Augmentation with pre-emptive macrogol-based osmotic laxative does not significantly improve standard bowel preparation in unselected patients: A randomized trial

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Abstract

Background and Aim: The addition of a laxative prior to a standard bowel preparation (BP) has shown variable results in efficacy, safety, and tolerability of the BP. This study compared the efficacy and tolerability of a macrogol-augmented BP (M-BP) with standard BP for routine colonoscopy in unselected patients.

Methods: Adults undergoing outpatient colonoscopy were randomized to either M-BP (one sachet of macrogol-based osmotic laxative (MBOL) twice daily for eight doses prior to standard preparation) or BP (split-dose of polyethylene glycol and sodium picosulfate). Bowel cleansing was assessed using the Ottawa BP scale. Risk factors for poor BP, patient satisfaction, and tolerance were recorded.

Results: This randomized trial was stopped due to futility after 14 months; at that point, 92 subjects were randomized to the study arm and 102 to the control arm. M-BP had a success rate of 71.7% (95% CI: 58.5–82.7%), while the BP had a success rate of 67.7% (95% CI: 54.9–78.8%), with a Pearson $\chi^2$ test $P$-value of 0.639, which exceeded the cut-off for futility (0.313). In subgroup analyses, there were statistically significant decreases in the rates of successful BP in patients taking regular opioids and regular laxatives. Both preparations were well tolerated, with no difference between groups (BP – 5.3% and M-BP – 6.6% $P = 0.66$).

Conclusion: The addition of MBOL prior to a standard BP in unselected subjects does not significantly improve bowel cleanliness at routine colonoscopy. The role of this laxative in patients at high risk of poor preparation warrants further investigation.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world, with the highest estimated rates in Australia and New Zealand.1,2 Colonoscopy and polypectomy are associated with a reduction in CRC-related morbidity and mortality.2 However, the effectiveness of colonoscopy depends on adequate bowel preparation (BP).3–5 Despite its importance, inadequate BP remains a significant problem in many centers, with a reported prevalence of between 10 and 30%6–8.

The ideal BP for colonoscopy should be effective, tolerable, safe, and inexpensive.9 Available regimens consist of either high-volume iso-osmotic polyethylene glycol (PEG)-based preparations; low-volume, hyperosmolar sodium phosphate or sodium picosulfate-based preparations;10–12 or a combination of the two. All preparations have limitations with respect to efficacy, tolerability, and safety. High-volume PEG-based preparations can be poorly tolerated and have shown suboptimal colon cleansing in several studies.13,14 Oral sodium phosphate or low-volume sodium picosulfate preparations are better tolerated and can result in superior cleansing compared with PEG.10,15,16 Reports of renal impairment and electrolyte disturbances associated with sodium phosphate and sodium picosulfate remain a concern for patients with pre-existing renal impairment and the elderly,17–19 and PEG-based preparations are preferred in these patients. Despite their increasing use, there is limited evidence in relation to the safety and efficacy of combination PEG and sodium picosulfate preparations.11 Several adjunctive agents (e.g. stimulant laxatives, prokinetics, flavored electrolyte solutions, and antifoaming agents) intended to enhance BP have been investigated with limited benefit.20–24

While several predictors of poor BP have been reported, effective management strategies to improve BP in patients at high risk are unproven.25–27 Stimulant laxatives have shown some benefit when given prior to low-volume preparations.28 In some Australian centers, osmotic laxatives are given prior to standard BPs to improve bowel cleansing in patients at risk of poor BP, but the evidence for this approach is lacking. Movicol is an osmotic laxative that contains macrogol 3350 and
Electrolytes. Macrogol 3350 increases stool volume, which triggers colonic motility via the neuromuscular pathway. We hypothesized that the addition of a macrogol-based osmotic laxative (MBOL) given for several days prior to a standard BP consisting of split-dose PEG and sodium picosulfate would significantly improve bowel cleansing compared to standard BP alone. Secondary aims included determining whether patient tolerance, acceptance, and compliance were changed and whether completion rate of colonoscopy, the time taken to complete the procedure, and polyp detection rate were improved with MBOL-augmented BP.

Methods

Study design. This was a single tertiary center (The Alfred Hospital, Melbourne, Australia), investigator-initiated, endoscopist-blinded, randomized trial comparing BP augmented with one sachet of MBOL twice daily for eight doses prior to the standard preparation (macrogol-augmented bowel preparation [M-BP]) and standard preparation (BP) only. Standard BP is a combination of one sachet of PEG and two sachets of sodium picosulfate with magnesium citrate (SP/MC), taken in a split-dose manner. The study protocol was approved by the Human Ethics Committee at the Alfred Hospital, Alfred Health Melbourne, and was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000712404).

Study population. Consecutive patients scheduled to have elective routine colonoscopy were invited to take part in the study from May 2016 to July 2017. Inclusion criteria were adult patients aged ≥18 years undergoing outpatient colonoscopy for any clinically established indication. Exclusion criteria included standard contraindications to colonoscopy (including suspected bowel perforation, toxic megacolon, gastric outlet obstruction, severe colitis, and pregnancy or lactation), severe heart failure (New York Heart Association Class III or IV), advanced chronic kidney disease [estimated Glomerular Filtration Rate (eGFR) < 30], and type 1 diabetes. Patients with hypersensitivity to PEG or SP/MC and patients with phenylketonuria or Glucose-6-phosphate dehydrogenase deficiency (due to the presence of aspartamine or ascorbic acid in the BP) were also excluded. Considering the study invitation, patients perceived as being at high risk of poor BP were neither excluded nor sought.

Study protocol. After obtaining informed consent, patients were randomized on a 1:1 basis to one of two BP arms (Fig. 1) according to a computer-generated randomization schedule. Patients in both arms received instructions for a low-residue White Diet for 2 days prior to the procedure and split dose of the standard BP (PrepKit-C). Standard BP is a combination of one sachet of PEG (Glycoprep-C, consisting of macrogol 3350, sodium sulfate, sodium chloride, and potassium chloride, Fresenius Kabi Pty Ltd., Pymble, New South Wales, Australia) and two sachets of SP/MC (PicoPrep, consisting of sodium picosulfate 10 mg, magnesium oxide 3.5 g, citric acid 12.0 g, and aspartame 36 mg, Fresenius Kabi Pty Ltd.). In both study arms, the White Diet was continued until 17:00 h the day before the procedure, followed by clear fluids only. One sachet of SP/MC mixed with 250 mL of water was taken at 18:00 h, followed by 1 L of PEG at 20:00 h the evening before the procedure. For morning procedures, another sachet of SP/MC in 250 mL of water was taken at 04:00 h, with the patient fasting from 06:00 h, while for afternoon procedures, the last sachet was taken at 07:00 h, with fasting from 11:00 h. In addition, patients assigned to the study arm (M-BP) received MBOL twice daily over 5 days (a total of eight doses), starting at 17:00 h on day five prior to the procedure. Each sachet of the studied laxative contains macrogol-3350 13.125 g, sodium chloride 350.7 mg, sodium bicarbonate 178.5 mg, potassium chloride 46.6 mg, lemon flavor, and potassium acesulfame as a sweetener, mixed with 125 mL of water for ingestion.

On the day of the procedure, patients completed a questionnaire on the tolerability of the assigned BP and collected patient history of diabetes and the use of laxatives or other medications that may affect bowel habit (e.g. opioid-based medications, antidepressants, antipsychotics).

The proceduralist, nursing staff, and anesthetists were blinded to the allocated BP. Additional data collected by the proceduralist and endoscopy nursing staff included indication for the procedure, caecal intubation, terminal ileum intubation, previous

Figure 1 Flow diagram of the study protocol. BP, bowel preparation; M-BP, macrogol-augmented bowel preparation; MBOL, macrogol-based osmotic laxative.
bowel resection, number of polyps detected, number of polyps
retrieved, total procedure time, withdrawal time, and the quality
of bowel-cleansing cleanliness as assessed by the Ottawa Bowel
Preparation Quality scale (OBPS). All procedures were
performed by experienced gastroenterology consultants or
consultant-supervised trainees.

The primary end-point was successful BP determined by
the OBPS (Table 1), defined as the fulfillment of the following
two criteria: a score of two or less in each colonic segment for
cleanliness and a score of two or less for the fluid component.
Secondary outcomes included tolerability and adherence to the
allocated BP regimen; colonoscopy outcomes such as caecal
intubation rate, polyp detection rate, and withdrawal time; and
patient risk factors for poor BP.

Statistical analysis. A sample size of 362 patients for ran-
domization was calculated assuming a successful cleansing rate
of 85% for the conventional high-volume PEG-based BPs in
accordance with the available evidence and conjectured improve-
ment in the success rate of 10% (e.g. from 85 to 95%) in the aug-
mented BP (M-BP) arm.11 With a two-sided binomial test
(alpha = 5%), 145 patients were required in each arm to achieve
a power of 80% for the detection of the conjectured improve-
ment. Inflating the calculated sample size requirement by up to
20% to account for dropouts, 181 patients were intended to be
randomized to each arm to test the primary outcome.

The analysis of the primary efficacy end-point was con-
ducted on a modified intention-to-treat (mITT) subset of all ran-
domized patients (i.e. on a subset of the conventional ITT
analysis set). Any patient who met one or more of the following
criteria was excluded from the mITT subset.

| Table 1 Summary of the scoring system for the Ottawa bowel prepa-
ration scale |

| Part 1 | Endoscopic appearance | Comment |
|--------|------------------------|---------|
| 0      | Excellent              | Mucosal detail clearly visible. If fluid present, it is clear. Almost no stool residue |
| 1      | Good                   | Some turbid fluids or stool residue but mucosal detail is still visible. Washing and suctioning not necessary |
| 2      | Fair                   | Turbid fluid or stool residue obscuring mucosal detail and contour. However, mucosal detail becomes visible with suctioning. Washing not necessary |
| 3      | Poor                   | Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained |
| 4      | Inadequate             | Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning |

| Part 2 | Fluid | Small: 0 | Moderate: 1 | Large: 2 |

1. The procedure was canceled for any reason (including “patient did not take BP”)
2. The procedure was conducted before the scheduled date, and no data were collected
3. The patient was randomly allocated to the augmented BP arm (M-BP), but it was known that no macrogol sachets were taken prior to the procedure
4. Failed colonoscopy (secondary to any cause unrelated to BP)

Patients randomized to the interventional arm who took
fewer than six of the eight macrogol sachets were excluded from
a supplementary per-protocol analysis of the primary end-point.
This per-protocol set (PPS) was a subset of the mITT analysis
set. A blinded interim analysis of the primary outcome was
scheduled to be performed after 50% of the randomized patients
had been assessed. A total of 194 patients met inclusion criteria
at the time of the interim analysis. The interim and intended final
analyses used O’Brien-Fleming-like Lan and De Mets spending
functions to set both the test size (alpha) for efficacy and the beta
(Type II error rate) for futility. The actual information fraction at
the time of the interim analysis was calculated as:

\[
\left(\frac{n_1 \times n_2}{n_1 + n_2}\right) / (n/2)
\]

where \(n_1\) was the current number of patients in “arm 1” (or study group) of the mITT analysis set, \(n_2\) was the current number of patients in “arm 2” (or control group) of the mITT analysis set, and \(n\) was the planned number of patients in each arm of the mITT analysis set at the time of the final analysis (Fig. 2). At the time of the interim analysis, the information fraction was 66.7%, a \(P\)-value of ≤0.012 was the threshold for declaring the superior-
ity of one arm over the other, and a \(P\)-value ≥0.313 was the
threshold for declaring futility.

The method of repeated confidence intervals (RCI) was
implemented to calculate the overall 95% confidence interval for
the difference. In the computation of the 100% (1 − α) confi-
dence interval, the alpha used at the interim analysis was the same as the \(P\)-value threshold for superiority. The exact Clopper-
Pearson method was used to calculate the confidence intervals.
The exact Pearson \(\chi^2\) test was used to compare the arms, and the consequent \(P\)-value was used to make a decision to stop or con-
tinue the trial.

Logistic regression was used to conduct subgroup analyses
of the primary end-point for each of five potential risk factors for
suboptimal BP: regular opioid use, history of diabetes, regular
use of laxatives, polypharmacy (use of more than eight regular
medications), and poor mobility.33 Wald \(\chi^2\) tests were used to
investigate the main effects of the subgroup factor and the treat-
ment and also their two-way interaction. All analyses were con-
ducted using the SAS 9.4 statistical package (SAS Institute Inc.,
Cary, NC, USA).

Results

A total of 224 patients were initially recruited to the study, of
which 30 patients (12 for the BP group and 18 for the M-BP)
were excluded. Of the remaining 194, 102 had been randomized
to receive standard BP, and 92 had been randomized to the aug-
mented bowel preparation (M-BP) (Fig. 2). Baseline
characteristics, including demographics and indications for colonoscopy, were comparable between the groups (Table 2).

Based on the mITT analysis, augmentation of the standard BP with MBOL resulted in 71.7% successful BPs, while the standard preparation resulted in 67.7% (P = 0.639) (Table 3). The comparison of the treatment arms in the per-protocol analysis was also not significant (P = 0.731). For both analyses, the observed P-values of the χ² tests exceeded the cut-off for futility (0.313), and this supported a decision to close the trial early. There was also no difference in the caecal intubation rate (P = 0.36), polyp detection rate (P = 0.8), and polyp retrieval rate (P = 0.79) between the study groups.

Subgroup analyses of the primary end-point with each of the five potential risk factors for poor BP, namely, regular opioid use, history of diabetes, regular use of laxatives, polypharmacy (regular use of eight or more medications), and poor mobility, did not indicate treatment differences within the subgroups (Table 4). However, statistically significant differences in successful BP were observed for opioid use and laxative use.

Both BP regimens were well tolerated by the participants as evidenced by few adverse symptoms (BP 5.3%, M-BP 6.8%, P = 0.66). The addition of MBOL to standard BP did not cause significant additional discomfort to the participants, with only four (4.4%) patients reporting adverse symptoms (diarrhea [n = 1], abdominal cramps [n = 2], fecal incontinence [n = 1]).

### Discussion

Inadequate BP continues to be a major problem at colonoscopy. Split-dose 4 L PEG preparation is considered the gold-standard BP, but it is often poorly tolerated because of the large volume and side effects, including bloating, nausea, and vomiting. Low-volume BPs, such as sodium picosulfate, are better tolerated but may be less efficacious than split-dose PEG-based preparations. Therefore, BP regimens that combine optimal colon cleansing with high patient tolerability and safety are needed.

Split-dose combination PEG and SP/MC with low-residue White Diet for 2 days prior is the current standard BP at many Australian endoscopy centres. MBOL is effective and safe in the treatment of constipation. Given its utility in the management of constipation, it has been used to enhance the efficacy of BP despite a lack of supporting evidence. To our knowledge, this is the first study to assess the efficacy of an osmotic laxative...
Successful bowel preparation with 10% conjectured improvement in the success rate

Laxative,44 in addition to low-volume PEG (2 L), did not improve the percentage of successful bowel preparations. No opioid use, 72.7% (62.8%, 81.3%); Opioid use, 56.8% (41.2%, 72.8%).

BP, bowel preparation; M-BP, macrogol-augmented bowel preparation.

Table 3 Primary end-point – Successful bowel preparation assessed by modified intention-to-treat analysis (mITT) and per-protocol analysis (PPS) with 10% conjectured improvement in the success rate

| Primary end-point | Treatment arm | Total number of patients | Number of successful bowel preparations | Percentage of successful bowel preparations | Lower limit of confidence interval | Upper limit of confidence interval | Exact Pearson χ² test P-value |
|-------------------|---------------|--------------------------|----------------------------------------|-------------------------------------------|---------------------------------|---------------------------------|--------------------------------|
| Successful bowel preparation (mITT) | M-BP (study arm) | 92 | 66 | 71.7 | 58.5 | 82.7 | 0.639 |
|                     | BP (control arm) | 102 | 69 | 67.7 | 54.9 | 78.8 |          |
|                     | Difference       | 4.1 | -1.39 | 21.9 | 0.731 |
| Successful bowel preparation (PPS) | M-BP (study arm) | 72 | 52 | 72.2 | 57.1 | 84.4 |          |
|                     | BP (control arm) | 92 | 63 | 68.5 | 55.0 | 80.0 |          |
|                     | Difference       | 3.7 | -15.9 | 23.3 |          |

1Clopper-Pearson exact confidence interval (α = 0.012).

BP, bowel preparation; M-BP, macrogol-augmented bowel preparation.

Table 4 Primary end-point – Subgroup analyses with each of the five risk factors for suboptimal bowel preparation (mITT)

| Subgroup factor          | Main effect of subgroup factor (P-value) | Main effect of treatment (P-value) | Interaction (P-value) |
|--------------------------|----------------------------------------|-----------------------------------|----------------------|
| Opioid use               | 0.032†                                 | 0.263                             | 0.282                |
| Diabetes                 | 0.659                                  | 0.916                             | 0.257                |
| Laxative use             | 0.009†                                 | 0.326                             | 0.136                |
| Medications –            | 0.205                                  | 0.610                             | 0.900                |
| Eight or more            | 0.348                                  | 0.427                             | 0.988                |

1Percentage (confidence interval [CI]) of successful bowel preparations: No opioid used, 72.7% (62.8%, 81.3%); Opioid used, 56.8% (35.2%, 76.6%).

2Percentage (CI) of successful bowel preparations: No laxative used, 72.4% (63.1%, 80.5%); Laxative used, 41.2% (14.2%, 72.8%).

P-values refer to the Wald χ² test for each effect in each of the five subgroup analyses.

BP when compared with high-volume PEG (4 L).23 Administration of Bisacodyl several days before a standard BP also did not improve the quality of BP.28 Current guidelines do not support the routine use of adjunctive agents to enhance BP; however, they may be used in selected circumstances, including patients at high risk of poor preparation.42

The present study has several limitations. First, we note the low successful BP rate for both the study group (71.7 mITT and 72.2% PPS) and the control group (67.7% mITT and 68.5% PPS). In our study, successful BP was defined by an OBPS score ≤ 6 (range: 0–14), which may have been too stringent for determining the adequacy of BP. Recently, the United States Multi-Society Task Force (USMSTF) on CRC defined adequate BP as one that enables the endoscopist to follow the recommended screening and surveillance guidelines and the ability to detect lesions >5 mm in size (target of ≥85%). In our study, around one third (34%) of included patients were noted to have one or more risk factors for poor BP, such as diabetes, opioid use, reduced mobility, polypharmacy, and laxative use (as a marker of constipation). This relatively large proportion of the cohort may have lowered the overall BP success rates. It is plausible that, if we had only included patients at high risk of poor BP, we may have shown a benefit of the studied laxative augmentation; however, we wished to document the effect of MBOL in unselected patients. While the study was not powered to detect treatment differences within subgroups of high-risk patients, we nonetheless observed significant effects of opioid and laxative use on successful BP at the time of the interim analysis when approximately 67% of the target accrual had been completed. We accept that the results from our single-center study may not be representative of other endoscopy units and that a multicenter randomized trial may be more appropriate to determine the efficacy of MBOL as an adjunct prior to BP. Finally, biochemical abnormalities related to BP were not recorded in this study. Although the studied laxative is close to iso-osmotic, we do not know whether its addition to a standard BP may increase the risk of electrolyte disturbances, although patients at high risk were excluded from the study (i.e. severe heart failure, advanced chronic kidney disease [eGFR < 30]).

In summary, the results of this randomized study demonstrate that taking MBOL prior to a standard low-volume BP in unselected patients does not clearly increase the percentage of

used as an adjunct prior to BP. In our study, an interim analysis of the primary end-point, successful BP, met the prespecified threshold for stopping for futility. While this curtailed study does not demonstrate equivalence of BP and M-BP, the outcome suggests that MBOL administered over 5 days before a low-volume BP with standard BP results, at most, in a small and clinically nonsignificant improvement (our observed improvement was 4%, i.e. from 67 to 71%). This is despite high tolerability of the augmented BP (M-BP 94 vs BP 96%). The curtailed study did find significant reductions in successful BP associated with opioid use, and also laxative use, among the whole cohort.

Several adjuncts to BP have been investigated previously, including metoclopramide, simethicone, senna, bisacodyl, spasmytotics, probiotics, and olive oil. However, none have been shown to improve the quality of BP. Metoclopramide used as an adjunct to PEG-based BP did not improve colonic cleansing or patient tolerance. Similarly, the addition of simethicone to sodium phosphate failed to improve BP but did reduce air bubbles in the colon. Senna, an anthranoid laxative, in addition to low-volume PEG (2 L), did not improve

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patients with successful BPs. The question of whether or not macrogol augmentation can make a significant difference to the success rates in patients at higher risk of poor BP remains unresolved and should be investigated further with a large multicenter randomized trial.

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