

Equivalence in Efficacy between Approved Low- and High-Volume Split Regimens for Bowel Preparation

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Funding: Prof. James East was funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health;

Conflicts of interest: JE: Clinical Advisory Boards: Lumendi, Boston Scientific. Speakers fees: Falk, Olympus; CH Consultancy for Norgine, Alpha-Sigma. No conflict of interest for remaining authors.

Author contributions: CH, AR, MS, GV, PS, DKR: study concept and design; CH, MS, GV; drafting of the manuscript; all authors: acquisition of data; LF, LF: statistical analysis; all authors: analysis and interpretation of data.

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Background: Efficacy of bowel preparation is critical for the outcome of colonoscopy. There is uncertainty whether approved low-volume PEG and non-PEG regimens are equally effective than high-volume PEG regimens when adopted in a split dose.

Methods: This systematic review was carried out in according with the guidelines of the preferred reported items for systematic review and meta-analyses. Literature search with PubMed/MEDLINE, EMBASE and Scopus (up to January 31st 2019) was performed to identify full articles on comparison between low- and high-volume regimens in a split dose. Primary outcome was the rate of adequate cleansing overall and in the right colon, while patient experience was a secondary outcome (compliance, tolerability, willingness to repeat the same preparation). Relative risks (RR) and 95% Confidence Interval (CI) were calculated. Quality was assessed by the Cochrane risk bias tool. Heterogeneity among studies was assessed by using the I^2 statistic. (CRD42019128067)

Results: From a total of 2,029 records, 17 studies with 18 arms, including 7,528 patients (low-volume-PEG: 6,593; -non-PEG: 935) were included. Low- and high-volume split regimens were equivalent for the rate of adequate cleansing in all the colon (88.2% vs. 88.5%; RR: 1.00; 95% CI 0.98-1.01; $I^2=21\%$) and in the right colon (91.9% vs. 91.0%; RR 1.01; 95% CI 0.99-1.03; $I^2=24\%$), and such equivalence individually applied to low-volume PEG (88.0% vs. 88.2%; RR 1.00; 95% CI 0.98-1.02; $I^2=38\%$) and non-PEG (89% vs. 90.3%; RR 0.98, 95%CI 0.94-1.03; $I^2=0\%$) regimens, as well as to individual products. Low-volume split regimens were associated with a better patient experience (compliance: RR 1.06; 95% CI 1.02-1.10; tolerability: RR 1.39; 95% CI 1.12-1.74; and willingness to repeat: RR 1.41; 95% CI 1.20-1.66). Results were robust at multiple sensitivity analysis.

Conclusions: When used in split dose, approved low-volume regimens are equally effective and more acceptable than high-volume regimens, supporting their implementation in colonoscopy practice.

BACKGROUND

Adequate cleansing is critical for detection of colorectal neoplasia and to marginalize the risk of missed lesions and post-colonoscopy CRC [1–3]. In addition, it improves colonoscopy efficiency, as inadequate cleansing has been associated with shortened surveillance intervals [4,5], longer procedure time [6] and need for early repetition of colonoscopy [7].

Based on a favorable combination of high efficacy and high safety [8–10], a split regimen of high-volume (3-4 liters, L) Polyethylene Glycol (PEG) regimen has become the reference standard for bowel preparation [11,12]. However, suboptimal acceptability and compliance have been generally attributed to the large volume of liquids to be administered, affecting patient experience and willingness to repeat the procedure [8,13]. Bowel preparation has been consistently rated as the worst phase of colonoscopy experience.

When considering patient experience as a relevant outcome of bowel preparation, low-volume PEG and non-PEG split regimens appear as an attractive alternative, due to a substantial reduction of the volume to be administered, i.e. ≤ 2 L. Despite their hyperosmolality, these low-volume regimens appeared to be safe after exclusion of high-risk patients, i.e. those with renal or cardiovascular comorbidities [8,11–13].

Thus, it is clinically relevant to assess whether low-volume split preparations are equally effective as high-volume split PEG regimens in order to implement their use in clinical practice. Unfortunately, most of the previous meta-analysis did not differ between split and non-split regimens, only partially addressing such an issue [13,14]. In addition, the only systematic review focusing on split-administration included non-approved low-volume PEG regimens (i.e., Miralax-Gatorade) [8]. Not enough data were available for the comparison between high-volume PEG and most of the low-volume, non-PEG regimens. [8].

Primary aim of this meta-analysis is to assess whether low-volume PEG and non-PEG regimens are equally effective as high-volume PEG regimens when administered in a split dose.

METHODS

The methods of our analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [15]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) on March 2019. The following methods are reported in **Appendix 1**: data sources and search strategy, the selection process, data extraction and the quality assessment.

Inclusion and exclusion criteria

For the purpose of our meta-analysis, we considered all clinical studies meeting the following inclusion criteria:

- (I) Population: all adults undergoing elective colonoscopy, irrespective of the indication.
- (II) Intervention: all low-volume bowel preparation regimens administered in split dose.
- (III) Comparison: all high-volume PEG-based bowel preparation regimens administered in split dose.
- (IV) Outcome: bowel preparation efficacy was recorded as the primary outcome. Secondary outcomes included compliance with the recommend regimen, willingness to repeat the same bowel solution, palatability of the regimen, side effects.
- (V) Study design: only RCTs, published as full text in English language, were considered.

Studies were excluded if meeting at least one of the following exclusion criteria:

- (I) Essential information not available;
- (II) Studies investigating bowel preparation regimen in special patients, such as pediatric patients, patients with a history of colorectal resection, inflammatory bowel disease patients or patients with a previous poor bowel preparation.
- (III) Studies investigating bowel preparation regimens not approved and/or discouraged by European Guidelines (i.e., sodium phosphate).
- (IV) Studies investigating bowel preparation regimens obtained by a non-approved combination of two products (e.g. e.g. Miralax-Gatorade).

Outcome assessment

In our systematic review and meta-analysis, the primary outcome was regarded as the rate of patients with a successful bowel preparation in the 1) overall colon and 2) right colon. Considering the expected variation in outcomes nomenclature among the studies, we pre-defined as a successful bowel preparation a Boston Bowel Preparation Scale (BBPS)[16] score of ≥ 6 , an Ottawa Bowel Preparation Score (OBPS)[17] of < 5 , an excellent or good bowel preparation reported by the endoscopists using the Aronchik Scale [18], or other non-validated 3-, 4- or 5-point scales. A successful right colon preparation was defined as BBPS ≥ 2 or an OBPS ≤ 2 in the right colon. Data on tolerability and side effects were extracted from the results of non-standardized questionnaires generally administered to the patients before colonoscopy: compliance with bowel preparation was defined as consumption of 75-100% of the prescribed solution, according to the cut-off adopted in the different series. Further secondary outcomes were the proportion of patients willing to repeat the same bowel preparation and the rate of patients who reported a good/neutral palatability (tolerability) of the prescribed solution. Side effects such as abdominal bloating, nausea, vomiting, and abdominal pain/cramping were also reported. We included withdrawals in the intention-to-treat (ITT) analysis. When both were presented, values from ITT were preferred to per-protocol (PP).

Statistical Analysis

As the outcomes were dichotomous events, we ran traditional pairwise meta-analyses computing the risk ratio (RR) and its 95% confidence interval (95% CI). The measure of effect was pooled by means of a random effects model in case of significant heterogeneity, otherwise a fixed effect model was used [19]. Heterogeneity among studies was assessed by calculating the I^2 measure of inconsistency. An I^2 -value of 0-30%, 30-60%, 60-75% and 75-100% was indicated as low, moderate, substantial and considerable heterogeneity, respectively. Publication bias was assessed by funnel plot and by Egger's regression test. Sensitivity analysis was performed for the most clinically relevant variables. Statistical analyses were conducted with R.

RESULTS

Study characteristics and quality

The literature search resulted in 2,029 articles (**Figure 1**). After reviewing the title and abstract, 22 articles were retrieved as full text. Of these, 17 articles matched the selection criteria and were finally included in the systematic review [20–37].

Studies characteristics are briefly reported in **Table 1**. All studies were published between 2008 and 2019. Six of them were performed in Italy (4,928 patients), 5 studies (1,015 patients) in Korea, 4 (767 patients) in The Netherlands, and the remaining studies in Czech Republic (259 patients), Germany (359 patients) and Lebanon (200 patients), respectively. Eleven studies involved multiple centers, otherwise 7 studies were single-center experiences.

Regarding bowel preparation scales, the Aronchick scale was used in 5 studies, the Ottawa bowel preparation scale in 4, the Boston bowel preparation scale in 4, and non-validated scales were used in 8 studies.

Altogether, the 17 studies included 7,528 patients in the intention-to-treat analysis, 3,749 being in the low-volume split group and 3,779 in the high-volume split group. Baseline characteristics in terms of age and gender were comparable between the two groups. We used the Cochrane risk bias tool for randomized trial to assess methodological quality. Risk of bias was low for all but allocation concealment (i.e. blinding of endoscopists at randomization) and incomplete outcome data (i.e., for excluded patients) (**Figure 2**). Reasons to remain included at PP analysis are detailed in **Appendix 2**.

Regarding the type of low-volume regimen, 2L-PEG with ascorbic acid as adjuvant (PEG-A) was the low-volume adopted in 9 studies, a combination of 2L-PEG with citrate and simethicone (PEG-C) in 4 (with the addition of bysacodil in 2), sodium picosulfate with magnesium citrate (SPMC) in 3, and oral sulfate solution (OSS) in 2 studies.

Primary outcome: Efficacy (overall and right colon)

Low-volume PEG and non-PEG regimens vs. high-volume regimen in split dose (Figure 3 and 4)

Based on the data reported by all the 17 studies (7,528 patients, 36 arms of treatment), low-volume split bowel regimens had an equivalent proportion of patients with an adequate

bowel preparation compared with split-dose high-volume PEG (3,305/3,749, **88.2%** vs. 3,344/3,779, **88.5%**). As reported in **Table 2**, the pooled RR was 1.00 (95% CI 0.98-1.01; $I^2=21\%$; $p=0.2$) showing no statistically significant difference and no relevant heterogeneity (Figure 3).

In the trials reporting data on right colon (10 studies, 5,288 patients), no difference in efficacy between low-(PEG and non-PEG) volume and high-volume PEG was found (2,417/2,630, **91.9%** vs. 2,420/2,658, **91.0%**; RR 1.01; 95% CI 0.99-1.03; $I^2=24\%$; $p=0.22$, **Table 2**). No publication bias was shown according to Funnel plots and Egger's test ($p=0.13$ and $p=0.06$) for both the primary outcomes (**Appendix 3**).

-Low-volume PEG

Split-dose 2L-PEG with the adjuvant of ascorbic or citric acid had a comparable proportion of patients with an adequate bowel preparation compared with high-volume split PEG (13 studies: 6,593 patients; 2,894/3,287, **88.0%** vs. 2,917/3,306; **88.2%**; RR: 1.00; 95% CI: 0.98-1.02; $I^2=38\%$; $p=0.08$, **Table 2**). The moderate heterogeneity was related to three series [21,36,37]. When excluding such studies, the RR was 1.01 (95% CI: 0.99-1.03) with $I^2=13\%$.

For those trials reporting on right colon cleansing (7 studies: 4,805), no difference in efficacy between low- and high-volume PEG was found (1,889/2,390; **79.0%** vs. 1,884/2,415; **78.0%**; RR: 1.01; 95% CI: 0.99-1.04; $I^2=25\%$; $p=0.37$, **Table 2**). No publication bias was shown (Egger's test: $p=0.18$ and $p=0.32$) for the two end-points.

Separate analysis for PEG-A and PEG-C is reported in the **Table 2 and Appendix 4**.

-Low-volume non-PEG

As shown in **Table 2**, split-dose non-PEG regimens had a comparable proportion of patients with an adequate bowel preparation compared with high-volume split PEG (5 studies: 935 patients; 411/462, **89%** vs. 427/473, **90.3%**; RR: 0.98, 95%CI: 0.94-1.03; $I^2=0\%$; $p=0.64$).

For those trials reporting on right colon cleansing, no difference in efficacy between low-volume non-PEG and high-volume PEG regimens was found (3 studies: 483 patients; 218/240, **90.1%** vs. 216/243, **88.9%**; RR: 1.02; 95% CI: 0.96-1.08; $I^2=0\%$; $p=0.49$, **Table 2**). No publication bias was shown (Egger's test: $p=0.32$ and $p=0.90$) for the two end-points.

Separate analysis for SPMC and OSS is reported in **Table 2 and Appendix 3**.

Secondary outcomes: Patient experience (Table 3)

Compliance

In 13 studies (6,570 patients) assessing compliance to bowel preparation, patients receiving low-volume PEG and non-PEG regimens were more likely to complete the preparation than those receiving high-volume volume preparation (3,049/3,277, **93.0%** vs. 2,910/3,293, **88.4%**; RR: 1.06; 95% CI: 1.02-1.10; $I^2 = 85\%$; $p < 0.01$). Separate analysis for PEG and non-PEG low-volume regimens are provided in **Table 3**.

Tolerability

In 9 studies (5,364 patients) assessing tolerability (i.e. palatability/acceptability) of bowel preparation, the low-volume PEG and non-PEG group demonstrated statistically significantly higher tolerability as compared with the high-volume group (2,230/2,672, **83.5%** vs. 2,002/2,692, **74.4%**; RR: 1.39; 95% CI: 1.12-1.74; $I^2 = 98\%$; $p < 0.001$). Separate analysis for PEG and non-PEG low-volume regimens are provided in **Table 3**.

Willingness to repeat the same preparation

In the 4 studies (815 patients) assessing the willingness to repeat the same bowel preparation regimen, there was a significant difference in favour of low-dose PEG and non-PEG regimens as compared to high-volume PEG (366/407, **89.9%** vs. 271/408, **66.4%**; RR: 1.41; 95% CI: 1.20-1.66; $I^2 = 71\%$; $p < 0.001$). Separate analysis for PEG and non-PEG low-volume regimens are provided in **Table 3**.

Adverse events and sensitivity analysis

Data on side effects for each study, adenoma detection rate, and sensitivity analysis (per protocol analysis, validated scales, exclusion of BBPS, year of publication) are summarized in **Appendix 5 and 6**, respectively.

DISCUSSION

According to our meta-analysis, there is a statistical equivalence between approved low- and high-volume preparations used in split dose in terms of efficacy of cleansing both in the overall colon and in the right colon. Such equivalence was independent on the type – i.e. PEG or non-PEG – of low-volume regimens, as all the individual products analyzed showed a similar pattern of efficacy. In addition, our analysis confirms a better profile of patient experience, especially in terms of willingness to repeat the same preparation, with a low-volume regimen.

The clinical relevance of our analysis is the opposite result in terms of efficacy as compared with the previous meta-analysis showing the superiority of a high-volume PEG over a low-volume PEG regimen used in a split dose [8]. First, by including 7 and 3 additional trials on low-volume PEG and non-PEG regimens, respectively, we increased by 7- and 2-fold the study populations, respectively. This also allowed us to make statistically meaningful comparison between each individual non-PEG regimen and a high-volume regimen, as only one trial for each product was available in the previous review [8]. Secondly, we excluded non-approved regimens of low-volume PEG preparations, such as those based on the combination between PEG and Gatorade, as well as those discouraged, such as sodium phosphate. Both of these factors completely reversed the previous superiority shown for high-volume PEG split regimens, reassuring on the favourable clinical outcome of low-volume preparations. Although found in a previous meta-analysis [13], the equivalence we showed between low- and high-volume regimens was restricted to studies adopting a split regimen. As non-split series represent a mere confounder [11,12], our analysis was based on the most suitable and clinically meaningful setting for the decision-making process. Third, we did not limit the comparison to the level of cleansing in the overall colon [8,13], but we also showed the equivalence between low- and high-volume regimens in the right colon. This is clinically relevant, as both adenomatous and serrated lesions tend to be more frequently flat and subtle in the proximal colon, requiring a high level of cleansing to be detected.

Despite less critical than our primary end-point, the better patient experience achieved by low-volume product is also clinically relevant. Low-volume regimens were superior in each individual end-point we selected for patient experience, with a similar trend for most of the adverse events related with bowel preparation. When coupling the equivalent efficacy with a better experience, there is compelling evidence to recommend a low-volume split regimen

as alternative to the high-volume regimen, unless additional factors, such as cost or patient preferences, supports a different choice.

The consistency of the study results across products with different mechanism of action – such as PEG and non-PEG agents – is somewhat unexpected. This may indicate a clear hierarchy between the timing of administration – i.e. split vs. non-split – over the mere action of the hyperosmolar product. Thus, the split regimen is able to cover most of the efficacy by itself, leaving a residual efficacy to the intrinsic activity of the laxative agent that is fulfilled by virtually any of the available products. Of note, we also excluded that the main mechanism of efficacy of low-volume regimens is a higher compliance to low- versus high-volume for two reasons. First, the equivalence between low- and high-volume was nearly the same when passing from ITT to PP analysis, despite the main difference between ITT and PP is represented by the cut-off in the amount of product actually taken; secondly, the difference between low- and high-volume regimens in terms of compliance was limited to 6%.

The strength of our analysis is not only related with the large number of patients enrolled, but also by the very low inter-study heterogeneity found in most of the comparisons on primary outcomes, as well as by its robustness in any of the sensitivity analysis applied. This is to be related to the fact that the operators in such studies are fully blinded to the product used, while the fact that patients are unblinded may affect secondary rather than primary outcomes.

The main limitation of our analysis is that an intrinsic selection bias in high-quality randomized trials – i.e. the exclusion of patients with major comorbidities – limits the assessment of safety for the hyperosmolar low-volume regimens. Thus, caution is required when prescribing these agents to frail or severely-ill patients, whereas the isotonic high-volume regimen may be a safer choice. The same selection bias may apply to inpatients, patients with prior failed preps, those with prior resections, severe constipation or treated with opiates. We included studies using the Boston Bowel Preparation Scale that is somewhat suboptimal for assessing the efficacy of products as it is artificially influenced by intra-colonoscopy washing. However, only 4 studies actually used this scale, and the results were unchanged when these studies were excluded at sensitivity analysis.

In conclusion, our analysis unequivocally shows the equivalence between low- and high-volume regimens, when a split dose administration is adopted. The better patient

experience associated with such low-volume regimens indicates their potential as first-choice agents.

Table 1: Studies characteristics. ITT: intention-to-treat, PEG-A: Polyethylene Glycol plus Ascorbic Acid, PEG-C: Polyethylene Glycol-citrate, SPMC: Sodium picosulfate with magnesium citrate, OSS: Oral Sulfate Solution.

Study	Publication year	Country	Centers (n)	Low-volume regimen	Patients (ITT)	
					Low-volume	4L
Ell[21]	2008	Germany	14	PEG-A	180	179
Marmo[25]	2010	Italy	3	PEG-A	217	218
Corporaal[37]	2010	The Netherlands	1	PEG-A	62	73
Jansen[22]	2011	The Netherlands	1	PEG-A	188	182
Valiante[29]	2013	Italy	1	PEG-C	140	140
Mathus-Vliengen[20]	2013	The Netherlands	1	PEG-A	43	46
Moon[26]	2014	Korea	3	PEG-A	181	180
Munsterman[34]	2014	The Netherlands	1	SPMC	85	88
Kojecky[35]	2014	Czech Republic	3	SPMC	125	134
Kim[31]	2014	Korea	1	SPMC	50	50
Parente[28]	2015	Italy	5	PEG-C	193	189
Zorzi[27]	2015	Italy	14	PEG-A	924	938
				PEG-C	940	938
Sharara[36]	2015	Lebanon	1	PEG-A	100	100
Jung[23]	2016	Korea	3	PEG-A	74	77
Yang[33]	2016	Korea	3	OSS	105	105
Spada[30]	2017	Italy	6	PEG-C	45	46
Kwak[32]	2019	Korea	9	OSS	97	96

Table 2. Primary outcome in terms of efficacy of cleansing for the overall colon and right colon according to low-volume PEG and non-PEG split regimens as compared with high-volume split regimens at ITT. RR: Relative Risk; CI: Confidence Interval.

Low-volume regimens	N° of trials	Patients (ITT, n)	Relative Risk (95% CI) All colon	I ²	N° of trials	Patients (ITT, n)	Relative Risk (95% CI) Right colon	I ²
	Efficacy <i>all colon</i>				Efficacy <i>right-colon</i>			
PEG & non-PEG	18	7,528	1.00 [0.98, 1.01]	21%	10	5,288	1.01 [0.99-1.03]	22%
- PEG	13	6,593	1.00 [0.98, 1.02]	38%	7	4,805	1.01 [0.99-1.03]	49%
-PEG-A	9	3,962	1.00 [0.97, 1.02]	48%	5	2,647	1.00 [0.99, 1.04]	44%
-PEG-C	4	2,631	0.99 [0.96, 1.02]	38%	2	2,158	1.00 [0.98-1.03]	0%
- non-PEG	5	935	0.98 [0.94-1.03]	0%	3	483	1.01 [0.96-1.06]	0%
-SPMC	3	532	0.96 [0.90-1.03]	0%	2	273	1.01 [0.94-1.08]	0%
-OSS	2	403	1.01 [0.96-1.06]	0%	1	210	1.01 [0.93-1.09]	NA

Table 3. Secondary outcomes in terms of patient experience. CI: Confidence Interval.

Secondary end-point	Number of trials	Patients (ITT, n)	Relative Risk (95% CI)	I ²
<i>Compliance</i>				
-PEG & non-PEG	13	6,570	1.06 [1.02-1.10]	85%
-PEG	9	5,808	1.08 [1.03-1.14]	86%
-non-PEG	4	762	1.01 [0.96-1.05]	16%
<i>Tolerability</i>				
-PEG & non-PEG	9	5,364	1.39 [1.12-1.74]	98%
-PEG	5	4,566	0.92 [0.85, 0.99]	84%
-non-PEG	4	742	0.51 [0.27, 0.95]	96%
<i>Willingness to repeat</i>				
-PEG & non-PEG	4	815	1.41 [1.20-1.66]	71%
-PEG	3	622	1.46 [1.15-1.86]	74%
-non-PEG	1	193	1.37 [1.18-1.59]	NA

Figure 1. Study flow-chart.

Figure 2. Risk of bias across the included studies.

Figure 3. Forest plot for the primary outcome (rate of adequate level of bowel preparation in the overall colon) according to the low-volume PEG and non-PEG regimen adopted in the included studies.

Figure 4. Forest plot for the primary outcome (rate of adequate level of bowel preparation in the right colon) according to the low-volume PEG and non-PEG regimen adopted in the included studies.

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