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Novel regimen for colonoscopy bowel preparation with oral lactulose: a prospective comparative study

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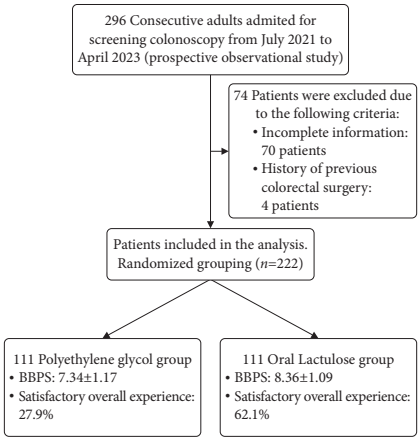
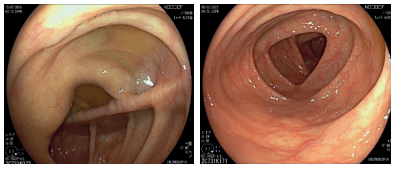


	Polyethylene glycol (*n*=111)	Lactulose (*n*=111)	*p*-value
Location			
Cecum	16 (14.4)	9 (8.1)	0.137
Ascending colon	25 (22.5)	22 (19.8)	0.622
Transverse colon	18 (16.2)	25 (22.5)	0.235
Descending colon	14 (12.6)	13 (11.7)	0.837
Sigmoid colon	8 (7.2)	15 (13.5)	0.123
Rectum	5 (4.5)	7 (6.3)	0.553
Macroscopic type (Paris Classification)			
0–IIa	37 (33.3)	6 (5.4)	<0.001
0–Is	43 (38.7)	78 (70.3)	<0.001
0–Ip	4 (3.6)	7 (6.3)	0.354
Others	2 (1.8)	0 (0)	0.155
Average size of lesion (mm)			
<5	37 (33.3)	52 (46.8)	0.040
5–10	43 (38.7)	36 (32.4)	0.326
>10	6 (5.4)	3 (2.7)	0.307
Colorectal polyp detection rate	86 (77.4)	91 (82.0)	0.404
Colorectal adenoma detection rate	49 (44.1)	66 (59.5)	0.022
Inadequate bowel preparation	9 (8.1)	2 (1.8)	0.030

	Polyethylene glycol (*n*=111)	Lactulose (*n*=111)	*p*-value
Side effects			
Nausea	44 (39.6)	35 (31.5)	0.207
Vomiting	7 (6.3)	17 (15.3)	0.031
Abdominal pain	29 (26.1)	0 (0)	<0.001
Bloating	33 (29.7)	0 (0)	<0.001
Tolerability			
Disagreeable flavor	51 (45.9)	4 (3.6)	<0.001
Excessive volume perception	78 (70.3)	0 (0)	<0.001
Difficulty in taking the preparation	43 (38.7)	16 (14.4)	<0.001
Satisfactory overall experience	31 (27.9)	69 (62.2)	<0.001



Bowel preparation with oral lactulose was superior to PEG as regards to colon cleansing, polyps and adenoma detection rate, tolerance and patient's overall experience.

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Background/Aims: Polyethylene glycol (PEG) is considered the gold standard regimen for bowel preparation; however, due to the necessity of a large volume, patient tolerance is impaired. Therefore, lactulose is a novel alternative for colonoscopy preparation. This study aimed to investigate the efficacy and safety of lactulose-based bowel preparations in comparison with PEG for colonoscopy.
Methods: This is a prospective, non-blinded, comparative study. Outpatients were randomly divided into two groups: group 1 (111 patients), PEG; and group 2 (111 patients), lactulose. The following clinical outcomes were assessed in each group: degree of bowel clearance using the Boston bowel preparation score, colorectal polyp detection rate, adenoma detection rate, tolerability, and side effects.
Results: The rate of inadequate bowel preparation was 8.1% and 1.8% for the PEG and lactulose groups, respectively (p=0.030). The Boston bowel preparation score for the entire colon was 7.34±1.17 and 8.36±1.09 for the PEG and lactulose groups, respectively (p<0.001). The satisfactory overall experience rates were 27.9% and 62.2% for the PEG and lactulose groups, respectively (p<0.001).
Conclusions: The novel bowel preparation with oral lactulose was superior to that with PEG in terms of colon cleansing, adenoma detection rate, tolerance, and patient experience.

Keywords: Adenoma; Colonoscopy; Lactulose; Polyethylene glycols

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide, according to the World Health Organization. Quality indicators in colonoscopy are crucial for optimal colonic evaluation, which is essential to achieve the early detection of colorectal neoplasms and avoid death from CRC. Thus, it is necessary to emphasize the improvement of the quality of colonoscopy screening.[1-3]

Bowel preparation is critical for high-quality colonic examination. Although clinical guidelines recommend polyethylene glycol (PEG) as the gold standard for colonoscopy preparation due to its adequate efficacy and safety profile, the major limitation of PEG as a preparation method is the requirement for high volumes of solution to achieve good colonic cleansing, which impairs patient tolerability, especially in the elderly population.[4-13] Several authors have proposed alternative bowel preparation schemes to overcome these limitations. However, side effects, limited availability, and high costs are important issues.[14-24]

In our center, we have used oral lactulose for bowel preparation for more than 10 years, and recent Asian studies have reported its usefulness for colonoscopic preparation, with adequate colonic cleansing and low rates of side-effects.[25-30] Nevertheless, the use of oral lactulose for bowel preparation remains to be standardized, including the dose (single or divided), volume of solution, timing of ingestion prior to the procedure, or requirement for other laxative drugs. Moreover, scientific evidence supporting the use of oral lactulose for bowel preparation is scarce, particularly from the West, and some manufacturers mention the risk of bowel explosion in the prospectus. This study aimed to assess the efficacy, safety profile, and tolerability of an oral lactulose-based regimen for bowel preparation during colonoscopy in comparison with the traditional PEG regimen.

METHODS

Patients

This was a prospective, observational, non-blinded comparative study (clinical trial registration number: NCT06282367). Data were extracted from a prospectively generated database, including consecutive outpatients who underwent diagnostic colonoscopy at two reference endoscopic centers in Brazil and Peru from July 2021 to April 2023.

Inclusion criteria were age ≥18 years with the following indications: CRC screening, lower gastrointestinal bleeding, iron deficiency anemia, and chronic diarrhea. Patients with previous colorectal surgery, pregnancy, emergency colonoscopy, use of any scheme or substance for bowel preparation other than those studied, incomplete information, or clinical conditions considered unsuitable for sedation or colonoscopy were excluded.

Primary outcomes

- Level of bowel clearance for colonoscopy
- Side effects rate associated with bowel preparation

Secondary outcomes

- Colorectal adenoma detection rate and colorectal polyp detection rate
- Characteristics of colorectal lesions found at colonoscopy
- Tolerability index for the bowel preparation schemes

The average detection rate of colorectal adenomas in the study group was 51.2%. All endoscopists who performed the procedures (JAR, DC, and VNA) have extensive experience in diagnostic and therapeutic endoscopy in high-volume reference centers in Brazil and Peru, and have also received multiple formal theoretical and practical trainings on the use of the Boston bowel preparation score (BBPS). The patients were randomly divided into two groups: group 1, bowel preparation for colonoscopy using PEG, and group 2, bowel preparation for colonoscopy using oral lactulose. The following data were collected for each group: age, sex, chronic constipation, pre-existing comorbidities, degree of bowel cleansing using the BBPS, colorectal polyp detection rate, colorectal adenoma detection rate, size and location of colorectal polyps, endoscopic morphology of colorectal polyps according to the Paris Classification,[1] inadequate bowel preparation rate, tolerability, side effects, excessive volume perception of the preparation by the patient, difficulty in ingestion, and overall satisfactory experience. Figure 1 shows a flowchart detailing the study design and registration process of the participants.

Adequate bowel preparation was considered when all colonic segments had a BBPS of 2 or 3 (according to the BBPS). All patients who presented with a score of 0 or 1 in at least one of the colonic segments were considered to have inadequate bowel preparation. The tolerability index and the presence of side effects associated with bowel preparation schemes were collected using a validated questionnaire before admission for the procedure.

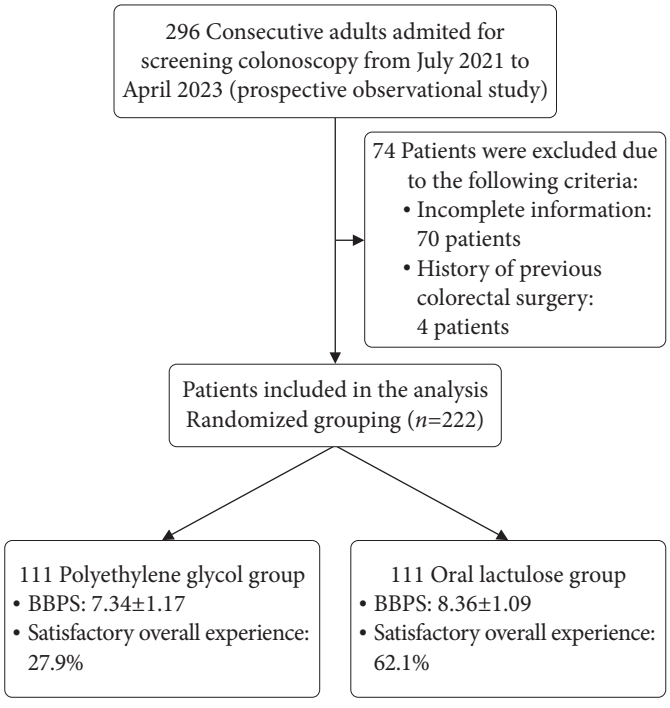

Fig. 1. Outline of the study design. BBPS, Boston bowel preparation score.

Bowel preparation

The bowel preparation scheme using PEG was performed following the recommendations proposed by the latest European[2] and American[3] guidelines, as follows: liquid diet without residues from 24 hours before the procedure associated with 4 units of PEG (110 g) diluted in 4 L of water with 15 mL of simethicone ingested in a split dose. These 4 L of preparation were ingested as follows: the initial 2 L the afternoon before the procedure and the other 2 L 6 hours before the colonoscopy.

The bowel preparation scheme using oral lactulose was performed as follows: liquid diet without residues from 24 hours before the procedure associated with 200 mL of lactulose 3.33 g/5 mL diluted in 600 mL of water with 15 mL of simethicone ingested in a single dose 6 h before the procedure. It is important to highlight that other coadjuvant laxative was administered in neither of the two schemes.

Statistical analysis

Data were tabulated using Microsoft Excel for Windows 2010 (Microsoft Corp.), and statistical analyses were performed using STATA ver. 16 (StataCorp.) and IBM SPSS ver. 25.0 (IBM Corp.). Due to the study design established in our research, we used univariate analysis as the statistical method because our study variables were independent and ideal for an isolated analysis (level of bowel cleansing for colonoscopy and side effects associated with each colonoscopy preparation scheme). Univariate analysis to compare the means of the continuous quantitative variables between groups was performed using Student *t*-test, while the chi-square test was used to compare the proportions of the qualitative variables between both groups. We proceeded to calculate the degree of statistical significance (p) for each of the study variables (considering a statistically significant result with a value of $p<0.05$).

Ethical statements

The authors declare that the study was a prospective observational evaluation of Western experiences using an innovative oral lactulose-based bowel preparation scheme for colonoscopy,

which was performed in accordance with the Declaration of Helsinki. This study was limited to the analysis and description of the statistical calculations of two research arms comparing two methods of colonoscopic preparation, which were performed in two reference endoscopic centers in Brazil and Peru, with the informed consent of all enrolled patients. This study was approved by the Institutional Review Board of the Hospital "José Agurto Tello" in 2023 (approval number: 03/2023).

RESULTS

During the study period, 296 patients underwent a complete colonoscopy. Seventy-four patients were excluded due to the following: 70 patients presented with incomplete information and four patients had a history of colorectal surgery. Of the 222 patients included in the analysis, 72 were male (32.4%) and 150 were female (67.5%). Both groups comprised of 111 patients. The baseline characteristics of the enrolled patients are shown in Table 1.

Bowel cleansing

The inadequate bowel preparation rates were 8.1% and 1.8% in the PEG and lactulose groups, respectively (p=0.030). The total score using the BBPS for determining the level of colonic cleanliness was 7.34±1.17 and 8.36±1.09 for group 1 and group 2, respectively (p<0.001). In addition, a superiority was observed in the level of bowel cleansing with the oral lactulose-based scheme in comparison with the standard scheme (PEG) in all colon segments, with statistically significant results in the right, left, and entire colon. Table 2 shows the comparative bowel cleanliness scores for each colonic segment based on the BBPS.

Table 1. Baseline characteristics of patients

Characteristic	Polyethylene glycol (n=111)	Lactulose (n=111)	p-value
Average age (yr)	58.0 (18–83)	57.9 (20–87)	0.937
Sex			0.626
Male	35 (31.5)	37 (33.3)	
Female	76 (68.5)	74 (66.7)	
Chronic constipation	11 (9.9)	14 (12.6)	0.524
Comorbidities			
Diabetes mellitus	15 (13.5)	13 (11.7)	0.686
High blood pressure	18 (16.2)	24 (21.6)	0.304
Others	4 (3.6)	7 (6.3)	0.354

Values are presented as median (interquartile range) or number (%).

Colorectal adenoma detection rate and characteristics of the lesions found

The colorectal adenoma rates were 44.1% for the PEG group and 59.5% for the lactulose group (p=0.022). In the lactulose group, a higher percentage of polyps smaller than 5 mm was observed compared to the PEG group (p=0.040). Likewise, a significantly higher number of Paris 0-Is polyps was observed in the lactulose group than in the PEG group 1. Table 3 shows the characteristics of colorectal lesions found in each group.

Side effects and tolerability

A higher percentage of side effects, such as nausea, abdominal pain, and bloating, were observed in the PEG group, with the

Table 2. Colon cleansing assessment of efficacy using the Boston bowel preparation score

	Polyethylene glycol (n=111)	Lactulose (n=111)	p-value
Right colon	2.29±0.57	2.76±0.46	<0.001
Transverse colon	2.77±0.43	2.85±0.37	0.069
Left colon	2.27±0.51	2.73±0.45	<0.001
Entire colon	7.34±1.17	8.36±1.09	<0.001

Values are presented as mean±standard deviation.

Table 3. Outcomes of lesions found during colonoscopy

	Polyethylene glycol (n=111)	Lactulose (n=111)	p-value
Location			
Cecum	16 (14.4)	9 (8.1)	0.137
Ascending colon	25 (22.5)	22 (19.8)	0.622
Transverse colon	18 (16.2)	25 (22.5)	0.235
Descending colon	14 (12.6)	13 (11.7)	0.837
Sigmoid colon	8 (7.2)	15 (13.5)	0.123
Rectum	5 (4.5)	7 (6.3)	0.553
Macroscopic type (Paris Classification)			
0–IIa	37 (33.3)	6 (5.4)	<0.001
0–Is	43 (38.7)	78 (70.3)	<0.001
0–Ip	4 (3.6)	7 (6.3)	0.354
Others	2 (1.8)	0 (0)	0.155
Average size of lesion (mm)			
<5	37 (33.3)	52 (46.8)	0.040
5–10	43 (38.7)	36 (32.4)	0.326
>10	6 (5.4)	3 (2.7)	0.307
Colorectal polyp detection rate	86 (77.4)	91 (82.0)	0.404
Colorectal adenoma detection rate	49 (44.1)	66 (59.5)	0.022
Inadequate bowel preparation	9 (8.1)	2 (1.8)	0.030

Values are presented as number (%).

last two side effects having statistically significant results. There were no severe adverse events or mortalities associated with bowel preparation schemes in either group.

The overall satisfaction rate was 27.9% (31/111) in the PEG group and 62.2% (69/111) in the lactulose group (p<0.001). Similarly, disagreeable flavor, excessive volume perception, and difficulty in preparation were significantly higher in the PEG group 1. Excessive volume perception hindering tolerability was reported in 70.3% (78/111) and 0% (0/111) of patients in the PEG and lactulose groups, respectively (p<0.001). The perception of unpleasant taste for each group was 45.9% (PEG group) and 3.6% (lactulose group) (p<0.001). Table 4 shows the comparative tolerability and frequency of adverse effects in each group.

DISCUSSION

This study adds further scientific evidence in favor of the use of low-volume solutions for bowel cleansing during colonoscopy and presents a new alternative based on oral lactulose with an efficacy-safety profile and a tolerability index superior to those of traditional regimens, such as PEG-based bowel preparation. The strength of our research is that it proposes an innovative colonoscopic preparation strategy that is widely available and accessible to the majority of the general population. To our knowledge, this is the first study to show this experience in a Latin American population.

Bowel cleansing is a crucial component of colonoscopy quality and is directly associated with missed lesion rate during the procedure, especially in the right colon (location with the highest incidence of interval CRC).[5-12] Froehlich et al.[13] prospectively enrolled 5,832 patients from 11 countries to evaluate the quality of colonoscopic cleaning, demonstrating that intermediate and high levels of bowel cleansing for colonoscopy allow for a complete evaluation of the entire colon and, consequently, a statistically significant reduction in the rate of missed colorectal polyps. These data reaffirm the positive clinical impact of adequate colonoscopy cleaning in decreasing the rate of missed polyps. Hassan et al.[2] recently proposed general recommendations for adequate bowel preparation before colonoscopy, recommending PEG in a split-dose scheme associated with simethicone as the substance of choice due to its high efficacy profile shown in different studies, either based on high-or low-volume regimens. Our study used the PEG-based regimen as the gold standard for comparison with the newly proposed regimen of colonoscopic preparations based on oral lactulose.

The main limitation of the traditional PEG-based colonoscopic preparation scheme is the need for a high volume of solution to achieve optimal colonic cleansing, which is poorly tolerated by most patients, particularly the elderly. In recent years, several studies have demonstrated the benefits of colonoscopic preparations with low-volume regimens (≤2 L) compared to those with high volumes (>2 L).[14-19] Spadaccini et al.[20] elaborated a meta-analysis of 17 randomized controlled trials (7,528 patients), in which they did not show statistically significant differences in relation to the effectiveness of low- and high-volume colonoscopy preparation schemes. However, they did demonstrate statistically significant results in favor of low-volume schemes with respect to the likelihood of completing the preparation and the tolerability rates. Similarly, recent studies have shown optimal efficacy-tolerability profiles using very low volume colonoscopic preparation schemes (≤1 L).[21-23] Maida et al.[24] prospectively included 1,289 patients divided into three groups (4 L-PEG, 2 L-PEG, and 1 L-PEG), demonstrating an optimal level of bowel cleansing in favor of very low-volume schemes with statistically significant results, even in the most proximal colonic segments. Our study reinforces these observations but using an innovative colonoscopic preparation scheme based on only 200 mL of oral lactulose diluted in 600 mL of water, showing an efficacy-tolerability profile superior to that of patients who received the traditional PEG-based scheme.

Multiple bowel preparation methods are available for colonoscopy. Nevertheless, some of these regimens have important limitations such as tolerability, cost, availability, and accessibility. Recently, a new bowel cleansing scheme based on oral

Table 4. Overall comparative outcomes of side effects and tolerability

	Polyethylene glycol (n=111)	Lactulose (n=111)	p-value
Side effects			
Nausea	44 (39.6)	35 (31.5)	0.207
Vomiting	7 (6.3)	17 (15.3)	0.031
Abdominal pain	29 (26.1)	0 (0)	<0.001
Bloating	33 (29.7)	0 (0)	<0.001
Tolerability			
Disagreeable flavor	51 (45.9)	4 (3.6)	<0.001
Excessive volume perception	78 (70.3)	0 (0)	<0.001
Difficulty in taking the preparation	43 (38.7)	16 (14.4)	<0.001
Satisfactory overall experience	31 (27.9)	69 (62.2)	<0.001

Values are presented as number (%).

lactulose was developed with a mechanism of action similar to that of PEG, but with a very low-volume regimen. There is little scientific evidence showing experience with this method of bowel preparation.[25-27] One of the few head-to-head studies comparing the conventional scheme with PEG and oral lactulose was conducted by Wenqi et al.,[28] and this study prospectively included 400 patients who were randomly divided into two groups of bowel preparation prior to colonoscopy: lactulose group (2 L lactulose) with 200 patients and PEG group (3 L-PEG) with 200 patients. Significantly better rates of bowel cleansing and colorectal adenoma detection were observed in the lactulose group, and a lower rate of side effects in the lactulose group than in the PEG group was noted ($p<0.001$). Finally, the study showed superior tolerability indices in favor of the lactulose scheme compared to the standard scheme ($p<0.001$). Our research group, with a methodology similar to that of the aforementioned study but using a very low-volume oral lactulose-based scheme (200 mL), reaffirms the superiority of colonoscopic preparation with oral lactulose over the conventional PEG scheme. Jagdeep et al.[29] prospectively analyzed 40 patients with lower gastrointestinal bleeding undergoing colonoscopy, who were divided into two groups, lactulose and PEG, demonstrating better pleasant taste rates in colonoscopy preparations with the lactulose scheme than with the PEG scheme. They also observed similar levels of bowel cleansing in both groups, with no statistically significant differences. Our results showed, in a larger cohort of patients, a better BBPS and a lower rate of inadequate bowel preparation in the lactulose group, with statistically significant differences in a Latin American population. Li et al.[30] prospectively included 176 patients divided into two groups, lactulose (88 patients) and PEG (88 patients), who underwent colonoscopy to evaluate the efficacy-safety profile of both methods, each consisting of 2 L of solution, and observed higher detection rates of colorectal polyps in the lactulose group than in the PEG group ($p<0.05$); they also showed a significantly lower rate of nausea in the lactulose group than in the traditional scheme. Our study showed similar results, but with a colonoscopic preparation scheme based on a single dose and a smaller volume of oral lactulose (800 mL in total). An important aspect to highlight is the high rate of side effects associated with the use of oral lactulose, bloating being one of the most frequent; however, in our study, no cases of bloating were observed, suggesting that by combining this amount of lactulose (200 mL) in the described dilution volume (600 mL) with simethicone, a synergism is generated that antagonizes its potential flatulent effect.

Our study had some limitations. It reports the experience of only two endoscopy centers; therefore, the data presented in this manuscript may not be representative of other endoscopy units and cannot be generalized. In addition, the lack of blinding in the applied scientific methodology could have biased the endoscopists' qualifications regarding bowel cleanliness. Therefore, future multicenter studies should be conducted to consolidate the information presented in our study. It is also important that prospective and blinded studies be developed with an adequate blinding system through the assignment of random numbers by a staff member who is not part of the research group, using equal containers for all patients in each group. Another limitation of our study was the lack of registered information related to body mass index that could potentially influence the bowel preparation results. Although the number of cases included in our study can be considered relatively small, to the best of our knowledge, this is the largest cohort of patients undergoing prospective randomization between PEG and oral lactulose for colonoscopy preparation, establishing itself as the largest experience with this method of bowel preparation in the West.

In conclusion, bowel cleansing for colonoscopy using an oral lactulose scheme is an excellent alternative to the traditional PEG regimens. The oral lactulose-based regimen is attractive to the general population because of its low cost, availability, high levels of colonic cleansing, colorectal adenoma detection rate, tolerability indices, and low rates of side effects. Nevertheless, studies with larger patient cohorts are required to confirm these results.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: all authors; Data curation: all authors; Formal analysis: all authors; Investigation: all authors; Methodology: all authors; Project administration: all authors; Resources: all authors; Software: all authors; Supervision: all authors; Validation: all authors; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors.

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