Clinical utility of purgative bowel preparation before capsule endoscopy: a multicenter, blinded, randomized controlled trial

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Background and Aims: Optimal bowel preparation before capsule endoscopy (CE) is currently unknown. In this multicenter, blinded, randomized controlled trial, we assessed clinical effectiveness of 2 types of purgative regimen and a control arm of clear fluid only.

Methods: Patients with suspected small intestinal bleeding were randomized into 3 arms: arm A, clear fluids only for 18 hours before CE and simethicone 200 mg in 150 mL water immediately before CE; arm B, same as A + 2 L of polyethylene glycol (PEG) 12 hours before CE; and arm C, same as A + 1 L PEG + sodium ascorbate 3 hours before CE. To assess diagnostic yield, lesions were classified either as highly relevant (P2) or less relevant (P0 or P1) lesions. Small-bowel visualization quality (SBVQ) was assessed using the Brotz score. Patient tolerability was assessed using the visual analog scale (0-10, with lower scores indicating better tolerability).

Results: Two hundred twenty-nine patients completed the study. The mean age was 58.7 years (95% confidence interval, 29.3-87.9), and 47.2% were men. There was no significant difference in diagnosis of P2 lesions in arms A, B, and C (48.7%, 48.0%, and 45.9%, respectively; $P = .94$). Overall SBVQ and distal SBVQ were similar across the 3 arms ($P = .94$ and $P = .68$, respectively). Patients reported better tolerability in arm A (mean score, 1.5) compared with arms B and C (mean score, 3.5 and 2.6, respectively; $P < .001$).

Conclusions: The use of a purgative bowel preparation before CE does not improve diagnostic yield or small-bowel visualization and is associated with lower patient tolerance. (Clinical trial registration number: ACTRN 12614000883617.) (Gastrointest Endosc 2022;96:822-8.)

Capsule endoscopy (CE) was first introduced in 2000, enabling noninvasive and complete examination of the entire small bowel.[1,2] The clinical application of CE has expanded over the years and is now the investigation of choice for assessment of suspected small intestinal bleeding.[3] In addition, CE has a role in the diagnosis and

Abbreviations: CE, capsule endoscopy; PEG, polyethylene glycol; RCT, randomized controlled trial; SBTT, small-bowel transit time; SBVQ, small-bowel visualization quality; VAS, visual analog scale.

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assessment of small-bowel Crohn's disease and in excluding small-bowel tumors in patients with inherited polyposis syndromes.[3]

Because CE lacks the ability to wash or suction intestinal contents, the overall diagnostic utility relies on adequate small-bowel preparation. Whether purgative bowel preparation taken before CE improves visualization and diagnostic yield of CE remains an area of controversy. Several randomized controlled trials (RCTs)[4-16] and systematic reviews and meta-analyses[17-23] have been performed over the years to assess the efficacy of purgative preparations on diagnostic yield and small-bowel visualization quality (SBVQ) at CE, yielding conflicting results. For example, earlier RCTs from the Netherlands,[13,16] China,[16] and South Korea[5,7] found improved SBVQ with varying doses of polyethylene glycol (PEG) preparation or sodium phosphate. Similarly, an RCT from Greece found improved SBVQ and diagnostic yield with PEG.[12] On the contrary, in several other RCTs, no improvement in SBVQ or diagnostic yield was observed with addition of purgative preparation compared with a clear-fluid diet alone.[4,6,8,9,11,14,15] There are several reasons for the observed heterogeneity, including small sample sizes and a lack of consistent or standardized definitions of diagnostic yield and SBVQ. Moreover, symptoms of GI intolerance are not uncommon with purgative preparations, and therefore in the context of available conflicting data, their routine use before CE needs to be further examined.[24,25]

We undertook a multicenter, blinded RCT to assess the clinical effectiveness of 2 types of purgative regimens (PEG 2 L and PEG 1 L + sodium ascorbate) and a control group (clear fluids only) in patients with suspected small intestinal bleeding undergoing CE. The primary aim of our study was to assess diagnostic yield. Secondary aims were to assess SBVQ, small-bowel transit time (SBTT), and patient tolerability.

METHODS

Study design

In this multicenter, blinded RCT, patients across 4 tertiary hospitals in Australia and 1 tertiary hospital in New Zealand participated in the trial. All assessments were performed between April 2014 and December 2019.

Study participants

All patients over age 18 years undergoing CE for investigation of suspected small intestinal bleeding were considered for inclusion in the study. Patients with any of the following were excluded: previous allergic reaction to PEG or any component of PEG-based preparation, contraindication to outpatient PEG-based preparation solution, chronic kidney disease stage V, heart failure (New York Heart Association class IV), fluid restricted to <2 L/day, currently pregnant or attempting pregnancy, known small- or large-bowel strictures, and history of capsule retention.

Randomization

Sequential outpatients were randomly allocated to 1 of 3 intervention arms using numbered opaque envelopes. The contents of the envelopes were determined using computer-generated random numbers centrally.

Study procedure

CE was performed using the Pillcam SB3 system (Medtronic, Minneapolis, Minn, USA) across all participating institutions. Detailed written and verbal information for preparation was provided to each patient after randomization. Iron supplements were stopped for all patients 5 days before CE. All patients were instructed to have a clear fluid–only diet 18 hours before the CE appointment (after a normal lunch the day before).

Patients assigned to arm A (control) were asked to take nothing by mouth for 6 hours before the procedure. Patients in arm B were instructed to drink 2 L of standard PEG (2 sachets of Glycoprep-C [Fresenius Kabi Mt Kuringgai, NSW, Australia] containing macrogol 3350 158.7 g, sodium chloride 7.8 g, potassium chloride 2.2 g, and sodium sulfate anhydrous 16.9 g as the active ingredients) 15 hours before CE (to be completed within 3 hours so that preparation was completed 12 hours before the test). Then, they were asked to continue a clear-fluid diet and take nothing by mouth for 6 hours before the CE appointment. Patients randomized to arm C continued a clear fluid–only diet 18 hours before the procedure. They were instructed to have 1 L of a PEG-based solution (Moviprep [Norgine, Frenchs Forest, NSW, Australia] containing macrogol 3350 100 g, sodium sulfate 7.5 g, sodium chloride 2.7 g, potassium chloride 1.0 g, ascorbic acid 4.7 g, and sodium ascorbate 5.9 g as active ingredients) 4 hours before the procedure (to be completed within 1 hour so that preparation was completed 3 hours before the test). Then, they were asked to take nothing by mouth until the CE appointment. On the day of the procedure, patients were instructed to swallow the capsule with simethicone 200 mg mixed in 150 mL of water.

Study outcomes

All CEs were reported by accredited gastroenterologists without prior information of the allocated intervention arm using a standardized datasheet (Appendix A, available online at www.giejournal.org). To assess diagnostic yield, lesions were classified either as highly relevant (P2) or less relevant (P0 or P1) based on the validated score proposed by Saurin et al.[26,27] Examples of lesions classified as P0, P1, and P2 are shown in Figure 1. Gastric transit time was defined as the length of time between the first gastric image and the first duodenal image. SBTT was defined as the length of time between the first duodenal image and the first cecal image. The overall SBVQ and distal SBVQ

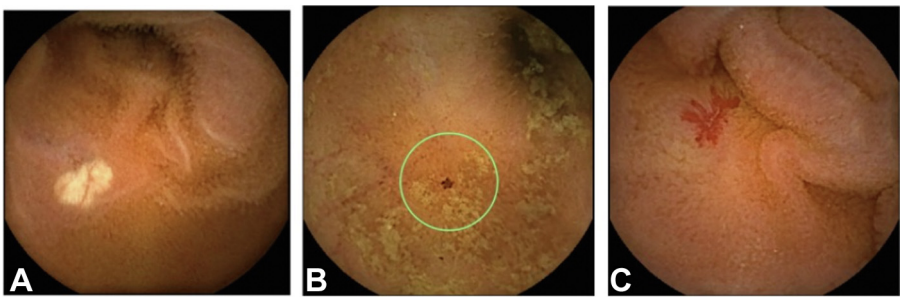

Figure 1. Examples of capsule endoscopy findings based on hemorrhagic potential. **A,** Xanthoma: no bleeding potential (P0 lesion). **B,** Mucosal red spot: uncertain bleeding potential (P1 lesion). **C,** Angioectasia: high bleeding potential (P2 lesion).

were separately assessed using a validated quantitative assessment score described by Brotz et al.[28] Patient tolerability was assessed using a self-reported visual analog scale (VAS; score of 0-10, with lower scores indicating better tolerability). A standardized telephone questionnaire was completed 30 days after the procedure to assess patient tolerance of the intervention (Appendix B, available online at www.giejournal.org).

Statistical analysis

Sample size calculation was based on the primary endpoint (detection of P2 lesions). We assumed 60% prevalence of P2 lesions in patients with suspected small intestinal bleeding undergoing CE. To detect a 15% improvement with an alpha of .05 and statistical power of .8, we calculated that 152 patients would be required per arm.

Continuous variables were summarized using means and their associated 95% confidence intervals (CIs) when normally distributed and using medians and their associated 95% bias-corrected CIs when non-normally distributed. *P* values for normally distributed variables were based on an analysis of variance F-test, whereas *P* values for non-normally distributed variables were based on the Kruskal-Wallis test. Categorical variables are summarized as percentages (and their associated 95% CIs) and were tested using a χ^2 test or Fisher exact test. All statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, Tex, USA).

The study was discontinued early based on a prespecified interim analysis performed at 50% enrollment on the grounds of likely futility with continuation of study recruitment. Based on the available complete data (sample sizes of 78 participants in arm A, 76 in arm B, and 75 in arm C), the Bayesian predictive probability of rejecting the null hypothesis, should the trial be allowed to complete intended recruitment, was assessed to be .064. The final analyses are presented below.

Ethical approval was obtained from individual governing ethical review boards. The trial was listed on the Australia and New Zealand clinical trials registry (ACTRN12614000883617).

RESULTS

From April 2014 to December 2019, 524 patients were screened across 5 centers for inclusion in the study (Fig. 2). Of these, 237 patients were randomized across the 3 arms in a 1:1:1 fashion. Eight patients were excluded after randomization (consent withdrawn in 4, procedure canceled in 3, and incorrect preparation in 1). A per-protocol analysis was conducted on 78, 76, and 75 patients, respectively, in arm A (control), arm B (PEG 2 L), and arm C (PEG 1 L + sodium ascorbate).

Median patient age was 60 years (interquartile range, 48-70), and 47.1% were men. Baseline characteristics for each group are described in Table 1. There was no significant difference in age, gender, body mass index, smoking, diabetes, nonsteroidal anti-inflammatory drug use, or overt GI bleeding preceding CE among the 3 groups. Small-bowel examination was incomplete in 18 patients (capsule remained in the stomach in 2 and small bowel was only partially examined in 16). The capsule passed in all patients as confirmed by an abdominal x-ray. There was no significant difference in the proportion of incomplete cases based on allocated intervention arms (5, 6, and 7 cases in arms A, B, and C, respectively; $P = .80$). Cases where the small bowel was at least partially examined were included for further analysis (except for SBVQ, gastric transit time, and SBTT assessment).

Primary outcome

Overall, P2 lesions were found in 47.6% of patients (95% CI, 41-54.1), whereas P0 and P1 lesions were detected in 28.2% of patients (95% CI, 22.3-34.1). There was no statistically significant difference in incidence of P2 lesions (48.7%, 48.0%, and 45.9% in arms A, B, and C, respectively; $P = .94$) or P0 and P1 lesions (28.2%, 32%, and 24.3% in arms A, B, and C, respectively; $P = .58$) (Table 2).

Secondary outcomes

Mean gastric transit time across arms A, B, and C was 38.5 minutes, 38.7 minutes, and 47.6 minutes, respectively ($P = .45$). Similarly, mean SBTT was found to be similar

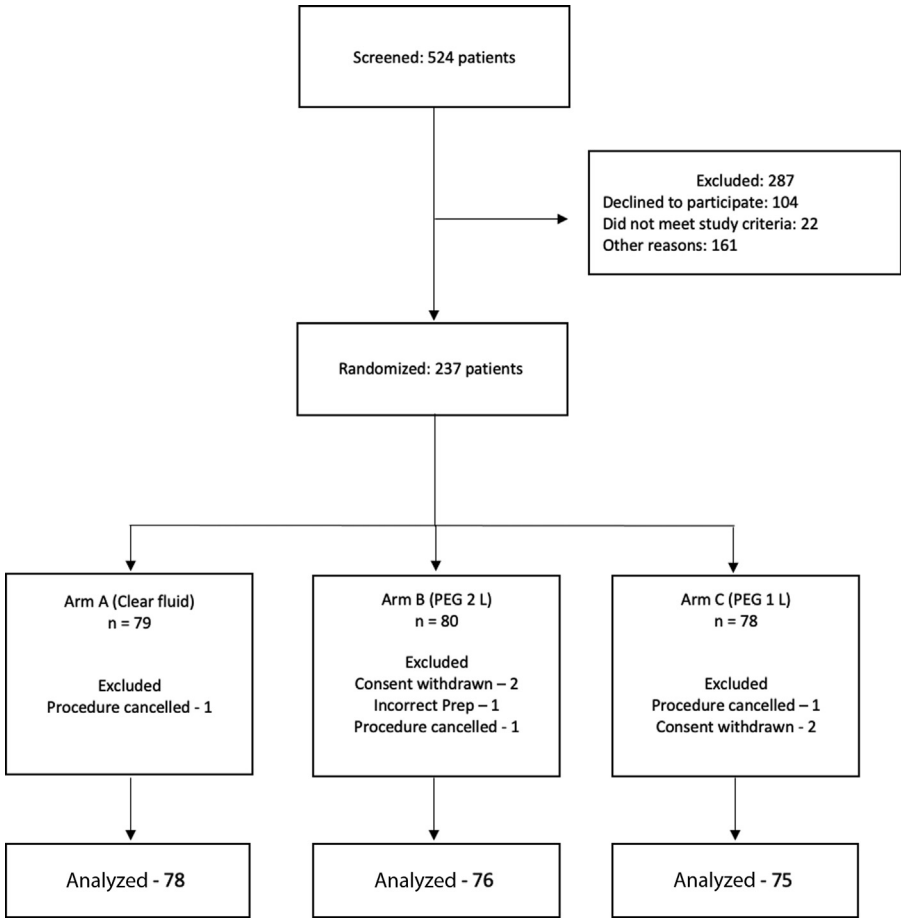

Figure 2. CONSORT diagram detailing patient flow through the trial. *PEG*, Polyethylene glycol; *CONSORT*, Consolidated Standards of Reporting Trials.

TABLE 1. Baseline patient characteristics

Characteristics	Arm A (control) (n = 78)	Arm B (polyethylene glycol 2 L) (n = 76)	Arm C (polyethylene glycol 1 L + sodium ascorbate) (n = 75)	*P* value
Mean age, y	60.6 (57.2-63.9)	56.1 (52.7-59.5)	59.3 (55.9-62.7)	.16
Gender, male, %	46.2 (35.3-57.3)	50 (38.8-61.2)	45.3 (34.4-56.8)	.83
Mean body mass index, kg/m^2	28.4 (26.8-30.1)	28.9 (27.2-30.6)	30.3 (28.6-31.9)	.26
Diabetes, %	19.5 (12-30)	22.4 (14.3-33.2)	30.7 (21.2-42.1)	.25
Smoker, %	46.7 (35.8-58)	52.6 (41.3-63.7)	44.6 (33.6-56.1)	.59
Nonsteroidal anti-inflammatory drug use in the last 30 days, %	23.7 (15.4-34.6)	25 (16.5-36.1)	28.2 (18.8-39.8)	.82
Overt GI bleeding, %	9.7 (4.7-19.4)	13.2 (7.2-22.9)	9.5 (4.5-18.7)	.73

Values in parentheses are 95% confidence intervals.

across study arms (244.7, 244.7, and 220.1 minutes, respectively, in arms A, B, and C; $P = .94$) (Table 3). There was no significant difference between overall SBVQ ($P = .96$) and distal SBVQ across the 3 study arms ($P = .72$).

Adverse effects reported by patients are described in detail in Table 4. Nausea, bloating, and abdominal pain were commonly reported by patients taking PEG 2 L (10.5%, 21.1%, and 17.3%, respectively) and PEG

TABLE 2. Incidence of P0-P1 and P2 lesions based on study arm

Type of lesion	Arm A (control) (n = 78)	Arm B (polyethylene glycol 2 L) (n = 75)	Arm C (polyethylene glycol 1 L + sodium ascorbate) (n = 74)	*P* value
P2, %	48.7 (37.7-59.8)	48 (36.8-59.3)	45.9 (34.9-57.5)	.94
P0-P1, %	28.2 (19.3-39.3)	32 (22.4-43.5)	24.3 (15.8-35.5)	.58

Values in parentheses are 95% confidence intervals.

TABLE 3. Capsule transit time and small-bowel visualization quality based on study arm

Characteristics	Arm A (control) (n = 73)	Arm B (polyethylene glycol 2 L) (n = 70)	Arm C (polyethylene glycol 1 L + sodium ascorbate) (n = 68)	*P* value
Gastric emptying, min	38.5 (29-47.9)	38.7 (28.3-49.2)	47.6 (31.4-61.8)	.45
Transit time to first cecal image, min	244.7 (224.3-265.1)	244.7 (223.5-265.9)	240.1 (231.2-255.2)	.94
Quantitative score SBVQ, overall small bowel	9.1 (8.8-9.4)	9 (8.6-9.4)	9.1 (8.9-9.3)	.95
Quantitative score SBVQ, distal half	8.3 (7.9-8.7)	8.1 (7.5-8.7)	8.4 (7.9-8.9)	.72

Values are mean (95% confidence interval).
SBVQ, Small-bowel visualization quality.

1 L + sodium ascorbate (10.7%, 11.1%, and 13.9%, respectively). No patients in arm A reported nausea, but bloating and abdominal pain were reported by 1.6% of patients.

Patient tolerability based on self-reported VAS for each study arm is described in Figure 3, with a lower score indicating better tolerability. The mean VAS score in arm A was .7 (95% CI, .4-1.1), which was significantly lower compared with 3.5 (95% CI, 3.0-4.1) in arm B and 2.6 (95% CI, 2.1-3.1) in arm C ($P < .001$). A higher proportion of patients in arm A (74%) reported no discomfort compared with patients in arms B and C (14.5% and 25%, respectively; $P < .001$).

DISCUSSION

Since the development of CE over 20 years ago, it has become an essential part of the diagnostic armamentarium for assessment of obscure GI bleeding. The American Gastroenterological Association guideline strongly recommends the use of a purgative preparation before CE, albeit supported by low-quality evidence.[29] Moreover, the effect of purgatives on the clinically relevant endpoint of diagnostic yield remains unclear.[30] Although several RCTs have been performed, because of limitations these have yielded heterogeneous results, and the clinical efficacy of purgatives remains unclear. Following the original recommendation by the device manufacturer (Given Imaging, Yoqneam, Israel), a clear fluid–only diet before capsule ingestion continues to be the preparation of choice across several centers, and the use of a purgative preparation before CE has therefore not been universally adopted. In the current blinded, multicenter RCT, we sought to assess the clinical efficacy of 2 types of purgative regimens compared with a clear fluid diet only in patients undergoing CE for the assessment of small-bowel bleeding.

In the present study, we assessed the efficacy of 2 purgative regimens: 2 L PEG (Glycoprep-C; Fresenius Kabi Australia) or 1 L PEG with sodium ascorbate (Moviprep; Norgine) in comparison with a diet containing clear fluid only before CE. All patients received 200 mg simethicone before CE. The most pertinent finding of our study was that no improvement was found in detecting P2 or P0 and P1 lesions with either purgative regimen compared with a clear fluid diet only. Our findings are in line with the most contemporary meta-analysis of RCTs assessing the utility of PEG preparations, where the effect of a purgative preparation on diagnostic yield was found to be nonsignificant (odds ratio, 1.17; 95% CI, .95-1.45).[23] Diagnostic yield has previously been assessed in several RCTs,[4,6,7,9,11,12,15,16] albeit with heterogeneous results. For example, Viazis et al[12] in an RCT from Greece demonstrated improved diagnostic yield with the use of 2 L PEG compared with a clear fluid diet. This, however, was not replicated in other RCTs.[4-9,11,15] Importantly, several RCTs had small sample sizes and therefore were underpowered to assess diagnostic yield.[7-9] Most of these studies classified culprit bleeding lesions as "positive/definitive" or "suspicious/probable," which may lack interobserver reliability, instead of using validated scores. We attempted to overcome this by adopting a validated score described by Saurin et al[26,27] for reporting clinically relevant small-bowel lesions, as has been recommended by the European Society of Gastrointestinal Endoscopy.[31]

We further assessed SBVQ across the 3 intervention arms using a validated quantitative index (Brotz score[28]) recommended by the European Society of Gastrointestinal Endoscopy. The effect of a PEG preparation on SBVQ has been investigated in previous RCTs using various scoring

TABLE 4. Adverse effects

Characteristics	Arm A (control) (n = 8)	Arm B (polyethylene glycol 2 L) (n = 76)	Arm C (polyethylene glycol 1 L + sodium ascorbate) (n = 75)	*P* value
Vomiting, %	0	5.3 (0-10.4)	0	.04
Nausea, %	0	10.5 (3.5-17.6)	10.7 (3.5-17.8)	.012
Bloating, %	1.6 (0-4.7)	21.1 (11.6, 31.79)	11.1 (3.7-18.5)	.001
Abdominal pain, %	1.6 (0-4.7)	17.3 (8.6-26.1)	13.9 (5.7-22.1)	.004

Values are mean (95% confidence interval).

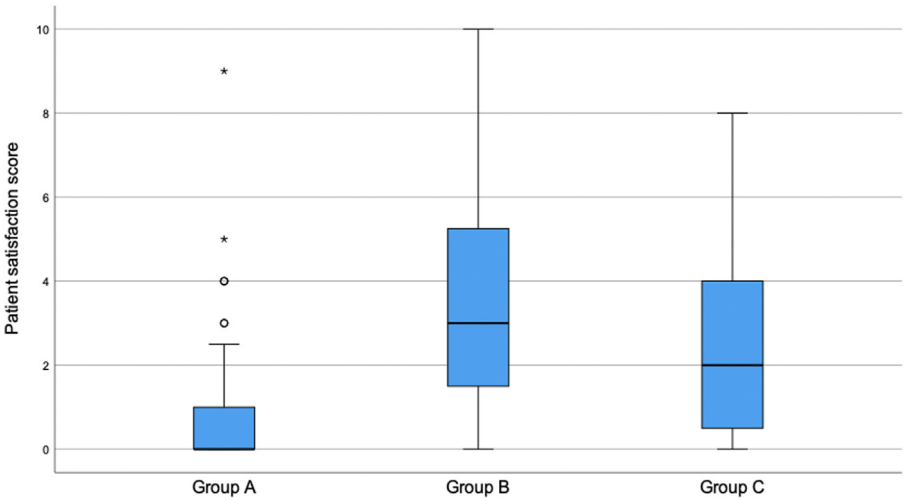

Figure 3. Patient satisfaction score based on visual analogue scale for each study arm type (lower score indicates better tolerability).

systems, including a binary score: if at least 90% of small-bowel mucosa was adequately visualized,[5,12,16] if at least 75% of small-bowel mucosa was adequately visualized,[13] variations of a 4- or a 5-point score,[4,6,7,14,15] and a computed assessment of a cleansing score.[11] We found that overall SBVQ and distal SBVQ were not statistically different in patients assigned to the control arm when compared with either of the purgative arms. Our results also contrast with findings of previous RCTs where improved visualization with purgatives was especially observed in the distal small bowel.[7,13,14]

Notably, in contrast to previous studies, we used simethicone as an adjunct in the control arm and both purgative arms.[5-8,12-16] Simethicone improves visualization by reducing surface tension and coalescing small bubbles into larger bubbles that pass easily.[32] A systematic review and meta-analysis by Wu et al[21] concluded that simethicone significantly improved SBVQ in patients undergoing CE (odds ratio, 4.4; 95% CI, 1.8-10.8). It did not appear to offer any added advantage when it was given in combination with a purgative preparation (odds ratio, 1.6; 95% CI, .8-3.3). In an RCT by Hookey et al,[11] when simethicone 80 mg was used in both control and purgative arms, no difference in SBVQ was observed. It is possible that the use of simethicone overcomes any advantage offered by the addition of a purgative regimen before CE.

We further assessed patient tolerability based on self-reported VAS and incidence of adverse events. Intuitively, significantly more patients assigned to the purgative arms (PEG 2 L and PEG 1 L + sodium ascorbate) reported nausea, bloating, and abdominal pain when compared with the control arm. Similarly, self-reported tolerance of the CE procedure was significantly better in the control arm than either of the 2 purgative arms.

Although our study is one of the largest RCTs investigating the efficacy of purgative bowel preparation before CE, it carries limitations that should be acknowledged. The trial was terminated early on the basis of interim analysis, because the diagnostic yield remained remarkably similar across the intervention arms. Based on statistical analysis, it was believed to be highly unlikely that a difference in diagnostic yield of 15% or more could have been demonstrated had the trial continued to full recruitment. It is therefore possible that our study was underpowered to detect smaller differences in the diagnosis of clinically relevant P2 lesions. However, given that we did not observe any added advantage of purgatives in overall or distal SBVQ, it is likely that purgatives do not offer a

clinically meaningful advantage over a clear fluid diet with simethicone. Second, our study recruited patients under investigation for suspected small intestinal bleeding. Consequently, generalizing findings to other population groups needs to be undertaken with caution.

In conclusion, in this blinded RCT, the use of a PEG preparation before CE did not result in improved diagnostic yield or SBVQ. Patients receiving PEG reported more adverse events and lower tolerance compared with patients on a clear fluid–only diet. Our results do not support the routine use of purgative preparation in patients undergoing CE.

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APPENDIX

Data Sheet - Capsule Endoscopy report data
Participant No: _____
Institution Code:

Reader's Initials	
Capsule Study Date	
Gastric Emptying Time (time elapsed from 1st gastric image to 1st small bowel image)	_ _ _ mins
Complete Study	Y/N
If Yes, Small Bowel Transit Time (time elapsed from 1st small bowel image to 1st caecal image)	_ _ _ mins
If No, Small Bowel Transit Time (time elapsed from 1st small bowel image to the end of the study)	_ _ _ mins
Findings	
Highly relevant (P2) (List for each lesion)	Y/N
Lesion type (ie. Angioectasia, ulcer)	
Location	Proximal/ Distal
(Proximal <50% of SBTT)	
(Distal >50% of SBTT)	
Less relevant (P0, P1) (List for each incidental finding)	Y/N
Lesion type (ie. Angioectasia, ulcer)	
Location	Proximal/ Distal
(Proximal <50% of SBTT)	
Distal >50% of SBTT)	
Mucosal image quality score	
Entire small bowel (score 0 - 10)	
Distal half of small bowel (score 0 - 10)	
Planned Intervention	
Has capsule led to change in management	Y/N
Further Imaging (radiological or nuclear medicine)	Y/N, Study type:
Repeat Capsule Endoscopy	Y/N
Enteroscopy (list method, oral or rectal, single or double balloon)	Y/N, Method:
Referral for surgery	Y/N

Data Sheet – 30 days follow up Questionnaire
Participant No: _____
Institution Code:

Reader's Initials	
Date of Call/Review	
Capsule Study Date	
Did you have any adverse effects during the month following the capsule endscopy?	Y/N
If yes:	
Did you need to see your GP or Emergency Dept?	
What for?	
Were you admitted to hospital?	
Which one?	
What treatment did you receive?	
Length of stay?	