

Clinical trial: an efficacy evaluation of reduced bisacodyl given as part of a polyethylene glycol electrolyte solution preparation prior to colonoscopy

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SUMMARY

Background

In an attempt to further improve patient preparation experience with reduced volume gut lavage solutions using 2-L sulphate-free electrolyte lavage solution plus 20-mg bisacodyl (HalfLyte[®] with Bisacodyl Tablets Bowel Prep Kit, Braintree Laboratories, Inc., Braintree, MA, USA), a low bisacodyl dose preparation was developed using 10 mg bisacodyl.

Aim

To compare preparation methods using the 10- or 20-mg bisacodyl with 2-L sulphate-free electrolyte lavage method.

Methods

At 10 US centres, 455 patients undergoing colonoscopy for routine clinical indications were equally randomized to receive 10- or 20-mg bisacodyl with 2-L sulphate-free electrolyte lavage method. Colonoscopists rated the efficacy of colon cleansing, blinded to the preparation assignment.

Results

Physician assessment of colon cleansing showed no difference between those randomized to receive the 10- or 20-mg bisacodyl preparations ($P = 0.52$). The 10-mg preparation had lower symptom scores for cramping ($P < 0.001$) and overall discomfort ($P = 0.001$). Other reported adverse experiences were few, mild and not different between groups.

Conclusion

Two-litre sulphate-free electrolyte lavage method solution with 10-mg bisacodyl is as effective as the 20-mg bisacodyl preparation for cleansing the colon prior to colonoscopy. The 10-mg bisacodyl regimen has an improved safety profile, with significantly reduced cramping, nausea and overall discomfort.

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INTRODUCTION

A reduced volume oral gastrointestinal preparation method (HalfLyte and Bisacodyl Tablets Bowel Prep Kit, Braintree Laboratories, Inc.) has been developed to improve the tolerance for colonoscopy cleansing. In a comparison to a standard 4-L sulphate-free electrolyte lavage method (SF-ELS, NuLYTELY, Braintree Laboratories, Inc.), the reduced volume method had similar cleansing efficacy with significantly less volume-related symptoms of fullness, nausea, vomiting and overall discomfort.¹ Occasional postmarketing adverse events of abdominal cramping have been received following ingestion of the 20-mg bisacodyl component. This study was designed to determine if a regimen using a 10-mg reduced bisacodyl dose would result in reduced preparation-related complaints while maintaining bowel cleansing efficacy.

METHODS

Study design

This was a single-blind, active control parallel study of adult out-patients undergoing routine elective colonoscopy. The trial was registered at <http://www.clinicaltrials.gov> # NCT00278967.

Study population

The study subjects were adult out-patients undergoing colonoscopy for routine clinical indications. Patients with ileus or suspected bowel obstruction, prior alimentary tract surgery, significant gastroparesis or gastric outlet obstruction, toxic colitis or megacolon, or those pregnant or lactating were excluded. Otherwise, all subjects were included regardless of underlying medical conditions or suspected colon pathology. Baseline evaluations included medical history, physical examinations and collection of demographic data.

Study centers

Data were collected at 10 US study sites. All used the same investigational protocol. Enrollment was competitive and subjects were recruited from physician practices. The experimental protocol and informed consent materials were approved by an Institutional Review Board before initiation of the study. Written informed consent was obtained for all participating patients.

Enrollment began on 16th January 2006, with the last subject completing on 19th April 2006.

Colon cleansing methods and study medication

Study subjects were advised to have clear liquids for breakfast, lunch and dinner on the day prior to their planned colonoscopy. A study coordinator interviewed each patient and provided written instructions for the preparation methods. Based on the randomization assignment, subjects were instructed to take two or four 5-mg bisacodyl tablets at noon on the day prior to their colonoscopy. After their first bowel movement or a maximum of 6 h later, patients were to drink 2-L SF-ELS 8 oz every 10 min. Patients were instructed to take nothing by mouth until after the scheduled colonoscopy the next day. Study subjects were asked to return the unused bowel preparation components.

Randomization

Study medications were provided by Braintree Laboratories in identically labelled kits and contained either two or four 5 mg bisacodyl tablets with 2-L lemon-lime SF-ELS. Subjects were randomly assigned in a 1:1 ratio at each participating site using a computer generated randomization schedule. The randomization schedule at each site was constructed by using random blocks of two balanced treatment assignments. Patients that met eligibility requirements were sequentially assigned a kit number from the randomization schedule.

Adequacy of cleansing

Bowel cleansing was scored by colonoscopists who were blinded to the preparation method. The 10- and 20-mg kits were provided to patients in identically labeled packages, with the only difference in the test preparations being the number of 5-mg bisacodyl tablets (2 or 4) contained in the kits. The colonoscopists were not allowed to perform any drug-related activity – randomization, dispensing, drug return or accountability. Cleansing was scored with a 4-point scale used in previous bowel cleansing studies¹⁻³ where 1 = 'poor' (large amounts of faecal residue requiring additional cleansing); 2 = 'fair' (enough feces or fluid to prevent a completely reliable exam); 3 = 'good' (small amounts of faeces or fluid not interfering with the exam); 4 = 'excellent' (no more than small bits of adherent feces/fluid). For the primary efficacy

variable, scores of 3 and 4 were considered 'successful' and scores of 1 or 2 were considered a 'failure'. Patients unable to tolerate their preparation or those who were not examined because of lack of bowel cleansing were also considered a 'failure'. Physicians were also asked to rate the cleansing as to clinical 'adequacy' for diagnostic purposes.

Patient tolerance

Patients maintained a bowel movement diary in which they recorded the time of each bowel movement and rating of associated symptoms. A treatment questionnaire was also completed by the patient over the course of their bowel preparation which recorded the times at which the patient took their bisacodyl tablets, started drinking the solution and a description of what they ate and drank on the day of the preparation. Finally, patients filled out an overall symptom questionnaire at the final visit where they rated symptoms associated with the entire preparation experience. Symptoms of fullness, abdominal cramping, nausea, vomiting and overall discomfort were scored on a 5-point scale used in previous bowel cleansing studies¹⁻³ where 1 = 'none'; 2 = 'mild'; 3 = 'bothersome'; 4 = 'distressing'; and 5 = 'severely distressing'. Symptoms reported as 'severely distressing' on the scale were documented as adverse events. In addition, investigators recorded any observed or patient-reported adverse experiences. Safety assessments also included adverse event monitoring as well as baseline and post-prep physical examination.

Data analysis

The sample size calculation, for a non-inferiority study, was based upon the normal approximation to the binomial distribution. Using the results from previous studies,¹⁻³ the overall treatment success for the 20-mg bisacodyl group was expected to be expected approximately 82%. A decrease of 15% in overall treatment success for HalfLyte with 10-mg bisacodyl (82-70%) would be considered clinically relevant. Assuming an 82% 20-mg bisacodyl response rate for overall treatment success, based on a one-sided chi-squared test, a sample size of 225 subjects per group will have 90% power to detect a treatment difference of 15% at the one-sided significance level of 0.05.

The primary efficacy analysis was based upon an intent-to-treat (ITT) analysis and included patients

who were randomized and received any treatment. Patients in this group had a determination of preparation success or failure based on the colonoscopists' score of cleansing. Patients who did not undergo colonoscopy because of inadequate preparation or preparation-related adverse events were considered failures. Success rate was analysed by using Cochrane chi-squared adjusting for the effect of investigator site.

Secondary endpoints were analysed in a manner similar to the primary analysis using Cochrane chi-squared adjusting for any site effects for counts (percentage) responses and two-way ANOVA with terms for treatment, site and their interaction for mean responses. Results were presented for the effect results (*P*-values) and 95% CI for the treatment difference.

Treatment emergent adverse event rates were descriptively presented by body system, preferred term, severity and relationship to treatment for each treatment group. Differences in adverse event rates between groups were assessed by using Fisher's exact test.

Statistical consultation was provided by G. Burton Seibert, PhD, StatNet Statistical Services Network, Plaistow, NH, USA.

The study was monitored by I3 Pharma Resourcing, Basking Ridge, NJ, USA and Braintree Laboratories, Inc.

RESULTS

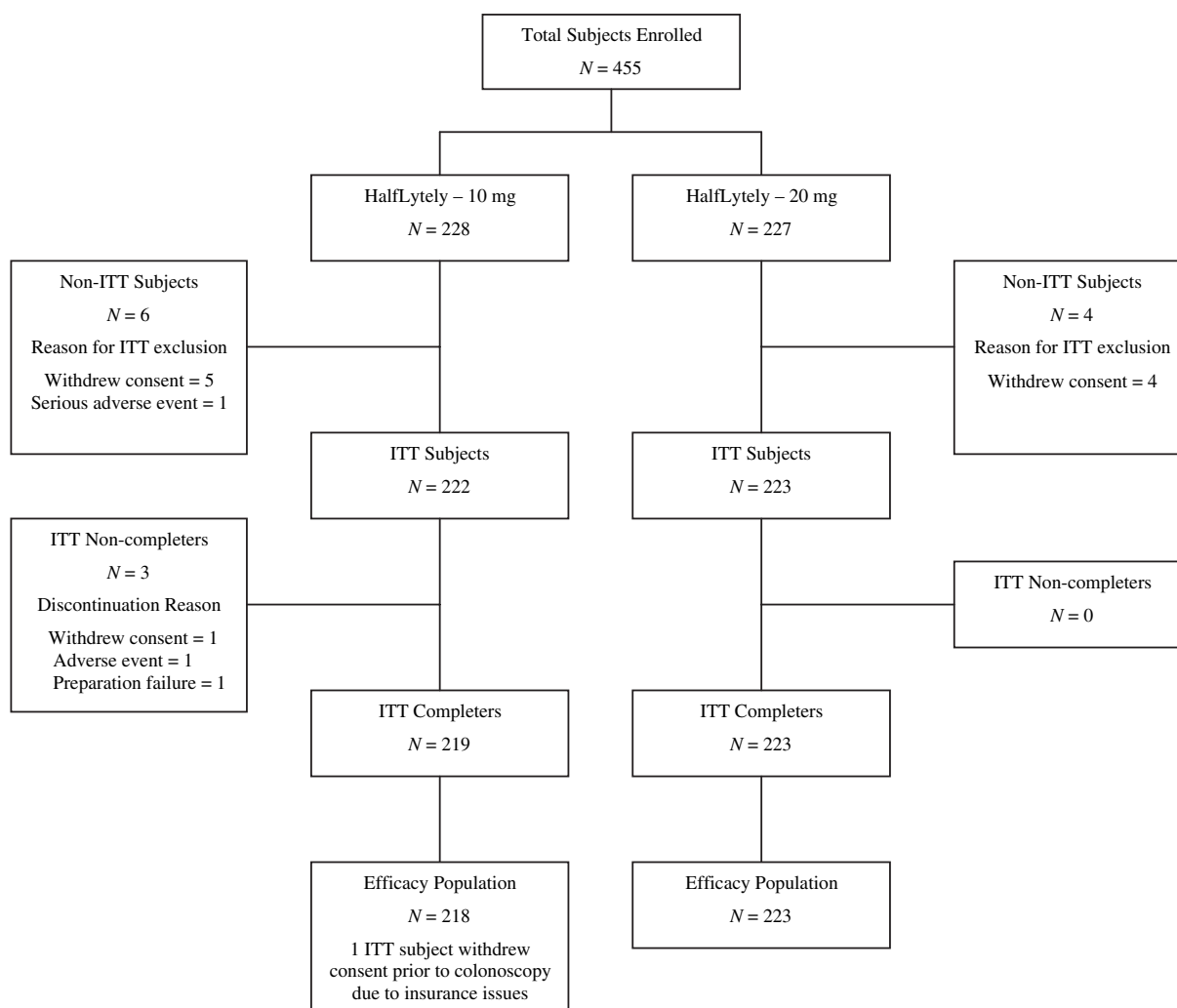
Demographics

Study subject allocation and disposition are recorded in Table 1. Four hundred and fifty-five subjects were enrolled including 123 elderly subjects aged 65 or older. Four hundred and forty-five received study medication and were included in the ITT analysis. The reasons for discontinuation are recorded in Table 1. Four hundred and forty-two of the 455 who received a study preparation fully completed the protocol.

There were equal proportions of male and female patients (47% and 53%, respectively) (Table 2). The treatment groups were similar to race and ethnicity distribution and weight at baseline. The average age in the study population was 57 years, ranging from 19 to 86 years of age. On average, the 10-mg bisacodyl group was 3 years older than the 20-mg group (*P* = 0.006).

Drug accountability performed at the end of the study revealed that treatment compliance was identical (*P* = 0.927) at 99 for each group.

Table 1. Subject disposition diagram



Efficacy

There was no difference in the primary efficacy variable of preparation 'success' or 'failure' (Table 3), with 87% of subjects in the 10-mg group and 88% of subjects in the 20-mg group experiencing successful preparation ($P = 0.521$). The percentage of successful preparations for both bowel cleansing preparations was similar and greater than that seen in previous studies of 2-L SF-ELS and 20-mg bisacodyl where successful preparations were seen in 79% and 86% of subjects, respectively^{1, 3}. In addition, preparation scoring by cleansing grade (poor to excellent) did not show any differences. No difference in preparation success was seen when the primary efficacy variable

was analysed by gender, race and age. Primary efficacy results at each of the 10 centres were consistent with the overall population, indicating no centre effect. Physicians rated nearly all preparations in the study adequate for colonoscopy, with no difference seen between the 10 (99%) and 20 mg (97%) preparations ($P = 0.503$).

Patient tolerance

Preparation-associated symptoms are reported in Tables 4 and 5. The 10-mg bisacodyl group experienced significantly less cramping, nausea and overall discomfort ($P \leq 0.001$). For nausea and overall discomfort, fewer patients reported bothersome to severe

Table 2. Demographics

	Bisacodyl 10 mg (<i>n</i> = 222)	Bisacodyl 20 mg (<i>n</i> = 223)	<i>P</i>
Age	58 (12)	55 (13)	0.006
Gender (%)			
Female	54	52	0.738
Male	46	48	
Race (%)			
Caucasian	85	87	0.517
Black	10	9	
Other†	3	3	
Hispanic	8	6	0.455
Weight (lbs)*	186 (45)	185 (42)	0.792

* Mean (s.d.); † Some did not report data.

Table 3. Investigator grading of preparations

	Bisacodyl 10 mg (<i>n</i> = 219)	Bisacodyl 20 mg (<i>n</i> = 223)	95% CI	<i>P</i>
Primary efficacy (%)				
Success	192 (87)	196 (88)	-8-5	0.521
Failure*	29 (13)	27 (12)		
Scoring by grade (%)				
Excellent	103 (47)	110 (49)		
Good	89 (40)	86 (39)		
Fair	25 (11)	22 (10)		
Poor	2 (1)	5 (2)		
Mean rating	3	3		

* Subjects unable to complete the preparation method because of prep-related adverse experiences were considered failures.

Table 4. Mean symptom ratings*: all subjects

	Bisacodyl 10 mg (<i>n</i> = 221)	Bisacodyl 20 mg (<i>n</i> = 223)	<i>P</i>
Cramping	1.56 (0.66)	1.86 (0.86)	<0.001
Stomach bloating	1.65 (0.71)	1.70 (0.76)	0.437
Nausea	1.55 (0.83)	1.81 (0.92)	<0.001
Vomiting	1.16 (0.62)	1.26 (0.80)	0.195
Overall	1.78 (0.77)	2.00 (0.81)	0.001

* Mean (s.d.).

Table 5. No. of subjects reporting bothersome to severely distressing symptoms

	Bisacodyl 10 mg (<i>n</i> = 221) <i>n</i> (%)	Bisacodyl 20 mg (<i>n</i> = 223) <i>n</i> (%)	<i>P</i> *
Cramping	16 (7)	31 (14)	<0.001
Stomach bloating	24 (11)	28 (13)	0.967
Nausea	28 (13)	47 (21)	0.005
Vomiting	11 (5)	17 (8)	0.722
Overall	31 (14)	45 (20)	0.037

**P*-value for difference between treatments for all severity categories (none – severely distressing).

symptoms in the 10-mg preparation (13%) compared with the 20-mg preparation (21%). With respect to cramping, the observed difference between the treatments was clearly driven by a nearly complete absence of 'distressing' and 'severely distressing' ratings for the 10-mg group. Indeed, about 6% of patients (13/223) treated with the 20-mg preparation reported that they had had distressing to severely distressing cramping when compared with 1% of patients (1/221) treated with the 10-mg preparation.

Analysis of symptom ratings in study subjects age 65 or older tended to have less cramping (*P* = 0.057) and significantly less nausea (*P* = 0.018) in the 10-mg bisacodyl group.

As listed in Table 6, there were no differences between groups for treatment emergent side effects. Similar findings were seen in the elderly subpopulation.

There were no on-study deaths. There were no clinically significant changes in physical examination, weight, temperature, pulse or blood pressure.

DISCUSSION

Osmotically balanced, electrolyte-balanced gut lavages provide safe and effective colon cleansing for diagnostic and surgical procedures.⁴⁻⁸ Removal of sodium sulphate made SF-ELS (NuLytely) more palatable.^{2, 9, 10} Various flavors were added to improve the taste, but volume-related discomfort and adverse experiences prompted further bowel preparation studies.

To reduce the volume of solution that must be ingested, various laxatives and solution volumes have been evaluated.¹⁰⁻¹³ Bisacodyl was chosen as a preparation adjunct because of these works and clinical

Table 6. Treatment emergent adverse events

	Bisacodyl 10 mg (n = 222)	Bisacodyl 20 mg (n = 223)	95% CI	P-value
Number of patients	17 (8)	17 (8)	(-5, 5)	1.000
With any event				
Number of events	18	25		
Gastrointestinal	10 (5)	12 (5)	(-5, 3)	0.828
Abdominal distension	2 (1)	2 (1)	(-2, 2)	1.000
Abdominal pain	1 (1)	5 (2)	(-4, 0.3)	0.216
Anal discomfort	1 (1)	0	(-0.4, 1)	0.499
Dyspepsia	0	2 (1)	(-2, 0.3)	0.499
Nausea	3 (1)	4 (2)	(-3, 2)	1.000
Oral discomfort	0	1 (0)	(-1, 0.4)	1.000
Rectal haemorrhage	1 (1)	0	(-0.4, 1)	0.499
Vomiting	2 (1)	5 (2)	(-4, 1)	0.499
Investigations	0	1 (0)	(-1, 0.4)	1.000
Weight decrease	0	1 (0)	(-1, 0.4)	1.000
Nervous system	5 (2)	3 (1)	(-2, 3)	0.503
Dizziness	1 (1)	0	(-0.4, 1)	0.499
Headache	4 (2)	3 (1)	(-2, 3)	0.724
Respiratory-epistaxis	0	1 (0)	(-1, 0.4)	1.000
SKIN-hyperhidrosis	1 (1)	1 (0)	(-1, 1)	1.000
Vascular	2 (1)	0	(-0.3, 2)	0.248
Hypertension	1 (1)	0	(-0.4, 1)	0.499
Hypotension	1 (1)	0	(-0.4, 1)	0.499

experience with its use as part of diet, laxative and cathartic methods of cleansing.^{6, 7} In a study of 200 out-patients, DiPalma *et al.* demonstrated equivalent colon cleansing with bisacodyl 20 mg with 2-L SF-ELS (HalfLyte) compared with 4-L SF-ELS (NuLYTELY) with greatly reduced volume-related patient complaints.¹ In particular, patients reported significantly reduced nausea, fullness and vomiting. However, patient reports of cramping were not significantly different between the preparations. The present protocol was, therefore, developed to demonstrate reduced complaints including cramping while maintaining bowel cleansing efficacy by reducing the required dose of bisacodyl.

This study was designed as a single blind study similar to previous bowel cleansing investigations.¹⁻³ Therefore, patients (but not investigators) were aware

of their preparation assignment. This would not be expected to affect the study outcome adversely, however, as the two preparations were nearly identical (with identical labelling and packaging) and the only difference being two or four bisacodyl tablets. Informed consent forms noted only that the two preparations were being compared for safety and efficacy. Patients were not informed of the study hypothesis, thereby limiting potential bias.

In this work, patient compliance was excellent and the preparations were equivalent with respect to physician rating of colon preparation. A reduction in preparation-related side effects was seen favouring the reduced dose of bisacodyl with less cramping, nausea and overall discomfort. Only one patient (<1%) in the 10-mg group had 'distressing' or 'severely distressing' cramping when compared with 6% of the 20-mg bisacodyl group.

This study shows that bisacodyl 10 mg with 2-L SF-ELS (HalfLyte) is as effective as a preparation using 20-mg bisacodyl and that the 10-mg dose regimen has substantially reduced cramping, nausea and overall discomfort.

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