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More Is Not Always Better: A Randomized Trial Of Low Volume Oral Laxative, Enemas, And Combination Of Both Demonstrate That Enemas Alone Are Most Efficacious For Preparation For Flexible Sigmoidoscopy

Lawrence Hookey, MD[1], Samson Haimanot, MD[1], Katherine Marchut, MD[1] and Stephen Vanner, MD[1]

OBJECTIVES: Colon cleansing for flexible sigmoidoscopy using a standard fleet enema does not provide adequate cleansing in a significant number of patients. We tested whether the addition of a low-volume oral cleansing agent could mitigate this challenge without significantly compromising patient tolerance. Hypothesis: Oral picosulfate with magnesium citrate (P/MC) would enhance the colon cleansing of patients undergoing sigmoidoscopy, as assessed by the modified Ottawa Bowel Preparation Score.

METHODS: A randomized single blinded trial comparing (1) a single dose (i.e., one sachet) of oral sodium picosulfate plus magnesium citrate (P/MC) administered the night before, (2) a single dose oral P/MC the night before plus sodium phosphate enema 1 h before leaving home, and (3) sodium phosphate enema alone 1 h before leaving home for flexible sigmoidoscopy was conducted on outpatients referred for sigmoidoscopy for symptom assessment.

RESULTS: A total 120 patients were randomized to the study groups. The main indication for sigmoidoscopy was investigation of rectal bleeding ($n = 80$). There was no significant difference in bowel cleansing quality, measured by the endoscopist blinded to preparation, between P/MC, P/MC plus enema, and enema alone as measured by the modified Ottawa Bowel Preparation Scale ($P = 0.34$) or the Aronchick Scale ($P = 0.13$). Both oral P/MC regimens were associated with higher incidence of nausea, abdominal pain, bloating, and interrupted sleep than enema alone ($P < 0.05$).

CONCLUSIONS: A single dose of oral P/MC administered the night before did not result in better colon cleansing for sigmoidoscopy when used alone or with an enema and was associated with more side effects (NCT 01554111).

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INTRODUCTION

Flexible sigmoidoscopy maintains an important role in the diagnostic algorithm of several clinical presentations (for example, painless rectal bleeding in younger patients)[1–3] and is a proven screening modality for colorectal cancer.[3–10] As with all endoscopic procedures, it is important that flexible sigmoidoscopy be done efficiently and with adequate visualization of the bowel. Having an effective cleansing preparation is key to both of these factors. Rectal enemas, usually sodium phosphate based, have been the mainstay of sigmoidoscopy preparations for many years.[11–13] However, there is a need for better preparations, evidenced by trials looking at oral preparations combined with enemas[14,15] or double enema preparations.[12,16]

Oral preparations have been a mainstay of colon cleansing for colonoscopy as they cleanse the proximal as well as the distal colon and are superior to rectal enemas in this regard. There are three main categories of oral colon cleansing agents: large-volume preparations, small-volume preparations, and a hybrid combination of both. One approach to enhanced cleansing for flexible sigmoidoscopy would be to use a standard colonoscopy cleansing. Although each of these three cleansing regimens can provide adequate cleansing, the large-volume polyethylene-based solutions (polyethylene glycol) solutions are not nearly as well tolerated by patients and can be an obstacle to patients agreeing to undergo investigations.[17–23] In contrast, previous studies have shown that small-volume preparations are well tolerated and much better accepted by patients. Furthermore, our previous studies[24] have shown that a single dose (half dose of standard colon cleansing regimen) induces multiple bowel movements and hence could be an ideal adjunct to optimize cleansing for sigmoidoscopy while maintaining patient acceptance of the tolerability of the preparation.

A few previous studies have attempted to enhance cleansing for flexible sigmoidoscopy using oral preparations, but the results have been variable. Some have shown improved tolerance and cleansing whereas others have shown no difference or even negative results compared with standard sodium phosphate enemas.[11,13–15,25–27] These

[1]Gastrointestinal Diseases Research Unit, Department of Medicine, Queen's University, Kingston, Ontario, Canada
Correspondence: L Hookey, MD, Division of Gastroenterology, Hotel Dieu Hospital, 166 Brock Street, Kingston, Ontario K7L 5G2, Canada. E-mail: hookeyl@hdh.kari.net
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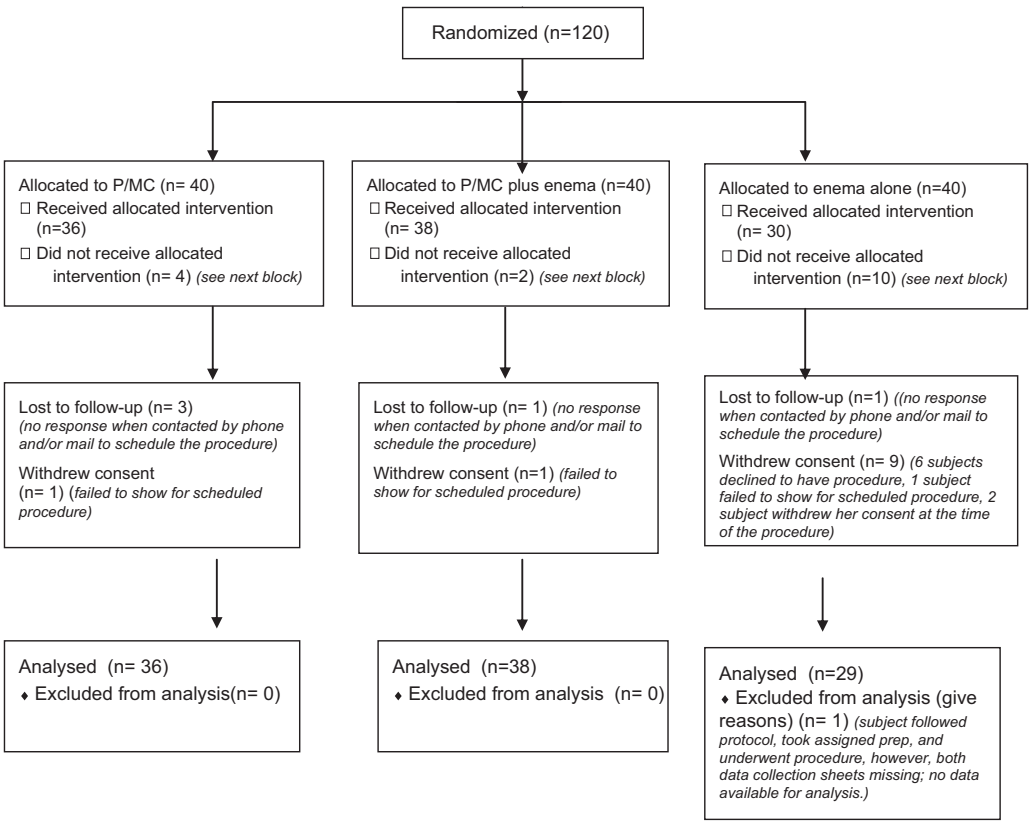

Figure 1 Patient flow through study. P/MC, sodium picosulfate plus magnesium citrate.

studies, however, have not examined the combination of a low-volume preparation and a single fleet enema, and we hypothesized that this combination would provide the ideal balance of enhanced efficacy and high patient tolerability. We chose the low-volume preparation sodium picosulfate plus magnesium citrate (P/MC) because recent studies had shown that it was particularly well tolerated compared with polyethylene glycol and sodium phosphate[21,28,29] and was also efficacious. Our previous prospective diary studies had shown that a single dose of P/MC stimulated an average of five additional bowel movements.[24]

To create the necessary comparator groups, the current study examined patient tolerability and efficacy of (1) a single sachet of P/MC (half the recommended colonoscopy dosing recommendation) administered the night before, (2) single sachet of P/MC administered the night before followed by a sodium phosphate enema 1 h before leaving home, and (3) sodium phosphate enema alone administered 1 h before leaving home, for colon cleansing before flexible sigmoidoscopy.

METHODS

Patients. Consecutive male and non-pregnant female patients aged 18 years or older who required outpatient flexible sigmoidoscopy at either the Kingston General Hospital or Hotel Dieu Hospital endoscopy units were considered for the study. Exclusion criteria included previous colorectal surgery and patients with reduced renal function (defined as eGFR less than normal range in 3 months before enrollment) or other medical conditions (such as ascites, congestive heart failure) that would increase the risk of receiving P/MC.

Study design. The participants undergoing flexible sigmoidoscopy were randomized to one of three separate preparations: (1) one sodium phosphate enema taken 1 h before leaving their home on the day of the procedure (2) one sachet of P/MC (Picosalax Ferring, Ferring Pharmaceuticals, North York, Ontario, Canada) at 7 PM the evening before the procedure and (3) combination of both one sachet P/MC at 7 PM the evening before the procedure and one sodium phosphate enema 1 h before leaving home. No dietary restrictions were given to the patients.

All the patients were recruited from outpatient gastroenterology clinics with no subjects being seen directly in endoscopy. The patients were consented and randomized by a clinical research assistant who received the assignment by opening an opaque envelope. Randomization was from an independently prepared list with permuted random-size block design (ranging in size from 6 to 12).

The study was approved by the Queen's University Health Sciences Research Ethics Board and was registered in an international research database (NCT 01554111).

Statistics. The primary outcome of the study was efficacy of cleansing, which was measured using the modified Ottawa Bowel Preparation Scale score, a validated instrument.[30] The modified scale uses the recto/sigmoid section of the scale.

Table 1 Patient demographics and technical results of flexible sigmoidoscopy

	Group			*P*-value
	P/MC alone ($n=36$)	P/MC plus sodium phosphate enema ($n=38$)	Sodium phosphate enema alone ($n=29$)	
Age (mean plus range)	44.4 (20–74)	39.6 (18–77)	43.2 (20–65)	0.38
Male (percentage)	36	63	55	0.06
Indication for sigmoidoscopy				
Rectal bleeding	28	28	24	0.60
Diarrhea	3	0	0	
Other (weight loss, incontinence, abnormal CT, rectal pain, proctitis)	5	10	5	
Insertion depth of exam (mean (cm) ± s.d.)	56 (±14)	54 (±12)	55 (±17)	0.87
Polyps detected (% of patients)	17	18	21	0.91

CT, computed tomography; P/MC, sodium picosulfate plus magnesium citrate.

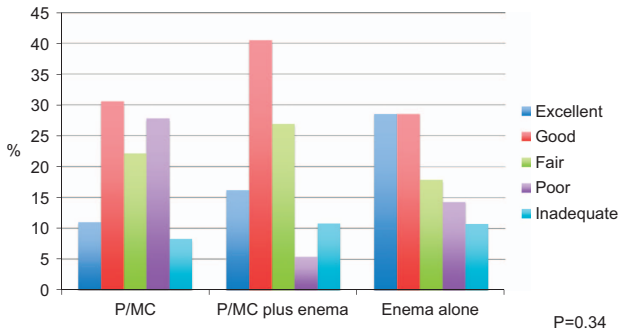

Figure 2 Bowel cleansing results as per the Modified Ottawa Bowel Preparation Scale. P/MC, sodium picosulfate plus magnesium citrate.

The endoscopist, who was blinded to the cleansing regimen, recorded the score at the end of each procedure. A score of 0 was the best possible score (Excellent) and a score of 4 was representative of an inadequate cleansing for a reasonable exam.

Power calculation. Due to the lack of prior data on this scale in sigmoidoscopy, we assumed that the scale is uniformly distributed and the s.d. would be 1.7. This was a conservative estimate. With a within-group s.d. of 1.7, we would require 34 patients in each of the three arms to achieve 90% power using an F-test at an alpha of 0.05. This would be to detect a mean difference of 1.5 points between the highest and lowest groups.[31] We assumed a 15% dropout rate, and thus aimed to recruit 120 patients.

Secondary outcomes. Each subject completed a tolerance questionnaire when they arrived in the endoscopy suite, used previously in numerous studies.[21,32–35] The questionnaire includes questions regarding acceptability of the bowel preparation (rated on a five-point scale), the patient's compliance with the regimen, and whether the patient would have the same bowel preparation regimen again for another sigmoidoscopy. Specific side effects that were queried via yes or no answers were fecal incontinence, sleep disturbance, abdominal pain, nausea, vomiting, bloating, dizziness, and rectal bleeding.

Other data collected included the maximum length of scope inserted, whether an additional enema was required to complete an adequate examination, the amount of fluid suctioned during the exam, the Aronchick score for bowel cleansing, and whether polyps were detected.

Continuous data were analyzed using the analysis of variance, ordinal data with Kruskal–Wallis, and nominal data with chi-square or Fisher's exact test, depending on the number of patients in each group.

RESULTS

A total of 120 patients were recruited from the outpatient gastroenterology clinics at Hotel Dieu Hospital between July 2012 and February 2014. Sixteen patients withdrew from the study (**Figure 1**). They withdrew because they no longer wanted to proceed with the procedure ($n=12$), had a change in symptoms resulting in a colonoscopy being arranged ($n=1$), withdrew consent ($n=2$), or chose to have the procedure done at another center ($n=1$). One additional patient was excluded due to missing tolerance and preparation quality data. The data were thus available on 103 patients undergoing sigmoidoscopy by one of six gastroenterologists all of whom were experienced using the Ottawa Bowel Preparation Scale.[36]

The mean age of the study population was 42 years (range 18–77) and the groups were well matched for age and gender (**Table 1**). Indications for sigmoidoscopy were similar between groups with the large majority being done for rectal bleeding. The majority of patients underwent sigmoidoscopy before 11 AM (with no differences in proportions waiting longer between groups) and all were compliant with their preparation instructions.

Efficacy. There were no significant differences seen in the preparation quality when assessed by either the modified Ottawa Bowel Preparation Scale ($P=0.34$) or the modified Aronchick scale ($P=0.13$, **Figure 2**). The need for additional enemas was not different between groups, nor was the mean distance reached during sigmoidoscopy (mean = 56 cm). Patients in the groups assigned to preparations with P/MC had more fluid suctioned during the exam than those taking the enema alone (**Table 2**).

Table 2 Sigmoidoscopy cleanliness data

	Group			*P*-value
	P/MC alone ($n=36$)	P/MC plus sodium phosphate enema ($n=38$)	Sodium phosphate enema alone ($n=29$)	
Mean Modified Ottawa Bowel Prep Score	1.92 (s.d. = 1.2)	1.54 (s.d. = 1.3)	1.50 (s.d. = 1.2)	0.30
Preparation rated good or excellent	41.7	56.8	57.1	0.34
Ottawa Bowel Prep Score (% of patients)				
Amount of fluid suctioned during exam	143 ml (±191)	106 ml (±124)	47 ml (±71)	**0.04**
Needed additional enema (%)	8	5.3	3.4	0.69

P/MC, sodium picosulfate plus magnesium citrate.
Bold value highlight the *P*-value <0.05.

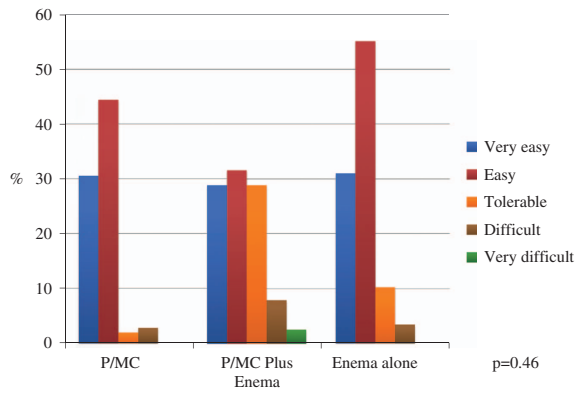

Figure 3 Tolerability of preparations. P/MC, sodium picosulfate plus magnesium citrate.

Given that the enema-only group did not meet the targeted completion number, we performed a *post hoc* imputation analysis. The best and worst possible Ottawa and Aronchick scores were imputed for seven additional cases (to match the number of patients in the P/MC group alone). There remained no significant difference between the groups.

Tolerance. The majority of patients in each group ranked their preparation regimen as very easy or easy (**Figure 3**) using a five-point global assessment of tolerance ranking the preparation regimen from very easy to very difficult. No significant differences were observed between the groups ($P=0.46$). In addition, greater than 90% of patients in each group said that they would take their assigned preparation again in the future. However, there were some differences in the experiences of patients taking the preparations. The patients in the groups taking P/MC were more likely to report nausea (although no difference in vomiting was seen), bloating, abdominal pain, dizziness, and trouble sleeping (**Table 3**). Despite this, no adverse events or serious adverse events occurred during the study.

DISCUSSION

The major advantages of flexible sigmoidoscopy are that it can be completed more quickly than colonoscopy and it requires no sedation. As a result, shorter booking intervals enable more cases to be completed during the daily endoscopy schedule. However, if the cleansing is poor, a second enema is often administered in the endoscopy suite resulting in significant delays and disruption to the schedule. Alternatively, the patients would be re-booked causing further delays in the diagnosis and treatment as well as greater use of resources. Despite the intuitive advantage of adding an oral cleansing supplement to the standard fleet enema to overcome these issues, we found no differences in efficacy between the three preparations—oral P/MC, oral P/MC plus sodium phosphate enema, or sodium phosphate enema alone. The reasons for this are unclear, but one possible explanation is that oral preparation advances stool from the right colon to the left, and paradoxically does not diminish the burden of stool for the enema to clear. Another reason for this may be the timing of the preparations, as evidence now firmly supports administering colonoscopy preparation within 4–6 h of the exam itself.[37] Whether this principle applies to sigmoidoscopy is not yet determined, given the partial cleansing provided, but will be worth investigating further.

Our results differ from several previous studies that reported better tolerance of the oral preparation than enemas.[11,13,15,25,26] There are several potential explanations for this. One is that patients recruited to the current study provided consent before enrollment (unlike several other studies), and were informed of the fact that there would be enemas in the two arms of the trial. Thus, the people enrolled into the current study were already prepared to use an enema, if required. Atkin *et al.*[27] randomized patients taking part in a larger trial but the patients were unaware of the intervention arms. Similarly, Bini *et al.*[15] randomized all patients referred without consenting them to the study, thus potentially including patients who would normally refuse an enema. Thus, the design of the current study is more likely to assess the true tolerance of the preparations, as opposed to pre-study biases of patients against certain agents such as enemas.[38,39] Nonetheless, there were aspects of the current study that could have influenced the tolerability and efficacy scores. For example, timing of preparation may have been a factor. Atkin *et al.* used an earlier time point in the day to administer P/MC and thus patients likely experienced less sleep disturbance. Similarly timing of the enema dosing has varied between the studies. In several studies, it was administered 1 h before the exam, often by a health-care professional, whereas in the current study, patients self-administered it 1 h before leaving the house. This may have increased patient tolerance of the enema but could also have resulted in poorer preparations

Table 3 Patient symptoms after completing colon cleansing regimens

Symptom	Group			*P* value
	P/MC alone (*n* = 36) %	P/MC plus sodium phosphate enema (*n* = 29) %	Sodium phosphate enema alone (*n* = 38) %	
Nausea	33	18	3	0.01
Vomiting	2	2	0	0.6
Abdominal pain	38	23	10	0.03
Dizziness	16	5	0	0.03
Bloating	38	15	10	0.01
Interrupted sleep	16	34	0	0.002

P/MC, sodium picosulfate plus magnesium citrate.

if there was a delay between the scheduled time of the sigmoidoscopy and the real start time. However, other studies have varied the timing of the enemas as well as administered a second enema,[12,14,16,25] with no major differences observed. All the exams in this study were scheduled for the morning, but the use of a morning dose of oral purgative may be worth investigating for afternoon sigmoidoscopy.

The study design did have some advantages compared with several previous studies, including the one-on-one patient instruction, consent process, intention to treat analysis, and power to detect clinically significant differences. There was a dropout rate (13.3%), mostly attributable to people deciding against undergoing the test. In our experience, this is not uncommon, especially when relatively minor symptoms such as rectal bleeding have resolved in younger patients. In fact, compared with other studies, the dropout rate was better than that described in many.[16,40] Given that all the flexible sigmoidoscopies in this study were conducted in the morning, it would be inappropriate to draw conclusions about afternoon exams; but given the longer delay between the evening before P/MC ingestion and the exam, it is difficult to hypothesize that cleansing would be enhanced. The current study also differs from others in the age of the study population as well. A majority of the patients in this study were undergoing sigmoidoscopy as an investigation of symptoms as opposed to as a screening procedure, and thus the mean age was 42 years compared with the older screening populations of other studies.[15,25,27] Given the results of the current study, it is unlikely that older age would positively impact either the tolerability or the efficacy.

In conclusion, when an oral low-volume colon cleansing agent is administered alone or as an adjunct to standard fleet enema for distal bowel cleansing, the oral preparation did not improve the quality of colon cleansing. Furthermore, although well tolerated, the oral preparation was associated with more side effects, such as nausea, abdominal bloating, and sleep disturbance.

CONFLICT OF INTEREST

Guarantor of the article: Lawrence Hookey, MD.
Specific author contributions: Lawrence Hookey: conception of study, development of protocol, data collection, data analysis, and drafting of manuscript. He approves the final version of the manuscript. Samson Haimonot: conception of study, development of protocol, data collection, data analysis, and drafting of manuscript. He approves the final version of the manuscript. Katherine Marchut: data collection, data analysis, and drafting of manuscript. She approves the final version of the manuscript. Stephen Vanner: conception of study, development of protocol, data collection, data analysis, and drafting of manuscript. He approves the final version of the manuscript.
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TRANSLATION STATEMENT

The results of this clinical trial demonstrate that improvement in the efficacy of preparation for flexible sigmoidoscopy is not achieved through the addition of agents, and efforts should focus on education and timing of enemas.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Preparation for flexible sigmoidoscopy remains a challenge, with several trials investigating alternatives and additives to enemas.

✓ Most studies have failed to show a distinct advantage of one regimen over another.

WHAT IS NEW HERE

✓ The addition of oral preparation, in the form of oral sodium picosulfate plus magnesium citrate, to enemas did not enhance bowel cleansing, and was associated with poorer patient satisfaction scores.

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