Efficacy and Tolerability of High and Low-volume Bowel Preparation Compared: a Real-life Single-blinded Large-population Study

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Research article

Keywords: Bowel preparation, Colonoscopy, Colonic Polyp, Adenoma

Posted Date: December 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-123588/v1

Version of Record: A version of this preprint was published at World Journal of Gastrointestinal Endoscopy on December 16th, 2021. See the published version at https://doi.org/10.4253/wjge.v13.i12.659.

Abstract

Background: Low-volume (LV) preparations for colonoscopy have shown similar efficacy compared to high-volume (HV) ones in trials. However, real-life clinical outcomes data are lacking. Our aim was to assess patients' free choice among HV preparations (4L polyethylene glycol, PEG) and LV (2L PEG plus bisacodyl) and to compare efficacy and tolerability.

Methods: Consecutive outpatients referred for colonoscopy could choose either LV or HV preparation with schedules (day-before or split-dose) depending on their appointment time. Adequate bowel preparation according to Boston Bowel Preparation Scale, clinical outcomes and self-reported tolerability of HV and LV were blindly assessed.

Results: 2,040 patients were enrolled and 1,815 (age 60.6 years, 50.2% men) finally included. LV was chosen by 52% of patients (50.8% of men, 54.9% of women). Split-dose schedule was more common with HV (44.7% vs. 38.2%, p=0.0055). HV and LV preparations showed similar adequate bowel preparation rates (89.2% vs. 86.6%, p=0.0983) but HV ones resulted higher in detection rates for polyps (PDR; OR 1.30, 95% CI 1.03–1.64, p=0.0254), adenomas (ADR; OR 1.28, 95% CI 0.99–1.65, p=0.0519) and advanced adenomas (AADR; OR 1.54, 95% CI 0.96–2.46, p= 0.0723) after adjustment for sex, age, indications. Visual Analogue Scale tolerability scored equally (7 [5-9]) but a ≥75% dose intake was more frequent with LV.

Conclusions: in a real-life setting, LV preparation confirms similar efficacy and tolerability compared to HV. However, with higher PDR and a trend toward higher ADR and AADR, HV should still be considered the reference standard for clinical trials.

Background

The clinical performance of colonoscopy is markedly influenced by the quality of bowel preparation. In fact, inadequate bowel preparation has proved to have a detrimental effect on different clinically significant outcomes, such as complete colonoscopy rate(1–3), polyp (PDR) and adenoma detection rates (ADR)(4–6). Moreover, inadequate preparation may require to repeat the procedure, with the subsequent increase in waiting times, risks and costs(7,8).

Large volumes (4 liter) of polyethylene glycol (PEG) have been classically prescribed to achieve adequate cathartic effect. Over the last years, several low-volume preparations have been developed to increase the patients' acceptability, compliance and willingness to repeat the procedure. Randomized clinical trials (RCTs) and meta-analyses have shown that low-volume preparations have similar efficacy compared to high-volume preparations(9–15), but the direct comparison of clinical outcomes is available only in a minority of trials. Moreover, real-life data is both scarce and conflicting.

Therefore we have performed a real-life study to assess patients' free choice between high-volume and low-volume bowel preparation and to compare efficacy (both in terms of bowel cleansing and clinically

relevant colonoscopy outcomes) and tolerability of such preparations when administered according to two different schedules (day-before or split-dose regimens).

Methods

Study design and subjects

We prospectively enrolled the consecutive patients referred for colonoscopy to the Digestive Endoscopy Outpatient Service of IRCCS Policlinico San Donato between 1 December 2014 and 31 December 2016. The patients enrolled in the regional colorectal cancer screening program were not included as in our Center they are all advised to use high-volume PEG-based preparation. If a patient underwent multiple colonoscopies during the study period, only the first procedure was taken into account for the study.

The exclusion criteria were: inability to give informed consent, use of cleansing products different from the recommended ones, incomplete patient forms as to the type of preparation used, incomplete colonoscopy because of a pathological stricture.

At the time of booking the examination, all the patients received written detailed instructions about the diet regimen (no fruit, legumes, or vegetables for 3 days before the procedure; light breakfast and lunch the day before colonoscopy, followed by clear liquids only) and about bowel preparation.

Patients were free to choose either a high-volume (HV) or a low-volume (LV) preparation. The HV preparation (SELG ESSE; Promefarm, Italy) was a PEG 4000 solution plus simethicone and electrolytes that had to be diluted in 4L still water, while the LV preparation was a combination of a PEG 4000 solution plus simethicone and electrolytes (Lovol-Esse; Alfasigma, Italy) diluted in 2L still water and the stimulant laxative bisacodyl (Lovoldyl; Alfasigma, Italy). Both the preparations are equally recommended by international guidelines(16,17). In the written instructions handed to the patients, the two preparations were listed with the HV preparation first.

For the procedures planned before 12:00 a.m., the patients were instructed to take the entire quantity of the PEG solution the evening before colonoscopy, starting from 7 pm; in case of LV preparation, 4 tablets (20 mg) of bisacodyl were also taken at 3:00 pm. For procedures planned after 12:00 a.m. a split-dose regimen was prescribed: half the dose of PEG was taken in the afternoon before and half the dose at 7:00 a.m. in the morning on the day of the colonoscopy; in case of LV preparation 20 mg bisacodyl was taken at sleep time.

The study was approved by the local Ethics Committee of San Raffaele Hospital and a specific written informed consent was taken from all the study participants. The study was conducted in accordance with the Declaration of Helsinki 1975 and subsequent amendments.

Colonoscopy

All the procedures were performed under mild-to-moderate sedation (midazolam ± pethidine i.v.) by 5 experienced endoscopists (> 1000 colonoscopies overall, > 300/year), well-trained in the use of bowel preparation rating scales and blinded to the content of the patient form and to the preparation taken. The indication for colonoscopy was collected by the endoscopist matching medical prescription and pre-colonoscopy interview, following the standard clinical protocol. The endoscopes used were either standard or high-definition scopes by Pentax (Tokyo, Japan).

Data collection

On the morning of colonoscopy, the patients were asked to fill a specific questionnaire covering the kind of bowel preparation used (HV or LV), amount of PEG solution taken (the 75% threshold was chosen to define the PEG intake as "full"), time of the exam, demographics, morphometrics, social circumstances (living alone, instruction level) and clinical data. The questionnaire included a specific section about personal bowel habits (Bristol stool chart, frequency of bowel movements per week). Constipation was defined as Bristol stool chart type 1–2 and less than 3 bowel movements/week, and/or chronic constipation as indication for colonoscopy. The form also contained a section about general satisfaction about the used preparation (evaluated by VAS score, from 0='absolutely unsatisfied' to 10='perfectly satisfied') and symptoms (nausea, vomit, bloating, abdominal pain) experienced during the preparation.

The quality of bowel preparation was assessed using the Boston bowel preparation scale (BBPS)(18). Bowel preparation was defined adequate if a global score ≥ 6 with segmental scores ≥ 2 in all colonic segments was achieved. For any patients with previous bowel resection, the preparation was considerate adequate if all the segmental sub-scores were ≥ 2.

The number, size and final histology of lesions resected or biopsied during the procedures were collected. Polyp detection rate (PDR), adenoma detection rate (ADR), right-colon ADR, advanced adenoma (adenomas ≥ 1 cm or with villous component or harboring high-grade dysplasia) detection rate (AADR), sessile/serrated lesion detection rate (SDR, excluding hyperplastic polyps) and cancer detection rate were calculated for all the patients overall and for the cohort of patients older than 50 years.

Aims of the study

Primary aim of the study was to compare efficacy of HV and LV preparations by means of adequate bowel preparation rate and detection of colonic lesions. Secondary aims were to compare efficacy of day before and split-dose schedules and to compare self-reported tolerability of different regimens.

Statistical analysis

The descriptive statistics were expressed as counts and percentages for categorical variables and mean (SD) or median (interquartile ranges) for continuous variables, as appropriate. Normality assumption was to be tested in continuous variables by visual inspection of the qq-plot.

The association between bowel preparation and baseline variables was investigated with the Chi-square test for categorical variables; the continuous variables were compared by analysis of variance ANOVA or

by the non-parametric Kruskal–Wallis test for non-normally distributed data.

Univariate and multi-variable logistic regression was used to identify if adequate bowel preparation and volume of bowel preparation were independently associated with clinical outcomes (PDR, ADR, AADR, SDR and cancer). Odds ratios (ORs) with their corresponding 95% CIs were calculated, and P values were considered statistically significant if they were less than 0.05.

Statistical analysis was carried out by computer software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

2,040 patients were totally enrolled; after excluding 225 patients (study flowchart in Supplementary Fig. 1), 1,815 patients were included (mean age 60.6 years, 50.2% male); 750 patients (41.3%) had their colonoscopy scheduled in the afternoon and thereafter used a split-dose regimen; 944 patients (52%) chose a LV preparation, while 871 patients (48%) preferred a HV preparation. The use of a split-dose regimen was more common in the HV group (44.7% vs. 38.2%, p = 0.0055).

Indications for colonoscopy were: symptoms (altered bowel movements, anemia or bleeding, abdominal pain) in 60.6%, post-polypectomy or post-colorectal cancer surveillance in 24.0%, positive fecal blood test (FBT) in 8.3% and follow-up of known IBD in 7.1% of the cases. The patients in the HV preparation group were more frequently male, had higher BMI and more frequently had a cardiac disease and a low-level education. There were no statistically significant differences in terms of age and other possible risk factors for poor bowel preparation (previous abdominal/pelvic surgery, constipation, living-alone status or non-adherence to low-fiber dieting before colonoscopy) (Table 1).

Table 1
Demographic and clinical features of the study population.

Characteristics	All patients n = 1,815	High volume n = 871	Low volume n = 944	p-value
Split-dose	750 (41.3%)	389 (44.7%)	361 (38.2%)	**0.0055**
Age	60.6 ± 14.8	61.2 ± 14.3	60.1 ± 14.6	0.0919
Male sex	911 (50.2%)	463 (53.2%)	448 (47.5%)	**0.0153**
Indication				
Symptoms	1,101 (60.7%)	538 (61.8%)	563 (59.6%)	
Surveillance:				**< 0.0001**
Post polypectomy	288 (15.9%)	134 (15.4%)	154 (16.3%)	
Post colonic resection for CRC	146 (8.0%)	73 (8.4%)	73 (7.7%)	
Positive FBT	151 (8.3%)	94 (10.8%)	57 (6.1%)	
IBD	129 (7.1%)	32 (3.6%)	97 (10.3%)	
BMI, mean ± SD §	25.3 ± 4.3	25.5 ± 4.3	25.0 ± 4.0	**0.0147**
Previous abdominal surgery	194 (10.7%)	98 (11.3%)	96 (10.2%)	0.4561
Constipation	152 (8.4%)	66 (7.6%)	86 (9.1%)	0.2389
Systemic Co-morbidities				
Heart disease	155 (8.5%)	90 (10.3%)	65 (6.9%)	**0.0087**
Diabetes	137 (7.5%)	72 (8.3%)	65 (6.9%)	0.2659
Stroke/dementia	44 (2.4%)	19 (2.2%)	25 (2.6%)	0.5182
Severe CKD	36 (2%)	21 (2.4%)	15 (1.6%)	0.2095
Cirrhosis	25 (1.4%)	12 (1.4%)	13 (1.4%)	0.9991
GERD	411 (22.6%)	192 (22.0%)	219 (23.2%)	0.5568
Waiting time > 1 month	1055 (59.5%)	485 (55.7%)	570 (60.4%)	**0.0900**
Non-adherence to low fiber diet	203 (11.3%)	91 (10.5%)	112 (11.9%)	0.3287
Lives alone §	272 (15.6%)	123 (14.8%)	149 (16.3%)	0.3945

CRC, colorectal cancer; FBT, fecal blood test; IBD, inflammatory bowel disease; BMI, body mass index; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

§BMI available for 1,727 patients; information about living alone available for 1,747 patients; instruction level available for 1,662 patients.

Characteristics	All patients n = 1,815	High volume n = 871	Low volume n = 944	p-value
Low instruction §	279 (16.8%)	157 (19.6%)	122 (14.1%)	**0.0017**

CRC, colorectal cancer; FBT, fecal blood test; IBD, inflammatory bowel disease; BMI, body mass index; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

§BMI available for 1,727 patients; information about living alone available for 1,747 patients; instruction level available for 1,662 patients.

Overall, adequate preparation was observed in 1,595/1,815 (87.9%) patients. Complete colonoscopy was possible in 1,793 patients (98.8%). Among the 1,380 patients older than 50 years, PDR, ADR and AADR were 33.1%, 25.0% and 5.9%, respectively. Cancer was found in 33 patients (3.4%), sessile lesions in 26 (1.9%). PDR, ADR, AADR and cancer rates were higher in the positive FBT group, followed by the surveillance, symptoms and IBD groups (Supplementary Tables 1 and 2).

Adequate bowel preparation was associated with a higher complete colonoscopy rate (99.7% vs. 92.5%, OR 24.05, 95% CI 7.82–73.92, p < 0.0001), higher PDR (34.9% vs. 22.0%, OR 1.89, 95% CI 1.31–2.73, p = 0.0006) and ADR (26.2% vs. 17.7%, OR 1.65, 95% CI 1.11–2.46, p = 0.0132), while no significant differences were found in AADR, cancer detection and SDR (Table 2 and Supplementary Table 3).

Table 2
Clinical outcomes according to the quality of preparation (patients ≥ 50 years).

Outcome	Adequate preparation n = 1,193	Inadequate preparation n = 187	OR (95% CI)	p-value
Complete examination	1,189 (99.7%)	173 (92.5%)	**24.05 (7.82–73.92)**	**< 0.0001**
PDR	416 (34.9%)	41 (22%)	**1.89 (1.31–2.73)**	**0.0006**
ADR	312 (26.2%)	33 (17.7%)	**1.65 (1.11–2.46)**	**0.0132**
AADR	74 (6.2%)	8 (4.3%)	1.48 (0.70–3.12)	0.3035
Cancer	26 (2.2%)	7 (3.7%)	0.57 (0.25–1.34)	0.1985
SDR	24 (2.0%)	2 (1.1%)	1.90 (0.45–8.10)	0.3863

PDR, polyp detection rate; ADR, adenoma detection rate; AADR, advanced adenoma detection rate; SDR, sessile lesion detection rate

Efficacy of bowel preparation

High vs. low volume

The adequacy of preparation was independent of the use of high or low-volume PEG (89.2% vs. 86.6%, p = 0.0983). There was no difference among HV and LV preparation also considering the two different schedules (HV split-dose 93.8% vs. LV split-dose 93.6%, p = 1; HV day-before 85.5% vs. LV day-before 82.3%, p = 0.1820) (Fig. 1). The efficacy of HV and LV preparations was similar in all the colonic segments (supplementary Fig. 2), irrespective of the use of the day-before or a split-dose schedule (supplementary Fig. 3).

Day-before vs. split-dose

The split-dose schedule resulted in a higher adequate preparation rate compared to day-before for HV preparation (93.8% vs. 85.5%, p = 0.0001) or LV preparation (93.6% vs. 82.3%, p = 0.0001) (Fig. 1). The use of split-dose regimens was associated with better preparation in all the colon segments, although the difference was highest in the right colon (OR 3.03, 95%CI 2. 12–4.34 for the right colon; OR 2.62, 95% CI 1.47–4.67 for the transverse colon; OR 2.77, 95% CI 1.64–4.70 for the left colon; all p values < 0.05) (Supplementary Table 4).

Clinical endpoints

High vs. low volume

As compared to LV preparation, HV preparation was associated with higher PDR (36.7% vs. 29.6%, OR 1.38, 95% CI 1.10–1.72, p = 0.0055), ADR (28.0% vs. 22.0%, OR 1.38, 95% CI 1.08–1.76, p = 0.0100) and AADR (7.5% vs. 4.5%, OR 1.72, 95% CI 1.09–2.73, p = 0.0203) without differences in cancer detection and SDR. After adjustment for age, sex and indication for colonoscopy, the difference remained statistically significant for PDR (adjusted OR 1.30, 95% CI 1.03–1.64, p = 0.0254) and for ADR (adjusted OR 1.28, 95% CI 0.99–1.65, p = 0.0519) but not for AADR (adjusted OR 1.54, 95% CI 0.96–2.46, p = 0.0723) (Table 3).

Table 3
Clinical outcomes according to the volume of bowel preparation (patients ≥ 50 years).

Outcome	High volume n = 685	Low volume n = 695	OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
PDR	251 (36.7%)	206 (29.6%)	**1.38 (1.10–1.72)**	**0.0055**	**1.30 (1.03–1.64)**	**0.0254**
ADR	192 (28%)	153 (22%)	**1.38 (1.08–1.76)**	**0.0100**	**1.28 (0.99–1.65)**	**0.0519**
AADR	51 (7.5%)	31 (4.5%)	**1.72 (1.09–2.73)**	**0.0203**	1.54 (0.96–2.46)	0.0723
Cancer	18 (2.6%)	15 (2.2%)	1.22 (0.61–2.45)	0.5688		
SDR	14 (2.0%)	12 (1.7%)	1.19 (0.55–2.59)	0.6652		

PDR, polyp detection rate; ADR, adenoma detection rate; AADR, advanced adenoma detection rate; SDR, sessile lesion detection rate.

*Adjustment for age (as a continuous variable), sex and indications for colonoscopy.

The same values were also observed within the overall population, thereby also including those patients with age ≤ 50 years (Supplementary Table 5).

Day-before vs. split-dose

The use of the split-dose schedule was not linked with better clinical outcomes as compared to day-before, for either HV or LV preparations (Table 4 and Supplementary Table 6).

Table 4
Clinical outcomes of high and low-volume preparations according to different schedules (patients ≥ 50 years old).

Outcome	High volume Day before n = 380	High volume Split-dose n = 305	p-value	Low volume Day before n = 427	Low volume Split-dose n = 268	p-value
PDR	137 (36.2%)	114 (37.4%)	0.7402	127 (29.7%)	79 (29.5%)	0.9407
ADR	100 (26.3%)	92 (30.2%)	0.2651	92 (21.6%)	61 (22.8%)	0.7066
AADR	28 (7.4%)	23 (7.5%)	0.9319	17 (4.0%)	14 (5.2%)	0.4933
Cancer	10 (2.6%)	8 (2.6%)	0.9944	6 (1.4%)	9 (3.4%)	0.0846
SDR	5 (1.3%)	9 (3.0%)	0.1328	8 (1.9%)	4 (1.5%)	0.7074

PDR, polyp detection rate; ADR, adenoma detection rate; AADR, advanced adenoma detection rate; SDR, sessile lesion detection rate.

Tolerability

High vs. low volume

Overall, HV and LV preparations were equally well tolerated (median VAS score 7, interquartile range 5–9 for both preparations). 860 patients (47.4%) reported gastrointestinal symptoms during preparation: nausea (26.5%) and bloating (19.9%) were the most frequently self-reported symptoms. The occurrence of nausea, vomiting and abdominal pain was more frequent among the patients in the LV group (Table 5). Self-reported incomplete (i.e., ≤ 75%) intake of the PEG solution was more common in the HV group (7.9% vs. 5.4%, p = 0.00318).

Table 5
Self-reported tolerability of bowel preparations according to volume.

	Total n = 1,815	High volume n = 871	Low volume n = 944	p-value
Global tolerance, VAS score*, median [interquartile range]	7 [5–9]	7 [5–9]	7 [5–9]	0.6274
Incomplete preparation (< 75% of PEG assumed)	116 (6.6%)	67 (7.9%)	49 (5.4%)	**0.0318**
Any symptom during preparation	860 (47.4%)	369 (42.4%)	491 (52%)	**< 0.0001**
Bloating	363 (20%)	183 (21%)	180 (19.1%)	0.3013
Nausea	480 (26.5%)	187 (21.5%)	293 (31%)	**< 0.0001**
Vomiting	174 (9.6%)	55 (6.3%)	119 (12.6%)	**< 0.0001**
Abdominal pain	281 (15.5%)	104 (11.9%)	177 (18.8%)	**< 0.0001**

*Visual Analogue Scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1,772 patients.

Split vs. day-before

For the HV preparation the split-dose regimen was related to better tolerability (higher VAS score) as compared to day-before, even if with no differences in terms of reported symptoms. For the LV preparation, the split-dose regimen was related to lower incidence of symptoms (in particular nausea and bloating) (Table 6).

Table 6
Tolerability of high and low-volume preparations according to different schedules.

	High volume one-day n = 482	High volume split dose n = 389	p-value	Low volume one-day n = 583	Low volume split dose n = 361	p-value
Global tolerance, VAS score*, median [interquartile range]	7 [5–8]	7 [5–9]	**0.0062**	7 [5–9]	7 [5–9]	0.0329
Incomplete preparation (< 75% of PEG assumed)	37 (7.9%)	30 (7.9%)	0.9935	31 (5.5%)	18 (5.2%)	0.8396
Any symptom during preparation	211 (43.8%)	158 (40.6%)	0.3843	324 (55.6%)	167 (46.3%)	**0.0054**
Bloating	103 (21.4%)	80 (20.6%)	0.7722	126 (21.6%)	54 (14.9%)	**0.0114**
Nausea	112 (23.2%)	75 (19.3%)	0.1575	196 (33.6%)	97 (26.9%)	**0.0294**
Vomiting	33 (6.9%)	22 (5.7%)	0.4725	73 (12.5%)	46 (12.7%)	0.9208
Abdominal pain	54 (11.2%)	50 (12.9%)	0.4553	105 (18.0%)	72 (19.9%)	0.4593

*Visual Analogue Scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1772 patients.

Discussion

The standard high-volume PEG-based preparation is safe and effective, but even in clinical studies a significant proportion of patients is unable to take all the prescribed dose(19) with detrimental effect on its efficacy. RCTs and meta-analyses have shown a comparable efficacy of different low-volume preparations compared to high-volume PEG(9,10,13–15), and the use of these preparations is now recommended in both the European(16) and North American(17) guidelines. However, most RCTs did not compare clinically relevant outcomes such as ADR. This comparison is short of the newer LV preparations such as 2L PEG plus citrate and 1L PEG plus ascorbate. While the former was compared to high-volume PEG at least in terms of efficacy and tolerability(14), the latter has been compared only with other low-volume preparations(20–22). Moreover, real-life data are conflicting: a recent prospective observational study has shown better cleansing results and higher ADR and AADR with 4L PEG compared to lower volume preparations(23).

In our real-life setting, only a slight majority of patients (52%) preferred the LV preparation over the standard HV. This may be partially explained by the order in which the two preparations were listed in the instructions handed to the patients (HV preparation listed first). However, among the patients with IBD,

frequently reluctant to perform bowel preparation, the use of the LV preparation was much more frequent than the HV one (75.2%). Women also used more frequently the LV preparation, while we did not find any age-related difference. Even if stated equally effective in the instructions given, it is possible that the patients perceived more effective a high-volume preparation and leaned towards that choice, especially for “strong” indications such as positive FBT. Interestingly, 52% of patients with colonoscopy planned in the afternoon chose the HV preparation. This may suggest that the possibility to reduce the volume of PEG was not felt so compelling once given the possibility to split its assumption.

Overall, 87.9% of our patients achieved adequate preparation. This result is in line or superior to the results reported in the literature(24,25), even if slightly inferior to the 90% target proposed by the European Society of Gastrointestinal Endoscopy (ESGE) in 2019(26). We confirmed that the low-volume PEG plus bisacodyl preparation is equally effective than HV in all the colonic segments (while some studies have shown worse performances of low-volume preparations in the right colon(27)) and irrespective of the intake schedule. In particular, the split LV preparation was as effective as the split HV preparation, confirming the results achieved in a recent meta-analysis(28).

Our real-life setting results confirm the importance of bowel preparation in terms of relevant outcomes such as complete colonoscopy rate, PDR and ADR, while we did not find differences in terms of AADR, SDR and cancer detection. Advanced adenomas and cancers are usually bigger lesions, easier to find even in a not well-prepared colon(6), while the SDR result can be explained by their low prevalence in our population.

Quite surprisingly, despite similar efficacy, the use of the HV preparation was related to higher PDR (OR 1.37), ADR (OR 1.38) and AADR (OR 1.72) compared to the LV preparation. To remove confounding factors due to the absence of randomization, we adjusted the OR considering three main characteristics related to the prevalence of colorectal lesions (age, sex and indication). Even after this adjustment, the HV preparation showed better results, with a statistically significant difference for PDR (adjusted OR 1.30, $p = 0.0254$) and differences very close to significance for ADR (adjusted OR 1.28, $p = 0.0519$) and AADR (adjusted OR 1.54, $p = 0.0519$). Despite better cleansing results with the split-dose as compared to the day-before regimen (93.7% vs. 82.8%, $p < 0.0001$), we did not find any correlation with clinical outcomes in both the HV and LV group. LV split-dose was inferior to either HV day-before or split-dose.

LV preparations(10,14) and in particular 2L PEG plus bisacodyl(9) were found to be better tolerated as compared to high-volume PEG in previous RCTs. On the contrary, we have observed more self-reported gastrointestinal symptoms such as nausea, vomiting and abdominal pain in the LV group. This result can be explained by the real-life observational design of our study, rather than reflecting an intrinsic lower tolerability of the LV preparation. Nonetheless, these GI symptoms affected neither the patients’ adherence nor tolerability. In fact, the LV preparation was judged as tolerable as the HV preparation according to the VAS scale, and it was more frequently taken completely. The use of a split-dose regimen increased the reported tolerability of both the HV (higher VAS score) and the LV (less frequent symptoms) preparations, as previously shown in RCTs and meta-analyses(29,30).

Our study has several limitations. Firstly, the single-center observational design implies the risk of sub-optimal reproducibility. However, the large sample size and the prospective nature of this study support our results. Secondly, as compared to RCTs, the real-life patients-determined allocation among different study groups could result in an unbalanced distribution of risk factors. Notably, the baseline characteristics of the two study groups (HV, LV) were mostly comparable and the few relevant differences (mainly sex and indication for colonoscopy) were adjusted when comparing the endoscopic performance measures between the groups. Thirdly, it is important to acknowledge that the application of the day-before schedule is no longer recommended by the 2019 ESGE guidelines because of its inferior efficacy when compared to split-dose, as confirmed by our results. Due to the extension of the metropolitan area served by our center, however, we decided to maintain the possibility to choose a day before regimen. In fact, living far from the endoscopic centers has been demonstrated to be a significant limitation for adherence to split dose regimen, especially for early morning scheduled colonoscopy(31). On the other hand, additional strengths of our study consist in the blindness of the endoscopists to the type of preparation taken and the use of a well-validated bowel preparation scale.

Conclusions

To resume, this large prospective single-blinded real-life study reveals that unselected outpatients still show only a slight preference for the LV preparation compared to the standard 4-liter PEG. Women, IBD patients and in general those patients who are going to receive a day-before regimen usually choose a LV preparation, while positive-FBT patients a HV preparation. Despite both the HV and LV preparations are perceived as equally tolerable, more patients in the LV group take the entire dose of PEG and report symptoms during preparation. The split regimen increases the bowel preparation tolerability both using HV and LV preparations. Adequate bowel cleansing can be equally achieved by means of either HV or LV preparation, showing better result with split dosage. In the real-life setting the HV preparation is associated with higher PDR and slightly increased ADR and AADR as compared to the LV preparation, thereby suggesting that the HV preparation should still be proposed as one of the preferred options in screening colonoscopy. Looking forward to large multi-center real-life studies, we believe that 4L PEG should be still considered the reference standard for new RCTs assessing both the bowel cleansing and the ADR in screening colonoscopy.

List Of Abbreviations

PDR, polyp detection rate; ADR, adenoma detection rate; PEG, polyethylene glycol; RCT, randomized controlled trial; HV, high volume; LV, low volume; BBPS, Boston Bowel Preparation Scale; AADR, advanced adenoma detection rate; SDR, sessile lesion detection rate.

Declarations

Ethics approval and consent to participate:

The study was approved by the local Ethics Committee of San Raffaele Hospital and a specific written informed consent was taken from all the study participants. The study was conducted in accordance with the Declaration of Helsinki 1975 and subsequent amendments.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare they have no competing interests.

Funding:

None

Acknowledgments:

Not applicable

Contribution of authors:

VO: acquisition, analysis, and interpretation of data, drafting and critical revision of the manuscript. PS, FB, MLA, FC, SV, MV: acquisition of data and critical revision of the manuscript. VM: statistical analysis of data. ER: analysis and interpretation of data, critical revision of the manuscript. LP: acquisition, analysis and interpretation of data, critical revision of the manuscript. GET: study concept and design, acquisition, analysis and interpretation of data, critical revision of the manuscript and study supervision.

References

1. Aslinia F, Uradomo L, Steele A, Greenwald BD, Raufman JP. Quality assessment of colonoscopic cecal intubation: An analysis of 6 years of continuous practice at a University hospital. American Journal of Gastroenterology. 2006.
2. Radaelli F, Meucci G, Sgroi G, Minoli G. Technical performance of colonoscopy: The key role of sedation/analgesia and other quality indicators. Am J Gastroenterol. 2008;
3. Hsu CM, Lin WP, Su MY, Chiu CT, Ho YP, Chen PC. Factors that influence cecal intubation rate during colonoscopy in deeply sedated patients. J Gastroenterol Hepatol. 2012;
4. Adler A, Wegscheider K, Lieberman D, Aminalai A, Aschenbeck J, Drossel R, et al. Factors determining the quality of screening colonoscopy: A prospective study on adenoma detection rates, from12 134

examinations (Berlin colonoscopy project 3, BECOP-3). Gut. 2013;

5. Clark BT, Rustagi T, Laine L. What level of bowel prep quality requires early repeat colonoscopy: Systematic review and meta-analysis of the impact of preparation quality on adenoma detection rate. American Journal of Gastroenterology. 2014.
6. Sulz MC, Kröger A, Prakash M, Manser CN, Heinrich H, Misselwitz B. Meta-analysis of the effect of bowel preparation on adenoma detection: Early adenomas affected stronger than advanced adenomas. PLoS One. 2016;
7. Rex DK, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. Am J Gastroenterol. 2002;
8. Kingsley J, Karanth S, Revere FL, Agrawal D. Cost effectiveness of screening colonoscopy depends on adequate bowel preparation rates - A modeling study. PLoS One. 2016;
9. Clark RE, Godfrey JD, Choudhary A, Ashraf I, Matteson ML, Bechtold ML. Low-volume polyethylene glycol and bisacodyl for bowel preparation prior to colonoscopy: A meta-analysis. Ann Gastroenterol. 2013;26(4):319–24.
10. Xie Q, Chen L, Zhao F, Zhou X, Huang P, Zhang L, et al. A meta-analysis of randomized controlled trials of low-volume polyethylene glycol plus ascorbic acid versus standard-volume polyethylene glycol solution as bowel preparations for colonoscopy. PLoS One. 2014;
11. Moon CM, Park D Il, Choe YG, Yang DH, Yu YH, Eun CS, et al. Randomized trial of 2-L polyethylene glycol+ascorbic acid versus 4-L polyethylene glycol as bowel cleansing for colonoscopy in an optimal setting. J Gastroenterol Hepatol. 2014;
12. Zorzi M, Valiante F, Germanà B, Baldassarre G, Coria B, Rinaldi M, et al. Comparison between different colon cleansing products for screening colonoscopy. A noninferiority trial in population-based screening programs in Italy. Endoscopy. 2016;48(3):223–31.
13. Lieshout I van, Munsterman ID, Eskes AM, Maaskant JM, van der Hulst R. Systematic review and meta-analysis: Sodium picosulphate with magnesium citrate as bowel preparation for colonoscopy. United European Gastroenterology Journal. 2017.
14. Spada C, Cesaro P, Bazzoli F, Saracco GM, Cipolletta L, Buri L, et al. Evaluation of Clensia®, a new low-volume PEG bowel preparation in colonoscopy: Multicentre randomized controlled trial versus 4L PEG. Dig Liver Dis. 2017;
15. Yang HJ, Park SK, Kim JH, Im JP, Yeom DH, Seo GS, et al. Randomized trial comparing oral sulfate solution with 4-L polyethylene glycol administered in a split dose as preparation for colonoscopy. J Gastroenterol Hepatol. 2017;
16. Hassan C, East J, Radaelli F, Spada C, Benamouzig R, Bisschops R, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2019. Endoscopy. 2019;
17. Saltzman JR, Cash BD, Pasha SF, Early DS, Raman Muthusamy V, Khashab MA, et al. Bowel preparation before colonoscopy. Gastrointest Endosc. 2015;

18. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc. 2009;
19. Kelly NM, Rodgers C, Patterson N, Jacob SG, Mainie I. A prospective audit of the efficacy, safety, and acceptability of low-volume polyethylene glycol (2 L) versus standard volume polyethylene glycol (4 L) versus magnesium citrate plus stimulant laxative as bowel preparation for colonoscopy. J Clin Gastroenterol. 2012;
20. DeMicco MP, Clayton LB, Pilot J, Epstein MS, Bekal PKT, DeMicco M, et al. Novel 1 L polyethylene glycol-based bowel preparation NER1006 for overall and right-sided colon cleansing: a randomized controlled phase 3 trial versus trisulfate. Gastrointest Endosc. 2018;
21. Schreiber S, Baumgart DC, Drenth JPH, Filip RS, Clayton LB, Hylands K, et al. Colon cleansing efficacy and safety with 1 L NER1006 versus sodium picosulfate with magnesium citrate: A randomized phase 3 trial. Endoscopy. 2019;
22. Bisschops R, Manning J, Clayton LB, Ng Kwet Shing R, Álvarez-González M. Colon cleansing efficacy and safety with 1 L NER1006 versus 2 L polyethylene glycol + ascorbate: A randomized phase 3 trial. Endoscopy. 2019;
23. Waldmann E, Penz D, Majcher B, Zagata J, Šinkovec H, Heinze G, et al. Impact of high-volume, intermediate-volume and low-volume bowel preparation on colonoscopy quality and patient satisfaction: An observational study. United Eur Gastroenterol J. 2019;7(1):114–24.
24. Gandhi K, Tofani C, Sokach C, Patel D, Kastenberg D, Daskalakis C. Patient Characteristics Associated With Quality of Colonoscopy Preparation: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;
25. Mahmood S, Farooqui SM, Madhoun MF. Predictors of inadequate bowel preparation for colonoscopy: A systematic review and meta-analysis. European Journal of Gastroenterology and Hepatology. 2018.
26. Kaminski MF, Thomas-Gibson S, Bugajski M, Bretthauer M, Rees CJ, Dekker E, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. United European Gastroenterology Journal. 2017.
27. Corporaal S, Kleibeuker JH, Koornstra JJ. Low-volume PEG plus ascorbic acid versus high-volume PEG as bowel preparation for colonoscopy. Scand J Gastroenterol. 2010;
28. Spadaccini M, Frazzoni L, Vanella G, East J, Radaelli F, Spada C, et al. Efficacy and Tolerability of High- vs Low-Volume Split-Dose Bowel Cleansing Regimens for Colonoscopy: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;
29. Bucci C, Rotondano G, Hassan C, Rea M, Bianco MA, Cipolletta L, et al. Optimal bowel cleansing for colonoscopy: Split the dose! A series of meta-analyses of controlled studies. Gastrointestinal Endoscopy. 2014.
30. Martel M, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A. Split-Dose Preparations Are Superior to Day-Before Bowel Cleansing Regimens: A Meta-analysis. Gastroenterology. 2015;

31. Radaelli F, Paggi S, Repici A, Gullotti G, Cesaro P, Rotondano G, et al. Barriers against split-dose bowel preparation for colonoscopy. Gut. 2017;

Figures

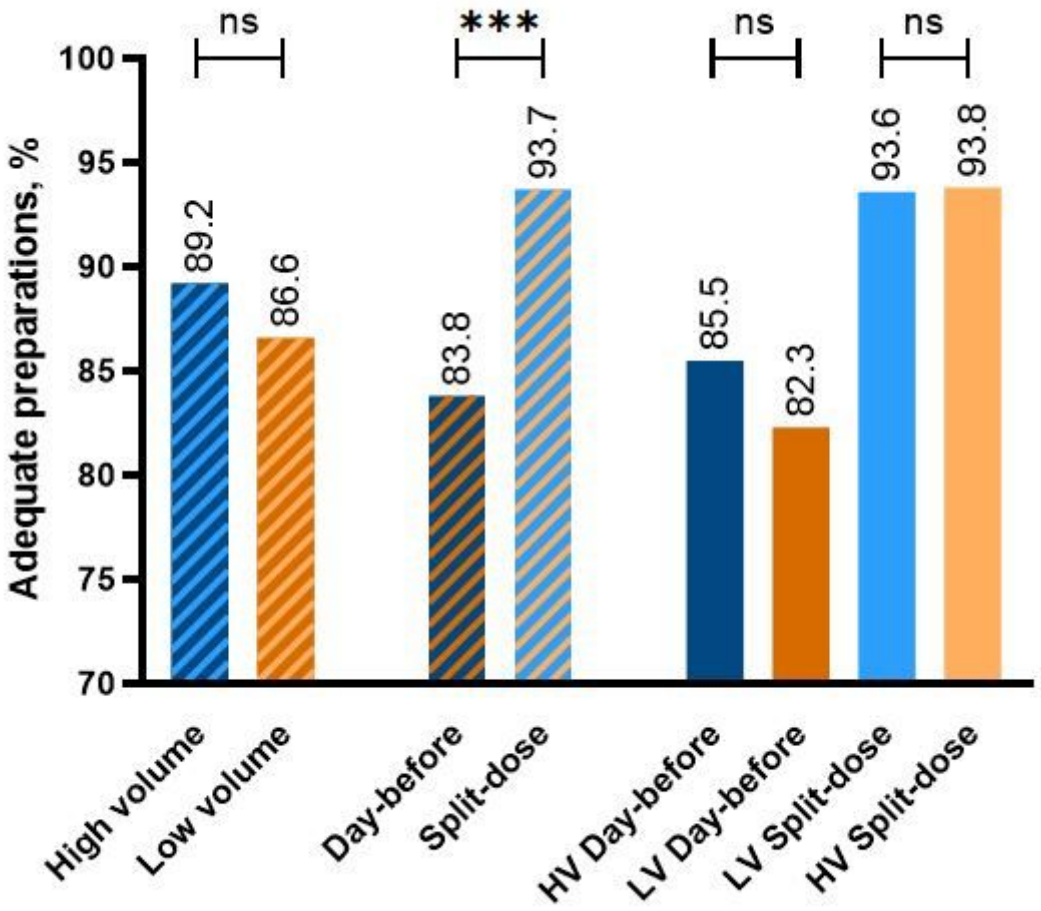

Figure 1

Frequency of adequate preparations (Boston Bowel Preparation Scale BBPS ≥2 in all bowel segments) according to volume and schedules of preparations.

Supplementary Files

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