquids versus 3-L polyethylene glycol electrolyte for colonoscopy bowel preparation

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Abstract

Background Polyethylene glycol electrolyte solution (PEG-ELS) is the standard for bowel preparation but often suffers from poor patient compliance and tolerability due to its high-volume requirement. This prospective, single-blinded, non-inferiority, randomized control trial aims to investigate the efficacy and safety of a lactulose-based regimen as an alternative for bowel preparation.

Methods Two hundred nine patients were randomly allocated to receive either a combination regimen consisting of 133.4 g lactulose in 200 mL, 800 mL carbohydrate-containing clear liquid, 2L additional water, and 5 g simethicone (n = 104) or 3L PEG-ELS with 5 g simethicone (n = 105), both administered in a split-dose format. The primary outcome was the rate of adequate bowel preparation, measured by the Boston bowel preparation score (BBPS). Adequate bowel preparation was defined as a BBPS score of 2 or 3 in all colon segments. Secondary outcomes included the percentage of high-quality bowel preparation (defining as a total BBPS score of 8 or 9), polyp detection rate (defining as the percentage of procedures where at least one polyp was detected), willingness to repeat the bowel preparation, adverse events, and changes in blood glucose and electrolyte levels.

Results The rate of adequate bowel preparation (96.2% vs. 97.1%, p = 0.691), the percentage of high-quality preparation (62.5% vs. 66.7%, p = 0.529), average total BBPS scores (p = 0.607), polyp detection rates (66.3% vs. 77.1%, p = 0.083), and tolerability and acceptability outcomes, including satisfaction (p = 0.729) and willingness to repeat preparation (p = 0.744), were not statistically different between the two arms. Adverse events and changes in blood glucose and electrolytes showed no significant differences (all p > 0.05).

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Conclusion The combination of oral lactulose and carbohydrate-containing clear fluids was non-inferior to 3L PEG-ELS for bowel preparation adequacy and polyp detection, without statistically significant differences in terms of tolerability and safety.

Keywords Colonoscopy, Bowel preparation, Lactulose, Carbohydrate-containing clear liquids, Polyethylene glycol electrolyte

Background

Colorectal cancer (CRC) is among the leading causes of cancer-related mortality worldwide [1], with nearly 1.93 million new cases and approximately 940,000 deaths reported in 2020 [2]. Early detection through effective screening methods such as colonoscopy significantly improves patient outcomes [3]. However, the diagnostic accuracy and safety of colonoscopy depend heavily on adequate bowel preparation [4, 5]. Adequate bowel preparation is considered a critical quality metric and has been shown to significantly reduce CRC mortality rates [6]. A benchmark of achieving ≥ 90% adequate preparation, as assessed by the Boston bowel preparation score (BBPS), is considered essential to ensure high-quality colonoscopy outcomes [7]. An ideal bowel preparation regimen should efficiently cleanse the colon without causing mucosal damage, significant patient discomfort, or electrolyte imbalance while being cost-effective and easy for patients to tolerate [8]. Despite advancements, inadequate bowel preparation remains a challenge, particularly in high-risk populations such as elderly patients and individuals with chronic constipation or obesity (body mass index [BMI] > 28 kg/m^2) [9].

Various bowel cleansing agents are employed for bowel preparation, ranging from osmotic and contact laxatives to prokinetics and defoamers. However, single-agent laxatives, such as sodium picosulfate and magnesium citrate, often fail to achieve optimal bowel cleansing outcomes and ensure patient comfort [10]. More importantly, sodium picosulfate and magnesium citrate, while effective, are associated with significant side effects such as dehydration, electrolyte imbalances, and suboptimal right colon cleansing, particularly in elderly or at-risk patients [10]. Although compound polyethylene glycol electrolytes (PEG-ELS), including formulations such as PEG-3350 and PEG-4000, is generally recommended by relevant guidelines as the preferred method for colonoscopy bowel preparation due to its safety and effectiveness [11, 12], the poor taste and the large intake of liquid (3–4 L) of the standard PEG-ELS significantly compromise patients' tolerance and compliance to the regimen [13–15].

Lactulose, a non-absorbable disaccharide, is well-tolerated and palatable, particularly among pediatric and sensitive populations [16, 17]. Its efficacy as a bowel preparation agent for colonoscopy has been studied, yielding varied findings. Specifically, some studies report comparable preparation quality to PEG with improved tolerability [18, 19], while others [20, 21] show improved bowel cleanliness with compromised palatability and tolerability. Recent efforts have focused on optimizing lactulose-based regimens, with emerging interest in carbohydrate-containing clear liquid, which are available in formulations compromising simple carbohydrates (e.g., Gatorade) or complex carbohydrates (e.g., maltodextrin) [22]. These liquids are increasingly recognized for perioperative benefits, such as enhanced patient comfort and reduced metabolic stress [23]. Building upon these findings, this study presents a prospective, single-blinded, non-inferiority randomized controlled trial to investigate the efficacy and safety of a novel bowel preparation regime combining lactulose with carbohydrate-containing clear liquids versus 3-L PEG-ELS for colonoscopy.

Materials and methods

Study design

This prospective, single-blinded, non-inferiority, randomized controlled trial was conducted at the digestive endoscopy department of Chongqing General Hospital from March to December 2023. The study received ethical approval from the Ethics Committee of Chongqing General Hospital (Ethical Number: KYS2022-020-01). Meanwhile, the study protocol was registered on the Chinese Clinical Trial Registry platform on Jun 20, 2022, with the register number of ChiCTR2200062035, and was also registered on the Chinese National Health Security Information Platform, with the filing number of MR-50-23-006796.

Study population

Inclusion criteria included consecutive adult participants aged 18 years and above, scheduled for a colonoscopy, signed and dated informed consent form, and commitment to comply with the study procedures and to cooperate with the implementation of the study. Exclusion criteria were: allergy to bowel preparation-related medication, American Society of Anesthesiologists (ASA) Physical Status Classification System grade ≥ III, diabetes, gastroparesis, gastric or intestinal stenosis or obstruction, and emergency cases. Diabetic patients were excluded

due to potential risks of hyperglycemia or hypoglycemia associated with the carbohydrate-containing clear liquids used in the study, which could affect their metabolic control during the preparation period. Patients could be withdrawn from the study for inability to adhere to treatment, severe adverse reactions, worsening symptoms of concurrent diseases requiring urgent intervention, voluntary withdrawal, or termination by researchers for medical reasons. Informed consent was obtained from all participants.

Sample size calculation

Sample size calculation was performed using PASS 11.0 software. This study primarily aimed to evaluate the non-inferiority of oral lactulose combined with carbohydrate-containing clear liquid compared to 3L PEG-ELS regarding the rate of adequate bowel preparation. Non-inferiority was defined as the upper limit of the confidence interval for the difference in the rate is less than 15%, a threshold commonly used in bowel preparation studies [24]. Based on an assumed overall success rate of 91.9% for both arms [25], a non-inferiority margin of 10%, and a one-sided significance level of $p < 0.025$, the required sample size was calculated as 67 participants per arm to achieve a statistical power of at least 85%. To account for an anticipated dropout rate of 20%, the final theoretical sample size was adjusted to 94 participants per arm.

Bowel preparation

Based on the results of our previous meta-analysis [26], all patients were instructed to adhere to a low-residue diet starting 24 h before their scheduled colonoscopy. Furthermore, in accordance with the recommendations made by relevant guidelines [11, 12], a split-dose bowel preparation regimen was implemented for all patients.

In the 3 L PEG-ELS arm, patients scheduled for morning colonoscopy (defining as procedures commencing between 08:00 and 12:00 a.m.) were instructed to consume 1 L of PEG-ELS solution (Fortrans®, BEAUFOUR IPSEN Industrie, France; 1 sachet of PEG-ELS powder diluted in 1 L of water) between 20:00 and 21:00 on the evening preceding the colonoscopy, followed by the remaining 2 L of PEG-ELS solution (a total of 2 sachets of PEG-ELS powder were used, with each sachet dissolved in 1 L of water) between 4:30 and 6:30 on the morning of the procedure. For patients scheduled for afternoon colonoscopy (defining as procedures starting at or after 14:00), 1L of PEG-ELS solution was consumed between 21:00 and 22:00 on the evening prior to the colonoscopy, with the remaining 2L PEG-ELS administered between 9:00 and 11:00 on the day before the procedure.

In the combination regimen arm, patients scheduled for morning colonoscopy were instructed to firstly consume a solution comprising 66.7 g of lactulose (Lidong®, 66.7 g/100mL, 100 mL/bottle, Beijing Hanmei Pharmaceutical Co., Ltd., China.) dissolved in 1 L of water, along with 400 mL of carbohydrate-containing clear liquids (Out FAST® Shuneng, 200 mL/bottle, Yichang Renfute Medical Food Co., Ltd., China.) between 20:00 and 21:00 on the evening preceding the colonoscopy. The same procedures were repeated with the same agents between 4:30 and 6:30 on the morning of the colonoscopy. For patients scheduled for afternoon colonoscopy, the bowel preparation solution was firstly administered between 21:00 and 22:00 on the evening before colonoscopy, with the same procedures repeated with the same agents between 9:00 and 11:00 on the morning of the colonoscopy.

Patients were instructed to consume 250 mL of the solution every 15 min. Additionally, all patients were required to take 5g of oral simethicone (Jianheng®, 2.5g/bottle, Jianeng Pharmaceutical Co., Ltd., China.) diluted in 12 mL of water within 30 min they fully consumed bowel preparation solutions.

Randomization and blinding

Randomization was performed using computer-generated random numbers sealed in opaque envelopes. Odd numbers represented the lactulose combined with carbohydrate-containing clear liquid, and even numbers represented the 3L PEG arm. Participants were randomly assigned (1:1) to either arm after eligibility screening, informed, and baseline assessment by a dedicated nurse. To ensure blinding, the examiners and investigators were unaware of the allocation.

Study outcomes

The primary outcome was the rates of adequate bowel preparation, measured by the Boston bowel preparation score (BBPS). Adequate bowel preparation was defined as a BBPS score of 2 or 3 for all colon segments [27]. To ensure consistent scoring, three experienced endoscopists, each with over 10 years of expertise in performing colonoscopies, underwent standardized training in use of the BBPS, including reviewing instructional materials, scoring sample videos, and achieving $\geq 90\%$ agreement with expert scores during a certification.

Secondary outcomes included the percentage of high-quality bowel preparation defined as achieving a total BBPS score of 8 or 9, total BBPS score, segment scores, polyp detection rate defined as the percentage of procedures where at least one polyp was detected, the acceptability and tolerability of the bowel preparation, and safety. The assessment of acceptability and tolerability included three aspects: comfort level, satisfaction

level and willingness to repeat the bowel preparation. These were assessed using a self-designed questionnaire administered to patients on the day of their colonoscopy, before any pre-procedure sedation. Patient responses were recorded on an ordinal scale answer (comfort level: "good", "fair", "poor", or "bad"; satisfaction level: "high", "moderate", or "low"; willingness to repeat prep: "yes" or "no"). The questionnaire items were as follows: (1) "How would you rate your overall comfort during the bowel preparation?", (2) "How satisfied are you with the bowel preparation process overall?", and (3) "Would you choose the same bowel preparation regimen again if another colonoscopy is required in the future?". Safety was assessed based on the incidence of adverse events, vital sign measurements, and blood tests for glucose and electrolyte level changes. Adverse events were systematically documented from the time of the procedure until study completion using a comprehensive approach. This included a combination of patient-reported issues collected through structured questionnaires specifically designed to capture potential side effects (e.g., nausea, vomiting, or other related symptoms), spontaneous patient reports, and clinically observed abnormalities identified by the investigator. Blood samples were collected on the day of inclusion in the study and just before the colonoscopy, and were tested for serum electrolytes, including potassium, calcium, sodium, and chloride.

Statistical analysis

We employed an intention-to-treat (ITT) analysis for data analysis in this study. Categorical data were expressed as frequencies or rates and analyzed using the Chi-square test or Fisher's exact test. Continuous data were presented as (mean ± standard) deviation (SD) and compared using independent sample *t* test. Repeated measures analysis of variance was used for analyzing repeated measurement data. A significance level of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.3.3 and IBM SPSS 26.0 software.

Results

Patient characteristics

A total of 209 patients were enrolled in the trial (Fig. 1), with 104 patients allocated to the lactulose arm and 105 to the 3L PEG-ELS arm. Baseline characteristics, including demographic, physiological, and clinical parameters, were well-balanced between the two arms, with no statistically significant differences observed (Table 1).

Rate of adequate bowel preparation

The rate of adequate bowel preparation was comparable in the both bowel preparation regimens ($\chi^2 = 0.158$, $p = 0.691$), with 96.2% (n = 100) and 97.1% (n = 102) in the lactulose solution and 3L PEG-ELS arm, respectively.

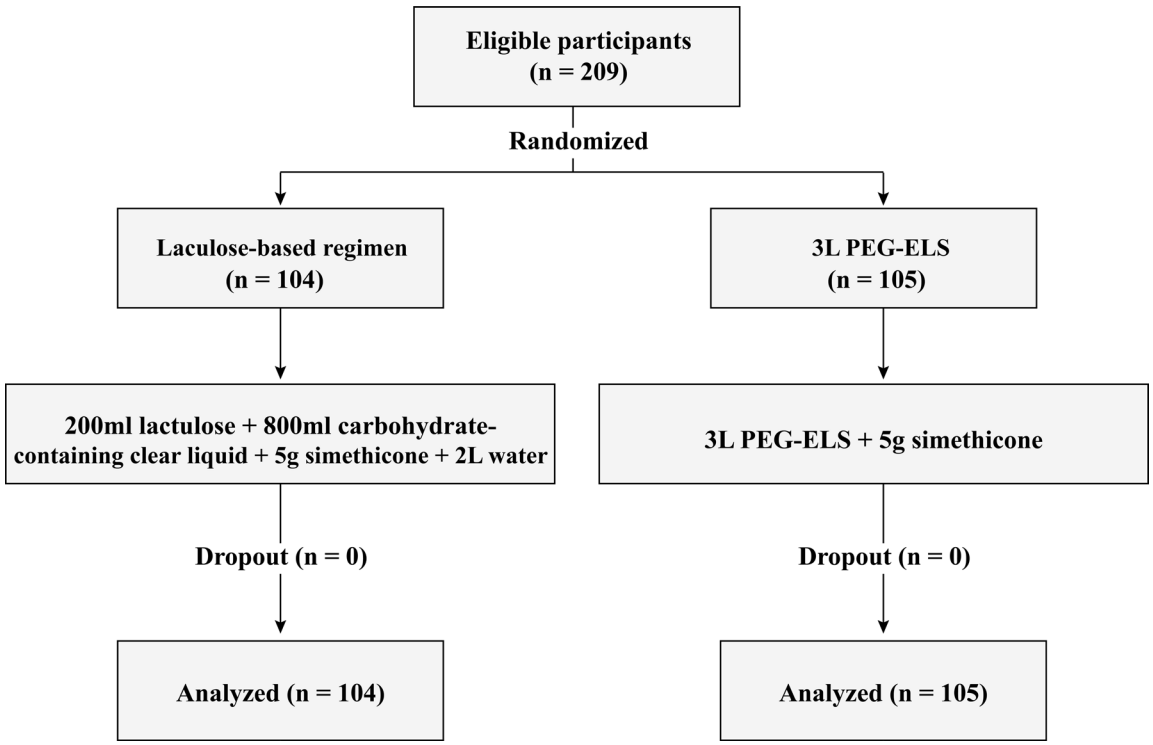

Fig. 1 Study procedure

Table 1 Baseline characteristics of patients between the two groups

Variables	Lactulose arm	3L PEG-ELS arm
Sample size, n	104	105
Age, years	55.22 ± 10.60	55.36 ± 11.59
Gender, n (%)		
Male	44 (42.3)	45 (42.9)
Female	60 (57.7)	60 (57.1)
Height, cm	162.5 ± 8.3	161.7 ± 7.4
Weight, kg	60.6 ± 10.7	60.8 ± 9.8
BMI, kg/m^2 (mean ± SD)	22.8 ± 2.9	23.2 ± 2.7
ASA classification, n (%)		
I	18 (17.3)	20 (19.1)
II	96 (92.6)	85 (80.9)
Colonoscopy indication, n (%)		
Diarrhea	4 (3.8%)	5 (4.8%)
Constipation	2 (1.9%)	1 (1.0%)
Abdominal pain/distention/discomfort	22 (21.2%)	20 (19.0%)
Colorectal cancer screening	31 (29.8%)	29 (27.6%)
Medical checkup	20 (19.2%)	24 (22.8%)
Others	25 (24.1%)	26 (24.8%)
Previous colonoscopy history, n (%)		
Yes	57 (54.8)	53 (50.5)
No	47 (45.2)	52 (49.5)
Heart rate, beats/min	76.33 ± 12.37	72.69 ± 10.38
Systolic blood pressure, mmHg	122.02 ± 15.32	128.00 ± 16.74
Diastolic blood pressure, mmHg	77.19 ± 10.71	78.48 ± 11.84
Oxygen saturation, %	97.54 ± 1.43	97.77 ± 1.71
Respiratory rate, times/min	19.42 ± 0.96	19.19 ± 1.06
Blood glucose, mmol/L	5.91 ± 1.08	6.10 ± 1.49
K^+, mmol/L	4.05 ± 0.24	4.07 ± 0.30
Ca^{2+}, mmol/L	2.22 ± 0.09	2.21 ± 0.09
Na^+, mmol/L	139.68 ± 1.79	140.02 ± 1.78
Cl^-, mmol/L	102.27 ± 1.97	102.64 ± 2.08

BMI body mass index, *ASA* American Society of Anesthesiologists, *SD* standard deviation

The percentage of high-quality preparation were also comparable between the two bowel preparation regimens ($\chi^2 = 0.397$, p = 0.529), with 62.5% (n = 65) in the lactulose arm and 66.7% (n = 70) in the 3L PEG-ELS arm. As shown in Table 2, the average total BBPS scores and segmental BBPS scores for the right, transverse and left colon were also not statistically significant between the two bowel preparation regimens.

Polyp detection rate

Polyps were detected in 69 patients in the lactulose arm and 81 patients in the 3L PEG-ELS arm, with polyp detection rates of 66.3% and 77.1%, respectively; however, the difference in polyp detection rates was not statistically significant ($\chi^2 = 3.006$, p = 0.083).

Tolerability and acceptability

Table 3 presents a detailed comparison of tolerability and acceptability outcomes between the two bowel preparation regimens. There were no statistically significant differences observed across comfort level ratings, satisfaction or willingness to repeat the preparation method. Specifically, a proportion of patients reported "poor" comfort in both the lactulose arm (15.4%, n = 16) and the 3L PEG-ELS arm (6.7%, n = 7). Similarly, high satisfaction levels noted in both arms, with 97.1% in the lactulose arm (n = 101) and 95.2% in the 3L PEG-ELS arm (n = 100). Willingness to repeat the preparation method was not significantly different between the two bowel preparation regimens, with 96.2% of the lactulose arm (n = 100) and 95.2% of the 3L PEG-ELS arm (n = 100).

Adverse events during bowel preparation

The results showed no statistically significant differences in the incidence of adverse events between the lactulose and 3L PEG-ELS arms. Overall, 33.7% (n = 35) of participants in the lactulose arm and 40.0% (n = 42) in the 3L PEG-ELS arm experienced at least one adverse event (p = 0.342). As shown in Table 4, rates of specific adverse events, including nausea/vomiting, abdominal bloating, thirst, abdominal pain, dizziness, headache, and

Table 2 Colon cleansing assessment of efficacy between the two groups using the Boston bowel preparation score

Variables	Lactulose arm (n = 104)	3L PEG-ELS arm (n = 105)	χ^2/t	*p*-value
Adequate bowel preparation, n (%)	100 (96.2%)	102 (97.1%)	0.158	0.691
High-quality preparation, n (%)	65 (62.5%)	70 (66.7%)	0.397	0.529
Total BBPS score, mean ± SD	7.971 ± 1.242	8.057 ± 1.167	0.516	0.607
Right colon, mean ± SD	2.577 ± 0.552	2.619 ± 0.507	− 0.575	0.566
Transverse colon, mean ± SD	2.827 ± 0.548	2.800 ± 0.402	0.405	0.686
Left colon, mean ± SD	2.606 ± 0.491	2.619 ± 0.544	− 0.185	0.852

BBPS bowel preparation quality score

Table 3 Comparison of acceptability and tolerability between the two arms from patient questionnaire

Variables	Lactulose arm (n = 104)	3L PEG-ELS arm (n = 105)	χ^2	*p*-value
Comfort level [n (%)]				
Good	1 (1.00)	0 (0.00)	6.141	0.105
Fair	86 (82.69)	98 (93.33)		
Poor	16 (15.31)	7 (6.67)		
Bad	1 (1.000)	0 (0.00)		
Satisfaction level [n (%)]				
High	101 (97.12)	100 (95.24)	0.120	0.729
Moderate	3 (2.88)	5 (4.76)		
Low	0 (0.00)	0 (0.00)		
Willingness to repeat preparation [n (%)]	100 (96.15)	100 (95.24)	0.106	0.744

Table 4 Incidence of adverse events between the two arms

Adverse events	Lactulose arm (*n* = 104)	3L PEG-ELS arm (*n* = 105)	*p*-value
Any adverse events [*n* (%)]			
No	69 (66.35)	63 (60.00)	0.342
Yes	35 (33.65)	42 (40.00)	
Nausea/vomiting [*n* (%)]			
No	94 (90.38)	91 (86.67)	0.531
Yes	10 (9.62)	14 (13.33)	
Abdominal bloating [*n* (%)]			
No	86 (82.69)	85 (80.95)	0.883
Yes	18 (17.31)	20 (19.05)	
Thirst [*n* (%)]			
No	92 (88.46)	92 (87.62)	1.000
Yes	12 (11.54)	13 (12.38)	
Abdominal pain [*n* (%)]			
No	96 (92.31)	100 (95.24)	0.555
Yes	8 (7.69)	5 (4.76)	
Dizziness/headache [*n* (%)]			
No	102 (98.07)	102 (97.14)	1.000
Yes	2 (1.93)	3 (2.86)	
Palpitations [*n* (%)]			
No	103 (99.04)	105 (100.00)	0.498
Yes	1 (0.96)	0 (0.00)	

Adverse events were systematically documented using a combination of patient-reported issues collected through structured questionnaires specifically designed to capture potential side effects (e.g., nausea, vomiting, or other related symptoms), spontaneous patient reports, and clinically observed abnormalities identified by the investigator

palpitations, were similar between the two bowel preparation regimens.

Blood glucose and electrolytes

As presented in Table 5, no significant changes in blood glucose, potassium, calcium, sodium, or chloride levels were observed between the lactulose and 3L PEG-ELS arms after bowel preparation (all $p > 0.05$).

Discussion

This prospective, single-blinded, non-inferiority, randomized controlled trial showed no statistically significant differences between lactulose combined with carbohydrate-based clear liquid and the 3L PEG-ELS alone in terms of efficacy, safety, and patient tolerability and acceptability. Both bowel regimens achieved high rates of adequate (96.2% vs. 97.1%, $p = 0.691$) and high-quality (62.5% vs. 66.7%, $p = 0.529$) bowel preparation, with comparable and consistently high BBPS scores observed across both arms. Polyp detection rates were also not significantly different between the arms (66.3% vs. 77.1%, $p = 0.083$), and patient satisfaction, as well as willingness to repeat the preparation, remained consistently high in the both arms. The incidence of adverse events and changes in both blood glucose and electrolyte levels were not significantly different, further confirming the safety profiles of the lactulose regimen.

Our study evaluated a novel bowel preparation regimen combining lactulose with carbohydrate-containing clear liquid showing comparable efficacy to the 3L PEG-ELS, with a rate of adequate bowel preparation of 96.2% for the lactulose arm and 97.1% for the 3L PEG-ELS alone arm. The rate of high-quality preparation was also not statistically different, at 62.5% for the lactulose arm and 66.7% for the 3L PEG-ELS alone arm. Additionally, the average total BBPS scores were consistently high and comparable between the two arms, with the lactulose arm achieving a mean score of 7.971 and the 3L PEG-ELS arm achieving a mean score of 8.057. Our findings are consistent with those of Jagdeep et al. [19], who reported similar BBPS scores for lactulose- and PEG-based regimens, with mean scores of 6.25 and 6.35 for the lactulose and PEG arms, respectively. However, the numerically higher BBPS scores reported in our study which may be attributed to our larger sample size. Moreover, a recent meta-analysis conducted by Zhang et al. [28] revealed that combining lactulose with PEG significantly enhanced bowel preparation efficacy compared to PEG alone, suggesting the potential synergistic effects of lactulose in improving bowel cleansing. Although our study did not include an arm evaluating the combination of PEG and lactulose, our results are consistent with this evidence, emphasizing lactulose's potential to improve preparation outcomes, particularly when paired with complementary agents. Future studies are warranted to directly compare

Table 5 Comparison of changes in blood glucose and electrolyte levels before and after bowel preparation between the two arms

Variables	Lactulose arm, $n=104$ (mean ± SD)	3L PEG-ELS arm, $n=105$ (mean ± SD)	*t*	*p*-value
GLU, mmol/L				
Pre-preparation	5.91 ± 1.08	6.10 ± 1.49	− 0.24	0.840
Post-preparation	5.59 ± 1.40	5.55 ± 0.82		
Difference	− 0.32 ± 1.76	− 0.55 ± 1.72		
K^+, mmol/L				
Pre-preparation	4.05 ± 0.24	4.07 ± 0.30	− 0.71	0.578
Post-preparation	3.87 ± 0.25	3.99 ± 0.27		
Difference	− 0.18 ± 0.35	− 0.08 ± 0.41		
Ca^{2+}, mmol/L				
Pre-preparation	2.22 ± 0.09	2.21 ± 0.09	0.07	0.941
Post-preparation	2.16 ± 0.10	2.18 ± 0.09		
Difference	− 0.06 ± 0.13	− 0.03 ± 0.13		
Na^+, mmol/L				
Pre-preparation	139.68 ± 1.79	140.02 ± 1.78	− 1.04	0.456
Post-preparation	138.26 ± 10.01	139.50 ± 12.66		
Difference	− 1.42 ± 10.18	− 0.52 ± 12.79		
Cl^-, mmol/L				
Pre-preparation	102.27 ± 1.97	102.64 ± 2.08	− 0.23	0.150
Post-preparation	101.02 ± 2.17	101.59 ± 2.05		
Difference	− 1.25 ± 0.50	− 1.05 ± 0.55		

GLU the blood glucose, *SD* standard deviation

the performance of PEG-lactulose combination with lactulose combined with carbohydrate-based clear liquid to better understand the relative advantages of these regimens.

Notably, there are some studies [25, 29, 30] revealed higher rates of adequate bowel preparation were observed in the lactulose scheme than PEG scheme. It is noted that 4L PEG was used as comparison in the study performed by Ramos et al. [25], as authors stated, the excessive volume perception undoubtedly hindered patients' tolerability, thereby decreasing the rates of adequate bowel preparation (91.9% vs. 98.2%). While both lactulose and PEG use osmotic mechanisms [31], lactulose is partially metabolized by gut flora, producing short-chain fatty acids and gases, which may affect tolerability and patient preference, unlike the entirely non-absorbable PEG [32]. Two additional studies [29, 30] administered 3L PEG-ELS to patients in the control arms, similar to our approach, where 3L PEG-ELS was also used for comparison. However, both of these studies used a lower volume (2L) of lactulose to patients in the experimental arms. In our study, a 3L volume of lactulose was prescribed, which may have been more challenging for patient tolerability. Notably, a recent network meta-analysis has identified 2L PEG-lactulose as one of the top-performing regimens for bowel cleansing success, with significant improvements over other low-volume regimens [33]. Therefore, this difference in volume of lactulose solution could explain why our study did not detect a significant difference in bowel preparation quality compared to the control bowel regimen.

Effective bowel cleansing is essential for accurate detection of colorectal lesions and reducing the risk of missed lesions, particularly in the right colon, where interval colorectal cancer (CRC) is most commonly observed [34–36]. In our study, the polyp detection rates showed no statistically significant difference between the lactulose combined with carbohydrate-containing clear liquid arm and the 3L PEG-S arm ($p=0.083$). This result is unsurprising, given the absence of significant differences in the rates of adequate and high-quality bowel preparation between the two arms, as reflected in the BBPS scores. Our findings are consistent with previous studies. For example, Zhang et al. [37] reported no significant difference in polyp detection rates between a lactulose-PEG combination arm and a PEG-alone arm in both high-risk and low-risk patients, which also corresponded to similar rates of adequate bowel preparation. However, some studies have reported conflicting results. Ramos et al. [25] observed a higher adenoma detection rate in the lactulose-based regimen arm compared to PEG-based regimen arm. Similarly, Sun et al. [29] found

that lactulose-based regimen achieved a higher adenoma detection rate than PEG-based regimen (50.0% vs. 33.5%). These discrepancies can be explained by the higher rates of adequate bowel preparation achieved with lactulose-based regimens in the studies by Ramos et al. [25] and Sun et al. [29], which likely contributed to improved visibility for higher adenoma detection. Taken together, these results emphasize that the quality of bowel preparation is positively associated with enhanced detection of colonic lesions [38].

Patient tolerability and acceptability are pivotal factors in evaluating bowel preparation regimens. In our study, both bowel preparation regimens showed satisfaction levels exceeding 95%, with no statistically significant differences observed in participants' willingness to repeat the preparation again. Our study also indicated a numerically higher proportion of participants reporting poor comfort in the lactulose arm compared to those in the 3L PEG-ELS arm. These findings are consistent with those reported by Jagdeep et al. [19], who observed that the lactulose regimen exhibited superior tolerability indices, particularly in terms of taste and patient comfort.

Adverse events such as nausea, bloating, and abdominal pain are common concerns during bowel preparation. In our study, the combination of lactulose with carbohydrate-containing clear liquid resulted in a numerically lower incidence of adverse events compared to the 3L PEG-ELS arm. Similar findings were reported by Sun et al. [29], who observed a lower rate of adverse effects with lactulose compared to PEG-S, and by Zhang et al. [28], who reported a reduction in abdominal pain and nausea. Notably, while bloating is commonly associated with lactulose due to its fermentation in the colon, our study did not find significant bloating among patients, as also noted by Zong et al. [39]. This might be attributable to the inclusion of carbohydrate-based clear liquids, which could modulate fermentation rates in the colon. The addition of carbohydrate-based clear fluids, aligned with ERAS principles, further supports the safety and comfort of lactulose regimen [23], supporting its consideration as a viable alternative to PEG-ELS.

Our study has several limitations. First, it was conducted at a single center, potentially limiting the generalizability of the findings. Second, diabetic patients were excluded, restricting the applicability of our findings to this subgroup. Third, although adequately powered for the primary outcome, the sample size may have been underpowered to detect differences in secondary outcomes, such as adverse events and polyp detection rates. Fourth, our study did not assess microbiome changes or follow-up at 4 weeks post-procedure, as these were outside our scope. Given the potential microbiome-modulating effects of lactulose noted in the literature, future studies should incorporate microbiome analyses and longer-term follow-ups to explore the broader implications of lactulose usage. Finally, patients with inflammatory bowel disease (IBD) were not included [40], necessitating future studies to evaluate the safety and efficacy of lactulose regimen in this population [41].

Conclusions

In conclusion, this single-blinded, non-inferiority, randomized controlled trial shows that oral lactulose combined with carbohydrate-containing clear liquid is as effective and safe as the standard 3L PEG-ELS regimen. Both regimens achieved high and comparable rates of adequate bowel preparation, and showed no statistically significant differences in mean total BBPS scores and polyp detection rates, with favorable tolerability and high patient acceptability.

Author contributions

Conceptualization, C.H. and J.B.L.; methodology, C.H. and H.L.L.; software, C.H., Z.X. and J.L.; validation, C.H. and Z.X.; formal analysis, C.H., H.L.L. and Z.X.; investigation, C.H. and H.L.L.; resources, C.H. and H.L.L.; data curation, C.H. and H.L.L.; writing-original draft preparation, C.H.; writing-review and editing, H.L.L, J.L., Z.X., X.T. and J.B.L.; visualization, C.H. and H.L.L.; supervision, X.T. and J.B.L.; project administration, C.H.; funding acquisition, C.H. All authors have read and agreed to the published version of the manuscript. C.H. and H.L.L. have contributed equally to this work as the joint first author.

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Availability of data and materials

The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval of the research protocol by the Ethics Committee of Chongqing General Hospital (Ethical Number: KYS2022-020-01).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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