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Double blinded randomized clinical trial to assess the effectiveness of several preparations for colonoscopy

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ABSTRACT

Introduction: Colonoscopy is the screening gold standard to investigate several conditions in the colon. The excellence of preparation is a determining factor for a quality colonoscopy.

Objective: Compare the quality of colon preparations for colonoscopy with different kinds of laxative medications in a public hospital of Belo Horizonte, Brazil.

Method: A prospective double blind randomized clinical trial was conducted from June 2016 to March 2017. A total of 117 Patients were randomised in four groups to receive a type of preparation (Sodium picosulfate, Mannitol, Lactitol, Lactulose). The patients answered a questionnaire and peripheral blood samples were collected before and after the preparation. The quality of the cleansing was accessed according to the Boston Bowel Preparation Scale.

Results: 99.1% of patients have taken the recommended dose and 79.5% reported a good tolerability. Endoscopists performed complete colonoscopy in 89.7%, with an polypectomy rate of 47%. The total effectiveness rate of the solutions were 88%. There were no statistically significant differences between groups ($p = 0.271$). Regarding the laboratory parameters, differences were seen in the pre- and post-test values of sodium, chlorine and creatinine but without exceeding reference values.

Conclusion: The four preparations were effective for colon cleansing, with good acceptance, differing only as for costs.

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Ensaio clínico randomizado duplo cego para avaliar a eficácia de várias preparações para colonoscopia

R E S U M O

Palavras-chave:

Colonoscopia
Qualidade
Preparação do intestino
Picossulfato sódico
Manitol
Lactitol
Lactulose

Introdução: a colonoscopia é o padrão ouro de triagem para pesquisa de várias doenças colônicas. A excelência de preparação é um fator determinante para uma colonoscopia de qualidade.

Objetivo: Comparar a qualidade das preparações do cólon para colonoscopia com diferentes tipos de medicamentos laxantes em um hospital público de Belo Horizonte, Brasil.

Método: Foi realizado um ensaio clínico randomizado duplo cego prospectivo de junho de 2016 a março de 2017. Um total de 117 pacientes foi randomizado em quatro grupos para receber um tipo de preparação (picossulfato sódico, manitol, lactitol, lactulose). Os pacientes responderam a um questionário e amostras de sangue periférico foram coletadas antes e depois da preparação. A qualidade da limpeza foi acessada de acordo com a Boston Bowel Preparation Scale.

Resultados: 99,1% dos pacientes tomaram a dose recomendada e 79,5% relataram boa tolerabilidade. Os endoscopistas realizaram colonoscopia completa em 89,7%, com taxa de polipectomia de 47%. A taxa de eficácia total das soluções foi de 88%. Não houve diferenças estatisticamente significantes entre os grupos ($p = 0,271$). Em relação aos parâmetros laboratoriais, foram observadas diferenças nos valores pré e pós-teste de sódio, cloro e creatinina, mas sem exceder os valores de referência.

Conclusão: As quatro preparações foram eficazes para limpeza do cólon, com boa aceitação, diferindo apenas quanto aos custos.

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Introduction

Colonoscopy is the screening gold standard to investigate several conditions in the colon and terminal ileum, particularly to screen colorectal cancer.¹ This procedure allows both the identification and the excision of polyps and premalignant lesions, thus contributing to the reduction of cancer mortality.^{2,3} However, the success of the test depends on the appropriate preparation of the colon enabling broad visibility of the mucosa, from the anal verge to the ileocecal valve.

The excellence of preparation is a determining factor for a quality colonoscopy.⁴ A good preparation reduces the rate of undiagnosed adenomas, from 33%–46% to 15%–32%.⁵ Patients with a regular preparation have the effectiveness of their tests affected, and require repeating the procedure in short notice, increasing the costs and the risks of complication.

Several agents are available in the market: Polyethylene Glycol – PEG, Sodium phosphate, Sodium picosulfate with Magnesium citrate, Mannitol and Lactulose. They are all used for orthograde colon washing. Despite several options, it has not been defined which of these agents would be considered as “gold-standard”, since none of them meets all criteria of an ideal preparation: complete colon cleansing with no damage to mucosa, associated with a complete tolerance with no side effects and low costs.^{6,7}

Polyethylene glycol is one of the most commonly used agents due to its safety and little incidence of hydroelectrolytic disorders, particularly in patients with multiple comorbidities,⁸ in addition to its high effectiveness. However,

it should be taken in large volumes and has low palatability.⁶ As for the solutions of sodium phosphate and sodium picosulfate with magnesium citrate, they are taken in smaller volumes and have shown to be equally effective in comparative studies.^{8,9,10} Nevertheless, they may cause significant side effects, such as changes in ion concentrations.

Regarding mannitol, there is a consensus in North America and Europe regarding not to use it due to the risk of colonic explosion and of severe hydroelectrolytic disorders.⁷ Nevertheless, this solution is widely used in Brazil, since it is considered as a good intestinal preparation method, with the best cost and with appropriate effectiveness and safety.^{1,11}

Lactulose, nonabsorbable disaccharide, which undergoes bacterial action, was chosen as intestinal preparation because it is widely available, affordable costs and with effectiveness results similar to those of mannitol.¹²

Lactitol, as well as lactulose, have both been used as options of intestinal preparation with good results reported by the manufacturer. Nevertheless, there are few studies in the literature showing their suitability.

The current scenario shows that the main formulae used are equally effective to detect lesions, but differ as for palatability, adherence to the recommended dosage and the occurrence of adverse reactions.¹⁰ In this context, the present study has the objective of comparing the quality of colon preparations, tolerability and adverse effects among sodium picosulfate, magnesium oxide, anhydrous citric acid – Sodium picosulfate, Mannitol, Lactitol, Lactulose, in patients from a public Hospital of Belo Horizonte, Brazil, which carries out 200 tests a month. It is important to emphasize that the choice

seeks to validate their use, since there are no clinical trials and virtually no evidence in the literature.

Materials and methods

A prospective double blind randomized clinical trial was conducted from June 2016 to March 2017, at a public Hospital of Belo Horizonte, Brazil. Patients with indication to colonoscopy of both genders, and in the age group of 40–79 years were selected. Patients were randomised in four groups, as for gender and age similar to those assisted in the facility to receive a type of intestinal preparation for the colonoscopy (Sodium picosulfate, Mannitol, Lactitol, Lactulose). The methodology ensured blinding of all of those involved (the endoscopist, researchers and the physician in charge of the pre-test interview) as for the type of preparation. Patient allocation in the groups (1, 2, 3 and 4) was randomized and stratified by gender (female, male) and age group (40–49, 50–59, 60–69, 70–79). The preparations were drawn within each stratum of age and sex. The allocation was planned by one of the authors (Souza, A.), a statistician who did not participate in the clinical stage.

The study was approved by the Ethics and Research Committee of the hospital – CAAE's number: 56445516900005129. All of the patients signed the Free and Informed Consent form to take part in the study.

The following were considered as exclusion criteria: having decompensated systemic diseases and being allergic to any of the components of the preparations.

Data collection and analyses

Patients with an indication of elective colonoscopy were first submitted to a pre-colonoscopy interview and were randomly allocated to receive one of the four types of preparation and had their tests scheduled.

On the day of the exam, patients responded to a questionnaire concerning tolerability, adverse effects. Peripheral blood samples were collected at the moment of the first evaluation and after the completion of the preparation. They were analysed for serum sodium, potassium, chlorine and creatinine.

Colonoscopy was performed by one of two staff endoscopists with the existing infrastructure, with no information on the preparation taken by the patient.

About the preparation

Patients took two tablets of Bisacodyl the day before the test. All preparations were taken in split doses: the first half 9 h before the test and the second half 5 h after the test.

Randomised participants of the Lactulose and Lactitol groups consumed a total of 200 mL of the medication: every 100 mL diluted in 400 mL of water.

Members of the Mannitol group were told to drink 500 mL of the medication, being 250 mL diluted in 250 mL of cold water. In the Sodium picosulfate group, they ingested two sachets each one diluted in 200 mL of water at first and then seven additional glasses of clear liquid.

In all groups, patients followed the same instructions on diet.

Main objective

The main objective of this study has been defined as the quality of the cleansing of the colon with the preparations. This parameter was accessed according to the Boston Bowel Preparation Scale, with scores from 0 to 3 for each region of the colon – ascending colon and cecum, transverse colon and descending colon, with a total score of 9. The preparation was considered appropriate when the score achieved was greater than or equal to 6.

Secondary objectives

Secondary objectives have been defined as palatability and tolerability of the preparation, caecal intubation rate, polyp detection rate and patients' willingness to take the solution again if necessary.

Statistical analysis

The size of the sample was calculated using statistical parameters to compare means using analysis of variance (ANOVA) of a factor. The comparison variable was the total amount of fluid. There were four comparison groups; greater difference to be detected corresponds to 0.3 and standard deviation 0.5, level of significance 5% and e power of the sample 80%. An additional 10% was added in case of losses. Calculations were performed using the STATA software version 12.

These parameters led to a number of 140 patients to be distributed in 4 groups of 35 individuals. Individuals were distributed in groups according to age and gender of patients assisted in the service, obtained by a previous study.

Results were analysed using the SPSS program version 22 (SPSS INC. Chicago, IL, USA) with continuous variables being expressed as means and standard deviation, while categorical variables were expressed as absolute and relative frequencies and were compared using X^2 tests. Significance level was set at $p < 0.05$.

Results

One hundred and forty patients were selected to take part in the study. Twenty patients refused and 120 were randomised, 3 were excluded due to incomplete data and 117 were allocated as follows: 30 in the Lactulose group, 28 in the Lactitol group, 28 in the Mannitol group and 31 in the sodium picosulfate group as shown in Fig. 1.

The characteristics of patients from the four groups are described in Table 1. Groups have been compared as for demographic characteristics and found similar.

Regarding the presence of associated comorbidities, 33 patients (28.2%) reported not carrying diseases. According to those who reported carrying a disease, the most common was hypertension (52 patients, 44.4%) followed by diabetes mellitus (23 patients, 19.7%) and hypothyroidism (16 patients, 13.7%). The most prevalent indications for the test were: positive faecal occult blood test (25 patients, 21.4%), followed by age > 50 years (21 patients, 17.9%) and haematochezia (19 patients,

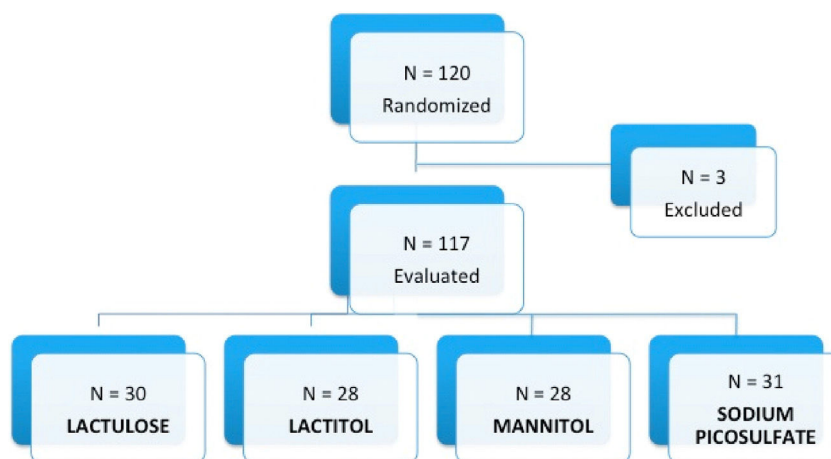


Fig. 1 – Flow chart of patients.

Table 1 – Characteristics of patients according to the type of preparation. Hospital Municipal, BH, MG, 2016.

Variables	Total n (%)	Preparation				p
		Lactulose n (%)	Lactitol n (%)	Mannitol n (%)	Sodium picosulfate n (%)	
Gender						
Female	83 (70.9)	21 (70.0)	19 (67.9)	20 (71.4)	23 (74.2)	0.959
Male	34 (29.1)	9 (30.0)	9 (32.1)	8 (28.6)	8 (25.8)	
Age group (years)						
40–50	19 (16.2)	5 (16.7)	6 (21.4)	3 (10.7)	5 (16.1)	0.992
50–59	51 (43.60)	14 (46.7)	10 (35.7)	13 (46.4)	14 (45.2)	
60–69	36 (30.8)	9 (30.0)	9 (32.1)	9 (32.1)	9 (29.0)	
70–79	11 (9.4)	2 (6.7)	3 (10.7)	3 (10.7)	3 (9.7)	
Schooling						
Complete primary school	20 (17.1)	4 (13.3)	3 (10.7)	8 (28.6)	5 (16.1)	0.242
Incomplete primary school	47 (40.2)	6 (20.0)	17 (60.7)	11 (39.3)	13 (41.9)	
Complete secondary school	30 (25.6)	12 (40.0)	5 (17.9)	5 (17.9)	8 (25.8)	
Incomplete secondary school	2 (1.7)	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.2)	
Complete higher education	10 (8.5)	4 (13.3)	2 (7.1)	3 (10.7)	1 (3.2)	
Not able to inform	8 (6.8)	3 (10.0)	1 (3.6)	1 (3.6)	3 (9.7)	

16.2%). No significant differences have been observed among groups as for these variables (Table 1).

In respect of the preparation, 99.1% of patients have taken the recommended dose and 79.5% reported it was easy to digest the solution. As for the taste, 92.3% stated that the solution has a pleasant or acceptable taste. If necessary, 93.2% would take the solution again.

During the preparation of the solution, 53 patients (45.3%) described some side effects, with nausea being the most frequent (20 patients, 17.1%), followed by weakness (16 patients, 13.7%) and headache (15 patients, 12.8%). No differences were seen among groups. Furthermore, the symptoms described have not prevented the test from being carried out and no patient had to interrupt the treatment or to be taken to hospital (Table 2).

Endoscopists performed complete colonoscopy in 89.7% (105 patients) of tests. The other findings are described at Table 3.

In relation to the effectiveness of the solutions, 88% (103) of all tests scored ≥ 6 on the Boston Bowel Preparation Scale.

There were no statistically significant differences regarding different groups ($p = 0.271$) (Table 4).

Regarding the analysis of Laboratory parameters, differences were seen in the pre- and post-test values of sodium and chlorine in the sodium picosulfate group and of creatinine in the Lactulose and Mannitol groups, but without exceeding reference values (Table 5).

Discussion

Colorectal cancer is the third most common in the United States according to data from the American Cancer Society, with almost 100,000 new cases in 2017.¹³ In Brazil, data from 2016 show virtually 35,000 new cases according to Instituto Nacional do Câncer – INCA (National Cancer Institute).¹⁴ In order to screen and prevent this disease, colonoscopy is an important tool since it allows detecting and removing premalignant lesions, thus contributing to a decrease in cancer mortality.^{1,12} Nevertheless, to be an test of excellence,

Table 2 – Characteristics of patients as for the presence of comorbidities and indication for the test according to the type of preparation. Hospital Municipal, BH, MG, 2016.

Variables	Total n (%)	Preparation				p
		Lactulose n (%)	Lactitol n (%)	Mannitol n (%)	Picosulfate n (%)	
Comorbidities						
SAH	52 (44.4)	11 (36.7)	16 (57.1)	12 (42.9)	13 (41.9)	0.445
DM	23 (19.7)	4 (13.3)	7 (25.0)	6 (21.4)	6 (19.4)	0.724
Hypothyroidism	16 (13.7)	2 (6.7)	6 (21.4)	4 (14.3)	4 (12.9)	0.440
GERD	12 (10.3)	4 (13.3)	2 (7.1)	4 (14.3)	2 (6.5)	0.663
CHF	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	0.361
Dyslipidemia	15 (12.8)	3 (10.0)	7 (25.0)	2 (7.1)	3 (9.7)	0.171
Depression	4 (3.4)	1 (3.3)	1 (3.6)	0 (0.0)	2 (6.5)	0.603
Indication						
FOBT+	25 (21.4)	3 (10.0)	8 (28.6)	7 (25.0)	7 (22.6)	0.331
Age > 50 years	21 (17.9)	3 (10.0)	6 (21.4)	6 (21.4)	6 (19.4)	0.617
Haematochezia	19 (16.2)	7 (23.3)	3 (10.7)	5 (17.9)	4 (12.9)	0.563
Post polypectomy follow-up	16 (13.7)	4 (13.3)	3 (10.7)	6 (21.4)	3 (9.7)	0.561
Family history +	14 (12.0)	6 (20.0)	4 (14.3)	2 (7.1)	2 (6.5)	0.321

Table 3 – Findings of colonoscopy by type of preparation. Hospital Municipal, BH, MG, 2016.

Variables	Total n (%)	Preparation				p
		Lactulose n (%)	Lactitol n (%)	Mannitol n (%)	Picosulfate n (%)	
Colonoscopy						
Cecum	48 (41.0)	9 (30.0)	13 (46.4)	11 (39.3)	15 (48.4)	0.862
Ileum	57 (48.7)	18 (60.0)	11 (39.3)	15 (53.6)	13 (41.9)	
Incomplete	12 (10.3)	3 (10.0)	4 (14.3)	2 (7.1)	3 (9.7)	
Tumor	5 (4.3)	2 (6.7)	1 (3.6)	1 (3.6)	1 (3.2)	
Polyps	55 (47)	12 (42)	16 (53)	15 (50)	14 (45)	
LST	2 (1.7)	0 (0)	0 (0)	2 (1.7)	0 (0)	
Diverticula	32 (27.4)	8 (26.7)	8 (28.6)	8 (28.6)	8 (25.8)	

Table 4 – Quality of the preparations by type and total – Boston Bowel Preparation Scale. Hospital Municipal, BH, MG 2016.

Variables	Total n (%)	Preparation				p
		Lactulose n (%)	Lactitol n (%)	Mannitol n (%)	Picosulfate n (%)	
Ascending colon and cecum						
Inappropriate/bad	4 (3.4)	0 (0.0)	1 (3.6)	2 (7)	1 (3)	0.754
Good/excellent	104 (88.9)	28 (93.3)	24 (85.7)	25 (86)	27 (87)	
Not testined	9 (7.7)	2 (6.7)	3 (10.7)	1 (3.6)	3 (9.7)	
Transverse colon						
Inappropriate/bad	4 (3.4)	0 (0.0)	1 (3.6)	2 (7.1)	1 (3.2)	0.628
Good/excellent	105 (89.7)	29 (96.7)	24 (85.7)	25 (89.3)	27 (87.1)	
Not testined	8 (6.8)	1 (3.3)	3 (10.7)	1 (3.6)	3 (9.7)	
Descending colon						
Inappropriate/bad	6 (5.1)	0 (0.0)	3 (10.7)	1 (3.6)	2 (6.5)	0.574
Good/excellent	108 (92.3)	29 (96.7)	24 (85.7)	26 (92.9)	29 (93.5)	
Not testined	3 (2.6)	1 (3.3)	1 (3.6)	1 (3.6)	0 (0.0)	
Total						
1-5	14 (12.0)	1 (3.3)	4 (14.3)	3 (10.7)	6 (19.4)	0.271
6-9	103 (88.0)	29 (96.7)	24 (85.7)	25 (89.3)	25 (80.6)	

the quality of the preparation is a determining factor, since patients whose preparation is regular have the effectiveness of their test affected, leading to an increase in costs and also a lower polyp detection rate.^{11,12} Furthermore, solutions should be safe and e with acceptable patient tolerance.¹⁵

Our results suggest that the ingestion of any of the four types of preparation is equally effective as for the quality of the cleansing of the colon. Out of the 117 tests performed, 103 (88%) had an appropriate score (≥ 6 in the Boston Bowel Preparation Scale), with no differences among groups ($p=0.271$).

Table 5 – Values of serum sodium and chlorine and serum creatinine pre- and post-test in groups by preparation. Hospital Municipal, BH, MG, 2016.

Variable	Preparation	Measurement	n	Mean	SD	Minimum	Maximum	p
Na (mmol/L)	Lactulose	Pre-test	24	139.08	2.19	135.00	143.00	0.922
		Post-test	24	139.00	4.10	131.00	148.00	
	Lactitol	Pre-test	23	139.65	2.55	135.00	145.00	0.329
		Post-test	23	140.48	3.49	135.00	148.00	
	Mannitol	Pre-test	20	139.50	1.88	136.00	143.00	0.211
		Post-test	20	140.45	3.56	133.00	147.00	
	Sodium picosulfate	Pre-test	23	139.43	2.87	132.00	145.00	0.055
		Post-test	23	137.70	3.66	128.00	143.00	
	Total	Pre-test	90	139.41	2.38	132.00	145.00	0.916
		Post-test	90	139.37	3.83	128.00	148.00	
Chlorine	Lactulose	Pre-test	24	102.71	2.73	98.00	109.00	0.589
		Post-test	24	102.29	3.20	95.00	109.00	
	Lactitol	Pre-test	23	103.52	2.57	100.00	108.00	0.880
		Post-test	23	103.65	3.23	99.00	113.00	
	Mannitol	Pre-test	20	103.55	2.33	100.00	109.00	0.384
		Post-test	20	102.85	3.23	97.00	111.00	
	Sodium picosulfate	Pre-test	24	103.38	3.16	95.00	109.00	<0.001
		Post-test	24	99.67	3.90	90.00	108.00	
	Total	Pre-test	91	103.27	2.71	95.00	109.00	0.004
		Post-test	91	102.07	3.68	90.00	113.00	
Creatinine	Lactulose	Pre-test	24	0.88	0.20	0.60	1.30	0.001
		Post-test	24	0.99	0.20	0.60	1.40	
	Lactitol	Pre-test	20	0.88	0.22	0.60	1.50	0.107
		Post-test	20	0.92	0.19	0.60	1.30	
	Mannitol	Pre-test	19	0.84	0.19	0.50	1.10	0.005
		Post-test	19	1.00	0.16	0.80	1.30	
	Sodium picosulfate	Pre-test	19	0.81	0.18	0.60	1.30	0.301
		Post-test	19	0.85	0.17	0.60	1.30	
	Total	Pre-test	82	0.86	0.20	0.50	1.50	<0.001
		Post-test	82	0.94	0.19	0.60	1.40	

This outcome is similar to those found in the literature, from studies with similar designs.¹⁶ However, it is worth mentioning that, virtually all trials compare Polyethylene Glycol (PEG) solutions and sodium phosphate formulations and, in a smaller number, there are also publications about the use of Mannitol.¹⁷ Nevertheless, there are virtually no randomized studies on Lactulose and Lactitol, despite the growing use of these formulations, particularly in Brazil. The use of these formulations as a colon preparation was based on practical experience rather than on the scientific evidence of its effectiveness. Thus, the present study contributes to ensure its use for this purpose by studying the effectiveness of these solutions.

Quality analysis per segment of the colon has not shown differences among groups: cecum and ascending colon: $p=0.754$, transverse colon: $p=0.628$ and descending and sigmoid colon: $p=0.574$. A proper cleansing of the ascending colon is particularly important, since sessile polyps⁹ usually found in this segment are more difficult to identify because they are flat and hidden by the effluent from the small intestine with mucus on its surface.⁹

In this study, 89.7% of tests reached the cecum (48 tests) or the terminal ileum (57 tests). Tumour detection rate was 4% and the polyp detection rate was 47%, with no difference among groups ($p=0.320$). Rates were higher than those described in the literature.¹⁸ This finding may be explained by the demographic profile of patients submitted to the test who

had the following main indications for colonoscopy: positive faecal occult blood test (FOBT+), with 21.4% of the tests followed by: age > 50 years (17.9%), haematochezia (16.2%) and post-polypectomy follow-up (13.7%). These indications are not restricted only to the cancer screenings in asymptomatic patients.

The present study has not shown differences between palatability and tolerability of solutions. When asked about the taste of the solution, 108 patients (92.3%) answered that the taste was good or acceptable ($p=0.898$). All four preparations had a good acceptance and 93.2% of patients were comfortable to use the preparations in a further test, if necessary. These findings are consistent with the literature, in papers with similar designs.¹⁹

With respect to side effects, 53 patients (45.3%) reported feeling at least one, with nausea, weakness and headache as the most common ones. None of the symptoms reported changed the test.

Regarding the laboratory findings, changes were found in sodium values before the test: 139.43 and after the test: 137.70, in the sodium picosulfate group ($p=0.055$). Changes were also seen in chlorine before the test: 103.36 and after the test: 99.76, in the Sodium picosulfate group ($p<0.001$) and in the values of creatinine in the Lactulose group: before the test: 0.87 and after the test: 0.99 ($p<0.001$) and in the Mannitol group: before the test: 0.85 and after the test: 1.00, ($p=0.003$). However, it is worth highlighting that these changes have not translated into

clinical changes and all values remained within the reference range, which corroborates the safety of its use.

With the increased demand for colonoscopy as the gold standard screening examination, it is also important to evaluate the cost of formulations. In this study, after evaluating and concluding about the similarity of results, it is worth verifying the cost of the solutions used which varied from R\$9,29 (Mannitol) to R\$27,30 (Sodium picosulfate) and R\$39,90 (Lactitol and Lactulose). This feature may define the choice of the solution used since they have similar effectiveness and tolerability.

Conclusion

The four preparations were effective for colon cleansing, with a good acceptance, absence of complications related to hydroelectrolytic disorders and high adenoma detection rates differing only as for costs, which enables a more appropriate choice to the management of public resources and expansion of its use.

Conflicts of interest

The authors declare no conflicts of interest.

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