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The Effect on Colon Visualization During Colonoscopy of the Addition of Simethicone to Polyethylene Glycol-Electrolyte Solution: A Randomized Single-Blind Study

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OBJECTIVES: Colonic bubbles associated with polyethylene glycol-electrolyte solution (PEG-ELS) are common and obscure mucosal visualization. This study aimed to determine whether adding simethicone decreases the incidence of bubbles.
METHODS: Prospective, single-blind, randomized comparison of split dose PEG-ELS vs. PEG-ELS + simethicone (PEG-S) for outpatient colonoscopy. Bubble severity for colonic segments was assessed on withdrawal as A = no/minimal bubbles, B = moderate bubbles/interfere with detecting 5 mm polyp, C = severe bubbles/interfere with detecting 10 mm polyp. Primary end point was Grade B or C bubbles in any colon segment. Secondary end points were cleansing quality, incidence and severity of side effects, and polyp detection.
RESULTS: One hundred and thirty nine patients enrolled; 13 withdrew before colonoscopy. Of 123 patients evaluated, 62 took PEG-S and 61 PEG-ELS. The incidence of grade B or C bubbles was much lower with PEG-S compared with PEG-ELS (2% vs. 38%; $P = 0.001$). Overall cleansing (excellent or good) quality was not significantly different for either the whole colon (89% PEG-ELS, 94% of PEG-S, $P = 0.529$) or right colon (88% PEG-ELS, 94% PEG-S, $P = 0.365$). More PEG-S patients had excellent rather than good preps (whole colon 53% vs. 28%, $P = 0.004$; right colon 53% vs. 35%, $P = 0.044$). Need for any flushing was less with PEG-S (38% vs. 70%, $P = 0.001$). The groups were not significantly different with respect to total procedure and withdrawal times, incidence or severity of side effects, or number of polyps/patient or adenomas/patient.
CONCLUSIONS: Adding simethicone to PEG-ELS effectively eliminates bubbles, substantially reduces the need for flushing, and results in more excellent preparations.
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INTRODUCTION

Effective bowel purgation is requisite for performance of high quality colonoscopy.[1–3] Bowel preparation may be inadequate in up to 25% of patients undergoing colonoscopy and may result in missed lesions during colorectal cancer screening.[4–6] Subsequently, reporting the adequacy of colon cleansing using one of the several available scales is an important measure of colonoscopy quality.[7–9] Such scales consider the presence, character, and quantity of residue as well as the ease with which it may be removed by means of flushing and suctioning. Besides liquid and solid debris, adherent chyme may be an important limitation in the evaluation of the proximal colon—particularly in patients with a long interval between the last dose of purgative and the colonoscopy.[10]

Another variable affecting mucosal visualization is colonic bubbles. Although presence and severity of bubbles are not typically commented on when describing preparation quality, the widespread practice of adding simethicone to water flushes during the performance of colonoscopy suggests that impaired mucosal visibility from bubbles is commonplace. In fact, up to one-third of patients receiving polyethylene glycol-electrolyte solution (PEG-ELS) have bubbles at the time of colonoscopy that may potentially interfere with polyp detection.[1,11–14] Simethicone, which eliminates bubbles by decreasing surface tension, is a well-tolerated over-the-counter medication used for gas and bloating.[1,13]

The purpose of this study was to evaluate whether the addition of simethicone to PEG-ELS, administered as a split dose the evening before and morning of colonoscopy, reduces the incidence of colonic bubbles that could interfere with polyp detection.

METHODS

This was a prospective, randomized, investigator-blinded study comparing 2 l PEG-ELS to PEG-ELS with simethicone (PEG-S), both administered as a split dose, in patients undergoing elective outpatient colonoscopy. All patients provided written informed consent. The study was conducted at a single university, and was approved by the university's

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Institutional Review Board. The study was registered nationally with clinicaltrials.gov, number NCT01209806.

Subjects. Patients 18 years of age or older scheduled to undergo elective outpatient colonoscopy were eligible to participate. Exclusion criteria included pregnancy, breast feeding, known or suspected gastroparesis, known or suspected bowel obstruction, severe constipation ($\leq$1 bowel movement per week), $>$50% colon resection, glucose-6-phosphate dehydrogenase deficiency, PEG allergy, significant psychiatric illness, or inability to provide informed consent.

Study design: randomization and protocol. Using a randomization schedule generated by the website *Randomization.com*, (http://www.randomization.com), eligible patients were randomly assigned to PEG-ELS or PEG-S by an investigator not involved in the colonoscopy procedure. Commercially available 2 l PEG-ELS containing sodium sulfate, sodium ascorbate, and ascorbic acid (MoviPrep, Salix Pharmaceuticals, Morrisville, NC) and liquid simethicone (Qualitest Pharmaceuticals, Huntsville, AL) were used. Subjects were provided with a standard PEG-ELS kit and given detailed instructions regarding preparation of the PEG-ELS, the addition of simethicone if randomized to that treatment arm, and routine instructions for colonoscopy including diet, hydration, and when to begin fasting. The patient's endoscopist was not involved in the randomization process and remained blinded for the duration of the study.

Subjects randomized to PEG-ELS took 1 l of PEG-ELS plus 500 cc of clear liquids at 6 PM the night before colonoscopy, and this was repeated 4 h before colonoscopy PM/AM dosing. Subjects randomized to PEG-S also consumed 1 l of PEG-ELS plus 500 cc of clear liquids at 18:00 hours the night prior and 4 h before the colonoscopy. However, 400 mg of simethicone was added to each liter of PEG-ELS as follows. PEG-ELS was mixed as instructed by the manufacturer and refrigerated before each 1 l was taken. Immediately before consuming the purgative, simethicone was added to chilled PEG-ELS by filling a 0.6 ml dropper with liquid simethicone (40 mg simethicone/0.6 ml) 10 times. The dropper had a line clearly indicating 0.6 ml, and this procedure was reviewed with the patient at the time of randomization. Patients were instructed to gently shake the PEG-S solution until the simethicone was dispersed and the solution clear. Prior investigation demonstrated that complete dissolution occurs rapidly and PEG-S remains clear even when refrigerated for more than 12 h (unpublished).

Diet instructions were identical for both the study groups. The day before colonoscopy, patients were permitted a low-residue breakfast up to 10:00 AM, followed by clear liquids up to 2.5 h before the colonoscopy except for medications, which were permitted with sips of water. Patients received specific instructions regarding a low-residue diet, including a list of acceptable and unacceptable foods (Supplementary Appendix A).

An investigator not performing the colonoscopy contacted patients within 1 week of their scheduled procedure to review the instructions. All study procedures were performed by an attending physician and fellows did not participate. All patients got monitored anesthesia care administered by a certified registered nurse anesthetist.

Assessments. At the time of randomization, demographic data were collected, including age, gender, indication for procedure, past medical history, medications, and history of prior colonoscopy.

On the day of colonoscopy, before the procedure, a safety assessment was performed including vital signs and orthostatic assessment. Also before colonoscopy, patients completed questionnaires evaluating compliance, side effects, sleep, satisfaction, and willingness to repeat the purgative. Side effects were measured using a 10-point Likert scale from 0 (none) to 10 (severe). Sleep quantity was measured by comparing the average number of hours the patient normally sleeps to the number of hours they slept the night before colonoscopy. Sleep quality was rated on a 5-point scale: very poor, poor, average, good, and very good.

During colonoscopy, the following were recorded: total procedure and withdrawal time (excluding interventions), cecal intubation, findings, and specific information regarding polyps including the number, location, size, morphology, and method of excision. The endoscopist graded the presence and severity of bubbles in segments during the procedure. By convention this was performed on withdrawal of the colonoscope and recorded after leaving each segment of colon. The Bubble Scale used for this study graded 4 segments of the colon—cecum, right colon and hepatic flexure, transverse colon and splenic flexure, and colon distal to the splenic flexure. Each colon segment was graded using a 3-point scale where A = no/minimal bubbles, B = moderate bubbles/interfere with detecting a 5 mm polyp, and C = severe bubbles/interfere with detecting a 10 mm polyp. Before the start of the study, both participating endoscopists attended a bubble scale training session during which multiple images demonstrating examples of grades A, B, and C were reviewed.

The endoscopist also graded the quality of preparation for the whole colon and the right colon (excellent, good, fair, or poor; excellent or good considered ''adequate'' cleansing). A descriptor of each preparation grade was available for the endoscopist to review at the time of assigning the grade (Supplementary Appendix B). The endoscopist also estimated the amount of flushing required (none, $<$50, 50–100, or $>$100 cc), and this was performed without simethicone except where specifically required to clear bubbles not responsive to standard flushing. When simethicone was used, it was immediately following withdrawal from a segment with Grade B or C bubbles, which could not be cleared with water flush.

When final pathology was available, an investigator not involved in performing the colonoscopy recorded the histology results (hyperplastic, adenomatous, cancer, other). For adenomas, the presence of high-grade dysplasia and villous component was recorded.

Masking. To ensure blinding, randomization assignments were concealed in a sealed envelope. After consent, the investigator would open the envelope to learn the patient assignment. In order to maintain blinding, patients were instructed by an investigator not to discuss their preparation assignment with the endoscopist. In addition, all preparation instructions were given in a closed exam room without the

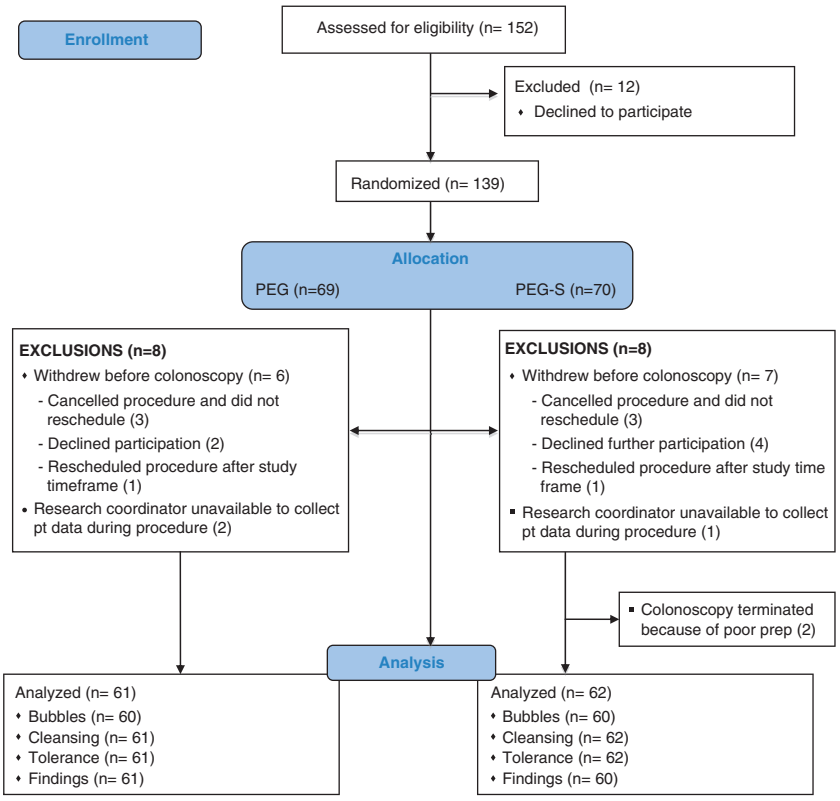

Figure 1 (**a**) With Polyethylene Glycol-Electrolyte Solution (PEG-ELS), 38% of patients had grade B or C bubbles in at least 1 colon segment compared with 2% with PEG-ELS + simethicone (PEG-S). (**b**) Preparation adequacy was similar with PEG-ELS and PEG-S. (**c**) Significantly less flushing was required with PEG-S. (**d**) Mean total procedure time and withdrawal time was not significantly different between the study groups.

endoscopist present. At the time of colonoscopy, the endoscopists documented whether they had remained blind to the patients' preparation through completion of the colonoscopy and grading of the prep.

Outcome measures. The primary trial end point was the presence of grade B or C bubbles in any colon segment for each patient. Secondary end points were quality of cleansing, need for flushing, total procedure and withdrawal time, incidence and severity of side effects, and polyp detection. Polyp assessment was done per patient and in total for both groups, and included the number of all polyps, adenomas, and high-risk adenomas defined as size >1 cm, high-grade dysplasia, or villous component.

Statistical analyses. The trial was designed and analyzed as a superiority trial on all end points (PEG-S better than PEG-ELS). Under the assumption that the incidence of bubbles would be about 10% in the simethicone group and 33% in the control group, a sample size of 60 patients per group yields 88% power (using a two-sided alpha of 0.05).

All patients were analyzed according to the group they were assigned to, but patients who canceled the procedure or withdrew from the study before undergoing colonoscopy were excluded. For dichotomous end points, the difference in proportions between the simethicone and control groups was estimated, along with a 95% exact confidence interval. Testing for dichotomous end points was based on the exact version of Barnard's test and for ordered categorical end points on an exact permutation test. For continuous end points, the mean or median difference was estimated, along with a 95% confidence interval. The analyses were conducted in SAS 9.2 (SAS Institute, Cary, NC) and StatXact 9 (Cytel, Cambridge, MA).

RESULTS

Participant flow and follow-up. From December 2009 to July 2010, 152 patients referred for outpatient colonoscopy were offered entry and 12 declined to participate (Figure 1). One hundred and thirty nine patients were randomized, and 13 patients withdrew before taking any preparation. Two patients in the PEG-ELS group and one patient in the PEG-S were excluded because of inability to collect key data (Figure 1). The final analyses included 123 patients, of whom 62 received PEG-S and 61 received PEG-ELS. The majority (113) of the 123 procedures were performed by the study's principal investigator, D.K. Endoscopist masking was maintained for all cases. Cecal intubation was accomplished for all but three cases in the PEG-S group (two because of poor preparation, and one because of stricture) and two in the PEG-ELS group (one because of technical difficulty and one patient did not have a cecum but did have intubation of an ileocolonic anastomosis). Compared with the PEG-ELS group, the PEG-S group had a higher fraction of women and a longer interval between preparation and procedure. Table 1 summarizes the characteristics of the study groups and colonoscopy-related variables.

Table 1 Patient and clinical characteristics

	PEG-ELS^{+} ($N=61$)	PEG-S^{++} ($N=62$)
Age (years), n *(%)*		
≤50	18 (30)	17 (27)
51–60	22 (36)	26 (42)
61+	21 (34)	19 (31)
Sex, n *(%)*		
Male	32 (52)	24 (39)
Female	29 (48)	38 (61)
Any medical conditions, *n* (%)	41 (67)	42 (68)
Number of medical conditions, mean ± s.d.[a]	1.7 ± 1.5	1.5 ± 1.5
Hypertension, *n* (%)	25 (41)	20 (32)
Hyperlipidemia, *n* (%)	22 (36)	14 (23)
Diabetes, *n* (%)	8 (13)	8 (13)
Any prior surgery, *n* (%)	20 (33)	18 (29)
Any medications, *n* (%)	52 (82)	53 (85)
Number of medications, mean ± s.d.[b]	2.3 ± 1.6	2.0 ± 1.5
Antihypertensive medications, *n* (%)	22 (36)	18 (29)
Cardiac medications, *n* (%)	21 (34)	11 (18)
Acid suppression medications, *n* (%)	14 (23)	17 (27)
Aspirin, NSAIDs, or acetaminophen, *n* (%)	19 (31)	12 (19)
Vitamins, herbs, or supplements, *n* (%)	24 (39)	28 (45)
Indication for colonoscopy, n *(%)*		
Screen/surveillance	44 (72)	41 (66)
Symptoms	17 (28)	21 (34)
First colonoscopy, *n* (%)	20 (33)	25 (40)
Interval between last prep and colonoscopy, n *(%)*		
<4 h	27 (44)	18 (29)
>4 h	34 (56)	44 (71)
Starting time of colonoscopy,[c] n *(%)*		
Before 10:00 hours	10 (17)	12 (20)
10:00 hours to noon	22 (37)	19 (32)
Noon to 14:00 hours	12 (20)	21 (35)
After 14:00 hours	16 (27)	8 (13)

NSAID, non-steroidal antiinflammatory drug; (+) PEG-ELS, polyethylene glycol-electrolyte solution (control); (++) PEG-S, polyethylene glycol-electrolyte solution plus simethicone.
Percentages may not sum to 100 because of rounding.
[a]Most common conditions listed.
[b]Most frequent medications listed.
[c]Data unavailable for one PEG-ELS and two PEG-S patients.

Preparation quality. Preparation quality was measured for the 123 patients who underwent colonoscopy and is summarized in Table 2. A total of 24 patients had grade B or C bubbles in at least one of the four colon segments assessed, and all but one of these patients received PEG-ELS (incidence = 2% PEG-S vs. 38% PEG-ELS, $P=0.001$) (Figure 1a).

Controlling for time elapsed between preparation and procedure, the differences in bubble incidence remained statistically significant. For time <4 h, incidence was 0% (0/18) in PEG-S vs. 52% (14/27) in PEG-ELS ($P=0.001$), whereas for time >4 h, incidence was 2% (1/42) and 27% (9/33), respectively ($P=0.002$). A total of eight patients in the PEG-ELS group and none in the PEG-S group had the most severe, grade C, bubbles. Thirty-nine of the 236 colon segments in the PEG-ELS patients, and one of the 238 colon segments in the PEG-S patients, showed grade B or C bubbles.

Prep efficacy results are summarized in Table 2. The two groups were not significantly different in the adequacy of cleansing for the entire colon (PEG-ELS = 89%, PEG-S 94%; $P=0.529$) and the right colon (PEG-ELS = 88%, PEG-S = 94%; $P=0.365$) (Figure 1b). Significantly more patients in the PEG-S group had "excellent" rather than "good" cleansing of both the entire colon (PEG-S = 53%, PEG-ELS = 28%; $P=0.004$) and the right colon (PEG-S = 53%, PEG-ELS = 35%; $P=0.044$). Furthermore, the need for any flushing was significantly less in the PEG-S group ($P=0.001$) (Figure 1c). No statistically significant differences were found in withdrawal time (mean = 7.0 min in PEG-S vs. 7.3 min in PEG-ELS, $P=0.462$) or total procedure time (mean = 12.6 min in PEG-S vs. 13.4 min in PEG-ELS, $P=0.277$) (Figure 1d).

Purgative completion, tolerance, and side effects. Table 3 summarizes the results for measures of purgative tolerance. Preparation completion was virtually identical across the two groups. There were no statistically significant differences in the incidence of side effects or in the severity of those reported side effects (results not shown). Severe symptoms rated 7 or higher on the 10-point scale were reported by seven patients in the PEG-S group vs. eight in the PEG-ELS group. Measures of duration and quality of sleep, and overall satisfaction, were also not significantly different across the two groups. A high percentage of patients in both groups indicated a willingness to repeat the assigned purgative in the future.

Colonoscopy findings. Table 4 summarizes the results of the colonoscopy findings. The proportion of patients in whom polyps were detected was not significantly different between the two groups (38% PEG-S vs. 48% PEG-ELS, $P=0.319$), nor was there a significant difference in adenoma detection (25% PEG-S vs. 33% PEG-ELS, $P=0.380$). The number of polyps per patient and the number of adenomas per patient were also not significantly different across the two groups.

DISCUSSION

Adequate bowel preparation directly impacts several measures of colonoscopy quality including cecal intubation, physician adherence to published surveillance guidelines, and adenoma detection.[4,6,15–17] To date, colonic bubbles have not been formally considered in scales measuring colon cleansing. However, colonic bubbles are frequently encountered by endoscopists who often address this problem by adding simethicone to their flushes.

We believe the impact of bubbles on prep adequacy may be underestimated. In a prior prospective study looking at split dose PEG-ELS, we detected bubbles having the potential to interfere with polyp detection in 35% of patients. Colonic bubbles may be a ubiquitous finding with a variety of purgatives. The presented findings are similar to the 32% incidence of bubbles with 5 l PEG-ELS administered on the day of colonoscopy, and 30% incidence with split dose sodium phosphate liquid.[13,18] In both the studies, the addition of simethicone significantly reduced the incidence of bubbles. Our study examined the effect of simethicone on the incidence

Table 2 Preparation efficacy end points

	PEG-ELS ($N=61$)		PEG-S ($N=62$)		PEG-S—PEG-ELS		
	n	**%**	***n***	**%**	**Δ**	**95% CI**	***P***
Grade B or C bubbles[a]	23	38	1	2	−36.7	−50.2, −24.2	0.001
Cecum[b]	8	14	0		−13.8	−25.1, −6.5	0.003
Right and hepatic flexure[b]	14	24	0		−24.1	−37.1, −14.7	0.001
Transverse and splenic flexure[a]	13	22	1	2	−20.0	−32.7, −9.6	0.001
Distal to splenic flexure[a]	4	7	0		−6.7	−16.7, −0.3	0.045
Number of colon segments w/Grade B or C bubbles[a]							0.001
0	37	62	59	98			
1	13	22	1	2			
2	5	8	0				
3	4	7	0				
4	1	2	0				
Adequate cleansing, whole colon	54	89	58	94	5.0	−6.1, 16.7	0.529
Adequate cleansing, right colon[c]	53	88	58	94	5.2	−6.0, 17.0	0.365
Flushing[a]							0.001
None	23	38	42	70			
<50 ml	9	15	11	18			
50–100 ml	8	13	3	5			
>100 ml	20	33	4	7			

Δ, difference (%) between PEG-S (simethicone) and PEG-ELS (control) groups; CI, confidence interval.
[a]$N=60$ in each group; data unavailable for a control patient for whom data were not collected and 2 simethicone patients because of aborted procedure (poor prep).
[b]$N=58$ in control and 59 in simethicone group; data unavailable for the 5 patients with no cecal intubation (see text) plus an additional control patient for whom data were not collected.
[c]$N=60$ in control and 62 in simethicone group; data unavailable for 1 control patient whose right colon was not intubated (tortuous colon).

of bubbles having the potential to interfere with polyp detection. All patients received low volume (2 l) PEG-ELS with sodium ascorbate and ascorbic acid (MoviPrep) administered as a PM/AM split dose, with 400 mg of liquid simethicone added to each dose of purgative in the PEG-S group. Similar to past studies, we found a high incidence of bubbles in those receiving PEG-ELS, and a marked and significant reduction in bubbles with the addition of liquid simethicone to the purgative. Along with this, the group receiving simethicone had significantly more excellent preps and required significantly less flushing.

Although this study was not powered for the secondary outcomes assessed, the remainder of comparisons between the two study groups did not demonstrate significant differences. Specifically, there were no significant differences between the two groups with respect to total procedure and withdrawal time, gastrointestinal adverse events, and polyp detection.

With respect to bubble and polyp detection, as per the study protocol, patients with bubbles that could not be cleared without adjuvant use of simethicone added to the water flush were analyzed per protocol assignment. We observed that vigorous flushing with water alone often exacerbated the severity of bubbles. Two patients in the PEG-ELS group required a simethicone flush. One of these had both distal segments rated as "A" (no/minimal bubbles) and a single adenoma was detected in one of these segments. The second patient had both distal segments rated as "B" (moderate bubbles/interfere with detecting 5 mm polyp) and no adenoma detected. To properly power this study to demonstrate a 25% improvement in adenoma detection with PEG-S would have required a study with an $N \sim 1750$.

Luminal bubbles are not a problem unique to colonoscopy, and have been described as a limiting factor for capsule endoscopy. Here, the consequences are even greater as there is no possibility of flushing with simethicone. The use of simethicone before capsule endoscopy, often with PEG-ELS, has become an accepted practice and its small bowel cleansing superiority has been demonstrated in a meta-analysis.[19] Bubbles are one of the five criteria in a validated scoring system for small bowel cleansing for capsule endoscopy.[20] Whether bubbles form spontaneously in the colon is unknown, but on numerous occasions we have witnessed copious bubbles flowing through the ileocecal valve into the cecum during routine colonoscopy. That the small bowel is a primary source of bubbles is suggested by our observation that the lowest frequency of colonic bubbles occurs distal to the splenic flexure.[14]

Simethicone has been available over-the-counter for over 50 years, and its use in infants, children, and adults is considered quite safe. As an adjunct to colon purgation, past studies have evaluated the addition of simethicone to both aqueous sodium phosphate liquid and 4 l PEG-ELS. Similar to our study, these studies consistently found a high incidence of bubbles with the control purgative, and a striking diminution of bubbles with the addition of simethicone. Although there has been speculation that bubbles are more of an issue with PEG, these referenced studies suggest bubbles occur at least as often with sodium phosphate.

Simethicone's effect on prep efficacy has yielded mixed results. Shaver *et al.*[13] showed significantly better colon cleansing with simethicone and alluded to improvement in the right colon, a region more likely to be affected by adherent dense chyme. Tongprasert *et al.*[1] showed that simethicone added to sodium phosphate improved visibility by diminishing bubbles. In the same study, there was a trend toward better colon cleansing with the addition of simethicone to sodium phosphate, though it did not reach statistical significance. McNally *et al.*[21] evaluated the

Table 3 Preparation tolerance

	PEG-ELS ($N=61$)		PEG-S ($N=62$)		PEG-S – PEG-ELS		
	n	%	*n*	%	Δ	95% CI	*P*
>90% prep completion	55	90	56	90	0.2	−11.3, 11.6	1.000
>90% pm prep completion	57	93	58	94	0.1	−10.1, 10.3	1.000
>90% am prep completion	56	92	56	90	−1.5	−12.7, 10.1	1.000
Any side effects	40	66	39	63	−2.7	−19.6, 14.4	0.783
Nausea	18	30	22	36	6.0	−11.3, 22.5	0.501
Vomiting	3	5	3	5	0.0	−10.1, 9.8	1.000
Abdominal pain	21	34	17	27	−7.0	−23.8, 10.0	0.422
Bloating	32	53	25	40	−12.1	−30.0, 5.8	0.207
Light headedness	15	25	17	27	2.8	−12.9, 18.8	0.799
Any severe side effects (7+ score)	8	13	7	11	−1.8	−14.3, 10.6	0.829
Severe nausea	4	7	4	7			
Severe vomiting	1	2	2	3			
Severe abdominal pain	0		1	2			
Severe bloating	5	8	3	5			
Severe light headedness	0		1	2			
Slept <50% of usual time	13	21	10	16	−5.2	−19.5, 9.8	0.522
Awake at night	43	70	41	66	−4.4	−20.8, 12.7	0.633
Number of times up[a]	Median = 2		Median = 2				0.704
Number of times to the bathroom[a]	Median = 2		Median = 2				0.557
Quality of sleep							0.522
Very poor	6	10	3	5			
Poor	10	16	13	21			
Average	17	28	26	42			
Good	18	30	13	21			
Very good	10	16	7	11			
Satisfaction							0.769
10 (High)	21	34	20	32			
9	0	18	1	2			
8	11	2	15	24			
7	1	21	1	2			
6	13	2	10	16			
5	1	7	3	5			
4	4	3	4	6			
3	2	7	0	6			
2	4	7	4	6			
0 (low)	4		4				
Would use prep again	46	75	50	81	5.2	−10.0, 20.5	0.515

Δ, difference (%) between PEG-S (simethicone) and PEG-ELS (control) groups; CI, confidence interval.
[a]Only among those who awoke during the night.

Table 4 Colonoscopy findings

	PEG-ELS ($N=61$)		PEG-S ($N=62$)		PEG-S – PEG-ELS		
	n	%	*n*	%	Δ	95% CI	*P*
Patients with polyp(s) detected[a]	29	48	23	38	−9.2	−26.6, 9.1	0.319
Number of polyps per patient[a]							0.562
0	32	52	37	62			
1	12	20	8	13			
2	10	16	5	8			
3+	7	12	10	17			
Patients with adenoma(s) detected[a]	20	33	15	25	−7.8	−23.8, 9.1	0.380
Number of adenomas per patient[a]							1.000
0	41	67	45	75			
1	8	13	6	10			
2	6	10	3	5			
3+	6	10	6	10			
Patients with high-risk adenoma detected[a]	2	3	0		−3.3	−11.5, 2.9	0.209

Δ, difference (%) between PEG-S (simethicone) and PEG-ELS (control) groups; CI, confidence interval; High-risk adenoma, adenoma >1 cm or with high grade dysplasia or with villous component.
[a]$N=61$ in control and 60 in simethicone group; data unavailable for 2 simethicone patients because of aborted procedure (poor prep).

effectiveness of simethicone in improving visibility by rating degree of bubbles as well as haziness. Haziness was defined as blurriness of vision independent of preparation adequacy and was rated according to the amount of water required to clear the endoscope lens. Patients with simethicone added to the colon purgative had significantly lower haziness scores and mean bubble scores compared with patients who did not receive simethicone, resulting in improved colonic visibility.

As gastrointestinal adverse events are a common problem with all purgatives, interventions to lessen this would be welcomed. Lazzaroni *et al.*[22] described significantly reduced malaise and sleep disturbance, and a trend toward improved tolerance, when simethicone was used in conjunction with PEG-ELS. Tongprasert *et al.*[1] found superior patient satisfaction with simethicone, though specific gastrointestinal adverse events were not different between study groups. Endoscopists in the simethicone arm were also more satisfied, likely due to better visualization and less need to flush. Our study did not find fewer adverse events in the simethicone group.

There are several weaknesses to our study. This study was greatly underpowered (more than 10-fold) to detect potentially important secondary outcomes such as actual differences in adenoma detection or side effects. Second, patients in the control arm did not receive a simethicone placebo, which may have impacted measures obtained by patient self-assessment (GI adverse events, prep completion, sleep, satisfaction, and willingness to repeat the preparation). For none of these measures did we detect a statistical difference between the study groups, but further studies should utilize a simethicone placebo. Furthermore, the majority of colonoscopies were done by one physician who developed the grading scale. Though an education session was performed before starting the study to ensure consistent (intra-observer) grading, too few cases were done by the other endoscopist to assess differences between the two. Although the readers were blinded to the assigned purgative, overestimation of the impact of bubbles on polyp detection could have resulted in a high proportion of patients deemed to have significant (grade B or C) bubbles. It is somewhat reassuring that the 38% incidence of bubbles in this study's control group is similar to four past published studies (30%—Sudduth, 33%—Rubin, 32%—Shaver, 42% Tongprasert), though this is the first to specifically include bubbles that could potentially impact the detection of polyps ≥ 5 mm.[1,13,14,18]

In summary, the addition of simethicone to each 1 l dose of split PEG-ELS resulted in a marked and significant reduction of luminal bubbles that could interfere with polyp detection. Larger studies will be needed to assess whether the addition of simethicone results in additional benefits such as reduced adverse events, greater endoscopist efficiency, and actual superior polyp detection.

CONFLICT OF INTEREST

Guarantor of the article: David Kastenberg, MD

Specific author contributions: Conception and design: D.K., data collection and data entry: R.M., K.T., V.G, analysis and Interpretation of data: C.D., drafting of article: R.M., D.K., critical revision of the article for important intellectual content: R.M., C.D., D.K., D.K. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All authors approved the final draft for submission.

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Potential competing interests: D.K. has applied for a patent for polyethylene glycol-electrolyte solution with simethicone (PEG-S). All other authors declare no conflicts of interest.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Colonic bubbles are commonly encountered during colonoscopy with both hyperosmotic and isosmotic purgatives.
- The clinical relevance of colonic bubbles is suggested by the common practice of adding simethicone to water flushes during colonoscopy.

WHAT IS NEW HERE

- Using the current "best practice" of split dosing, the addition of simethicone to low volume PEG-ELS effectively eliminates colonic bubbles.
- The addition of simethicone to PEG-ELS also reduces the need for any intra-procedure flushing and improves the proportion of patients with excellent colon cleansing.

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Supplementary Information accompanies this paper on the *Clinical and Translational Gastroenterology* website (http://www.nature.com/ctg)