International Journal of Gastroenterology
2020; 4(2): 54-62
http://www.sciencepublishinggroup.com/j/ijg
doi: 10.11648/j.ijg.20200402.16
ISSN: 2640-1681 (Print); ISSN: 2640-169X (Online)

A Randomized Clinical Trial Evaluating Mannitol, Lactitol, and Polyethylene Glycol Macrogol as Oral Solutions for Colonoscopy Preparation

Lourianne Nascimento Cavalcante[1, 2, *], Adriana Ribas[1], Alexandre Pithon Lins[1], Luciana Rodrigues Leal da Silva[1], Flora Maria Lorenzo Fortes[1], Valdeck Sodre Bispo Jr[1], Marcus Vinicius Matos de Almeida[1], Maira Cintra de Oliveira[1], Camila Silveira[1], Marcos Clarencio Batista[1], Igelmar Barreto Paes[1, 2]

[1]Hospital Geral Roberto Santos, Digestive Endoscopy and Gastroenterology Services, Salvador, Bahia, Brazil

[2]Medicine School, Federal University of Bahia, Salvador, Bahia, Brazil

Email address:

lourianne@gmail.com (L. N. Cavalcante)

[*]Corresponding author

To cite this article:

Lourianne Nascimento Cavalcante, Adriana Ribas, Alexandre Pithon Lins, Luciana Rodrigues Leal da Silva, Flora Maria Lorenzo Fortes, Valdeck Sodre Bispo Jr, Marcus Vinicius Matos de Almeida, Maira Cintra de Oliveira, Camila Silveira, Marcos Clarencio Batista, Igelmar Barreto Paes. A Randomized Clinical Trial Evaluating Mannitol, Lactitol, and Polyethylene Glycol Macrogol as Oral Solutions for Colonoscopy Preparation. *International Journal of Gastroenterology*. Vol. 4, No. 2, 2020, pp. 54-62. doi: 10.11648/j.ijg.20200402.16

Received: August 11, 2020; **Accepted**: August 26, 2020; **Published**: September 23, 2020

Abstract: Colonoscopy is an important tool for diagnosing and treating bowel injuries and reducing colorectal cancer incidence. Adequate bowel preparation is necessary to ensure the effectiveness of the procedure for detecting injuries. In this trial the aim was to compare effectiveness of lactitol, mannitol, and polyethylene glycol (PEG) oral solutions for bowel cleansing prior to colonoscopy. This is a randomized, blinded clinical trial. The primary endpoint was to evaluate the adequacy of colon cleansing according to the Boston Bowel Preparation Scale (BBPS). A total of 294 patients were randomized into three groups. The overall adequacy of bowel cleansing was achieved in 98.8% in the mannitol, followed by 93.5% in the lactitol and 92.3% in the PEG group. When comparing lactitol and mannitol, the efficacy to bowel preparation was greater in the mannitol group, but without statistical significance (P=0.164). The adequacy to bowel preparation was slightly better in the mannitol group than PEG (98.8% vs. 92.2%, respectively), but with P-value of 0.073. In adjusted analysis, the results were similar. The frequency of hypernatremia after bowel preparation was 25.3% in the mannitol group, followed by 7.3% and 5.2% in the PEG and lactitol, respectively. Considering tolerance for bowel preparation solution there was no difference between the mannitol and lactitol groups (P=0.07); but lactitol was better tolerated when compared to PEG (P=0.001). In conclusion, mannitol, lactitol and PEG are effective as intestinal cleansing solutions before colonoscopy, but adverse events, taste and tolerability must be considered before choosing.

Keywords: Intestinal Preparation, Bowel Cleansing, Colonoscopy, Lactitol, Mannitol, Polyethylene Glycol

1. Introduction

Colonoscopy is a minimally invasive procedure that is widely used for the diagnosis and treatment of colon disease. It is an important public health tool that reduces colon cancer rates worldwide [1–10]. However, unlike other tests, colonoscopy depends on effective bowel preparation [4, 11].

Inadequate bowel cleansing is responsible for almost 20% of colonoscopy failures, and it can also lead to suboptimal efficiency of the procedure, underdiagnosis, and reduced therapeutic potential [4, 12, 13]. Bowel preparation is inversely associated with lesion screening results, leading to error or delay in diagnosis, prolonged cecal intubation time and withdrawal time, decreased success rates for cecal intubation, and a need for further testing. Ideally, the colon cleansing agent should be effective, safe and agile, not cause damage to the intestinal mucosa, lead to low rates of electrolyte changes, and be largely

accepted by doctors and patients [4, 12, 13]. Osmotic laxatives are the most frequent choice for bowel cleansing.

Mannitol is a polyalcohol obtained by hydrogenating fructose from sucrose. It is a commonly used osmotic laxative associated with successful colonic cleansing compared to other solutions, although it is related to adverse events in more than 10% of cases (nausea, vomiting, headache, dehydration, and hypovolemia) [14–16]. Polyethylene glycol (polyethylene glycol [PEG]) has a molecular weight greater than 3,000 kDa and functions as a non-absorbable osmotic agent, retaining water molecules through hydrogen bonds; it is considered a good option for bowel preparation [14, 15, 17]. Other solutions composed of sodium picosulfate and sodium phosphate have also been used for bowel preparation before colonoscopy, with diverse results related to efficacy and patient tolerability [18].

Lactitol (galactose and sorbitol) is a synthetic nonabsorbable disaccharide, commonly used as an osmotic laxative to treat constipation and hepatic encephalopathy; however, it is also identified as a sweetener due to its characteristics [19–21]. The use of lactitol for bowel cleansing may be a safe, effective, and possibly more palatable option for patients and may broaden the range of solutions currently available. However, there are no clinical trials regarding the applicability of lactitol for this purpose.

The aim of this randomized clinical trial was to compare the efficacy of oral solutions of lactitol, polyethylene glycol, and mannitol for colon cleansing prior to colonoscopy.

2. Patients and Methods

This was a prospective, randomized, double-blind clinical trial (Clinical Study Record No. RBR-5psg4w). The study was approved by the Research Ethics Committee of Hospital Geral Roberto Santos (Salvador, Brazil), and was conducted in accordance with the Declaration of Helsinki. All enrolled subjects provided written informed consent. The subjects were enrolled between March 2018 and May 2019.

The primary outcome was to compare the adequacy of oral solutions for colon cleansing before colonoscopy. Adequacy was assessed with the Boston Bowel Preparation Scale (BBPS). Secondary outcomes included other preparation quality criteria, such as polyp detection and ileal intubation rate; safety was evaluated according to the frequency of serious adverse events.

2.1. Eligibility Criteria

Patients older than 18-years-old referred for endoscopy service with an indication for colonoscopy were included. Exclusion criteria were: previously diagnosed heart attack; decompensated kidney, heart or liver disease; bowel occlusion; previous colectomy; allergy or contraindication to any component of the study medications; pregnancy or active breastfeeding; any severe medical condition that made participation inappropriate due to increased risk or lack of benefit of screening; significant laboratory abnormality; international normalized ratio > 2.5; platelets < 40.000 cells/mm^3.

2.2. Study Procedures

Subjects underwent a screening visit to assess eligibility. Demographic information, medical and surgical records were obtained; laboratory tests dated up to 4 wk at screening visits were also evaluated. Patients who met the eligibility criteria were electronically randomized into three groups (Table 1). Patients, nursing and endoscopy staff were blind to the type of preparation administered. Only a non-blind researcher prepared solutions. Each group received a total of 700 mL cleansing solution in citrus flavor, composed of lactitol monohydrate (66.7 g/100 mL), mannitol 20% (200 mg/mL), or polyethylene glycol macrogol (each sachet contained 13.125 g polyethylene glycol, sodium bicarbonate 0.1775 g, sodium 0.3507 g, potassium chloride 0.0466 g, excipients qsp.). On day 1, all patients were instructed to take a liquid diet from 12:00 pm and to take bisacodyl 10 mg per oral at 5:00 pm. On day 2, a bowel-cleansing solution was taken, and all patients received 5% 1000 mL intravenous glucose solution; colonoscopy was performed after at least 4h of fasting. Blood samples were collected (serum sodium, potassium, urea, creatinine) at the screening visit and just prior to colonoscopy (Table 1).

An expert specialist team used high-definition equipment to perform the colonoscopies. Sedation was performed by anesthetists according to a local protocol. The quality of bowel cleansing was assessed by endoscopists with previous proficiency in BBPS application [6]. According to the BBPS, the right colon (cecum and ascending segments), transverse (hepatic and splenic flexion), and left colon (descending colon, sigmoid and rectal) were assessed separately. They assigned a score from 0 to 3 for each colon segment, with the lowest score 0 (inadequate cleansing) and the greatest 9 (very appropriate cleansing). At least 2 points in each colon segment (right, transverse, and left colon) were necessary to be considered adequate preparation. At least two images were captured from each colonic segment to document the quality of the cleansing. The ileum intubation and polyp detection rates were also computed, considering the number of ileum intubation and detected polyps ($n \geq 1$) divided by the number of colonoscopies performed.

Table 1. *Study procedures according to types of solution for bowel preparation before colonoscopy.*

Day 0†	Screening visit
Day 1†	Liquid diet after midday plus Bisacodyl 10 mg at 5:00 pm
Day 2‡	Group A: Lactitol oral solution 400 mL plus citrus juice 300 mL Group B: Mannitol 20% oral solution 500 mL plus citrus juice 200 mL Group C: 20 sachets of polyethylene glycol macrogol (PEG) in citrus flavor diluted in 700 mL water

Notes: † Day 0 and day 1, the procedures were the same for all groups; ‡Glucose solution 5% intravenous was used for all patients and colonoscopy was performed after 4 h fasting; blood samples were collected to perform laboratory tests before and after oral solution intake.

It was computed as a failure if colonoscopy was not performed or discontinued due to technical reasons related to inadequate bowel cleansing. Blood pressure, heart rate, and oxygen saturation were systematically monitored during the procedure.

2.3. Safety

Adverse events were recorded and classified as serious or non-serious. Non-serious adverse events were classified as mild, moderate, or severe. Serious adverse events were any unfavorable medical occurrence that resulted in death, threat to or risk of life, hospitalization, persistent or significant disability, significant medical occurrence, and congenital anomaly. Adverse event causality was assessed according to validated scale [22]. Palatability was assessed using a 7-point scale and satisfaction with bowel preparation was assessed after oral solution intake and before the colonoscopy procedure, using a 3-point Likert scale [23]. Tolerance to bowel preparation was assessed before colonoscopy, using a visual analogue scale questionnaire with point range from 1 to 5 [11, 24].

2.4. Statistical analysis

Sample size calculation was performed and revealed that 90 subjects would be required in each group to detect a two-sided difference in treatment success, with error alpha=0.05, power=80%, and an equal size (1:1:1) for each group. Descriptive statistics included percentages and frequencies for categorical variables, means and standard deviations for continuous variables. The adequacy of intestinal cleaning measured by BBPS was the dependent variable. The solutions of lactilol, polyethylene glycol and mannitol (reference solution) were the main independent variables (intervention) and the variables sex, age (categorized in two intervals: <60 and ≥60), presence of comorbidity were the covariates of the model of Poisson regression used in the statistical analysis, in order to directly obtain the crude model adjusted association measures, given the possibility of confounding potentials in the association between intervention and outcome. The crude model was performed containing only the intervention variable and the adjusted model with all independent variables considering the significance level less than 0.05 of each variable in the adjusted model as a criterion for its permanence in the final model. In addition, quantification of confounding bias was adopted as one more criterion, assuming arbitrarily a minimum difference of 10% between the relative risks of the crude to the adjusted model. The goodness of fit of the models was assessed using the Akaike Information Criterion and residue analysis [25]. For the assessment of the assumption of no overdispersion, the reason for the deviance residues was observed by their degrees of freedom [26]. Even if there was no violation of this assumption, it was decided to robustly estimate the standard errors of all models [27]. The association statistics obtained from the Poisson regression were: relative risk (RR), the absolute increase in cleaning risk (AAR) or the (absolute cleaning risk reduction - ARR), the relative risk increase (ARR - direct measure of effectiveness) or (relative cleaning risk reduction - RRR) cleaning and number needed to treat (NNT) [28]. Then, adverse reactions were considered as the presence of nausea, vomiting, hypernatremia and dizziness in order to calculate the probability that, on average, patients would benefit and harm simultaneously (LLH), by combining the incidences of adverse effects with the benefit of colon cleansing (NNT) of solutions compared to mannitol [27, 29]. All analyses were performed using the R Project software [30].

3. Results

A total of 294 patients were randomized (98 each group); but one patient was excluded in the polyethylene glycol group after randomization due to exclusion criteria detected (previous left colectomy); and 10 patients did not show up on the scheduled day for colonoscopy (5 in the PEG group and 5 in the mannitol group), corresponding to 3.8% of the sample. A total of 283 patients drank the oral solution for colon cleansing and were allocated into three groups: lactitol (*n*=98, 34.6%) patients in the lactitol group, (*n*=93, 32.9%) mannitol and (*n*=92, 32.3%) polyethylene glycol.

The mean age was 55.7 (12.0) years and 204 subjects were older than 50 years. The main reason for colonoscopy was colorectal cancer surveillance, followed by hematochezia (Table 2). The more frequent findings of colonoscopy were polyps (*n*=101, 34.4%), diverticular colon disease (*n*=63, 21.4%), and inflammatory bowel disease (*n*=33, 11.2%). Baseline patient characteristics are reported in Table 2 and no significant differences were observed among groups.

Table 2. *Baseline characteristics of patients and colonoscopy according to the colon preparation solution group.*

	Lactitol, *n*=98	**Mannitol, *n*=98**	**PEG, *n*=98**
Female, *n* (%)	68 (35.6)	62 (32.5)	61 (31.9)
Age, mean (SD)	55.6 (11.3)	55.5 (13.8)	55.9 (10.9)
BMI in kg/m2 (SD)	26.3 (3.8)	26.4 (4.6)	26.4 (4.7)
Diabetes type 2	14 (46.7)	7 (23.3)	9 (30)
Hypertension	38 (37.6)	30 (29.7)	33 (32.7)
IBD	7 (29.2)	10 (41.7)	7 (29.2)
Hemoglobin (SD)	13.3 (1)	13 (1.4)	12.9 (1.6)
Urea† (SD)	30.5 (7.8)	28.2 (8.6)	26.9 (7.8)
Creatinine† (SD)	0.8 (0.2)	0.8 (0.2)	1.38 (4.1)

	Lactitol, *n*=98	Mannitol, *n*=98	PEG, *n*=98
Sodium† (SD)	140 (2.4)	139.8 (2.6)	131.9 (31.9)
Potassium† (SD)	4.36 (0.5)	4.29 (0.3)	4.36 (0.5)
Reason for colonoscopy, n (%)			
Abdominal pain	13 (48.1)	6 (22.2)	8 (29.6)
Anemia	1 (40)	4 (40)	2 (20)
CCR surveillance	40 (40.8)	26 (26.5)	32 (32.7)
Chronic diarrhea	6 (25)	13 (54.2)	5 (20.8)
Constipation	12 (31.6)	11 (28.9)	15 (39.5)
Hematochezia	17 (31.5)	17 (31.5)	10 (18.5)
IBD	9 (39.1)	11 (47.8)	3 (13)
Loss of weight	5 (55.6)	1 (11.1)	3 (33.3)
Other	11 (39.3)	8 (28.6)	9 (32.1)
Colonoscopy findings, n (%)			
Angiectasis	2 (20)	3 (30)	4 (4.9)
Diverticulum	21 (18.9)	22 (34.9)	20 (31.7)
IBD	11 (33.3)	17 (51.5)	5 (15.2)
Neoplasia	1 (25)	2 (50)	1 (25)
Normal	36 (41.9)	22 (25.6)	28 (32.6)
Polyps	41 (40.6)	31 (30.7)	29 (28.7)
Portal colopathy	11 (33.3)	1 (33.3)	1 (33.3)
Colonoscopy features			
PDR (%)	36.7	33.3	91.5
Ileum intubation rate	77.8	80.7	80.7
Bubbles, *n* (%)	15 (21.7)	7 (13.5)	12 (21.8)

BMI: Body mass index; CCR: Colorectal carcinoma; IBD: Inflammatory bowel disease; PDR: Polyp detection rate; SD: Standard deviation.
†The serum laboratory tests were performed before the bowel cleansing solution intake.

The overall adequacy of bowel cleansing was achieved in more than 90% of patients, 98.8% in the mannitol group, followed by 93.5% in the lactitol and 92.3% in the PEG group. When comparing patients who used the preparation with lactitol and mannitol, the adequate preparation was greater in the mannitol group, but without statistically significant difference (RR 0.94; CI95% 0.86-1.03; P=0.164), with 5.9% of relative risk reduction of inadequacy with number needed to treat (NNT) 18 (Figure 1 and Table 3). When comparing patients who used the preparation with mannitol and PEG, there was a slight better performance in mannitol group (mannitol 98.8% vs. PEG 92.2%), but without significant differences (RR 0.91; CI95% 0.82-1.01; P=0.073), with 8.8%of relative risk reduction of inadequacy and NNT 12 (Figure 1, Table 3).

Table 3. *Adequacy of colon preparation considering Mannitol, Lactitol and PEG solutions. Crude and Adjusted Relative Risk, Absolute and Relative Risk Reduction (effectiveness) and Number Needed to Treat Adjusted by Poisson Regression.*

Variable	Adjusted Model*			Crude Model**						Δ RR%
	RR	[CI] 95%	P-value	RR	[CI] 95%	P-value	ARR	RRR%	NNT	
Lactitol	0.95	[0.87-1.03]	0.192	0.94	[0.86-1.03]	0.164	0.056	5.9	18	1.05
Mannitol	1	-	-	1	-	-	-	-	-	-
Age (yr)	-	-		-	-	-	-	-	-	-
< 60	0.96	[0.88-1.04]	0.274	-	-	-	-	-	-	-
≥ 60	1	-	-	-	-	-	-	-	-	-
Gender	-	-		-	-	-	-	-	-	-
Female	0.98	[0.89-1.08]	0.635	-	-	-	-	-	-	-
Male	1	-	-	-	-	-	-	-	-	-
Comorbidity	-	-		-	-	-	-	-	-	-
No	0.93	[0.86-1.01]	0.072	-	-	-	-	-	-	-
Yes	1	-	-	-	-	-	-	-	-	-
PEG	0.91	[0.82-1.00]	0.059	0.91	[0.82-1.01]	0.073	0.083	8.8	12	0
Mannitol	1	-	-	1	-	-	-	-	-	-
Age (yr)	-	-		-	-	-	-	-	-	-
< 60	1.04	[0.93-1.15]	0.492	-	-	-	-	-	-	-
≥ 60	1	-	-	-	-	-	-	-	-	-
Gender	-	-		-	-	-	-	-	-	-
Female	1.08	[0.99-1.18]	0.099	-	-	-	-	-	-	-
Male	1	-	-	-	-	-	-	-	-	-

Variable	Adjusted Model*			Crude Model**						Δ RR%
	RR	[CI] 95%	P-value	RR	[CI] 95%	P-value	ARR	RRR%	NNT	
Comorbidity	-	-		-	-	-	-	-	-	-
No	0.95	[0.87-1.05]	0.313	-	-	-	-	-	-	-
Yes	1	-	-	-	-	-	-	-	-	-

Notes:
*Confidence intervals and p values calculated from the Robust Standard Error estimated through the heteroscedasticity-consistent covariance matrix of the model coefficients. Akaike Information Criterion (AIC): Crude AIC: 343.9; AIC adjusted: 349.6. **Adjustment Goodness Test for the Poisson model (Residual deviation: RD) Gross: 0.1889 (p=1); Adjusted AD: 0.19007 (p=1).
The difference in RRs between the adjusted and crude models was <10% (Δ=1.05%), meaning that the RR of the group variable in the presence of the other variables was little different from the RR of the group variable without the covariables. As the RRs calculated were close to 1 and the respective p values were> 0.05, the crude model was chosen.
RR: Relative Risk; [CI] 95%: Confidence interval for RR; Δ RR%: Difference of risks in% between definitive model and crude model (criterion: be> 10%).
ARR: Absolute Risk Reduction; RRR%: Relative Risk Reduction (effectiveness); NNT: Number Needed to Treat.

In adjusted analysis, lactitol and mannitol groups did not show any differences in bowel preparation adequacy considering age, gender, and comorbidities. The lack of comorbidities was possibly associated with bowel cleaning adequacy, but the analysis did not demonstrate differences (RR 0.93; CI95% 0.86-1.01; P=0.072) (Table 3). Adjusted analysis of mannitol and PEG groups showed a slight trend to significant adequacy in the mannitol group (P=0.059), with no differences when assessed other variables (Table 3).

Only 4 subjects were considered to have colon cleansing failure (unable to proceed with colonoscopy): one in the mannitol group, and 3 in the PEG group.

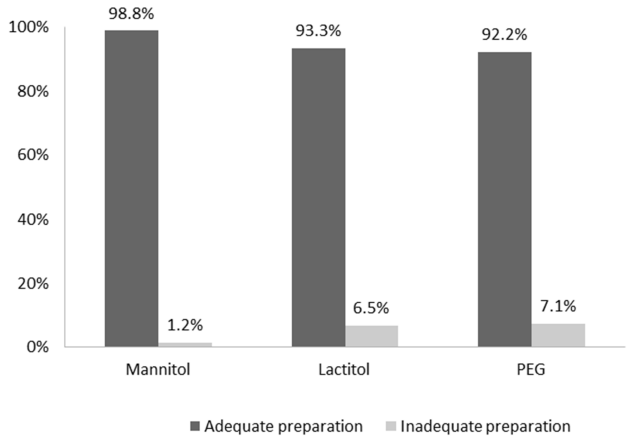

Figure 1. *Comparison of the adequacy of bowel cleansing solutions considering Boston Bowel Preparation Scale.*

Note: Fisher's exact test was performed and the P-value < 0.05 was considered statistically significant

The description of the average scores with respect to the adequacy of bowel preparation by BBPS in each bowel segment is presented in table 4. Regarding this criterion of evaluation, the mean of BBPS was greater in lactitol, followed by mannitol and PEG groups.

The average frequency of polyps detection was 34.1% (*n*=101), 40.6% in the lactitol group, 30.7% in the mannitol group, and 28.7% in the PEG group; significant differences were not noted in the analysis (lactitol *vs* mannitol *P*=0.660; lactitol *vs* PEG *P*=0.460). In patients older than 50 years, the polyp detection increased to 41.5% (*n*=88) but without differences among groups. Polypectomy was the most frequent procedure performed (*n*=86, 29.1%; Table 2). The ileum intubation rate reached was 79.7% (*n*=84), without significant differences among groups.

Table 4. *Description of the averages obtained with the BBPS score in the assessment of cleanliness of the colonic segments during colonoscopy.*

	Lactitol	Mannitol	PEG
Right colon	2.72 (0.47)	2.69 (0.62)	2.53 (0.56)
Transverse colon	2.79 (0.47)	2.61 (0.69)	2.61 (0.50)
Left colon	2.72 (0.59)	2.67 (0.68)	2.55 (0.56)
Entire colon	8.21 (1.52)	7.97 (1.86)	7.66 (1.62)

Note: Averages and standard deviations are presented.

No serious adverse events were reported, and abdominal pain, dizziness, dry mouth, and headache were similar among all groups. The frequency of hypernatremia after bowel preparation was 25.3% in the group that used mannitol, followed by 7.3% and 5.2% in the PEG and lactitol groups, respectively. The lactitol (RR: 0.2, 95%CI: 0.08-0.52) and PEG (RR: 0.29, 95%CI: 0.12-0.68) solutions showed a relative reduction in risk of progressing to hypernatremia, with a number needed to treat (referred to as NNT) of 5 and 6, respectively. Nausea was more common in the lactitol group (21.8%) compared to the mannitol group (8.6%), with an RR of 3.77 (95%CI: 0.84-17.02) needed to treat 8 subjects with lactitol so that one of them had nausea (number needed to harm, NNH). The frequency of nausea in the PEG group (21.7%) was similar to that observed in the lactitol group. Vomiting was more common in patients prepared with lactitol (8.1%) compared to mannitol (2.2%), with an RR of 2.54 (95%CI: 1.2-5.37). The absolute increase in risk in the treated group was 0.132 (95%CI: 0.129-0.135) and NNH of 17. The frequency of vomiting in the group prepared with PEG was 4.3% and the RR was 2.53 (95%CI: 1.17-5.44), bringing an absolute increase in risk in the treated group of 0.131 (95%CI: 0.128-0.135) with a NNH of 46. The adverse events and likelihood of being helped or harmed according to the bowel preparation solution were described in table 5.

The visual analog scale showed that tolerance for bowel preparation solution was higher in the mannitol group (4.52), followed by the group treated with lactitol (4.31) and PEG (3.85). There was no difference between the mannitol and lactitol groups (*P*=0.07); however, lactitol was better

tolerated compared to PEG (P=0.001). In the mannitol group, 94.6% were satisfied with the bowel preparation, followed by 91% in lactitol and 85.9% in the PEG group.

Considering the palatability of the bowel preparation solutions, 65 of 283 patients classified the oral solutions to taste very or moderately unpleasant; of these, 63.1% were in the PEG group, 29.2% in the lactitol group, and 7.7% in the group treated with mannitol ($P < 0.001$).

Table 5. *Likelihood of being helped or harmed according to the bowel preparation solution group.*

Lactitol group						
AE	**Incidence of AE (z)**	**Incidence of AE %**	**NNT for intestinal cleansing**	**Expected number of AE considering the NNT ****	**NNH AE**	**LLH=(1/NNT) / (1/NNH)***
Nausea	0.218	21.8	18	3.92	8	0.44
Vomiting	0.081	8.1	18	1.46	17	0.94
Hypernatremia	0.052	5.2	18	0.94	5	0.28
Dizziness	0.045	4.5	18	0.81	29	1.61

Polyethylene glycol macrogol (PEG) group						
AE	**Incidence of AE (z)**	**Incidence of AE %**	**NNT for intestinal cleansing**	**Expected number of AE considering the NNT****	**NNH AE**	**LLH=(1/NNT) / (1/NNH)***
Nausea	0.217	21.7	12	2.60	8	0.67
Vomiting	0.043	4.3	12	0.52	46	3.83
Hypernatremia	0.073	7.3	12	0.88	6	0.5
Dizziness	0.054	5.4	12	0.65	23	1.92

*LLH (LLH is > 1, the subject under intervention will have more benefit regarding the risk of adverse effects); ** z X NNT (BATTAGGIA, 2006).

4. Discussion

The number of patients screened for colon injuries will increase over time, requiring effective and safe colon solution preparations. Factors increasing the risk of worse bowel preparation may include older age, lower education level, and nonadherence to preparation instructions; these issues need to be addressed when high-quality colonoscopy is desired [12, 31, 32]. In this trial, we proposed to compare three different oral solutions to bowel preparation before colonoscopy, including an unusual application of lactitol and the most commonly used solutions, such as mannitol and PEG.

The trials that evaluate the effectiveness of intestinal preparation solutions present heterogeneous methods; thus, any comparison becomes a difficult process. Mannitol solution is a frequent cleansing solution for bowel preparation of colonoscopy in Brazil, although it is not recommended by some societies due to reports of colon explosion and electrolyte disturbances [14–16, 18]. The PEG is presented as an effective alternative to bowel preparation solution, but with diverse ways to be applied. Lactitol is an osmotic disaccharide laxative produced by hydrogenation of lactose that increases fecal volume and stimulates peristalsis; it is well indicated for chronic intestinal constipation and hepatic encephalopathy [20, 21, 23]. There are no previous studies evaluating lactitol application for bowel cleansing.

In this trial lactitol, all studied solutions were found to be effective for bowel cleansing, but mannitol and lactitol showed higher proportion of adequacy considering at least 2 points in each colonic segment using BBPS, despite not reaching statistical significance. Group prepared with PEG solution revealed a worse performance than mannitol in bowel cleansing, despite not having statistical significance in crude or adjusted analysis. Although the sample size calculation, we believe that an analysis regarding a larger number of patients would be able to show significant differences between groups. A previous study conducted with 148 patients, who were randomized to receive PEG or mannitol, showed that there was no significant difference in terms of efficacy or adverse events, such as nausea, vomiting, pain, or bloating [33]. Beck *et al* [15] compared PEG and mannitol solutions for preoperative bowel preparation in 80 patients; both methods were considered safe and effective, with success rates of 70% and 100%, respectively.

In this study, PEG did not show a good performance when compared with previous data. We have used a cleansing solution with 20 sachets, each sachet containing 13.125 g polyethylene glycol macrogol and 700 mL water, with a worse BBPS score compared to mannitol 20% and lactitol. Some studies, especially those using PEG solution, did not clarify the PEG dose; in addition, dilutions have varied among trials (to dilute the sachet). Other trials have presented good-quality bowel cleansing with sodium phosphate and 10% mannitol solutions compared to sodium picosulfate in more than 90% of colonoscopies, mainly due to the presence of feces adhering to the right colon walls after cleansing with sodium picosulfate preparation; however, adverse events and flavor might be possible limiting factors [14].

Lactitol is a disaccharide analog of lactulose, which is not absorbed in the small intestine but is extensively metabolized by colonic bacteria. Some studies on hepatic encephalopathy and constipation have compared lactitol and lactulose, and the efficacy and tolerance of lactitol for adults were found to be similar; gastrointestinal adverse events were common, but generally with mild intensity [20]. A trial compared PEG electrolyte containing PEG-4000 (118 g), sodium sulfate (11.37 g), sodium bicarbonate (3.37 g), sodium chloride (2.93 g), and potassium chloride (1.48 g), which were reconstituted in 2 L water and lactulose solution (200 mL) plus 2 L water. The comparative efficacy of the bowel preparation was evaluated using the BBPS scoring system and the lactulose group showed superior bowel cleansing compared to the PEG

group, as evidenced by the higher BBPS scores for all segments of the colon [34]. The present findings of lactitol were similar if compared with lactulose in this analysis. The most significant limitations were related to heterogeneity in the preparation of the solutions, making it difficult to compare studies, in addition to several methods for measuring the quality of bowel preparation.

Adverse events and tolerability were the most interesting points to distinguish the solutions. In accordance with other analyses, we found a higher frequency of hypernatremia after bowel preparation in patients within the mannitol solution group, 20% and 18% greater than that in the lactitol and PEG groups, respectively. No patient had clinically significant symptoms. Considering the electrolytes disbalance, lactitol and PEG were safer, with an NNT of 5 and 6, respectively. There was no colon gas explosion reported and the local experience with mannitol did not show a similar record. Nausea was the more common adverse event observed, 2.5 higher fold in lactitol and PEG than mannitol group. Vomiting was also more frequently reported in the lactitol and PEG groups compared with mannitol. Previously published trials have revealed that patients in the mannitol preparation group have a significantly higher frequency of nausea, vomiting, abdominal pain, and abdominal distension than those in the PEG group [14–16]. The long-term safety profile of lactitol, compared to other bowel cleansing solutions needs further investigation.

Groups that obtained better scores on BBPS achieved higher rates of polyps' detection. We found a polyp detection frequency of 34.1%, with a slight proportion in the lactitol group (40.6%) compared with the mannitol (30.7%) and PEG (28.7%) groups. Currently, there are no anatomopathological assessments to detect the adenoma detection rate, despite the retrieval of more than 95% of removed polyps for histological analysis; this is an analysis limitation. Data have shown that the removal of adenomas from the colon reduces the risk of subsequent cancer [35]; and data have shown that screening colonoscopies with adenoma detection rates below 20% were more likely to have patients subsequently presenting with interval cancer [36].

Mannitol and lactitol had better palatability in this trial. The palatability of PEG solution was not positively evaluated, as it was a very or moderately unpleasant flavor by many people. Previous analyses have shown that PEG solution has better tolerability and acceptability than mannitol; when compared with lactulose, though, PEG appears to have a lower quality performance [16, 34]. There is no other data to compare lactitol in the similar conditions, but studies for intestinal constipation and hepatic encephalopathy, demonstrated good tolerability, especially for the possibility of use as a sweetener in cold and hot drinks. Some data have demonstrated that methods to achieve palatability and tolerability vary among studies; in addition, bowel preparation experience and cultural habits can influence the patient's preferences.

In conclusion, we observed that mannitol, lactitol and PEG are options for intestinal preparation before colonoscopy. Lactitol is a possible alternative to be used for this purpose but further head-to-head trials are necessary. The condition of the patient, the local experience must also be considered when choosing the most appropriate solution to bowel cleansing.

Author Contributions

Cavalcante LN, Batista MC, and Paes IB designed the report; Cavalcante LN, Ribas A, Lins AP, Leal da Silva LR, Fortes FML, Bispo Jr VS, Cintra de Oliveira M, Silveira C, Almeida MVM collected the patient's clinical data; Ribas A and Cavalcante LN analyzed the data and wrote the paper.

Declarations

The authors declare that there are no conflicts of interest. This study was approved by the Ethics Committee of Hospital Geral Roberto Santos (CAAE N° 83167418.5.0000.5028). The manuscript was prepared and revised in accordance with the CONSORT Statement 2010.

Acknowledgements

All authors participated equally in the realization of this trial.

We are grateful to Cifarma Científica Farmacêutica LTDA for donating medicines, Hospital Geral Roberto Santos and the Secretary of Health of the Bahia´s State (SESAB) for structural support.

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