

Randomized Trial of Gatorade/Polyethylene Glycol With or Without Bisacodyl and NuLYTELY for Colonoscopy Preparation

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OBJECTIVES: We assessed the safety, efficacy, and tolerability of a new preparation of Gatorade and polyethylene glycol (PEG) for colonoscopy with or without bisacodyl compared with NuLYTELY.

METHODS: We performed an investigator-blinded, placebo-controlled, randomized trial of 64 oz of Gatorade and 306 g of PEG (G/PEG) with or without 10 mg of bisacodyl and NuLYTELY. A total of 600 outpatients consumed their preparation the day before a morning colonoscopy. The primary endpoint was colon cleanliness assessed by the Boston Bowel Preparation Scale (BBPS). Tolerability was assessed using a subject questionnaire, and safety was assessed from a basic metabolic profile drawn before the colonoscopy.

RESULTS: Adding bisacodyl to G/PEG caused more abdominal bloating/cramps ($P < 0.01$) and did not result in a cleaner colon ($P = 0.66$) compared with G/PEG without bisacodyl. The BBPS scores in both the G/PEG arms and NuLYTELY arm were not significantly different ($P = 0.19$). Compared with subjects in the NuLYTELY arm, subjects in the G/PEG without bisacodyl arm had less nausea ($P < 0.04$), vomiting ($P < 0.02$), abdominal pain ($P < 0.02$), bloating ($P < 0.005$), difficulty drinking the liquid ($P < 0.0001$), and found the overall preparation easier to tolerate ($P < 0.0001$). Subjects in the combined G/PEG arms had a lower serum sodium ($P < 0.0007$), chloride ($P < 0.007$), and BUN ($P < 0.0001$) levels than those in the NuLYTELY arm, but this did not cause any clinical symptoms.

CONCLUSIONS: Bisacodyl added to G/PEG for colon lavage caused more side effects and did not result in a cleaner colon. The G/PEG preparations cleansed the colon as well as NuLYTELY, were far better tolerated, and were equally safe.

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INTRODUCTION

Colon cancer was the second leading cause of cancer death in the United States in 2008 (<http://seer.cancer.gov/faststat>). Colonoscopy is probably the most effective screening method for colon cancer, but in 2008, only 53.0–58.5% of the US population aged 50–75 years had undergone a colonoscopy in the past 10 years.¹ Concern about the bowel preparation was the most common reason cited by people older than age 50 years for not having a colonoscopy.²

Over the past few decades, attempts have been made to improve the tolerability and efficacy of the bowel preparations used for colonoscopy (see Table 1).

Four-liter polyethylene glycol 3,350 and electrolyte solutions (PEG-ELS)³ are not always well tolerated by patients (GoLYTELY, Braintree Laboratories, Braintree, MA, USA; CoLyte, Alaven Pharmaceutical, LLC, Marietta, GA, USA).⁴ Sulfate-free versions of PEG-ELS (SF-PEG-ELS)⁵ are only minimally better tolerated by patients (NuLYTELY, Braintree Laboratories; TriLyte, UCB, Brussels, Belgium).⁴ Safety concerns^{6,7} have limited the use of sodium phosphate preparations⁸ (VISICOL and OsmoPrep, Salix Pharmaceuticals, Raleigh, NC, USA).

Bisacodyl, a poorly absorbed diphenylmethane laxative that stimulates peristalsis, has been used with a 2-liter version

of SF-PEG-ELS (HalfLyte, Braintree Laboratories), but there is no evidence that bisacodyl is effective.⁴

Combinations of PEG (MiraLAX, Merck, Whitehouse Station, NJ, USA) in low ELS (e.g., Gatorade, The Gatorade Company, Chicago, IL, USA) and bisacodyl have been used in an attempt to improve the tolerability of the bowel preparation. Two investigator-blinded trials^{9,10} of 238–255 g PEG in 64 oz of Gatorade and 10–20 mg bisacodyl compared with a 4-liter PEG-ELS found better quality preparations with the PEG-ELS and only a minimal difference in tolerability.

Our uncontrolled observations with 238 g of PEG and 64 oz of Gatorade with or without 10–20 mg of bisacodyl were disappointing, with an unacceptably high number of sub-optimal colonoscopy preparations, and patients complained that the 306 g of PEG (G/PEG) preparation took longer to start working and kept them up at night.

We modified our protocol by increasing the PEG to 306 g given the day before the colonoscopy as 51 g at noon and 255 g from 1700 to 2100 h with 64 oz of Gatorade, and eliminated the bisacodyl. Our uncontrolled observations with the modified G/PEG protocol showed the quality of the preparations were similar to those with NuLYTELY. Patients seemed to tolerate the G/PEG preparation better than the commercial PEG preparations.

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Table 1 Select colon lavage preparations available for sale in the United States

	CoLyte or GoLYTELY	TriLyte or NuLYTELY	HalfLyte	MoviPrep	Gatorade+ PEG	VISICOL #32 tablets	SUPREP
Sodium bicarbonate (g)	6.74	5.72	2.86				
Sodium chloride (g)	5.86	11.2	5.6	5.38	1.19		
Sodium sulfate (g)		22.74		15			35
Sodium citrate (g)					0.68		
Sodium phosphate (g)						48	
Potassium-H ₂ -phosphate (g)					0.84		
Potassium chloride (g)	2.97	1.48	0.74	2.03			
Potassium sulfate (g)							6.26
PEG-3350 (g)	236	420	210	200	306		
Sodium ascorbate (g)				11.8			
Ascorbic acid (g)				9.4			
Magnesium sulfate (g)							3.2
Fructose/sucrose (g)					112		
Water (ml)	4000	4000	2000	2000	2247	2000	2839
Sodium (mmol)	500	260	130	363.6	38	416	493
Potassium (mmol)	40	20	10	28.4	6		71
Magnesium (mmol)							27
Chloride (mmol)	140	212	106	119.6	20		
Bicarbonate (mmol)	80	68	34				
Sulfate (mmol)	160					105.6	308
Phosphate (mmol)					6	326	
Ascorbate (mmol)				59.6			
Citrate (mmol)					6		
PEG-3350 (mmol)	70.4	125.2	62.6	59.2	91.2		
Cost (\$)	16.78	25.32	63.68	64.84	16.56	66.68	80.32

Contents obtained from the package inserts. Cost data for patients paying cash at Wal-Mart in January 2011 in Illinois, USA, for the least-expensive version (generic if available).

The objective of this study was to evaluate the safety, efficacy, and tolerability of a G/PEG preparation with or without 10 mg of bisacodyl compared with a preparation with NuLYTELY (or TriLyte). The study used an investigator-blinded, placebo-controlled, randomized trial format to compare the three preparations.

METHODS

Study design and oversight. The protocol was approved by the Adventist Midwest Region Institutional Review Board (AMH 2010-01-80, ClinicalTrials.gov NCT01063049). The trial was designed by the authors with no outside input. Adventist Hinsdale Hospital donated 171 basic metabolic profiles (BMPs) and waived the fee for the Institutional Review Board. All other expenses associated with this study were paid for by the authors. Subjects received no financial reward and paid for their preparations.

The study was an investigator-blinded, placebo-controlled, randomized trial of three bowel preparations as follows: (1) NU: NuLYTELY (or TriLyte) 4-liter (1 gallon) consumed from 1700 to 2100 h the night before the colonoscopy; (2) G/PEG + P: PEG 51 g in 355 ml (12 oz) of any clear liquid and a placebo (two 0.4 mg folic acid tablets) consumed at noon the day before the colonoscopy and PEG 255 g in Gatorade 1,872 ml (half gallon, 64 oz) consumed from 1700 to 2100 h the day before the colonoscopy; and (3) G/PEG + B: PEG 51 g in 355 ml (12 oz) of any clear liquid and bisacodyl (two 5 mg tablets, Major Pharmaceuticals, Livonia, MI, USA) consumed at noon the day before the colonoscopy and PEG 255 g in Gatorade 1,872 ml consumed from 1700 to 2100 h the

day before the colonoscopy. Subjects in the Gatorade arms were blinded to the inclusion of bisacodyl or placebo tablets, and were allowed to choose any non-red variety of Gatorade. Subjects were on clear liquids the day before the colonoscopy and instructed to consume nothing by mouth after midnight, except for medications taken in the morning. Subjects were instructed to take Fleets enemas if their stool was not clear on the morning of the colonoscopy.

Folic acid was chosen as a cost-effective placebo for bisacodyl, because both tablets were about the same color and size.

Subjects had their colonoscopy performed between February 2010 and February 2011 by one of three gastroenterologists (DG, JH, and MR) with 17 to 34 years of experience. Colonoscopies were scheduled to begin between 0800 h and noon in the gastrointestinal labs at our office or two community hospitals.

Subjects were outpatients undergoing elective colonoscopy and at least 18 years of age. Exclusion criteria included: (1) allergies or intolerances to any of the study drugs; (2) pregnancy; (3) those who required a multiple-day colon preparation for previous colonoscopies; or (4) those with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or toxic megacolon. Each subject signed an informed consent document.

Before the study began, it was determined that a total of 600 subjects would be enrolled with 200 subjects in each of the three bowel preparation arms. Our staffs were trained to screen and recruit all patients who met the inclusion criteria. Approximately 1,000 consecutive patients were invited to participate in the study to recruit the 600 subjects included in this study. The most common reasons patients declined to

participate in the study were that they wanted to choose their own bowel preparation, and they did not want to have blood drawn for a BMP. Randomization was performed using a computer-generated random number table in blocks of 30 subjects with 10 of each of the bowel preparation randomly distributed within each block. Each subject received an identical-appearing envelope with bowel-preparation instructions enclosed (see Supplementary Information (pages 1 and 2 online)). The envelopes for the G/PEG arms of the study contained two 5 mg bisacodyl or 0.4 mg folic acid tablets. Subjects were allowed to withdraw from the study until 24 h before their colonoscopy, and were replaced with another randomly selected subject who was given the same bowel-preparation regimen as the subject who withdrew. Beginning the day before the colonoscopy, all subjects were evaluated on an intention-to-treat basis, no matter what bowel preparation they actually used. Subjects could be switched to another bowel-cleaning regimen chosen by the physician on call if they could not tolerate the one assigned to them.

One author (DF) was responsible for monitoring the data for any adverse outcomes.

Measurements. A questionnaire was filled out by each subject immediately before the colonoscopy (see Supplementary Information (page 3 online)). Subjects were asked to rate their symptoms of nausea, vomiting, abdominal cramps/pain, and bloating on a scale of 0 to 3 as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Subjects were asked: if they had any other problems during their preparation; how much of the preparation they drank; if they needed to call the doctor for advice or help; if they needed to change their assigned preparation, because they could not drink it all; if they needed to take any Fleet enemas the morning of the procedure; if they had to wake up in the middle of the night to have a bowel movement; and if they would want to use the same preparation again if they needed a future colonoscopy. Subjects were asked to rate how difficult it was to drink the liquid, and overall, how difficult the preparation was. Both questions were answered on a scale of 0 to 3 as follows: 0 = easy, 1 = mildly difficult, 2 = moderately difficult, and 3 = very difficult. Subjects were asked if they had ever had a colonoscopy before, what preparation they consumed previously, and how was the study preparation compared with their previous preparation (i.e., easier, about the same, or more difficult).

A BMP was obtained before the intravenous line for the colonoscopy was started. Subjects known to have a creatinine ≥ 1.30 mg/dl had a baseline BMP drawn in the 30 days before the colonoscopy.

A questionnaire was filled out by the gastroenterologist immediately after the colonoscopy (see Supplementary Information (page 4 online)) rating the cleanliness of the bowel preparation. The questionnaire included the subject's age and race, the site at which the colonoscopy was performed, if the subject had a history of heart failure or renal insufficiency, the indications for the colonoscopy and the findings, if the subject had a previous colon resection, and whether the cecum (or most proximal extent of the remaining colon) was reached.

Table 2 The BBPS¹¹ and the OPS¹²

BBPS rating for each colon segment

- 0 = Unprepared colon segment with stool that cannot be cleared
- 1 = Portion of mucosa in segment seen after cleaning, but other areas not seen due to retained material
- 2 = Minor residual material after cleaning, but mucosa of segment generally well seen
- 3 = Entire mucosa of segment well seen after washing

BBPS is calculated by adding the ratings of the right, transverse and left colon segments. The overall BBPS is reported from 0 (very poor) to 9 (excellent)

OPS rating for each colon segment

- 4 = Inadequate (solid stool not cleared with washing and suctioning)
- 3 = Poor (necessary to wash and suction to obtain a reasonable view)
- 2 = Fair (necessary to suction liquid to adequately view segment)
- 1 = Good (minimal turbid fluid in segment)
- 0 = Excellent (mucosal detail clearly visible)

OPS rating for the amount of fluid in the whole colon

- 2 = Lots of fluid
- 1 = Moderate fluid
- 0 = Little fluid

OPS is calculated by adding the ratings of the right, transverse/descending and sigmoid/rectum colon segments, and rating for the fluid in the whole colon. The overall OPS is reported from 14 (very poor) to 0 (excellent)

Abbreviations: BBPS, Boston Bowel Preparation Scale; OPS, Ottawa Preparation Scale.

The primary endpoint of this study was the cleanliness of the colon on the Boston Bowel Preparation Scale (BBPS),¹¹ and a secondary endpoint was the cleanliness of the colon on the Ottawa Preparation Scale (OPS)¹² as reported by the gastroenterologist performing the colonoscopy (see Table 2).

For both bowel-preparation scales, any segment of the colon that had been completely resected or could not be reached due to difficulty advancing the colonoscope was not rated. Any segment that could not be reached due to more distal segments being poorly prepared was given the worst rating on each scale.

A secondary endpoint of the study was the cleanliness of the colon as rated by the gastroenterologist. A good-quality colonoscopy was defined as being able to see at least 95% of the mucosa of the visualized colon after washing and suctioning; otherwise, the preparation was rated as inadequate.

Before the study began, each participating gastroenterologist watched a video (media.bmc.org/Media/BostonBowelPreparationScale.wmv) as a calibration exercise for both the BBPS and OPS. During the study, any segments that proved difficult to rate were discussed among the authors.

Data analysis. Continuous variables were compared using Student's *t*-test (unpaired, two-tailed). Categorical variables were compared using Pearson's χ^2 -test (non-directional); however, when the observed frequencies were low, Fisher's exact test (two-tailed) was used. *P*-values of less than 0.05 were regarded as statistically significant.

When this study was designed, no studies using the BBPS had been published. Therefore, we based our sample size on prior studies of preparation quality and tolerability, and estimated that 600 patients (200 per arm) would have the

Table 3 Data from the questionnaire filled out by the gastroenterologists immediately after the colonoscopy

	1 NuLYTELY or TriLyte	2 Gatorade/PEG with placebo	P-value 1 vs. 2	3 Gatorade/PEG with 10 mg bisacodyl	P-value 2 vs. 3	P-value 1 vs. 3	4 Gatorade/PEG (both arms)	P-value 1 vs. 4
<i>N</i>	200	200		200			400	
Sex ratio (M:F)	119: 81	109: 91	0.31	101: 99	0.42	0.07	210: 190	0.06
MD (Gerard: Raiser: Holden)	100: 57: 43	95: 64: 41	0.75	85: 71: 44	0.60	0.25	180: 135: 85	0.39
Age in years (mean \pm s.d.)	60.2 \pm 13.2	59.7 \pm 13.8	0.71	61.3 \pm 12.5	0.22	0.39	60.4 \pm 13.1	0.86
<i>Race</i>								
Caucasian	173	168	0.48	173	0.48	1.00	341	0.68
African American	8	10	0.63	4	0.10	0.24	14	0.76
Hispanic	8	5	0.40	5	1.00	0.40	10	0.31
Other	11	17	0.24	18	0.86	0.18	35	0.16
<i>Procedure</i>								
Performed in our office	115	113	0.84	123	0.31	0.42	236	0.73
Start time (mean hour \pm s.d.)	10.2 \pm 0.9	10.3 \pm 1.0	0.29	10.2 \pm 1.0	0.29	1.00	10.3 \pm 1.0	0.23
History of heart failure	0	1	1.00	1	1.00	1.00	2	0.55
Baseline creatinine level \geq 1.30	9	7	0.61	5	0.56	0.28	12	0.35
Previous colon resection	8	9	0.81	10	0.81	0.63	19	0.68
<i>Indications (multiple indications possible)</i>								
Screening	70	67	0.75	59	0.39	0.24	126	0.39
History of polyps	41	56	0.08	62	0.51	< 0.02	118	< 0.05
History of colon cancer	4	6	0.52	8	0.58	0.24	14	0.31
FH colon neoplasia	28	29	0.89	30	0.89	0.78	59	0.81
Rectal bleeding	39	34	0.52	39	0.52	1.00	73	0.71
Anemia	14	11	0.54	6	0.21	0.07	17	0.15
History of IBD	3	3	1.00	10	< 0.05	< 0.05	13	0.16
Diarrhea	11	6	0.21	6	1.00	0.21	12	0.13
Recent diverticulitis	1	4	0.37	3	1.00	0.62	7	0.28
Abnormal GI X-ray	0	2	0.50	0	0.50	1.00	2	0.55
Change in bowel habits	0	5	0.06	1	0.22	1.00	6	0.19
<i>Findings (multiple findings possible)</i>								
Normal	61	59	0.82	53	0.50	0.37	112	0.52
Colon polyps	99	100	0.92	102	0.84	0.76	202	0.82
Colon cancer	1	2	1.00	3	1.00	0.62	5	0.67
Diverticulosis	78	59	< 0.05	61	0.82	0.07	120	< 0.03
Crohn's disease	1	0	1.00	8	< 0.008	< 0.04	8	0.28
Ulcerative colitis	2	5	0.45	5	1.00	0.45	10	0.35
Other colitis	4	4	1.00	2	0.69	0.69	6	0.74
Incomplete colonoscopy	3	1	0.62	3	0.62	1.00	4	0.69

Abbreviations: M, male; F, female; IBD, inflammatory bowel disease; GI, gastrointestinal tract.
P-values in bold signify significance levels < 0.05 .

power to detect statistically meaningful differences. In a *post-hoc* analysis with a sample size of 200 subjects per arm, the probability was 80% that the study would detect a difference between two arms at a two-sided 0.05 significance level, if the true difference between the BBPS of those arms was 0.28.

RESULTS

Subjects and endoscopic findings. The baseline characteristics of the 200 subjects in each of the three arms of the study were generally well balanced and are shown in Table 3. Six indications or findings were significantly more common in one arm than the other arm.

A total of 36 subjects (15 NU, 9 G/PEG + P, 12 G/PEG + B) withdrew at least 24 h before their scheduled colonoscopy and were replaced; 3 subjects (1 NU, 1 G/PEG + P, 1 G/PEG + B) decided not to undergo a colonoscopy; 14 subjects (3 NU, 4 G/PEG + P, 7 G/PEG + B) postponed their colonoscopy beyond February 2011; 5 subjects (4 NU, 1 G/PEG + B) wanted a different preparation than they were randomly assigned; 5 subjects (3 NU, 2 G/PEG + P) did not want to

have their blood drawn; and 9 subjects (4 NU, 2 G/PEG + P, 3 G/PEG + B) withdrew for unstated reasons.

A post-polypectomy bleed in one subject (1 G/PEG + P) was the only significant complication.

Colon polyps (including two colon cancers) were found in 102 of 196 (52.0%) average-risk subjects undergoing a screening colonoscopy. Colon polyps (including four colon cancers) were found in 203 of 404 subjects (50.2%, $P = 0.68$ vs. average risk subjects) undergoing colonoscopy due to increased risk or active symptoms.

The cecum (or most proximal extent of the remaining colon) was reached in 593 of 600 (98.8%) subjects. Of the seven incomplete colonoscopies, six (3 NU, 1 G/PEG + P, 2 G/PEG + B) were technically difficult, and one (1 G/PEG + B) had an obstructing sigmoid cancer. There was not a single subject in whom the cecum could not be reached due to an inadequate preparation.

Preparation quality and laboratory changes. The cleanliness data for each arm are shown in Table 4.

The laboratory data for each arm are shown in Table 5.

A total of 10 subjects (5 NU, 3 G/PEG + P, 2 G/PEG + B) declined to have their blood drawn, or the nurses forgot

Table 4 Colon cleanliness data from the questionnaire filled out by the gastroenterologists immediately after the colonoscopy

	1 NuLYTELY or TriLyte	2 Gatorade/ PEG with placebo	P-value 1 vs. 2	3 Gatorade/ PEG with 10 mg bisacodyl	P-value 2 vs. 3	P-value 1 vs. 3	4 Gatorade/ PEG (both arms)	P-value 1 vs. 4
BBPS								
Right colon (mean ± s.d.)	2.45 ± 0.67	2.49 ± 0.60	0.53	2.53 ± 0.63	0.52	0.22	2.51 ± 0.61	0.27
Transverse colon (mean ± s.d.)	2.70 ± 0.53	2.78 ± 0.48	0.11	2.74 ± 0.47	0.40	0.42	2.76 ± 0.47	0.16
Left colon (mean ± s.d.)	2.71 ± 0.58	2.77 ± 0.49	0.26	2.72 ± 0.55	0.44	0.86	2.75 ± 0.51	0.39
Total BBPS (mean ± s.d.)	7.86 ± 1.55	8.05 ± 1.28	0.18	7.99 ± 1.41	0.66	0.38	8.02 ± 1.34	0.19
OPS								
Right colon (mean ± s.d.)	1.18 ± 0.96	1.14 ± 0.95	0.68	1.07 ± 0.88	0.44	0.23	1.11 ± 0.91	0.38
Transverse/descending colon (mean ± s.d.)	0.66 ± 0.79	0.58 ± 0.83	0.32	0.57 ± 0.73	0.90	0.24	0.58 ± 0.79	0.24
Sigmoid/rectum (mean ± s.d.)	0.60 ± 0.86	0.53 ± 0.77	0.39	0.67 ± 0.87	0.09	0.42	0.60 ± 0.83	1.00
Fluid total colon (mean ± s.d.)	0.35 ± 0.55	0.32 ± 0.49	0.56	0.39 ± 0.59	0.20	0.48	0.36 ± 0.54	0.83
Total OPS (mean ± s.d.)	2.80 ± 2.24	2.58 ± 2.47	0.35	2.71 ± 2.47	0.60	0.70	2.65 ± 2.47	0.47
Inadequate preparation	11	7	0.33	9	0.61	0.65	16	0.40
Failed or inadequate Preparation	13	7	0.17	9	0.61	0.38	16	0.18

Abbreviations: BBPS, Boston Bowel Preparation Scale; OPS, Ottawa Preparation Scale.

to draw their blood on the day of colonoscopy. Another 14 subjects (6 NU, 5 G/PEG + P, 3 G/PEG + B) had hemolyzed samples, making the potassium result unusable. One subject's blood (1 NU) was so hemolyzed that all the values in the BMP were unusable.

Three subjects, all with no known pre-existing renal disease, had post-preparation serum sodium levels ≤ 130 mmol/l (1 NU = 129 mmol/l; 2 G/PEG + P = 120 and 129 mmol/l), and none had any obvious clinical symptoms. The subject who had a serum sodium level of 120 mmol/l had a baseline serum sodium level of 131 mmol/l (drawn for reasons unrelated to this study).

Two subjects, both with no known pre-existing renal disease, had post-preparation serum potassium levels < 3.0 mmol/l (1 G/PEG + P = 2.6 mmol/l, 1 G/PEG + B = 2.9 mmol/l) and neither had any obvious clinical symptoms.

One subject with no known pre-existing renal disease had a post-preparation serum creatinine ≥ 1.50 mg/dl (1 G/PEG + B = 1.57 mg/dl) and had no obvious clinical symptoms.

In the NU arm, the BBPS for subjects consuming 33–75% of their preparation was 7.27 ± 1.81 (*n* = 31), for those consuming 76–99% of their preparation was 8.13 ± 1.56 (*n* = 32), for those consuming 100% of their preparation was 7.93 ± 1.45 (*n* = 137, *P* < 0.04 vs. 33–75%), and for those consuming 76–100% of their preparation was 7.97 ± 1.48 (*n* = 168, *P* < 0.03 vs. 33–75%).

In all three arms combined, the BBPS for subjects scheduled to undergo colonoscopy from 0800 to 0900 h was 8.02 ± 1.47 (*n* = 130), from 0915 to 1000 h was 7.99 ± 1.41 (*n* = 209), from 1015 to 1100 h was 7.96 ± 1.25 (*n* = 170), and from 1115 to 1200 h was 7.82 ± 1.63 (*n* = 91, *P* = 0.34 vs. 0800 to 0900 h).

The correlation coefficient between the total BBPS and the total OPS was –0.796.

In all three arms combined (when all three colon segments were rated), inadequate preparations were found in 8 of 8 (100%) subjects with BBPS ≤ 3, 7 of 8 subjects (87.5%) with BBPS = 4, 10 of 17 subjects (58.8%) with BBPS = 5, 1 of 64 subjects (1.6%; colon segments: right = 1, trans-

verse = 3, left = 2) with BBPS = 6, 1 of 70 subjects (1.4%; colon segments: right = 1, transverse = 3, left = 3) with BBPS = 7, and 0 of 425 subjects (0%) with BBPS ≥ 8.

Preparation tolerance by subjects. The data from the subject questionnaire for each arm is shown in Table 6.

Only three subjects (3 NU) could not consume more than 50% of their preparation and were switched to G/PEG. All three were counted, on an intention-to-treat basis, in the NU arm: two had BBPS = 9 and one had a BBPS = 3 and an inadequate preparation.

DISCUSSION

Our investigator-blinded study found no statistically significant differences in the BBPS among the three preparation arms. There was no statistically significant difference between the BBPS of the G/PEG arms combined, and the NU arm, or in the OPS (a secondary endpoint of our study) among the three arms. This is the first randomized trial to show that Gatorade/PEG can be as effective in cleansing the colon as a 4-l PEG-ELS.

Only 27 subjects (4.5%) had colon preparations that were rated as inadequate for a good quality colonoscopy by the gastroenterologist. There was no statistically significant difference between the number of inadequate preparations in the G/PEG arms combined and the NU arm. If the three patients who were unable to tolerate the NuLYTELY were included with the inadequate preparations, the difference between the G/PEG arms combined and the NU arm would remain not statistically significant.

Subjects in the G/PEG + B arm had a statistically significant increase in abdominal cramps/pain compared with those in the G/PEG + P arm, but overall, did not find the preparation more difficult. One previous investigator-blinded study¹⁰ had compared a 255-g version of G/PEG with and without 10 mg of bisacodyl, and found no significant difference in the OPS between the two arms (*P*-value not reported).

Table 5 Data from the basic metabolic profiles drawn before the IV for the colonoscopy was started in subjects with no known pre-existing renal disease

	1 NuLYTELY or TriLyte	2 Gatorade/ PEG with placebo	P-value 1 vs. 2	3 Gatorade/ PEG with 10 mg bisacodyl	P-value 2 vs. 3	P-value 1 vs. 3	4 Gatorade/ PEG (both arms)	P-value 1 vs. 4
<i>Subjects with no known renal disease (N)</i>								
Na (mmol/l) (mean ± s.d.)	191	193	0.61	195	0.56	0.28	388	0.35
Na (mmol/l) (mean ± s.d.)	139.8 ± 2.6	138.8 ± 3.0	<0.0005	139.3 ± 2.5	0.08	0.05	139.0 ± 2.7	<0.0007
K (mmol/l) (mean ± s.d.)	4.29 ± 0.42	4.26 ± 0.44	0.49	4.25 ± 0.42	0.82	0.35	4.26 ± 0.43	0.43
Cl (mmol/l) (mean ± s.d.)	104.1 ± 2.7	103.4 ± 3.1	<0.02	103.4 ± 2.9	1.00	<0.02	103.4 ± 3.0	<0.007
CO ₂ (mmol/l) (mean ± s.d.)	23.7 ± 2.3	23.7 ± 2.3	1.00	23.8 ± 2.4	0.68	0.68	23.8 ± 2.3	0.62
BUN (mg/dl) (mean ± s.d.)	13.1 ± 3.9	11.3 ± 3.9	<0.0001	12.0 ± 4.2	0.09	<0.008	11.6 ± 4.0	<0.0001
Cre (mg/dl) (mean ± s.d.)	0.95 ± 0.18	0.94 ± 0.19	0.60	0.94 ± 0.18	1.00	0.59	0.94 ± 0.19	0.54
Ca (mg/dl) (mean ± s.d.)	9.38 ± 0.40	9.54 ± 0.48	<0.0004	9.50 ± 0.46	0.40	<0.007	9.52 ± 0.47	<0.0004
Na < 130 mmol/l	1	2	1.00	0	0.50	1.00	2	1.00
K < 3.0 mmol/l	0	1	1.00	1	1.00	1.00	2	0.55
3.0 mmol/l ≤ K < 3.5 mmol/l	5	3	0.72	4	1.00	1.00	7	0.76
Cre ≥ 1.30 mg/dl	4	6	0.75	6	1.00	0.75	12	0.60
<i>Subjects with known Cre ≥ 1.30 (N)</i>								
Change Na (mmol/l) (mean ± s.d.)	9	7	0.61	5	0.56	0.28	12	0.48
Change Na (mmol/l) (mean ± s.d.)	-2.0 ± 3.0	-0.7 ± 3.3	0.42	-2.0 ± 3.7	0.54	1.00	-1.2 ± 3.4	0.58
Change K (mmol/l) (mean ± s.d.)	-0.6 ± 1.8	-0.10 ± 0.54	0.49	-0.26 ± 0.31	0.56	0.69	-0.17 ± 0.45	0.43
Change Cl (mmol/l) (mean ± s.d.)	-0.8 ± 2.3	-0.3 ± 1.7	0.64	-1.8 ± 2.8	0.27	0.48	-0.9 ± 2.2	0.92
Change CO ₂ (mmol/l) (mean ± s.d.)	-1.8 ± 3.1	-2.0 ± 2.6	0.89	-3.0 ± 1.7	0.47	0.44	-2.4 ± 2.2	0.61
Change BUN (mg/dl) (mean ± s.d.)	-7.5 ± 7.7	-10.9 ± 7.5	0.39	-6.4 ± 4.2	0.26	0.77	-9.0 ± 6.5	0.63
Change Cre (mg/dl) (mean ± s.d.)	-0.12 ± 0.17	-0.12 ± 0.18	1.00	-0.04 ± 0.14	0.43	0.39	-0.09 ± 0.17	0.69
Change Ca (mg/dl) (mean ± s.d.)	-0.01 ± 0.41	0.23 ± 0.35	0.24	0.44 ± 0.61	0.46	0.12	0.3 ± 0.5	0.15

In subjects known to have a baseline creatinine ≥ 1.30 mg/dl, the data is shown as the change in electrolytes calculated from a baseline basic metabolic profile drawn before the bowel preparation and the basic metabolic profile drawn before the intravenous line for the colonoscopy was started.
P-values in bold signify significance levels <0.05.

Table 6 Data from the questionnaire filled out by the subjects immediately before their colonoscopy

	1 NuLYTELY or TriLyte	2 Gatorade/ PEG with placebo	P-value 1 vs. 2	3 Gatorade/ PEG with 10 mg bisacodyl	P-value 2 vs. 3	P-value 1 vs. 3	4 Gatorade/ PEG (both arms)	P-value 1 vs. 4
<i>Side effects</i>								
Nausea (mean ± s.d.)	0.64 ± 0.86	0.41 ± 0.72	<0.04	0.45 ± 0.71	0.58	<0.02	0.43 ± 0.72	<0.02
Vomiting (mean ± s.d.)	0.22 ± 0.64	0.06 ± 0.34	<0.02	0.11 ± 0.48	0.23	0.05	0.09 ± 0.42	<0.03
Abdominal cramps/pain (mean ± s.d.)	0.46 ± 0.70	0.31 ± 0.56	<0.02	0.46 ± 0.60	<0.01	1.00	0.39 ± 0.59	0.20
Bloating (mean ± s.d.)	0.96 ± 0.85	0.74 ± 0.71	<0.005	0.76 ± 0.74	0.78	<0.02	0.75 ± 0.72	<0.002
<i>Other side effects</i>								
Headache	4	10	0.10	6	0.31	0.52	16	0.20
Other	13	7	0.17	9	0.61	0.38	16	0.18
% Preparation consumed (mean ± s.d.)	93.4 ± 12.9	98.9 ± 5.3	<0.0001	99.3 ± 3.9	0.39	<0.0001	99.1 ± 4.6	<0.0001
Consumed 100% of Preparation	137	188	<0.0001	191	0.50	<0.0001	379	<0.0001
Incomplete % consumed (mean ± s.d.)	79.0 ± 14.9	82.3 ± 13.6	0.48	82.6 ± 10.2	0.96	0.49	82.4 ± 12.0	0.35
Called MD for advice	8	16	0.09	10	0.22	0.63	26	0.21
Needed Fleets enemas	23	28	0.45	31	0.67	0.24	59	0.27
Number of enemas (mean ± s.d.)	1.52 ± 0.73	1.54 ± 0.69	0.92	1.68 ± 0.65	0.43	0.40	1.62 ± 0.67	0.56
Changed preparation due to intolerance	3	0	0.25	0	1.00	0.25	0	<0.04
Woke up at night for bowel movement	104	127	<0.02	129	0.84	<0.02	256	<0.005
Would use the same preparation again	114	185	<0.0001	182	0.58	<0.0001	367	<0.0001
<i>How difficult was</i>								
Drink liquid (mean ± s.d.)	1.33 ± 0.97	0.41 ± 0.62	<0.0001	0.45 ± 0.70	0.55	<0.0001	0.43 ± 0.66	<0.0001
Overall preparation (mean ± s.d.)	0.97 ± 0.96	0.38 ± 0.63	<0.0001	0.42 ± 0.67	0.54	<0.0001	0.40 ± 0.65	<0.0001
Had previous colonoscopy	116	123	0.48	133	0.30	0.08	256	0.15
<i>Previous preparation</i>								
Any 4-liter PEG preparation	10E:77S:9M	79E:16S:5M	<0.0001	85E:15S:7M	0.84	<0.0001	164E:31S:12M	<0.0001
Any sodium phosphate pills	3E:4S:4M	6E:4S:1M	0.27	4E:5S:4M	0.38	1.00	10E:9S:5M	0.53
Fleets phospho-soda	0E:1S:4M	1E:3S:3M	0.56	2E:0S:2M	0.18	0.29	3E:3S:5M	0.62
Any 2-liter Gatorade/PEG	0E:1S:2M	0E:1S:1M	1.00	1E:6S:2M	0.62	0.62	1E:7S:3M	0.62

Abbreviations: PEG, polyethylene glycol; E, easier, S, same; M, more difficult.

For "previous preparation," the study preparation was E, S, M, compared with the previous preparation.

P-values in bold signify significance levels <0.05.

A study¹³ of 45 subjects compared the colon cleanliness after a 4-liter PEG-ELS solution with and without 10 mg of bisacodyl, and concluded that there was no significant difference between the arms. A study¹⁴ with 442 subjects compared versions of HalfLyte (2 ISF-PEG-ELS) with 10 and 20 mg of bisacodyl and found no difference in colon cleanliness, but fewer side effects were seen with the 10-mg version. An unpublished study with 308 subjects described in the HalfLyte package insert compared versions of the HalfLyte with 5 and 10 mg of bisacodyl, and found no difference in colon cleanliness. There are no published studies that show that bisacodyl is effective as part of a modern colon-cleansing preparation.⁴

Using low-ELS, such as Gatorade, as part of a preparation for colonoscopy could cause renal injury or electrolyte shifts to occur from the large quantity of PEG and water consumed. Subjects with no known pre-existing renal disease in both G/PEG arms combined had statistically significant lower serum sodium, lower serum chloride, lower serum BUN, and higher serum calcium levels compared with similar subjects in the NU arm. No significant differences in the serum creatinine or potassium levels were noted among the three preparation arms. Although the electrolyte differences were statistically significant, the absolute differences between arms were small and not associated with any clinical symptoms. The two previous studies^{9,10} comparing G/PEG preparations with GoLYTELY did not measure the subject's serum chemistries.

As baseline BMPs were not drawn in subjects with no known pre-existing renal disease, it is impossible to know how much their serum chemistries changed. Previous studies^{5,15,16} with NuLYTELY found small and inconsistent changes in serum chemistries after a preparation with NuLYTELY. In this study, the differences in serum chemistries between subjects in the NU arm and G/PEG arms combined were small, suggesting that the changes in serum chemistries after a G/PEG preparation were also small.

There is a case report¹⁷ of a 73-year-old woman who developed a seizure and was found to have a serum sodium level of 117 mmol/l following a preparation with 64 oz of Gatorade and 255 g of PEG. An abstract¹⁸ reported 14 patients with severe hyponatremia, following preparations with G/PEG. Our G/PEG has not been widely used, and studies with large numbers of subjects using this preparation would be reassuring.

In the 21 subjects with a baseline creatinine ≥ 1.30 mg/dl, who had both a baseline and pre-colonoscopy BMP drawn, no significant changes in serum chemistries were noted among the three preparation arms. The number of subjects with pre-existing renal disease was small and no subject with a creatinine > 2.45 mg/dl enrolled in our study.

Subjects in the G/PEG arms tolerated their preparations far better than subjects in the NU arm by almost every measure used in this study. Compared with subjects in the NU arm, subjects in the G/PEG + P arm had statistically significantly less nausea, vomiting, abdominal cramps/pain, and bloating. Compared with subjects in the NU arm, subjects in both G/PEG arms combined had statistically significantly less difficulty drinking the liquid, found the overall

preparation easier to tolerate, were able to consume 100% of the preparation more frequently, and were more willing to use the same preparation again for a future colonoscopy. Of the subjects who had used any 4-liter PEG preparation for their previous colonoscopy, more subjects found the preparations in the G/PEG arms combined easier to consume than the preparation in the NU arm. These findings were not only statistically significant, but in absolute terms, the differences were quite large. These findings are clinically important, as the consumption of the bowel preparation is the most commonly cited reason for not undergoing a colonoscopy.²

Compared with subjects in the NU arm, subjects in both G/PEG arms combined more frequently woke up at night to have a bowel movement.

Our 306 g version of G/PEG used a non-traditional split dose with 51 g of PEG at noon the day before the colonoscopy, which may have reduced the side effects compared with NuLYTELY, and accounted for the superior cleansing results compared with other trials^{9,10} with G/PEG. Our G/PEG had 51 to 68 g more PEG compared with other G/PEG studies,^{9,10} which might have cleansed the colon better. The Fleets enemas given to subjects whose stools were not clear on the morning of the colonoscopy may have salvaged some preparations, which otherwise would have been inadequate. SF-PEG ELS (NuLYTELY) is better tolerated than sulfate-containing solutions,⁴ such as GoLYTELY, making our findings even more clinically relevant.

The American College of Gastroenterology recommends¹⁹ that bowel preparations be given as PM/AM split doses. Two studies^{20,21} have compared the day before dosing of a 4-liter PEG-ELS preparation with the PM/AM split dosing of a similar preparation and found the split-dosing regimens produced significant better bowel preparations. The day before regimens produced good or excellent results in 39.4–56.2% of subjects, whereas the split-dosing regimens produced good or excellent results in 76.5–94.4%. In both studies, (1) subjects in the day before arms consumed a liquid diet the day before the colonoscopy; (2) subjects in the split-dosing arms consumed a regular diet the day before the colonoscopy; and (3) the 4-liter PEG-ELS preparations contained sodium sulfate.

All three arms of our study used day before dosing and had adequate preparations in 94.5–96.5% of subjects. These excellent results may have been because of the use of a sulfate-free 4-liter PEG lavage (NuLyte), the clear liquid diet given to our subjects the day before the procedure, or the Fleets enemas given to subjects whose stools were not clear on the morning of the colonoscopy.

If colonoscopy preparations are sufficiently well tolerated and efficacious, split dosing may be unnecessary for morning procedures. Only head-to-head comparisons in randomized trials of these different bowel preparations will definitively answer these questions.

In our study, 94.7% of subjects in the G/PEG arms combined were able to finish their preparations compared with 68.5% of subjects in the NU arm, but these findings do not explain why the colons were as clean in the G/PEG arms as they were in the NU arm. Subjects in the NU arm

actually consumed an average of 392 g of PEG (93.4% of the prescribed amount) compared with 303 g (99.1% of the prescribed amount) in both G/PEG arms combined. The 31 subjects (15.5%) who consumed 139–315 g of PEG in their NuLYTELY (33–75% of the prescribed amount) had a significantly lower average BBPS compared with that of the 169 subjects (84.5%) who consumed 319–420 g of PEG in their NuLYTELY (76–100% of the prescribed amount). If the 31 subjects who consumed 33–75% of their NuLYTELY were excluded from the NU arm, the BBPS of the remaining 169 subjects would be very similar to the BBPS for the 400 subjects in both G/PEG arms combined. This is further evidence that 238–255 g of PEG may not be enough to reliably lavage the colon.

Five studies^{15,22–25} have compared various 2-liter PEG-ELS solutions with 15–20 mg of bisacodyl to similar 4-liter PEG-ELS solutions without bisacodyl and concluded that there was no significant difference in cleanliness between the arms, and that the 2-liter preparations were better tolerated. None of these studies used both the SF-PEG-ELS and a sensitive and validated measure of colon cleanliness.

It has been reported that the quality of colonoscopy preparations declines as the time between the preparation and colonoscopy increases.²⁶ We found no significant difference between the BBPS of colonoscopies performed between 0800 and 0900 h compared with 1115 and 1200 h. It should be noted that by design in this study, no afternoon procedures were studied.

This is the first study to use both the BBPS and the OPS to rate colon cleanliness. The colon segments rated on the BBPS (right, transverse, and left) were easier for the gastroenterologist to define during colonoscopy than those rated on the OPS (right, transverse/descending, and sigmoid/rectum). The BBPS rated each segment after washing and suctioning, whereas the OPS rated each segment before cleaning was attempted. The BBPS was more clinically relevant, because the visualization of the mucosa is the primary goal of any bowel preparation. The OPS was more sensitive to truly outstanding colon preparations, as it distinguished between segments that required no cleaning and those that required some cleaning. Despite these differences, the results on the BBPS and OPS were moderately-to-strongly correlated ($r = -0.796$).

Both the BBPS and OPS suffer from poorly designed scoring systems that are not easily converted into the poor/fair/good/excellent subjective rating scale, which is often used by gastroenterologists in their colonoscopy reports. A colon with minor residual material throughout the colon would receive a BBPS = 6, and most gastroenterologists would consider this a good preparation. A colon with a clean transverse and left colon, but with stool that could not be cleared throughout the right colon, would receive the same BBPS = 6, but the preparation would be poor.

A segment of colon is rated 1 on the BBPS, when a portion of mucosa in a segment is seen after cleaning, but other areas are not seen due to retained material. The BBPS does not specify the percentage of a segment's mucosa that must not be seen for it to be rated 1. Our adequate/inadequate scale required at least 95% of the mucosa of the whole colon to be

well visualized for the preparation to be rated as adequate. It was possible for a segment of the colon to be rated 1 on the BBPS, yet the preparation of the whole colon on the adequate/inadequate scale to be rated as adequate. An improved scale to rate bowel cleanliness is needed to overcome these limitations.

This study is being reported as an investigator-blinded study of G/PEG + P vs. G/PEG + B rather than a double-blinded study, because the placebo (folic acid) pills and bisacodyl pills looked very similar, but were not identical. To the best of our knowledge, patients did not know which pill they were consuming.

In conclusion, we found the NU arm and both G/PEG arms produced statistically similar colon cleansing when consumed the day before a morning colonoscopy. Subjects in the G/PEG arms tolerated their preparations far better than those in the NU arm. G/PEG appears to be as safe as NU with small but statistically significant electrolyte differences among the arms, causing no clinical symptoms. G/PEG costs about 25% as much as commercially available low-volume colon-cleansing preparations, such as HalfLyte, MoviPrep, VISICOL tablets, and SUPREP (see Table 1). Although a formal cost effectiveness analysis was not performed, using the G/PEG preparation described here could result in a very significant cost savings. In our practice, the G/PEG (without bisacodyl) is used for most colon cleansings for colonoscopy.

Adding 10 mg of bisacodyl to G/PEG and 64 oz of Gatorade for colon lavage caused more abdominal bloating/cramps, and did not result in a cleaner colon. There is no evidence that bisacodyl is effective as part of a PEG colon-cleansing preparation and its widespread use as part of various colon-lavage preparations needs to be re-examined.

Future studies need to determine: (1) if the G/PEG used in this study provides the optimal balance of colon cleansing with patient safety and tolerance; (2) if any clear liquid could be substituted for Gatorade; (3) how the G/PEG preparation compares with other commercially available preparations; (4) the safety of the G/PEG preparation in larger numbers of patients, including those with renal insufficiency and CHF; and (5) if the inconvenience of a PM/AM split-dose G/PEG preparation is outweighed by the improved cleanliness for morning colonoscopies.

CONFLICT OF INTEREST

Guarantor of the article: David P. Gerard, MD.

Specific author contributions: David P. Gerard: all. John L. Holden and Manfred W. Raiser: concept, acquisition of data, analysis, drafting, and critical revisions. Diane B. Foster: acquisition of data, analysis, drafting, critical revisions, and administrative.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✔ Concern about the bowel preparation is the most common reason people do not have a colonoscopy.
- ✔ Low compliance with bowel preparations can result in suboptimal colon visualization.
- ✔ Preparations with Gatorade and PEG (up to 255 g) are not as efficacious as 4-liter electrolyte-PEG solutions.
- ✔ The safety of Gatorade and PEG preparations has not been assessed in a trial using BMPs.
- ✔ Bisacodyl has not been shown to be effective as part of a modern colon-cleansing preparation.

WHAT IS NEW HERE

- ✔ A new preparation using 64 oz of Gatorade and G/PEG is described.
- ✔ Adding bisacodyl to Gatorade/PEG caused more side effects and did not result in a cleaner colon.
- ✔ Gatorade/PEG (306 g version) and NuLYTELY are equally efficacious when given the evening before a morning colonoscopy.
- ✔ Gatorade/PEG (306 g version) was far better tolerated than NuLYTELY
- ✔ Gatorade/PEG resulted in lower serum sodium, chloride, and BUN levels than NuLYTELY, but these differences were small and not clinically important.

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