Digestive and Liver Disease 51 (2019) 837–842

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Comparison of asymmetric (low morning-dose) and standard split-dose regimen of PEG plus bisacodyl for bowel preparation: A randomized controlled trial

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ARTICLE INFO

Article history:
Received 11 July 2018
Accepted 16 December 2018
Available online 28 December 2018

Keywords:
Bowel preparation
Colonoscopy
Endoscopy
Polyethylene glycol
Screening

ABSTRACT

Background: Reducing the morning dose of PEG solution may be a reliable strategy to improve the patient compliance of split-dose regimens without affecting efficacy of bowel cleansing.
Aims: to compare the efficacy for bowel cleansing of an asymmetric split-dose regimen (25% of the dose on the day of colonoscopy and 75% on the day before) with the standard split-dose regimen.
Methods: Outpatients were enrolled in a randomized, single-blind, non-inferiority clinical trial. All subjects received a split-dose preparation with a 2L PEG-citrate-simethicone plus Bisacodyl. Patients were randomly assigned to: group A, asymmetric split-dose regimen; group B, symmetric split-dose regimen. Primary endpoint was the proportion of adequate bowel cleansing.
Results: Split-dose was taken by 81 and 80 patients in group A and B. Adequate bowel cleansing was achieved in 92.6% and 92.5% patients in group A and B ($p = 1.000$). No differences were observed regarding Boston Bowel Preparation Scale total score, adenoma detection rate and scores of each colon segment.
Conclusions: The reduction of morning dose of PEG in a split-dose regimen is not inferior to the standard split-dose regimen in achieving an adequate bowel cleansing. However, further studies are needed to evaluate whether asymmetric preparation is associated to a higher tolerability compared to symmetric split-dose regimen. (NCT03146052)

1. Introduction

Bowel preparation is one of the major determinants of quality of colonoscopy. It has been shown that inadequate bowel cleansing hinders procedural success and may lead to missed adenomas and failures of cecal intubation [1,2]. In addition, poor level of bowel cleansing leads to interrupt endoscopic procedures and to repeat the examinations, resulting in an increase of colonoscopy costs [3]. Therefore, optimization of bowel cleansing has a critical role to increase the quality and effectiveness of colonoscopy and to reduce costs.

To date, European and American guidelines recommend split-dose regimens of PEG solutions for routine bowel preparation [4,5]. However, the adoption of split regimens in clinical setting remains sub-optimal [6], especially in early morning colonoscopy [7]. Low adherence in this setting may be related to the patients' unwillingness to get up early on the day of colonoscopy and fear of bowel movements or soiling while traveling to the endoscopy services [7].

Conventionally, splitting of the dose means that half of the solution is taken the evening before and the other half is taken the morning of the colonoscopy. Reducing the morning dose of preparation may be a reliable strategy to increase patients' adherence to split-dose regimens and previous studies using 4 L PEG solutions have demonstrated that taking three fourth of preparation the day before and one fourth in the morning provided a better quality preparation compared to day-before preparation [8,9]. In addition, Manno et al. [8] demonstrated that this modified regimen was also associated to a better tolerability. However, no data are available about the efficacy and tolerability of a split-dose regimen with a low morning-dose using a low-volume formulation.

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https://doi.org/10.1016/j.dld.2018.12.012
1590-8658/

We hypothesized that halving the morning dose while maintaining the same total dose of preparation using a low volume formulation, might be not inferior to the standard split-dose regimen. Therefore, the present study aimed to compare the efficacy of bowel preparation using an asymmetric split-dose regimen (meaning that 75% of the dose is given on the day before of the procedure and 25% of the dose is given on the day of the procedure) with the standard split-dose regimen in patients undergoing screening and surveillance colonoscopy.

2. Materials and methods

2.1. Study design and population

This study was a prospective, randomized, single-blind, non-inferiority trial in adult patients undergoing screening or surveillance colonoscopy. The study was conducted at two high-volume endoscopy centers (Rho and Garbagnate Milanese) in a 3-months period (March 2017–May 2017). The study protocol was approved by the ethics committee of Milan — Area 3 on March 9, 2017 (n. 165-032017) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent. The trial has been registered in a publicly accessible registry (International Clinical Trials Registry registration number: NCT03146052).

All patients were aged from 50 to 75 years and scheduled as outpatient for screening or surveillance colonoscopy. Patients were excluded if they had any of the following conditions: inpatients; refusal of split-dose regimen for bowel preparation; previous history of colorectal resection; severe cardiac disease; advanced (stage IV and V) chronic kidney disease; pregnancy; ileus, suspected bowel obstruction or toxic megacolon; known inflammatory bowel disease; known or suspected allergy to PEG.

2.2. Randomization and study protocol

Eligible participants were randomly assigned, according to a computer-generated list with an allocation ratio of 1:1, to receive either asymmetric or symmetric split-dose regimen of a low-volume preparation by investigators who were not involved in the enrolment process. Detailed written instructions were administered to all patients who accepted to participate.

A low-fiber diet was prescribed three day before colonoscopy; participants in both groups were instructed to have a light lunch on the day before the colonoscopy and only clear liquid were allowed on the day of the exam. All endoscopic procedures were scheduled between 9:00 AM and 1:00 PM.

2.3. Study products and bowel cleansing methods

The preparation used in the study is a combination of a 2 L sulphate-free iso-osmotic formulation of of PEG-4000 added with citrates and simethicone (PEG-CS) (Lovol-esse; AlfaWassermann, Bologna, Italy. Kit contains 4 pouches, each containing 64.5 g of PEG, to be dissolved in 2 L of water.), and bisacodyl 5 mg tablets (Lovodyl; Alfa-Wassermann, Bologna, Italy).

All subjects were instructed to take 4 bisacodyl tablets at 4:00 PM on the day before the procedure. Subjects allocated to the asymmetric split-dose regimen group were invited to consume at 6:00 PM on the evening before the colonoscopy 3 sachets of PEG-CS in 1,5 L of water in a range from 90 to 120 min (about 250 mL every 15 min) and 4 h before the scheduled procedure 1 sachets in 0,5 L of water in a range from 15 to 30 min. Subjects allocated to the symmetric split-dose regimen group were invited to consume at 6:00 PM on the evening before the colonoscopy 2 sachets of PEG-CS in 1 L of water in a range from 60 to 90 min and 5 h before the scheduled procedure 2 sachets in 1 L of water in a range from 60 to 90 min. No additional fluids were recommended in the two groups.

2.4. Data collection and colonoscopy procedure

Unblinded investigators collected demographic (age, gender, weight, height; employment status) and clinical data with medical history (presence of diabetes mellitus, heart disease, hypertension, chronic renal failure, cirrhosis, stroke/dementia, depression, diverticulosis, inflammatory bowel disease, chronic constipation, history of polyps, previous abdominal surgery).

All patients filled in a nurse-administered, previously validated questionnaire to assess compliance, tolerability and safety of bowel preparation [10]. Compliance to the split-dose regimen was assessed by the amount of intake of study agents using a 3-point scale: 1 (100% intake), 2 ($\geq$ 75% intake), and 3 (< 75% intake). Tolerability was evaluated assessing how patient finds tolerable the bowel preparation by using a 4-point scale: 1 (Easy), 2 (Acceptable), 3 (Somewhat difficult), 4 (Very difficult). Safety was evaluated by the occurrence of adverse events such as bad taste in mouth, gastric fullness, nausea or vomiting, bloating, abdominal pain, headache, scored by a 4-point semiquantitative scale ranging from 0 = no symptom to 3 = severe distress. Willingness to repeat the same preparation in the future was also recorded.

Blinded experencied endoscopists performed endoscopic procedure in accordance with colonoscopy quality practice. If not contraindicated, endoscopies were performed using intravenous sedation with midazolam and/or fentanyl. During withdrawal of the colonoscope, the colonic mucosa was carefully inspected. Any effort was made to clean the colon from residual liquid and debris by washing and suctioning, in order to optimize colonic mucosa inspection.

Colonoscopy was defined as complete when there was visualization of appendiceal orifice or terminal ileum. Bowel preparation was evaluated by using Boston Bowel Preparation Scale (BBPS) score of the three colonic segment (right, transverse and left colon) [11]. The points were assigned as follows: 0 (unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared); 1 (portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid); 2 (minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment is seen well); and 3 (entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid). Each segment of the colon received a score from 0 to 3, and these segment scores were summed for a total BBPS score ranging from 0 to 9. The preparation was considered adequate when BBPS score was $\geq$6 with a score with at least 2 points in any segment.

Data on bowel cleansing, endoscopic procedures and findings (i.e. cancer, polyps, diverticula) were collected.

2.5. Endpoint measurement

The primary endpoint of the study was the proportion of adequate bowel cleansing in each group. The secondary endpoints were the total BBPS score and the BBPS score of each segment of the colon (right, transverse and left colon). We also considered as secondary endpoint the rate of patients with at least one adenoma (adenoma detection rate, ADR), the rate of the occurrence of adverse events, the compliance and the tolerability.

2.6. Statistical analysis

Sample size was calculated using an online calculator for binary outcome non-inferiority trial (https://www.sealedenvelope.com/

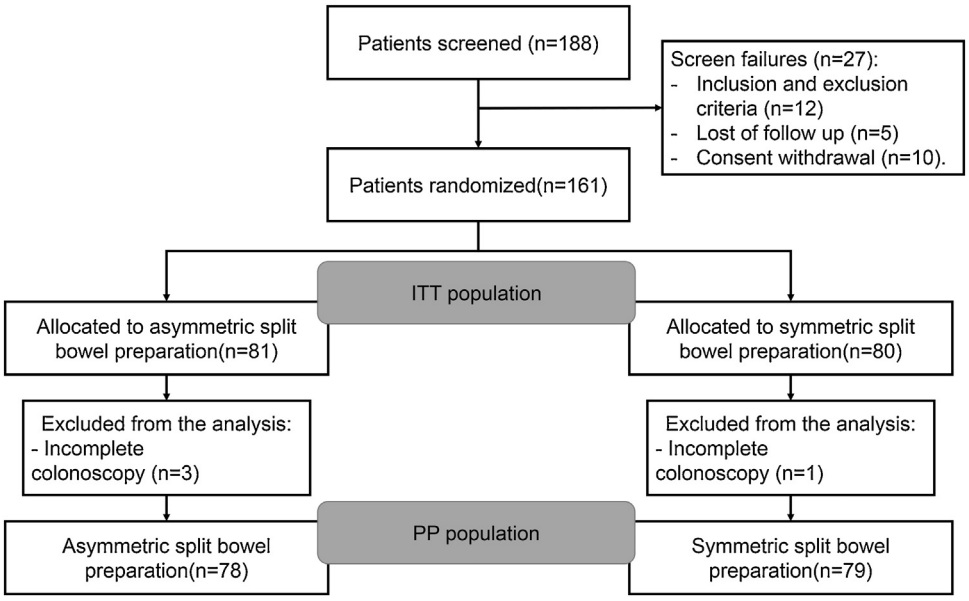

Fig. 1. Flow diagram of patient enrolment, randomization and analysis. ITT, Intention-To-Treat; PP, Per-Protocol.

Table 1
Demographics and clinical features.

	Asymmetric group (n = 81)	Symmetric group (n = 80)	*p* Value
Age (years), mean (SD)	60.2 (7.2)	60.2 (7.3)	0.998
Male sex, n (%)	34 (42)	42 (52.5)	0.208
Female sex, n (%)	47 (58)	38 (47.5)	
BMI (kg/m2), mean (SD)	26 (5.8)	25.4 (5.7)	0.588
Medical condition			
Diabetes mellitus	6 (7.4)	5 (6.2)	0.509
Arterial hypertension	23 (28.4)	17 (21.2)	0.362
Chronic constipation	23 (28.4)	20 (25)	0.722

power/binary-noninferior). In previous studies, the use of standard split-dose regimen with PEG-CS plus bisacodyl showed a rate of adequate preparation of about 93% [12,13]. According to previous studies, a non-inferiority margin of 10% was chosen [14–16]. Assuming a type I error of 5% and a power of 80%, a total number of 80 subjects was estimated to be needed per group.

The analysis was based on the intention-to-treat (ITT) population. Categorical variables and continuous variables were expressed as percentages and means ± standard deviations, respectively. A Student's t-test was used for the continuous variables, while Pearson's chi-squared test and Fisher's exact test were used for the categorical variables where appropriate.

All statistical analyses were performed with SPSS (version 19.0; SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered significant.

3. Results

3.1. Study population

One hundred eighty eight patients were included in the trial. Among them, twenty seven patients were excluded from the ITT population because of violation of inclusion and exclusion criteria (n = 12), lost of follow up (n = 5), consent withdrawal (n = 10). The remaining 161 patients were included in the study (Asymmetric group: n = 81 patients; Symmetric group: n = 80 patients) (Fig. 1).

Characteristics of participants are shown in Table 1. No significant differences in terms of age, sex, BMI and clinical data were observed in the two groups of patients.

Table 2
Comparison of technical performance of colonoscopy and endoscopic findings in the two groups of bowel preparation.

	Asymmetric group (n = 81)	Symmetric group (n = 80)	*p* Value
Cecal intubation time (minutes), mean (SD)	8 (2.2)	8 (2.3)	1.000
Withdrawal time (minutes), mean (SD)	7.9 (1.8)	7.5 (1.4)	0.110
Adenoma detection rate, n (%)	35 (43.2)	35 (43.8)	1.000
Adenocarcinoma, n (%)	0 (0)	1 (1.2)	0.497
Diverticula, n (%)	21 (25.9)	19 (23.8)	0.711
Inflammatory bowel diseases, n (%)	2 (2.5)	0 (0)	0.252
Others, n (%)	6 (7.4)	6 (7.5)	0.998

3.2. Colonoscopy procedures

Data on colonoscopy procedure are shown in Table 2. Failure of cecal intubation occurred in 3 patients in asymmetric group and 1 patient in symmetric group (3.7% vs 1.2%; p = 0.620). No differences were found between the two groups in cecal intubation time (8 ± 2.2 vs. 8 ± 2.3 min; p = 1.000) and withdrawal time (7.9 ± 1.8 vs 7.5 ± 1.4 min; p = 0.110) (Table 2). Adenoma detection rate was similar in the two group [35 (43.2%) vs 35 (43.8%; p = 1.000]. Similarly, no differences were observed in terms of other endoscopic findings, including adenocarcinoma [0 (0%) vs 1 (1.2%); p = 0.497], diverticula [21 (25.9%) vs 19 (23.8%); p = 0.711] and inflammatory bowel diseases [2 (2.5%) vs 0 (0%); p = 0.252) (Table 2).

3.3. Bowel cleansing efficacy

Adequate bowel cleansing was achieved in 92.6% (75 of 81 participants) of the asymmetric group and 92.5% (74 of 80 participants) in the symmetric group (p = 1.000) (Fig. 2, Table 3).

Overall BBPS score was similar in the two groups (6.8 ± 1.2 vs 6.9 ± 1.4, p = 0.627) (Fig. 2, Table 3), while the distribution of the scores at each segment (Right side colon, transverse colon, left side colon) was comparable in the two groups (Table 3).

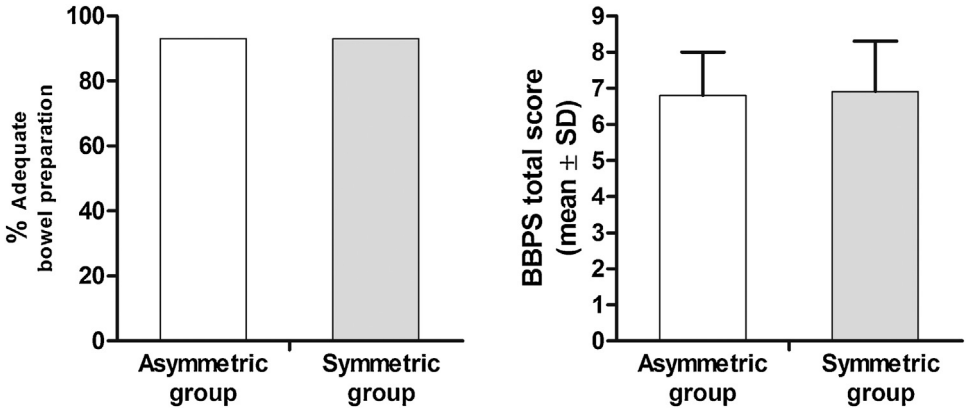

Fig. 2. Percentage of patients with adequate preparation and BBPS total score in the two groups.

Table 3
Cleansing comparison between quality of bowel preparation in the two groups of bowel preparation using the Boston Bowel Preparation Scale (BBPS).

	Asymmetric group (n = 81)	Symmetric group (n = 80)	*p* Value
Adequate bowel preparation, n (%)	75 (92.6)	74 (92.5)	1.000
Overall BBPS score, mean (SD)	6.8 (1.2)	6.9 (1.4)	0.627
BBPS score at each segment, n (%)			
Right side colon			
3	15 (19.2)	26 (32.9)	0.105
2	60 (76.9)	52 (65.8)	
1	3 (3.8)	1 (1.3)	
0	0 (0)	0 (0)	
Transverse colon			
3	29 (36.2)	30 (38)	0.337
2	51 (63.8)	47 (59.5)	
1	0 (0)	2 (2.5)	
0	0 (0)	0 (0)	
Left side colon			
3	35 (43.2)	32 (40)	0.242
2	45 (55.6)	43 (53.8)	
1	1 (1.2)	5 (6.2)	
0	0 (0)	0 (0)	

Table 4
Compliance, tolerability and occurrence of adverse events during the bowel preparation process in the two groups of bowel preparation.

	Asymmetric group (n = 81)	Symmetric group (n = 80)	*p* Value
Intake of study agent n (%)			
100% intake	74 (91.3)	75 (93.7)	0.765
≥75% intake	7 (8.7)	5 (6.3)	
<75% intake	0 (0)	0 (0)	
How patient finds bowel preparation n (%)			
Easy	36 (44.4)	31 (38.8)	0.303
Somewhat difficult	45 (55.6)	49 (61.2)	
Adverse events, n (%)			
Bad taste in the mouth	21 (25.9)	22 (27.5)	0.860
Gastric fullness	22 (27.2)	20 (25)	0.857
Nausea or vomiting	21 (25.9)	16 (20)	0.454
Bloating	25 (30.9)	22 (27.5)	0.918
Abdominal pain	15 (18.5)	16 (20)	0.729
Headache	12 (14.8)	12 (13.8)	1.000
Willingness to repeat the same preparation in the future	72 (88.9)	72 (90.0)	0.595

3.4. Compliance, tolerability and adverse events

The proportion of patients taking 100% of solution was high both in asymmetric and symmetric group [74 (91.3%) vs. 75 (93.7%); p = 0.765] (Table 4). A greater proportion of participants in the asymmetric group considered bowel preparation as easy [36 (44.4%) vs. 31 (38.8%)], but this difference was not statistically significant (p = 0.303).

No differences were found between two groups regarding adverse symptoms and willingness to repeat the same preparation (Table 4).

4. Discussion

In this study, an asymmetric (low dose in the morning) split-dose preparation with a low volume formulation (2 L PEG-CS plus bisacodyl) was not inferior to the standard split-dose regimen in achievement of adequate bowel cleansing in patients undergoing screening and surveillance colonoscopy. Both regimens were safe and well tolerated and similar results were achieved in terms of compliance.

The use of split-dose regimens of PEG solutions significantly improves the percentage of patients with satisfactory colon clean-

liness, increases patient compliance, and decreases adverse events such as nausea compared with the administration of the full dose of PEG solutions on the day before colonoscopy [17]. However, the adoption of split-dose regimens in clinical practice remains suboptimal, in particular in early morning [7].

A reliable strategy to improve the adherence and tolerability to split-dose regimens is the use of PEG solutions that require smaller volumes to intake. In fact, several randomized clinical trials have shown that PEG low volume preparations, administered in a split-dose regimen, achieved a non-inferior efficacy in colon cleansing, associated to a higher patients' tolerability and acceptability [13,18–21].

However, in a recent Italian multicentre prospective study of 1447 outpatients undergoing colonoscopy, the main patients' barriers for the choice of split-dose were the fear of bowel movements during traveling (49.9%) and the refusal to get up early in the morning (47.9%). In order to improve patients' adherence to split regimens, we proposed to halve the morning dose without reducing the total amount of PEG solution to intake using a low-volume formulation. Previous studies have demonstrated that taking three fourth of preparation day before and one fourth the morning of the procedure provided a better quality preparation than day-before preparation [8,9]. In comparison to these studies, we used a low-volume PEG preparation of PEG-CS plus bisacodyl to further reduce the volume of PEG solution to intake in the morning. In addition, this modified regimen was compared to the standard split-dose regimen. We found that asymmetric split-dose preparation is as effective as conventional split-dose preparation for bowel cleansing in subjects undergoing FOBT-positive screening colonoscopy and post-polipectomy surveillance examination.

In addition, we did not found significant differences in terms of ADR in the two groups of our study. ADR is a recommended quality measure of screening colonoscopy and several evidences have demonstrated that the detection of colonic adenomas lesions is strongly influenced by that quality of colon cleansing [1,2,22]. These results suggest that this modified regimen may be a reliable alternative in bowel preparation for screening and surveillance colonoscopy.

Reducing the morning dose of split-dose regimen for bowel cleansing has some advantages: the intake of a smaller volume of solution takes less time. In addition, 500 mL of fluids can be taken at a higher consumption rate without the occurrence of gastric discomfort, such as nausea or gastric fullness. These factors allowed us to postpone the start of bowel preparation of overall 1 h, reducing the drawback of early awakening. However, although a higher quote of patients who received low morning dose preparation defined it as "easy", we did not find significant differences in terms of tolerability, neither we found a lower rate of gastrointestinal symptoms (such as gastric fullness or abdominal pain) in the asymmetric preparation group. This may be due to the fact that sample size of the study was calculated to evaluate the efficacy of bowel cleansing. For this reason, we are not able to detect higher tolerability of asymmetric split-dose preparation in this setting. In addition, as discussed before, the higher advantages of this preparation should be in early morning colonoscopy, whereas in our study only a little part of colonoscopies were planned before 10:00 AM.

This study has some limitations. The reduction of morning dose of PEG solution led to postpone the start of bowel preparation of one hour. For this reason, we hypothesized that asymmetric preparation allows to gain one hour of sleep. However, in this study awakening times were not collected. Therefore, it is not possible to evaluate whether asymmetric preparation may reduce the drawback of early awakening. A second critical point would be our decision of using a 2-L solution of PEG associated to bysacodil, a drug associated to gastrointestinal symptoms, such as abdominal pain. The use of bysacodil could be a confounder and it could limit the reproducibility of the proposed regimen due to the tolerability and the side effects of the drug. However, no case of severe abdominal pain was reported by the partecipants included in this study.

In conclusion, we find that a modified split-dose regimen with a reduced dose of PEG volume in the morning of procedure using a low-volume preparation is as effective as standard split-dose preparation for bowel cleansing. Further studies are needed to assess whether asymmetric split-dose regimen is more tolerated than standard split-dose regimen, in particular for procedures scheduled in early morning.

Conflict of interest

None declared.

Guarantor of the article

Gianpiero Manes

Trial registration number

NCT03146052

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