

A Single or Split Dose Picosulphate/Magnesium Citrate Before Colonoscopy: Comparison Regarding Tolerance and Efficacy with Polyethylene Glycol. A Randomized Trial

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ABSTRACT

Background & Aims: To compare the efficacy and tolerance of sodium picosulphate/magnesium citrate (PMC) and polyethylene glycol (PEG) in a single or split dose regimen for colonoscopy bowel preparation.

Methods: A prospective, randomized, endoscopist-blinded, multicenter study. The patients were randomly assigned to receive PMC (PMC4/0) or PEG (PEG4/0) in a single dose 4L day before colonoscopy or a split dose 2+2L PMC (PMC2/2) or 3+1L PEG (PEG3/1) one day before and in the morning before the colonoscopy. Each patient was interviewed to determine his/her subjective tolerance of the preparation before the procedure. The quality of bowel cleansing was assessed in a blinded test performed by multiple endoscopists using the Aronchick scale.

Results: A total of 600 patients were enrolled, 88.2% were included in the analysis. Satisfactory bowel cleansing (Aronchick score 1 and 2) was significantly more frequent when a split dose was used irrespective of the solution type (81.6% PMC2/2, 87.3% PEG3/1 vs. 73.0% PEG4/0, $p = 0.024$). In single dose regimens, PMC performed better than PEG (82.6% vs. 73.0%). Single or split dose PMC preparations were comparable. A PMC based solution was generally better tolerated than PEG regardless of the regimen used ($p < 0.001$). Nausea was reported mostly after the 4L PEG (32.8%, $p < 0.001$), incontinence after a split PMC dose (34.4%, $p = 0.002$), and bloating after the 4L PEG (38.0%, $p < 0.001$). There was no significant difference in the prevalence of vomiting.

Conclusion: Colonic preparation with PMC yields similar results as a split PEG dose, regardless of whether PMC is administered in single or separate doses. PMC is better tolerated than any PEG-based preparation. A single 4L PEG the day before the colonoscopy is less appropriate for bowel cleansing.

Key words: colonoscopy – bowel preparation – sodium picosulphate – polyethylene glycol.

INTRODUCTION

Colonoscopy is one of the basic procedures used in gastrointestinal endoscopy. Despite technological developments its outcome is essentially dependent on the quality of bowel preparation. Insufficient bowel cleansing has a negative impact on the success rate of cecal intubation in 1/5 to 1/3 of patients [1], prolongs overall intubation time, decreases the polyp detection rate [2] and increases the cost of a colonoscopy by up to one-fifth [3].

An ideal preparation should result in a clean bowel without

causing significant changes in the mucosa. It should be well tolerated, with minimum adverse events, and should act rapidly. A substance that would meet these requirements is not available yet. The gold standard represents polyethylene glycol (PEG). A low-volume (2 L) PEG dose with an additional laxative or a combination of a stimulant laxative with osmotic acting magnesium citrate, e.g. sodium picosulphate/magnesium citrate (PMC) is gaining popularity.

Quality of bowel cleansing depends not only on the formula used, but the preparation regimen also plays a role. Split dosing of the laxative offers, in general, better cleansing than a single dose preparation [4]. Direct comparisons of modern formulas with conventional PEG, especially in similar dosing regimens, are missing. Most of the studies evaluated PEG and sodium phosphate solutions (NaP). PMC as a relatively novel agent has not been investigated extensively.

The aim of this study was to compare effectiveness of a PMC to PEG in conventional single or split dose regimens in terms

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of bowel cleansing and patient tolerance and to determine whether dividing PMC into two doses gains any advantage to standard dosing.

METHODS

This was a prospective, randomised, endoscopist-blinded, multicenter study. Patients referred to the endoscopy department of Bata regional Hospital in Zlin, Hospital Vsetin and University hospitals in Brno were enrolled.

The exclusion criteria included ileus, known or suspected bowel obstruction, pregnancy, presence of serious medical conditions, such as severe cardiac, renal, liver diseases, active bowel inflammation and a history of prior colonic or rectal surgery.

A total of 600 subjects were randomly allocated in a 1:1:1:1 ratio (150 in each group) to receive PMC or polyethylene glycol in different regimens. Eligible patients were sequentially numbered. Randomization was performed in each participating center by non-endoscopy physician using a sealed envelope system. The endoscopists who evaluated bowel cleansing quality were blinded, and the subjects were asked not to reveal the preparation used. The subjects received commercially available preparations.

Large bowel preparation

Each sachet of PMC (PicoprepTMplv. sol., Ferring Pharmaceuticals) contained 10 g of sodium picosulphate, 3.5 g of magnesium oxide, and 12.0 g of citric acid. One sachet of polyethylene glycol (FortransTMplv. sol., Ipsen Pharma) contained 64 g of polyethylene glycol 4000 and sodium bicarbonate, sodium and potassium chloride up to 74g.

Group 1 (PMC4/0) was prepared using PMC in the afternoon before the colonoscopy (2 sachets + 4 L of any clear-water-based drink). Group 2 (PMC2/2) used PMC in a split dose (1 sachet + 2 L of a drink in the afternoon, and the same dose early in the morning before the colonoscopy). Group 3 (PEG3/1) used 3 L of PEG in the afternoon before the colonoscopy and 1 L early in the morning before the colonoscopy. Group 4 (PEG4/1) used 4 L of PEG in the afternoon before the colonoscopy. All subjects were instructed to start a low-residue diet 2 days before the colonoscopy and were asked to follow the suggested preparation regimen.

All the colonoscopy procedures were performed between 7:00 AM and 12:00 noon and not earlier than 3 hours after last intake of the preparation. A complete preparation was regarded as ingestion of more than 3.5 L of the solution according to each patient's statement.

Bowel cleansing assessment

The quality of bowel preparation was assessed through a blinded test by 6 experienced endoscopists at the end of the colonoscopy using the Aronchick scale [5]. Grade 1: a small volume of clear liquid or greater than 95% of the surface was seen; grade 2: a large volume of clear liquid covering 5% to 25% of the surface, but greater than 90% of the surface was seen; grade 3: some semi-solid stool that could be suctioned or washed away, but greater than 90% of the surface was seen; grade 4: semi-solid stool that could not be suctioned or washed

away, and less than 90% of the surface was seen; and grade 5 – a repeated preparation and colonoscopy required.

Data collection

Shortly before the colonoscopy each patient filled out an anonymous questionnaire to assess the amount of ingested fluid during preparation, frequency of bowel movements within one week before the colonoscopy, weight, height, age and gender. Overall tolerance of the preparation was rated on a 5 point scale (1: the best, 5: the worst). Nausea, vomiting, abdominal pain, bloating and incontinence during the preparation were recorded and graded (0: none, 1: present).

A written informed consent was obtained from each patient and the study was approved by the local Ethical Committee.

The quality of bowel preparation according to the Aronchick scale and the overall tolerance of the preparation were considered as the primary endpoints of the study. For both of them, differences between the study groups were evaluated using the Pearson chi-squared test for contingency tables. An analysis of variance test was employed for continuous variables (based on a data normality check). The Pearson chi-squared test was used to assess the differences in other categorical variables as well. The Spearman correlation coefficient was used to examine the relationship between variables (IBM SPSS Statistics 22). A standard level of significance, $\alpha=0.05$ was considered. The power of the test was retrospectively evaluated using the Power and Precision software version 3.2

RESULTS

Patients' characteristics

Seventy one patients were excluded because the questionnaire was not filled in completely, or the patient did not follow the dietary recommendations, the schedule of preparation (mainly in the PMC2/2 group), or due to an incomplete colonoscopy.

There was no significant difference in the baseline characteristics between both groups (Table I) except for older age and the prevalence of diabetes in the PEG3/1 group compared to the other groups ($p < 0.001$). Stool frequency did not correlate with age in this group ($r = 0.07$, $p = 0.377$).

Bowel cleansing

The mean ingested amount of the solution was similar in all groups ($p = \text{NS}$). The frequency of incomplete preparations (ingesting less than 3.5L of the solution) was highest in the PMC2/2 group (23.2%). According to patient information it was caused mainly by misapprehension of the preparation instructions. Therefore, differences were not statistically analysed. The subjects in other groups did not complete the preparation mainly because of abdominal discomfort.

Satisfactory preparation (defined as Aronchick score 1 or 2) was present in 82.6% PMC4/0, 81.6% PMC2/2, 87.3% PEG3/1 and 73.0% PEG4/0. These rates were similar in all groups with the exception of PEG4/0 subjects ($p = 0.024$). A statistically significant difference was observed in the number of subjects with the best bowel cleansing (Aronchick score 1). The split dose of PEG or any of the PMC based regimens were superior to the PEG 4/0 (42.5% PEG3/1, 37.9% PMC4/0, 38.4% PMC2/2

Table I. Baseline characteristics of the patients

	PMC4/0 n = 132	PMC2/2 n = 125	PEG3/1 n = 134	PEG4/0 n = 137	P value
Age (yr), mean±SD	56.4 ± 15.3	56.8 ± 16.1	65.0 ± 14.7	59.5 ± 14.1	<0.001
Female, n (%)	63 (47.7)	62 (49.6)	69 (51.5)	58 (42.3)	NS*
BMI (kg/m ²), mean±SD	27.7 ± 4.6	27.9 ± 4.8	28.9 ± 6.1	28.2 ± 4.6	NS*
Diabetes, n (%)	9 (6.8)	20 (16.0)	35 (26.1)	22 (16.1)	<0.001
Stool a days, n (%)	1 110 (83.3)	103 (82.4)	106 (79.1)	116 (84.7)	NS*
	2 14 (10.6)	16 (12.8)	18 (13.4)	13 (9.5)	
	3+ 8 (6.1)	6 (4.8)	10 (7.5)	8 (5.8)	

* NS - not significant

vs. 22.6% PEG4/0, $p = 0.003$). Splitting the PMC preparation had no benefit (37.9% vs. 38.4%). When comparing single dose regimens, PMC performed better than PEG (37.9% vs. 22.6%) (Fig. 1). The quality of preparation was not dependent on age, number of stools, ingested volume, presence of diabetes or the tolerance in any of the groups. The quality of bowel cleansing, as assessed by the endoscopists, is shown in Table II.

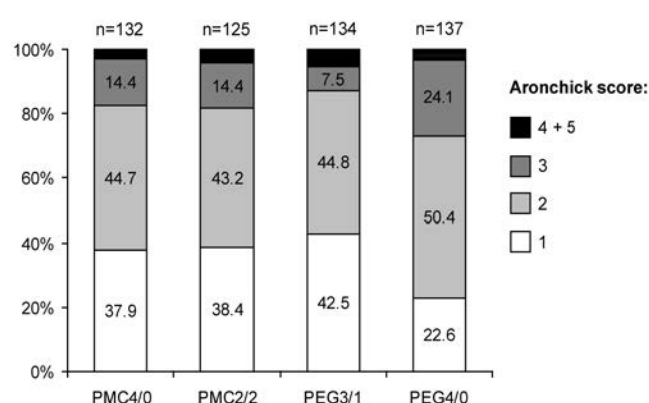
Tolerance

Overall tolerance

The PMC prepared subjects reported the best tolerance (score 1) more frequently than the PEG prepared ones (PMC4/0 vs. PEG4/0 or PEG3/1, PMC2/2 vs. PEG4/0 or PEG3/1, $p < 0.001$), without a difference in the PMC group (60.6% vs. 56.0%). Surprisingly the split dose of PEG was not tolerated better than the conventional 4 L of PEG (23.1% vs. 24.1%) (Fig. 2). Tolerance did not correlate with the amount of the solution used. The trend for better toleration of PMC4/0 in elderly subjects ($r = 0.2$, $p = 0.019$) and PEG3/1 in younger ones ($r = -0.19$, $p = 0.02$) was noticeable.

Complaints

Nausea occurred most frequently in the PEG4/0 group (32.8%) and less frequently after a single dose of PMC (6.1%, $p < 0.001$). Abdominal pain was reported less frequently after PMC4/0 (6.1%) when compared to other preparations ($p = 0.021$). Incontinence occurred most frequently in subjects prepared with PMC2/2 (34.4%, $p = 0.002$). PEG based regimens were associated with the highest prevalence of bloating (PEG4/0 38.0%, PEG3/1 25.4%, $p < 0.001$). There was no significant difference in the frequency of vomiting (Table III).

**Fig. 1.** Quality of bowel preparation with sodium picosulphate/magnesium citrate (PMC) and polyethylene glycol (PEG) in different regimens

Aronchick score 1: the best, 5: the worst; Satisfactory preparation: Aronchick score 1 or 2

DISCUSSION

The quest for optimal bowel preparation has been going on for years, but an ideal formula has not been discovered yet.

The consensus of the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) stated that PEG is the gold standard for colonoscopic bowel preparation, and sodium phosphate may serve as an alternative to PEG solutions [6]. In Europe, the European Society of Gastrointestinal Endoscopy (ESGE) recommends preparation

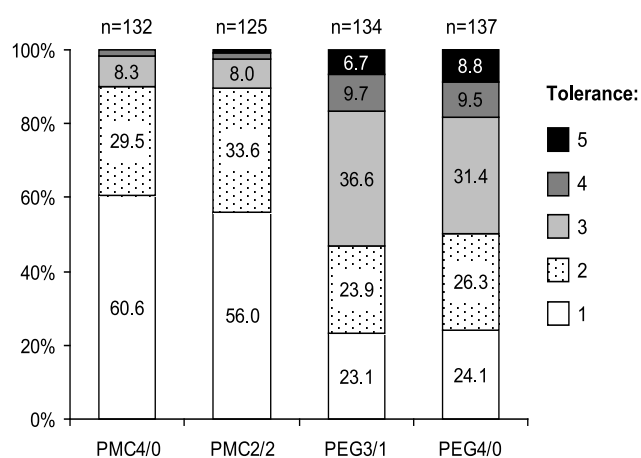
Table II. Bowel preparation quality

	PMC4/0 n = 132	PMC2/2 n=125	PEG3/1 n=134	PEG4/0 n=137	P value
Volume of preparation (L), mean±SD	3.9 ± 0.9	3.8 ± 0.8	4.0 ± 0.5	3.9 ± 0.4	NS*
Incomplete preparation, n (%)	30 (22.7)	29 (23.2)	26 (19.4)	20 (14.6)	NS*
Aronchick score, n (%)	1 50 (37.9)	48 (38.4)	57 (42.5)	31 (22.6)	0.003
	2 59 (44.7)	54 (43.2)	60 (44.8)	69 (50.4)	
	3 19 (14.4)	18 (14.4)	10 (7.5)	33 (24.1)	
	4 3 (2.3)	5 (4.0)	6 (4.5)	2 (1.5)	
	5 1 (0.8)	0 (0)	1 (0.7)	2 (1.5)	
Satisfactory preparation, n (%)	109 (82.6)	102 (81.6)	117 (87.3)	100 (73.0)	0.024

Incomplete preparation: ingestion less than 3.5L of solution; Satisfactory preparation: Aronchick score 1 or 2; * NS: not significant

Table III. Overall tolerance and prevalence of complaints during preparation

		PMC4/0 n=132	PMC2/2 n=125	PEG3/1 n=134	PEG4/0 n=137	P value
Tolerance, n (%)	1	80 (60.6)	70 (56.0)	31 (23.1)	33 (24.1)	<0.001
	2	39 (29.5)	42 (33.6)	32 (23.9)	36 (26.3)	
	3	11 (8.3)	10 (8.0)	49 (36.6)	43 (31.4)	
	4	2 (1.5)	2 (1.6)	13 (9.7)	13 (9.5)	
	5	0 (0.0)	1 (0.8)	9 (6.7)	12 (8.8)	
Nausea, n (%)		8 (6.1)	23 (18.4)	20 (14.9)	45 (32.8)	<0.001
Vomiting, n (%)		1 (0.8)	6 (4.8)	2 (1.5)	8 (5.8)	0.049
Pain, n (%)		8 (6.1)	22 (17.6)	20 (14.9)	24 (17.5)	0.021
Incontinence, n (%)		27 (20.5)	43 (34.4)	20 (14.9)	35 (25.5)	0.002
Bloating, n (%)		25 (18.9)	19 (15.2)	34 (25.4)	52 (38.0)	<0.001

**Fig. 2.** Tolerance of sodium picosulphate/magnesium citrate (PMC) and polyethylene glycol (PEG) in different regimens
Tolerance score 1: the best, 5: the worst

with a split regimen of the 4 L PEG solution (or a same-day regimen in the case of a colonoscopy performed in the afternoon), and as alternatives low-volume PEG of sodium picosulphate plus magnesium citrate [4].

The conventional 4L of PEG regimen is known to be safe and effective, but poorly tolerated due to intestinal volume expansion. There is an effort to circumvent this side effect by low-volume (2L) PEG with an additional laxative (e.g. ascorbic acid) or by magnesium citrate with stimulants (picosulfate) [7]. Picosulphate/magnesium citrate belongs to formulas with combined laxative action. Sodium picosulfate is hydrolysed by colonic bacteria to an active metabolite, which increases bowel peristalsis. The laxative effect of magnesium citrate is induced by osmotic retention of fluids in the colon. An adequate osmotic action requires the addition of a sufficient amount of any other hydration fluid.

The cleansing effect of PEG was compared mainly with oral sodium phosphate. According to the latest meta-analysis published in 2012 and including 31 studies performed from 1985 to 2010 both compounds appeared to be comparable [8]. When PMC was compared to oral sodium phosphate, the effect on bowel cleansing was similar. However, the tolerance of PMC was better and with fewer side effects such as nausea, vomiting or abdominal pain [9, 10]. In a randomised trial [11] Reggev et

al found PMC to be associated with better bowel cleansing and patient acceptability than PEG. However, the authors compared various doses and duration of the preparation (3L of PEG in the afternoon and 3 sachets of PMC from the morning the day before the colonoscopy). In another study, Worthington et al evaluated PMC and 2L of PEG containing ascorbic acid [12]. This formula is distinct from the PEG solution used in the present study, and thus, a comparison is not possible. In the SEE CLEAR II study PMC was not inferior to low-volume PEG; however PEG was combined with bisacodyl tablets [13]. Once again, no conclusion can be drawn.

The randomised trial by Voiosu et al [14] corresponds most closely to our study. The authors evaluated a split dose of 4 L PEG and a single dose of PMC. PEG performed slightly better than PMC (best cleansing 29.5% vs. 21.3%) in terms of bowel preparation, while PMC was better tolerated. Again, different regimens and volumes were used – a 4 L of split dose PEG to a single 3 L of PMC. The authors did not find any assessment of these preparations in similar dosages and/or volumes in literature.

The present study confirmed the benefits of a split dose preparation in the case of PEG. When PEG and PMC were used in this regimen, bowel cleansing was similar. It seems, at this point, that the division of PMC into more doses offers no benefit except for less interference with patient time schedule during preparation.

One may object to dividing PEG into 3 and 1L, which is distinct from PMC (2 and 2L) and may influence the results. When split doses with different volumes (4L vs. 3L) [15], (4L vs. 2L and 3L vs. 1.5L) [16] were compared, no differences were observed. There is only one study, in which 3L of PEG performed worse than 4L [17]. It is assumed that PEG in the proportion 3 + 1L has no significant impact on the results and may be applicable in clinical practice too.

It should be noted that the PEG3/1group was significantly older than the others, and one can imply an ingestion of lower volume, worse tolerance and preparation. However, this fact had no impact on the outcome. There was no correlation between age and any variables that may have an effect on the quality of preparation: the presence of constipation, volume of the formula ingested and/or its tolerance.

The cleansing quality depends not only on volume distribution, but also on the interval between bowel

preparation and the start of the colonoscopy. The shorter the delay, the better the cleansing, with the optimum being between 3 to 5 hours [18]. In our group, all patients were examined during the morning. In the case of a single dose PEG at least 10-12 hours had elapsed before testing, similarly to the PMC preparation. This experience also favours PEG preparation with the administration of the second dose of laxatives in the morning before the examination.

The quality of bowel preparation may be affected by other factors such as age, obesity, bowel resection, diabetes, constipation, etc [19]. In our group these factors were not evaluated with the exception of age, frequency of bowel movements and diabetes. No relation was found.

Subjective tolerance is what our patients are interested in. The preparation was successfully completed by 78-85% of our subjects. Other authors reported rates of 53-98% for PEG [20].

The number of subjects who will not have been able to drink the entire 4L-volume because of its intolerance will be smaller in reality. Some subjects in the PMC group did not drink the entire volume due to the fact that they did not quite understand the instructions for use.

No differences were found in the overall tolerance between PMC groups. Surprisingly nausea occurred less frequently after a single dose of PMC. Tolerance of PMC was subjectively rated better than PEG, regardless of whether PEG was used in a split or in a single dose. Better tolerance of PMC may be caused by dividing it into smaller quantities. A larger volume of the solution is generally less tolerated [21]. We consider this explanation unlikely. Of all the problems that may be caused by volume load (nausea, vomiting, bloating, pain) only nausea and bloating occurred less frequently after PMC. The same conclusion was drawn in the trial of Regev et al [11]. Better tolerance of PMC may be explained by properties of the compound itself. The role of sensory differences between solutions may play a part along with the fact that PMC can be supplemented with plain water or other drinks. This conclusion is consistent with other reports, in which PMC was better tolerated than a large volume of PEG [14, 22].

Safety issues must be taken into account. Side effects were not the subject of our study. PEG is considered to be safe [4]. PMC, if not ingested with a sufficient amount of fluids, may lead to dehydration. Mucosal irritation and inflammation were described after oral phosphates and PMC [23].

The present study has certain limitations. The baseline group characteristics were not fully comparable. It was not prospectively optimised according to sample size. However, based on the results observed in the 528 analysed patients in the four study groups, the power of the Pearson chi-squared test was calculated to be 94% for the quality of bowel preparation parameter (as expressed using the Aronchick scale), and almost 100% for the overall tolerance of the preparation.

CONCLUSION

This trial shows that bowel cleansing with PMC is comparable to a split PEG dose. Dividing the PMC preparation into two days does not improve the quality of bowel preparation and/or its tolerance. In both regimens PMC is better tolerated

than PEG irrespective of the regimen used. The single 4L of PEG the day before the colonoscopy is less effective.

Conflicts of interest. None to declare.

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