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# Colon Capsule Visualization Is Not Enhanced with Prucalopride: A Randomized Controlled Trial

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## INTRODUCTION

Colon capsule endoscopy is designed to be a less invasive method of examining the colon. Currently, its use has been largely limited to individuals who do not want to undergo a colonoscopy or have had an incomplete exam. A number of studies have examined the efficacy and reliability of the colon capsule, and the main limiting factor is the quality of the bowel preparation. The goals of bowel preparation for colon capsule differ from optical colonoscopy; for instance, the level of cleansing required is higher, as washing during the exam is not possible. In addition, the preparation needs to provide propulsion for the capsule in order for the entire colon to be examined prior to battery expiration (currently approximately 11 hours). This is often achieved with additional 'booster' doses of preparation such as sodium phosphate (NaP) (1).

The bowel preparation that has become the standard for the colon capsule in Europe was reported by Schoofs et al. (2). Patients consumed a clear liquid diet the day before the exam and then ingested 3 L of polyethylene glycol solution (PEG) solution the evening prior to and 1 L of PEG the morning of the exam. Fifteen minutes before ingesting the capsule, patients took domperidone 20 mg orally. Two hours after ingesting the capsule, they drank 45 mL of a NaP booster. If the capsule was not excreted three hours after the first booster, then a second NaP booster of 30 mL was administered. If the capsule was not excreted by seven hours, a bisacodyl suppository was administered. This intense regimen resulted in the colon capsule being excreted in 83% of patients, and the bowel preparation rated as good or excellent in 78% (2). However, since NaP is not available in North America due to safety concerns, there is a need for a colon capsule bowel preparation that is acceptable to patients and provides similar completion rates and visualization as colonoscopy.

Several trials have been published evaluating alternative preparations, with variable success rates (1–5). Most use additional doses of traditional bowel purgatives as boosters to move the capsule along into the colon, but sodium picosulfate and magnesium citrate (P/MC) has yet to be investigated for this. An orally administered small bowel and colonic prokinetic agent, such as prucalopride (Resotran, Janssen Inc., Toronto, Canada) has not been evaluated as a booster.

Prucalopride is a selective, high-affinity 5-hydroxytryptamine$_4$receptor agonist for the treatment of chronic constipation. It has been shown to increase intestinal motility in clinical trials of constipated patients (6). Its peak plasma concentration is reached at 2.1 hours, and it has an elimination half-life of 24–30 hours. A maximum plasma concentration of about 7 ng/mL is reached after 3 days of repeated dosing of a 2 mg dose (7).

A pilot study compared the colon cleansing and colon capsule completion rates with prucalopride used as a booster in patients taking PEG and P/MC preparations (8). While overall complete exam rates in the pilot study were poor, it was higher in those who received a second booster dose of prucalopride. This preliminary data suggested that higher doses of prucalopride might provide the 'booster effect' needed, without the safety concerns or tolerability issues associated with boosters such as sodium phosphate.

P/MC is a combination of a colonic prokinetic agent (sodium picosulfate) with an osmotic laxative (magnesium citrate). It is commonly used for preparation for colonoscopy and has the potential to be used as a substitute for NaP as a booster for colon capsule, as it has been shown to have similar efficacy for colon cleansing with a more favorable safety profile.

## HYPOTHESIS

In preparation for colon capsule examination, a regimen that involves daily oral prucalopride for 4 days and split dose PEG, with boosters of either an additional prucalopride dose or P/MC on the day of colon capsule exam, will improve the visualization of the colonic mucosa and the rate of complete exams.

## METHODS

This was a prospective, randomized, investigator-blinded, controlled study comparing colon capsule preparation and completion rates with split-dose PEG and 1) prucalopride 2 mg daily for 4 days; 2) prucalopride 2 mg daily for 4 days plus a prucalopride booster after ingestion of the capsule; and 3) prucalopride 2 mg daily for 4 days plus a P/MC booster, in out-patients referred for a routine colonoscopy at the Hotel Dieu Hospital in Kingston, Ontario.

Approval was obtained from the Health Sciences Research Ethics Board at Queen's University, and the study was registered in an international clinical trial database (NCT01864915).

### Patient Selection and Randomization

Consecutive male and female patients between the ages of 18 and 75, undergoing colonoscopy for screening, surveillance or symptom assessment, were considered for the study.

After being screened for study participation by a gastroenterologist, a research assistant met with each potential participant to explain the goals of the study, the study procedures, answer questions and obtain informed consent.

Exclusion criteria included the following: symptoms of dysphagia or problems with swallowing, bowel obstruction or ileus, known stricture or fistula, inflammatory bowel disease, previous small or large bowel surgery, severe gastroparesis or motility disorder, severe renal impairment (glomerular filtration rate [GFR] less than 55 within three months of study), congestive heart failure (New York Heart Association [NYHA] class III or IV), active ischemic heart disease, decompensated cirrhosis or severe hepatic dysfunction (ascites or INR>2), history of arrhythmia, diabetes on treatment with insulin or oral hypoglycemics, and pregnant or nursing women.

After consent was obtained, patients were randomized via sealed opaque envelopes containing assignment to either one of the following three groups: 1) prucalopride group: prucalopride 2 mg for 4 days, 2) prucalopride booster group: prucalopride 2 mg for 4 days plus a 2 mg prucalopride booster, or 3) P/MC booster group: prucalopride 2 mg for 4 days plus a P/MC booster. Assignment was by random computer-generated numbers, prepared by an independent biostatistician.

### Preparations and Patient Instruction

The study participants received their instructions for colon capsule and colonoscopy preparation on the date that the colonoscopy was ordered by the gastroenterologist (see Table 1 for timeline of preparation). All patients were instructed to take prucalopride 2 mg once daily, in the morning, starting 3 days before the colon capsule examination. They consumed a clear fluid diet the day before the capsule study.

All patients were asked to consume 2 L of PEG over a period of 2 hours, starting at 18:00 the evening before the capsule exam and 2 L of PEG starting at 05:00 the morning of the exam. The video capsule was ingested under supervision at 08:00, followed immediately by the fourth dose of prucalopride.

Patients assigned to the prucalopride booster group took an additional prucalopride 2 mg dose at the time of capsule ingestion, for a total of 4 mg. Those assigned to the P/MC booster group took a full sachet of P/MC 2 hours after capsule ingestion. If the capsule had not been excreted by 14:00 (6 hours after capsule ingestion), the data recorder emitted an alarm. Patients in the P/MC booster group were asked to take a second P/MC booster (half a sachet) when they heard the alarm.

Patients were permitted a light snack at 15:00. After 11 hours, patients removed the belt and data recorder. Colonoscopy was performed the following day. All patients continued a clear fluid diet and consumed an additional PEG 2 L at 07:00 the following morning, with the colonoscopy scheduled for 11:00.

### Outcomes

The primary outcome was the quality of the bowel preparation using a previously described scale (4).

The points on the cleansing level scale are as follows:

1. Poor: mucosa was largely obscured by opaque debris or turbid fluid
2. Fair: a portion of the mucosa was obscured by turbid fluid and/or debris large enough to prevent reliable visualization of polyps > 5 mm in size
3. Good: fluid was clear and any small pieces of debris or mucus were dispersed across the image or separated enough to not obscure polyps > 5 mm in size
4. Excellent: fluid was clear and image was either free of debris or had only small bits of scattered debris

Each study was saved with a random identifier and independently interpreted by two endoscopists, Lawrence Hookey and Robert Bechara, who each have experience in colonoscopy and video capsule endoscopy evaluations. The interpreters were blinded to the preparation taken by the individual patients. Colon capsule completion was defined as visualization of rectum or anal vasculature or an expelled capsule.

Secondary outcomes included the rate of complete exams, defined by visualization of the rectum and anal vascular arcade or expulsion of the capsule prior to the battery expiring, or both. Other secondary outcomes included patient tolerance of the preparations, as assessed with a survey questionnaire

**Table 1.** Bowel cleansing regimens

| | **Prucalopride** | **Prucalopride + Prucalopride Booster** | **Prucalopride + Picosalax Booster** |
|---|---|---|---|
| **Day 1** | | | |
| 0800 | Prucalopride 2 mg | Prucalopride 2 mg | Prucalopride 2 mg |
| **Day 2** | | | |
| 0800 | Prucalopride 2 mg | Prucalopride 2 mg | Prucalopride 2 mg |
| **Day 3** | Clear fluid diet | Clear fluid diet | Clear fluid diet |
| 0800 | Prucalopride 2 mg | Prucalopride 2 mg | Prucalopride 2 mg |
| 1800 | PEG 2 L | PEG 2 L | PEG 2 L |
| **Day 4** | | | |
| 0500 | PEG 2 L | PEG 2 L | PEG 2 L |
| 0700 | NPO | NPO | NPO |
| 0800 | Colon capsule<br>Prucalopride 2 mg | Colon capsule<br>Prucalopride 4mg | Colon capsule<br>Prucalopride 2 mg |
| 0900 | Clear fluid diet | Clear fluid diet | Clear fluid diet |
| 1000 | -- | | Picosalax full sachet |
| 1400 | - | - | If study not complete, Picosalax half sachet |
| 1500 | Light snack, then resume clear fluid diet | Light snack, then resume clear fluid diet | Light snack, then resume clear fluid diet |
| **Day 5** | | | |
| 0700 | PEG 2 L | PEG 2 L | PEG 2 L |
| 0900 | NPO | NPO | NPO |
| 1100 | Colonoscopy | Colonoscopy | Colonoscopy |

completed on the day of the colonoscopy (9–11), as well as polyp detection when compared to the colonoscopy the day after colon capsule exams.

### Statistics

This was a pilot study to assess the efficacy of the two booster medications in colon visualization and exam completion rates. Twenty patients per group were recruited to detect a difference in proportion of patients having a good or excellent preparation from 50% to 90%, based on our prior data and the clinical criteria for acceptable rate of poor preparation in colon capsule.

Continuous data were compared using ANOVA, while categorical data were compared with the chi-square test or Mann Whitney.

## RESULTS

Sixty patients were recruited for the study, and 48 underwent colon capsule exams. All 48 participants had a subsequent colonoscopy. Reasons for not completing the colon capsule included withdrawal of consent (n=9) and new diagnosis of renal insufficiency on screening bloodwork (n=3; see Figure 1, CONSORT flow diagram). Data are presented for all patients enrolled in the study who ingested any part of the preparation.

The mean age of the participants was 59.3 years, with no significant difference between groups in age, weight or gender distribution (Table 2). The majority of cases were performed for screening or surveillance.

The study completion rate was higher in the P/MC group, with 7 out of 13 having a complete study, compared to 2 out of 19 and 4 out of 16 in the prucalopride and prucalopride booster groups, respectively (0.025).

No difference was seen in quality of bowel preparation between the two prucalopride groups, while P/MC was associated with a significantly higher and thus better score (Table 3, p=0.002). There were no significant differences in subjects rating of preparation taste or the ease of completing the regimen (Table 4). Side effects reported after starting the prucalopride included mild abdominal pain (n=8), diarrhea (n=13), and headache (n=8).

The rate of complete colon capsule studies was low, and thus, limited the comparison to optical colonoscopy with respect to polyp detection. When all subjects were included (including incomplete colon capsules or colonoscopies), the overall adenoma detection rates for colon capsule and colonoscopy were 25% and 64.6%, respectively. In the 13 patients with complete colon capsule examinations, seven had one or more polyps detected during the capsule exam, and eight had polyps discovered during optical colonoscopy.

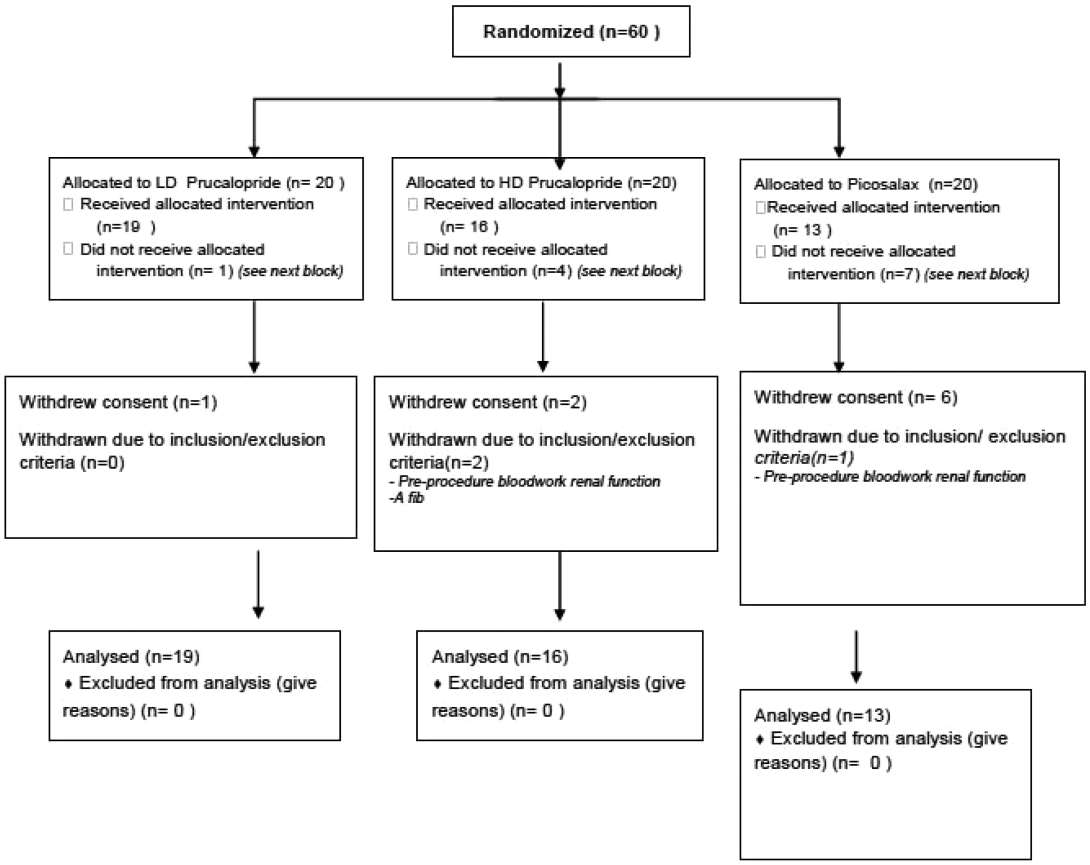


**Figure 1.**

## DISCUSSION

This randomized clinical trial investigated whether the results of the intense regimens described previously for colon capsule exams could be accomplished with a regimen based on a pill (prucalopride), supplemented by a higher dose prucalopride or P/MC booster. Unfortunately, despite all versions of the preparation being well tolerated, none had an acceptable rate of complete colon exams, with the highest being 54% in the P/MC group.

The trend toward better cleansing and higher completion rates suggests that perhaps P/MC can be leveraged further to increase the completion rates. This may potentially be accomplished with increasing the second dose from half a sachet to a full sachet. It also raises the question of which type of booster is most efficacious: prucalopride is a pure motility agonist, whereas P/MC combines osmotic laxative effects with stimulation of motility. Attempts at boosting with PEG, a non-osmotic, non-motility laxative, have not been particularly fruitful either (12). Further support of osmotic boosters comes from a trial using split-dose PEG and sodium sulfate (Suprep$^{tm}$, Braintree Laboratories Inc., Braintree) boosters which had promising results, with bowel preparation reported as good to excellent in 85%, and very high completion rates of > 95% (13). However,

**Table 2.** Baseline data

| | | Prucalopride n=19 | Prucalopride booster, n=16 | P/MC booster, n=13 | *P* value |
|---|---|---|---|---|---|
| Age, mean (SD) | | 57.9 (11.9) | 60.2 (8.2) | 60.2 (14.6) | 0.8 |
| Gender (n = male) | | 7 | 8 | 9 | 0.18 |
| Weight, kg, mean (SD) | | 83.2 (15.7) | 86.8 (14.8) | 94.6 (16.2) | 0.14 |
| Indication | Rectal bleeding/anemia | 2 | 1 | 1 | 0.31 |
| | Positive test (FOBT*, CT) | 0 | 1 | 0 | |
| | Screening/surveillance | 14 | 14 | 12 | |
| | Change in bowel habits | 3 | 0 | 0 | |

**Table 3.** Visualization quality in colon capsule examinations

| | Prucalopride, n=19 | Prucalopride booster, n=16 | P/MC booster, n=13 | *P* value |
|---|---|---|---|---|
| Average prep. Score | 1.84 (0.78) | 1.88 (0.59) | 2.66 (0.52) | 0.002 |

**Table 4.** Tolerance of preparations

| | | Prucalopride, n=19 | Prucalopride booster, n=16 | P/MC booster, n=13 | *P* value |
|---|---|---|---|---|---|
| Preparation Taste | Excellent | 0 | 2 | 1 | 0.15 |
| | Good | 3 | 2 | 3 | |
| | Okay | 8 | 10 | 5 | |
| | Poor | 5 | 1 | 4 | |
| | Bad | 3 | 1 | 0 | |
| Ease of preparation | Very easy | 2 | 1 | 0 | 0.13 |
| | Easy | 6 | 6 | 3 | |
| | Tolerable | 9 | 5 | 7 | |
| | Difficult | 2 | 1 | 2 | |
| | Very Difficult | 0 | 3 | 1 | |

this medication is currently only available in the United States, and these study results have yet to be replicated.

The current study has certain limitations. The number of patients declining to complete the study was higher than expected, for reasons that are unclear but may have involved the additional day of bowel cleansing and the additional hospital visits involved in undergoing two procedures. Thus, the power to detect small differences in colon capsule preparation or completion rates would be impaired. Nonetheless, the completion rates were so far from acceptable that the concept of further enrolment using these regimens does not seem reasonable.

Patient interest in colon capsule appears to remain high despite its challenges, which include those that are potentially surmountable (e.g., polyp detection rates less than colonoscopy, intense preparation regimens) and those inherent in the procedure (e.g., need for follow up colonoscopy in a substantial proportion of patients, incomplete exams). The continued high use of computer tomography colonography points to patients' desire for a less invasive procedure than colonoscopy. The myriad of screening options (flexible sigmoidoscopy, stool testing, CT colonography, colon capsule and colonoscopy) can result in complex conversations with patients, and no study to date has examined the effect of education and discussion around the available options. Although the process of how patients weigh these options has not been extensively investigated, some studies suggest that preparation intensity is key (14, 15). At this point, this factor would not favour colon capsule; however, patient discomfort and invasiveness of the test are also key components, thus encouraging further research into this new technology. With so many options becoming available, the reasoning behind patient decision-making deserves much more attention and research than it has currently received.

In conclusion, the colon capsule cleaning regimens evaluated in this study were inadequate to be recommended for regular use. Nonetheless, the option of taking a pill-supplemented cleansing regimen for colon capsule seems naturally aligned with patients' preference of a pill-based exam to colonoscopy. As other pro-kinetic agents are developed and marketed, future evaluation of their use in this area is warranted.

### Author Contributions

Lawrence Hookey developed the concept, co-designed the study, recruited patients, performed blinded review of the videos, performed data analysis, and drafted and revised the manuscript. Melissa Kelley developed the concept, co-designed the study, recruited patients, and revised the manuscript. Katherine Marchut co-designed the study, recruited patients, and revised the manuscript. Jordan Green co-designed the study, assisted in data collection and analysis, and revised the manuscript. Robert Bechara co-designed the study, recruited patients, performed blinded review of the videos, and drafted and revised the manuscript.

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