

Review

Efficacy of ultra-low volume (≤ 1 L) bowel preparation fluids: Systematic review and meta-analysisMilou L. M. van Riswijk, , Kelly E. van Keulen  and Peter D. Siersema 

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Background and Aims: High-quality bowel preparation is paramount for the diagnostic accuracy and safety of colonoscopy; however, it is often difficult for patients to adhere to high-volume laxatives, which may contribute to poor bowel preparation. This review aims to assess the efficacy of bowel preparation fluids of 1 L or less (≤ 1 L).

Methods: We performed a systematic review including all relevant randomized controlled trials on ultra-low volume (≤ 1 L) bowel preparation fluids for colonoscopy published since 2015. Primary endpoint was the percentage of adequately prepared patients. Secondary endpoints included adenoma detection rate (ADR) and safety.

Results: Bowel preparation with sodium picosulfate/magnesium citrate (SPMC; 19 trials, $n = 10,287$), 1L-polyethylene glycol with ascorbate (PEGA; 10 trials, $n = 1717$), sodium phosphate (NaP; 2 trials, $n = 621$), and oral sulfate solution

(OSS; 3 trials, $n = 597$) was adequate in 75.2%, 82.9%, 81.9%, and 92.1%, respectively, of patients; however, heterogeneity between studies was considerable (I^2 range: 86–98%). Pooled ADRs were 31.1% with SPMC, 32.3% with 1L-PEGA, 30.4% with NaP, and 40.9% with OSS. Temporary electrolyte changes were seen with all ultra-low volume bowel preparation fluid solutions but without sustained effects in most patients.

Conclusion: Ultra-low volume bowel preparation fluids do not always meet the 90% quality standard for adequate bowel preparation as defined by current guidelines. Nonetheless, they may be considered in patients intolerant for higher-volume laxatives and without risk factors for inadequate bowel preparation or dehydration-related complications.

Key words: cathartics, colonoscopy, endoscopy, laxatives, meta-analysis

INTRODUCTION

COLONOSCOPY IS CONSIDERED the gold standard for screening and surveillance of colorectal cancer (CRC) and its precursor lesions. However, diagnostic accuracy and safety of colonoscopy highly depend on the quality of preprocedural bowel preparation. Inadequate bowel preparation has been reported as frequent as 25% and is associated with a lower adenoma detection rate (ADR), lower procedure completion rate, longer procedure time, higher complication rate, and a higher need for repeat colonoscopy with associated increased healthcare costs.^{1–7} In light of this, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines advise that at least 90% of the colonoscopy patients should have adequate bowel preparation.^{1,8}

Inadequate bowel preparation is often linked to the high volume of laxatives patients need to drink.^{9,10} Moreover, the high burden of bowel preparation may be one of the reasons for patients not to undergo colonoscopy.^{11,12} In the past few years, several strategies have been developed to ensure adequate bowel cleansing, aiming to improve bowel preparation tolerability while maintaining an adequate cleansing effect. The reference standard for bowel preparation consisted for a long time of 3–4 L of polyethylene glycol (PEG) electrolyte solution^{1,2} due to its efficacy and favorable safety profile.¹³ More recent randomized clinical trials (RCT) and meta-analyses comparing lower volumes (2 L) of bowel preparation solutions to standard regimes, demonstrated that the former benefit patient compliance and show a higher willingness to repeat colonoscopy while still leading to a high bowel cleansing efficacy.^{14–16}

Nonetheless, even 2 L of poorly tasting laxatives is still less optimal for a subgroup of patients.^{9,17} In an effort to further optimize patient experience and compliance, several ultra-low volume bowel preparation fluids of 1 L or less have been developed, based on either hyperosmotic solutions or stimulant laxatives (Appendix S1). In a recently

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published observational study including 5000 patients, a 300 mL bowel preparation solution consisting of sodium picosulfate with magnesium citrate (SPMC) demonstrated a high willingness to repeat colonoscopy (93.5%) when compared to 4 L PEG (69.4%) and 2 L PEG with ascorbate (73.2%).¹⁸

The ESGE recommends both high-volume (>2 L) as well as low- (≤ 2 L), or ultralow-volume (≤ 1 L) laxatives in healthy patients, based on a non-inferiority outcome of individual studies. However, not all included studies investigating ultralow volume laxatives were found to meet the quality standard of a minimum of 90% adequate bowel preparation. Considering that the cleansing efficacy is even more important than tolerability,³ the scope of this review is to assess the efficacy and safety of ultra-low volume fluids (≤ 1 L) to achieve adequate bowel preparation for colonoscopy.

MATERIALS AND METHODS

Protocol and registration

THE PROTOCOL WAS designed in line with the PRISMA guidelines and registered in the PROSPERO database of systematic reviews (CRD42020181630).

Information sources and search strategy

The search was systematically performed on 17 April 2020 in three databases: PubMed, Embase (Ovid interface), and the Cochrane Library (CENTRAL). The search strategy and search terms were developed in collaboration with a medical librarian. Search terms included “colonoscopy”, “laxatives”, “cathartics”, “purgatives”, “bowel evacuant”, “bowel preparation”, “bowel cleansing”, “colon cleansing”, “visualization”, “lavage”. Alternative spelling was accounted for. The full search strategy is available in Appendix S2.

Eligibility criteria

We included RCTs that investigated bowel preparation fluids with a volume of ≤ 1 L, published between 1 January 2015 and 17 April 2020. We excluded studies that did not report original data, animal studies, studies focusing on a specific study population, and conference abstracts. The search was limited to articles either in English or Dutch, with full-text available through the university library or open access publishing.

Study selection

To remove duplicate records, we used Endnote X9.2 (Clarivate Analytics, Philadelphia, PA, USA), after which all remaining records were transported to the web-based

screening program Rayyan QCRI.¹⁹ Eligible studies were identified by one researcher (MvR). Uncertainties were resolved through discussion with the senior author (PS).

Outcome measures

Our primary endpoint was the proportion of adequately prepared patients on an intention-to-treat basis. Adequate bowel cleansing was defined as a Boston Bowel Preparation Scale (BBPS) score ≥ 6 , Aronchick Scale (AS) score ≤ 2 (good or excellent), Ottawa Bowel Preparation Scale (OBPS) score ≤ 5 , and Harefield cleansing scale (HCS) grade A or B.²⁰

If the outcome was reported with more than one preparation scale, BBPS and OBPS were preferred over AS, as previous studies have shown better interobserver consistency with a Cohen's kappa coefficient of 0.77, 0.94, and 0.77 for BBPS, OBPS, and AS, respectively. Furthermore, AS is preferred over HCS (kappa 0.457).^{20–22} Additionally, BBPS was preferred over OBPS because of more extensive validation and more frequent use in clinical practice.^{1,20}

Secondary endpoints included ADR and safety. If the primary outcome was not reported, the study was not included in the meta-analysis for efficacy, but only in the safety analysis.

Statistical analysis

We used a random-effects model to calculate the pooled proportion of adequately prepped patients and ADR per type of fluid, using the restricted maximum likelihood method.²³ A Freeman-Tukey double arcsine transformation was used to minimize the effect of extreme proportions (near 1 or 0) in study subsets with small sample sizes and to stabilize variances.²⁴ Additionally, subgroup analyses and meta-regression on predefined subgroups were conducted. We assessed the effects of the use of additives (i.e. adjunctive laxatives drugs prescribed besides the main laxative, e.g. bisacodyl), the dosing protocol (split-dose, same day, or day before), and diet (liquid diet, low-residue diet, or a combination).

Heterogeneity across the pooled studies was assessed using I^2 statistics, with low, moderate, and substantial heterogeneity defined as 25%, 50%, and 75%, respectively.²⁵ To further explore heterogeneity and to detect possible outliers, influence analyses were conducted, including leave-one-out sensitivity analyses and Baujat-plots.^{26,27} If more than 10 studies were available, a graphic display of study heterogeneity (GOSH plot) analysis was conducted.²⁸ All analyses were conducted in R3.6.2,²⁹ using the packages *meta*,³⁰ *metafor*,³¹ and *dmetar*.³²

Risk of bias assessment

To assess and visualize risk of bias in the included studies, the Cochrane Collaboration Risk of Bias 2 (RoB2) tool was used for randomized interventional trials.³³ Selection bias was assessed using funnel plots.

RESULTS

Search results

OUR SYSTEMATIC LITERATURE search yielded 5097 citations. After removing duplicates, 3029 were screened based on title and abstract. Based on potential relevance, 239 full-text articles were screened, of which 43 were included. The full selection process is shown in the PRISMA flowchart (Fig. 1).³⁴

Study characteristics

Of the 43 included studies, 26 evaluated SPMC,^{16,34–59} 12 1L-PEG with ascorbate (PEGA),^{46,58–68} four oral sulfate solution (OSS),^{61,69–71} four sodium phosphate solution

(NaP),^{38,72–74} two sennosides,^{72,75} and one magnesium citrate⁷⁶ (Table 1).

All studies were single- or multicenter assessor-blinded RCTs. Fourteen studies (32%) were sponsored by pharmaceutical companies.^{35,36,39,41,42,49,51,55,58,60,61,66,69,70} Study populations included outpatient patients with various indications for colonoscopy, i.e. screening, surveillance, and diagnostic. Exclusion criteria were commonly accepted contraindications for colonoscopy and contraindications for bowel preparation in general.

Adequately prepared patients per fluid

For SPMC, the percentage of adequately cleaned patients was reported in 19 studies comprising 10,287 patients, with a pooled percentage of 75.2% (95% confidence interval [CI] 67.6–81.4; $I^2 = 96\%$; Fig. 2). The pooled estimate was significantly higher in studies that used additives, such as bisacodyl ($n = 9714$), compared to studies that only used the standard dosage of 300 mL SPMC ($n = 573$; $P < 0.01$; Table 2, Fig. S1). Dosing subgroups (same-day, day before, split-dose) performed significantly different in subgroup

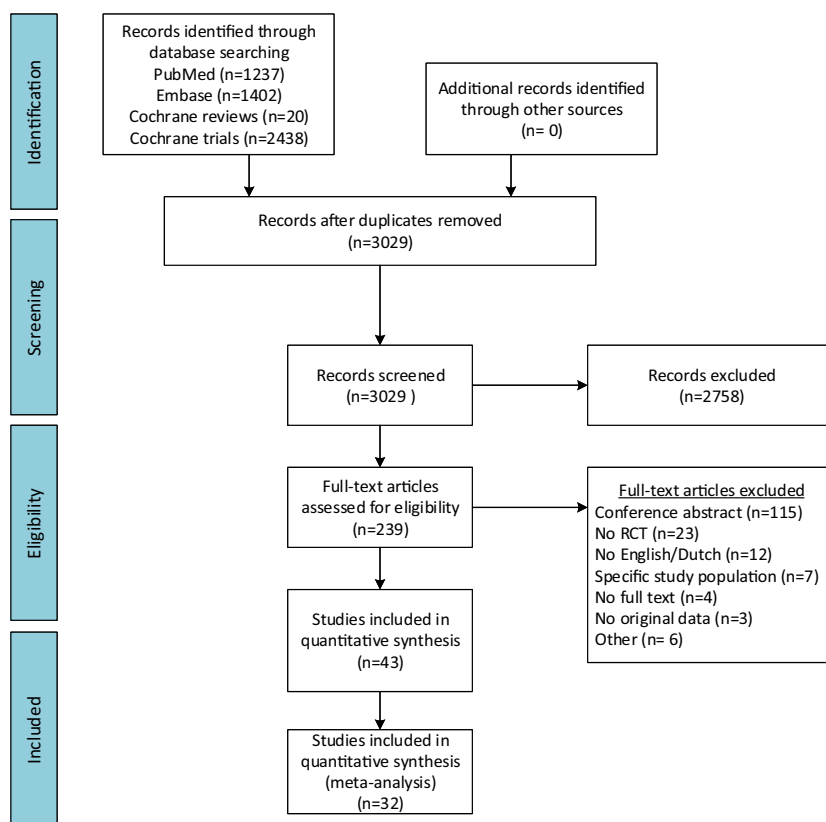


Figure 1 PRISMA flow diagram of study selection. RCT, randomized controlled trial.

Table 1 Ultralow-volume bowel preparation fluids, study characteristics

Author (year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Choi 2016 [‡]	Korea	SC, SB RCT	Diagnostic, therapeutic	1. 102	1. 49.9	1. Split 400 mL SPMC	2. Split 2 L PEGA (Coolprep) + 20 mL simethicone	1. 2 L
				2. 98	2. 51.6	(Picolight) + 10 mg bisacodyl		2. 1.5 L
Dwyer 2017 [‡]	Australia	SC non-inferiority RCT	Clinically accepted indications	1. 112	54 (full study)	1. Split 300 mL SPMC (Picosalax), white diet	2. 1 L PEG (Glycoprep-C) + split 300 mL SPMC (Picoprep), LQD	1. 0.2 L/h
				2. 118				2. 0.2 L/h
Gweon 2015	Korea	SC, SB, non-inferiority RCT	Various	1. 104	1. 47.7	1. SD split 300 mL SPMC + 10 mg bisacodyl (no product names reported)	2. Split 4 L PEG	1. Up to 4 L
				2. 105	2. 50.6			2. NR
Heetun 2016	Ireland	SC RCT	Diagnostic, screening, surveillance	1. 102	1. 56.4	1. Split 300 mL SPMC, LQD	2. 4 L PEG, LQD (no product names reported)	Extra fluids encouraged
				2. 107	2. 58.7	3. 240 mL NaP split/DB in morning procedures, LQD		
				3. 122	3. 56.8			
Hookey 2019 [‡]	Canada	MC, SB, non-inferiority RCT	Elective	1. 448	57.2 (full study)	1. Split 320 mL SPMC solution (Clenpiq), LQD	2. Split 2 L PEG (Kleanprep) + 5 mg bisacodyl, LRD	1. 2 L
				2. 453		2. Split 300 mL SPMC powder (Prepopik), LQD		2. 2 L
Hung 2020	Taiwan	MC, SB, non-inferiority RCT	Elective	1. 316	1. 47.7	1. Split 300 mL SPMC (Bowclean), LRD	2. Split 2 L PEG (Kleanprep) + 5 mg bisacodyl, LRD	1. 2 L
				2. 315	2. 49.4			2. None
Jun 2017 [‡]	Korea	SC, SB RCT	Screening, diagnostic	1. 99	1. 54.6	1. Split 450 mL SPMC (Picolight), LRD 3 days	2. Split 450 mL SPMC (Picolight) with flexible timing of second dose, LRD 3 days	1. 2.5 L
				2. 105	2. 54.3			2. 2.5 L
Kiesslich 2017 [‡]	Germany	MC, SB RCT	Elective	1. 131	1. 58.3	1. Split 300 mL SPMC (Picoprep)	2. DB 300 mL SPMC (Picoprep)	1. 2 L
				2. 73	2. 56.6			2. 2 L
Kim 2015	Korea	MC, SB, non-inferiority RCT	Screening, surveillance, diagnostic, treatment	1. 153	1. 53.5	1. Split 300 mL SPMC (Picolight) + 10 mg bisacodyl, 3 days LRD	2. Split 4 L PEG, 3 days LRD (product name NR)	1. 4 L
				2. 166	2. 53.8			2. None

Table 1 (Continued)

Author (year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Kim 2016	Korea	SC, SB RCT	Diagnostic	1. 59	1. 54	1. DB SPMC (Picolight) + NaP (Clicolon) + 10 mg bisacodyl, 1 day LRD 2. Split SPMC (Picolight) + NaP (Clicolon)+ 10 mg bisacodyl, 1 day LRD	3. DB SPMC (Picolight) + 1L-PEGA (Coolprep) + 10 mg bisacodyl, 1 day LRD 4. Split SPMC (Picolight) + 1L-PEGA (Coolprep) + 10 mg bisacodyl, 1 day LRD	1. 1 L
				2. 58	2. 53			2. 1 L
				3. 57	3. 53			3. 1.5 L
				4. 55	4. 55			4. 1.5 L
Kim 2020	Korea	SC, SB RCT	Screening, surveillance, diagnostic, treatment	1. 97	1. 56.5	1. Split 340 mL SPMC (Picosolution) + 10 mg bisacodyl, LRD 3 days 2. SD 1L-PEGA (Coolprep), 10 mg bisacodyl night before, LRD 3 days	3. Split 2 L PEGA (Coolprep), LRD 3 days	1. 2 L
				2. 99	2. 54.4			2. 1 L
				3. 99	3. 58.1			3. 1 L
Klare 2015	Germany	SC, SB RCT	NR	1. 99	1. 53.4	1. DB 300 mL SPMC (Picoprep), 1 day LQD 2. Split 300 mL SPMC (Picoprep), 3 days LRD	2. Split 2–4 L PEG (Oralav; until clear stool), 1 day LQD	1. 250 mL/h
				2. 101	2. 56.4			2. ≥1 L
Kojecy 2017	Czech Republic	MC, SB RCT	NR	973 [†]	NR	1. DB 300 mL SPMC (Picoprep), 3 days LRD 2. Split 300 mL SPMC (Picoprep), 3 days LRD	3. DB 2L-PEGA (Moviprep), 3 days LRD 4. Split 2 L PEGA (Moviprep), 3 days LRD	1 + 2. 2 L
								3–6. None
Kojecy 2018	Czech Republic	MC, SB RCT	NR	1 + 2.	1 + 2.	1. DB 300 mL SPMC (Picoprep), LRD 3 days 2. Split 300 mL SPMC (Picoprep), LRD 3 days	3. DB 2 L PEGA (Moviprep), LRD 3 days 4. Split 2 L PEGA (Moviprep), LRD 3 days 5. DB 4 L PEG (Fortrans), LRD 3 days 6. Split 3/1 L PEG (Fortrans), 3 days LRD	1 + 2. 2 L
				178	60.2			3 + 4. 1.5 L
				3 + 4.	3 + 4.			5 + 6.
				189	60.5			None
				5 + 6.	5 + 6.			
				181	62.4			
Munsterman 2015	The Netherlands	SC, SB RCT	Surveillance, diagnostic, treatment	1. 85	1. 57	1. Split 300 mL SPMC (Picoprep), LRD 2 days, LQD 1 day	2. Split 3/1 L PEG (Kleanprep), LRD 2 days, LQD 1 day	1. 4 L
				2. 88	2. 55			2. unspecified
Muñoz-Navas 2015 [‡]	Spain	SC, SB RCT	First-time diagnostic endoscopy	1. 224	1. 50.7	1. DB SPMC, LRD 2 days prior, LQD 1 day 3. SD 300 mL SPMC, LRD 2 days prior, LQD 1 day	2. DB 4 L PEG, LRD 2 days prior, LQD 1 day (no product names reported)	1. 250 mL/h
				2. 213	2. 53.6			2. 250 mL/h
				3. 53	3. 55.3			3. None

Table 1 (Continued)

Author (year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Pisera 2019	Poland	MC, SB RCT	Screening	1. 6752 2. 6745	55–62 (full study)	1. Mixed DB/split 300 mL SPMC (Citrafleet), 1 day LRD, 0.5 day LQD 2. DB 300 mL SPMC (Citrafleet), LRD 1 day, 0.5 day LQD	2. Mixed DB/split 4 L PEG (Fortrans), 1 day LRD, 0.5 day LQD 3. DB 2 L PEG, LRD 4 days, LQD 1 day 4. Split 2 L PEG, LRD 4 days, LQD 1 day (no product names reported)	1. 4 L 2. None
Pohl 2015 [‡]	Germany	MC, SB RCT	Diagnostic, screening, surveillance	1. 193 2. 200	1. 60.1 2. 59.5	1. DB 300 mL SPMC (Citrafleet), LRD 1 day, 0.5 day LQD 2. Split SPMC, LRD 4 days, LQD 1 day	2. Split 2 L PEGA (Moviprep), LRD 1 day, 0.5 day LQD	1. 250 mL/h 2. 1 L
Prieto-Frias 2016	Spain	MC stratified trial	Elective outpatient	1. 157 2. 148	1. 53.7 2. 55.7	1. Split SPMC (Citrafleet), LRD 2 days 2. DB 300 mL SPMC (Citrafleet), LRD 2 days		NR
Rostrom 2019	Canada	SC RCT	Screening, surveillance	1. 33 2. 28 3. 34 4. 36	1. 57.6 2. 56.4	1. DB SPMC, LRD 4 days, LQD 1 day 2. Split SPMC, LRD 4 days, LQD 1 day	3. DB 2 L PEG, LRD 4 days, LQD 1 day 4. Split 2 L PEG, LRD 4 days, LQD 1 day (no product names reported)	NR
Sahebally 2015	Ireland	SC, SB RCT	NR	1. 64 2. 66	1. 57.2 2. 59.3	1. DB 300 mL SPMC (Picolax), LQD 0.5 day 2. DB 300 mL SPMC, LRD 1 day, LQD starting preparation	2. DB 2 L PEGA (Moviprep), LQD 0.5 day (no product names reported)	1. 2 L 2. 2 L
Schulz 2016 [‡]	Germany	MC, SB RCT	Screening, surveillance, diagnostic, IBD	1. 156 2. 159	57.1 (full study)	1. DB 300 mL SPMC, LRD 1 day, LQD starting preparation 2. Split 300 mL SPMC, LRD 1 day, LQD starting preparation		1 + 2. 250 mL/h
Seo 2018	Korea	SC, SB RCT	Elective outpatient colonoscopy, screening, surveillance, diagnostic	1. 114 2. 109	1. 54.9 2. 56.1	1. Split 300/150 mL SPMC (Picolight), LRD 3 days, LQD 1 day 2. Split 300 mL SPMC, LRD 3 days, LQD 1 day	2. Split 2 L PEGA (Coolprep), LRD 3 days, LQD 1 day	1. 2 L 2. 1 L
Voiosu 2017	Romania	MC, SB RCT	Outpatient, first colonoscopy, screening, surveillance, diagnostic	1. 37 2. 37 3. 69 (34/35)	1. 58 2. 57 3. 54	1. Split 300 mL SPMC (Picoprep), 1 day LRD 3a. Individualized SPMC or PEG based on questionnaire	2. Split 4 L PEG (Fortrans), 1 day LRD 3b. Individualized SPMC or PEG based on questionnaire	1. 250 mL/h 2. None
Yoo 2015	Korea	SC, SB RCT	Screening, surveillance, diagnostic	1. 100 2. 100	1. 53.3 2. 57.0	1. Split 300 mL SPMC (Picolight), LRD 3 days, LQD starting preparation	2. Split 2 L PEGA (Coolprep), LRD 3 days, LQD starting preparation	1. 2 L 2. 1 L

Table 1 (Continued)

Author (year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Schreiber 2019 [‡]	Germany	MC, SB, non-inferiority RCT	Screening, surveillance, diagnostic	1. 251	1. 52.9	1. DB 300 mL SPMC (Citrafleet), LQD 0.5 day		1. 250 mL/h 2. 1 L
				2. 250	2. 54.6	2. DB 1L-PEGA (NER1006, Plenvu), LQD 0.5 day		
Bisschops 2019 [‡]	Belgium	MC, SB, non-inferiority RCT	Screening, surveillance, diagnostic	1. 275	1. 56.3	1. Split 1L-PEGA (NER1006, Plenvu), 1 day LRD, 0.5 day LQD	3. Split 2 L PEGA (Moviprep), 1 day LRD, 0.5 day LQD	Ad libitum
				2. 275	2. 54.9	2. SD 1L-PEGA (NER1006, Plenvu), 1 day LRD, 0.5 day LQD		
				3. 272	3. 54.3	3. SD 1L-PEGA (NER1006, Plenvu), 1 day LRD, 0.5 day LQD		
DeMicco 2019 [‡]	USA	MC, SB, non-inferiority RCT	Out/inpatient, screening, surveillance, diagnostic	1. 276	1. 57.5	1. Split 1L-PEGA (NER1006, Plenvu), 1 day LRD, 0.5 day LQD		1. 1 L 2. 2 L
				2. 280	2. 56.8	2. Split 1 L OSS (Suprep), 1 day LRD, 0.5 days LQD		
Choi 2018	Korea	SC, SB, non-inferiority RCT	Elective outpatient, screening, surveillance, diagnostic	1. 130	1. 55.3	1. Split 1 L PEGA (Coolprep) + 2 mg prucalopride, LRD 3 days prior	2. Split 2 L PEGA (Coolprep), LRD 3 days prior	1. 1 L 2. 1 L
				2. 130	2. 58.5	2. SD 1 L PEGA (Moviprep) + DB 5 mg mosapride citrate hydrate AC, 24 mg sennoside AN		
Kamei 2018	Japan	SC, non-inferiority trial	Outpatient, screening, surveillance, IBD	1. 68	45.5	1. SD 1 L PEGA (Moviprep) + DB 5 mg mosapride citrate hydrate AC, 24 mg sennoside AN	2. SD 2 L PEG (NIFLEC) + DB 5 mg mosapride citrate hydrate AC, 24 mg sennoside AN	1. 0.5 L 2. None
				2. 44	(full study)	2. SD 1 L PEGA (Coolprep) + 10 mg bisacodyl evening before, LRD 3 days prior		
Kang 2017	Korea	SC, SB RCT	Screening, surveillance, diagnostic, previous abdominal surgery	1. 100	1. 54.4	1. SD 1L-PEGA (Coolprep) + 10 mg bisacodyl evening before, LRD 3 days prior	2. Split 2 L PEGA (Coolprep), LRD 3 days prior	1. 1.5 L 2. 1 L
				2. 100	2. 56.8	2. SD 1L-PEGA (Clicool) + 20 mg bisacodyl, clear LQD evening prior		
Kim 2019	Korea	SC, SB RCT	Screening, surveillance, diagnostic	1. 83	1. 52.3	1. SD 1L-PEGA (Clicool) + 20 mg bisacodyl, clear LQD evening prior	2. Split 2 L PEGA (Clicool), clear LQD evening prior	1. 1 L 2. 1 L
				2. 85	2. 56.8	2. SD 1 L PEGA, evening prior		
Kwon 2016 [‡]	Korea	MC, SB, non-inferiority RCT	Elective	1. 91	1. 59.6	1. SD 1 L PEGA, evening prior	2. Split 2 L PEGA, LRD 3 days prior (no product names reported)	1. 1 L 2. 1 L
				2. 96	2. 56.0	2. SD 1 L PEGA, evening prior		

Table 1 (Continued)

Author (year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Banerjee 2016	India	SC, double-blind non-inferiority trial	Diagnostic, IBD, surveillance	1. 71	45.8	1. SD 1 L PEG (Peglec) + 24 mcg lubiprostone, clear LQD starting preparation	2. SD 1.5 L PEG (Peglec) + lubiprostone	NR
				2. 75	(full study)		3. SD 2 L PEG (Peglec) + lubiprostone	
				3. 221			4. SD 2 L PEG (Peglec)	
				4. 221				
Tian 2019	China	SC, SB RCT	Diagnostic, surveillance	1. 82	1. 52.3	1. Split 1L-PEGA + 30 mL castor oil + 20 mL simethicone, LRD 3 days (no product names reported)	2. Split 2 L PEG + 30 mL castor oil + 20 mL simethicone	1. 2 L
				2. 84	2. 52.3			2. 1 L
				3. 80	3. 49.0		3. Split 1–2 L PEG + 30 mL castor oil + 20 mL simethicone	3. None
Poyrazoglu 2015	Turkey	SC, SB RCT	Elective-screening, surveillance, diagnostic, IBD	1. 66	1. 47.7	1. Split 90 mL NaP, 3 days prior LRD, 1 day LQD	(No product names reported)	NR
				2. 62	2. 49.8	2. Split 500 mL 1000 mg Sen-nosides A and B calcium + 66.6 g sorbitol		
Hung 2019	China	SC RCT	NR	1. 93	1. 49.7	1. Split 90 mL NaP (Fleet)		1. 1.5 L
				2. 97	2. 48.9	Phospho-soda), LRD 2 days, 0.5 day LQD		2. 1.5 L
Kang 2015	Taiwan	SC, non-concurrent control group	Screening	1. 259	1. 47.7	2. SD 45 mL NaP (Fleet Phospho-soda), 2 mg prucalopride 8 pm DB, LRD 2 days, 0.5 day LQD		NR
				2. 172	2. 47.8	1. DB 90 mL NaP (Fleet Phospho-soda)		
Yang 2020 [†]	Korea	MC, SB, non-inferiority RCT	Diagnostic, screening, surveillance	1. 112	1. 48.2	2. Split 90 mL NaP (Fleet Phospho-soda)	2. DB 14 NaP tablets (PBK-1701TC, Pharmbio) + 2.5 L water, 1 day LQD	1. 2 L
				2. 112	2. 46.4	1. Split 946 mL OSS (Suprep), 1 day LQD		2. 2.5 L
Lee 2019 [‡]	Korea	SC, SB, non-inferiority RCT	Diagnostic, screening, surveillance, therapy	1. 93	60.2	1. Split 946 mL OSS (Suclear), LRD 3 days prior	2. Split 2 L PEGA (Coolprep), LRD 3 days prior	1. 2 L
				2. 94	(full study)			2. 1 L
Gerard 2017	USA	SC, SB RCT	Elective, screening, surveillance, diagnostic	1. 200	1. 60.6	1. Split 946 mL OSS (Suprep), 1 day LQD	2. Split 2 L PEGA (Moviprep), 1 day LQD	1. 2 L
				2. 200	2. 60.1			2. 1 L

Table 1 (Continued)

Author (Year)	Country	Study design	Reason for colonoscopy	Sample size (ITT)	Age (mean, years)	Intervention (low-volume)	Comparison (high-volume)	Additional fluid intake
Thukral 2019	USA	SC, SB RCT	Open-access screening and surveillance	1. 108 2. 107	1. 57.0 2. 55.8	1. Split 600 mL magnesium citrate, LRD 2. Split 600 mL magnesium citrate, LQD	(No product names reported)	1. 1 L 2. 1 L
Khorasanynejad 2017	Iran	SC, double-blind RCT	Screening, surveillance	1. 151 2. 160	50.0 (full study)	1. Split 180 mL C-lax syrup (containing 270 mg Sennosides), LRD 1 day	2. 5 L PEG DB, LRD 1 day prior (no product names reported)	NR

[†]No subgroup information provided.
[‡]Industry-funded trial.

AC, ante coenam; AN, ante noctem; CRC, colorectal carcinoma; DB, day before; IBD, inflammatory bowel disease; ITT, intention to treat; LQD, liquid diet; LRD, low-residue diet; MC, multicenter; NaP, sodium phosphate solution; NR, not reported; OSS, oral sulfate solution; PEGA, polyethylene glycol with ascorbate; RCT, randomized controlled trial; SB, single-blind; SC, single-center; SD, same day; Split, split-dose; SPMC, sodium picosulfate with magnesium citrate.

analysis ($P < 0.00001$), with a negative trend for day-before dosing (Table 2, Fig. S2). Bowel preparation efficacy did not differ significantly between diet subgroups (liquid, low-residue, or combined; Table 2, Fig. S3).

Ten studies comprising 1717 patients reported the proportion of adequately prepared patients using 1L-PEGA, with a pooled percentage of 82.9% (95% CI 74.4–90.1; $I^2 = 94\%$; Fig. 3). The pooled efficacy of seven studies ($n = 641$) using additives was comparable to the efficacy of NER1006, a 1L-PEG solution with a higher ascorbate concentration (Table 2, Fig. S4). In addition, subgroup analysis for dosing subgroups showed comparable efficacy of same-day or split dosing (Table 2, Fig. S5). Subgroup analysis for diet effect did not show a significant difference in bowel cleansing efficacy (Table 2, Fig. S6).

Two studies comprising 621 patients reported the efficacy of NaP, with a pooled percentage adequately prepared patients of 81.9% (95% CI 36.7–97.2; $I^2 = 98\%$; Fig. 4). For OSS, three studies comprising 597 patients reported on our primary endpoint, with a pooled percentage of 92.1% (95% CI 79.7–97.2; $I^2 = 86\%$; Fig. 5). Due to the small number of studies available, no subgroup analyses could be performed.

Furthermore, the two studies investigating the efficacy of sennosides did not report on preparation adequacy in a proportional manner.

Secondary endpoints

Adenoma detection rate

Adenoma detection rate was reported in 10 SPMC studies with a pooled ADR of 31.0% (95% CI 25.6–36.7; $I^2 = 83\%$) and in eight 1L-PEGA studies with a pooled ADR of 32.4% (95% CI 26.6–38.4; $I^2 = 83\%$). ADR was reported in one study in the NaP group and was 30.4% (95% CI 20.6–41.2), and in two studies in the OSS group with a pooled ADR of 40.9% (95% CI 28.3–54.2; $I^2 = 81\%$; Fig. 6a–d).

Safety

All included studies reported gastrointestinal symptoms such as abdominal pain and distention, anal irritation, nausea, and to a lesser extent vomiting as most frequent adverse events (AEs). Furthermore, headache, dizziness, and general malaise were reported with the use of all fluids.

Of the 26 SPMC studies, 22 reported on AEs, and six evaluated laboratory abnormalities. A range of 8.1–85.6% of the patients experienced at least some of the AEs as mentioned above. Moreover, three studies^{37,39,42} reported elevated serum magnesium in 3.6–10.5% of the patients,

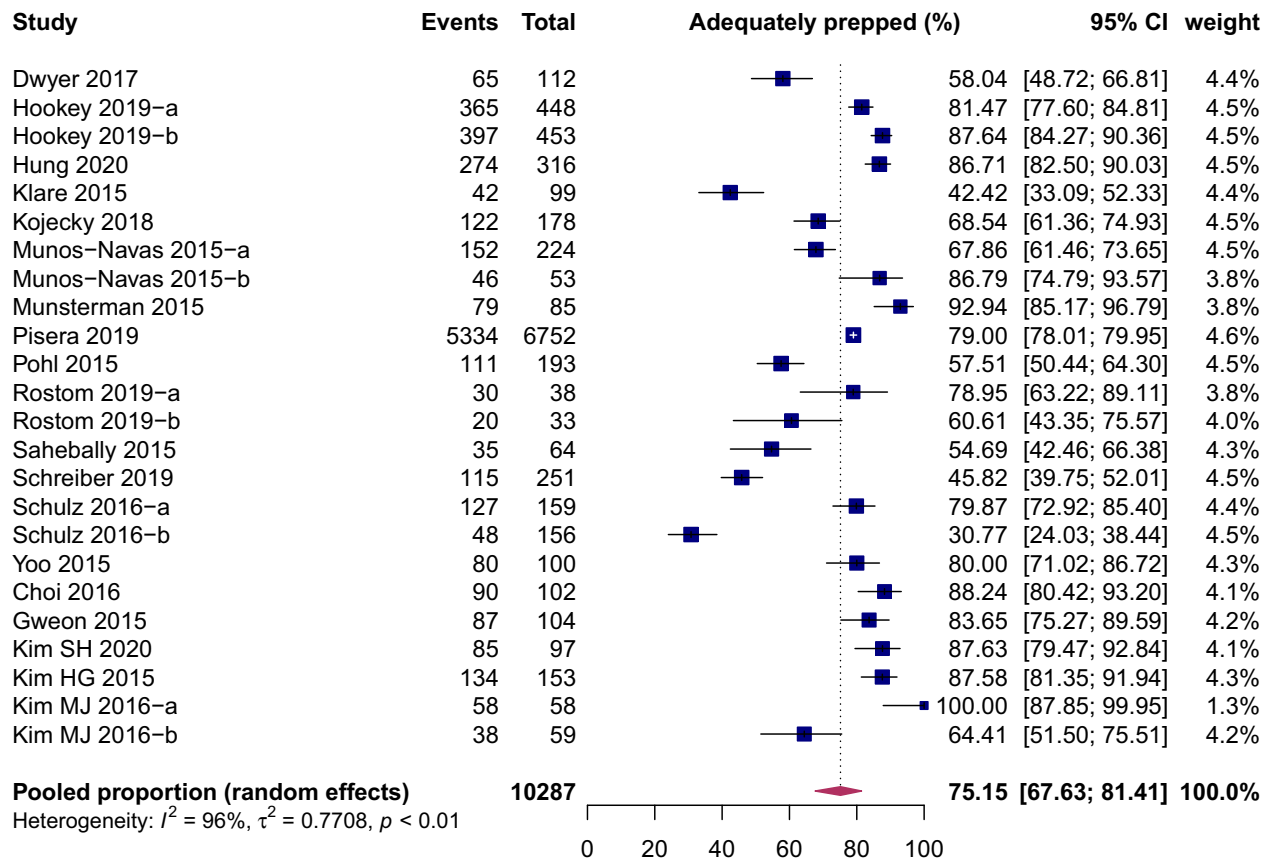


Figure 2 Pooled proportion for adequately prepped patients, sodium picosulfate with magnesium citrate (SPMC). CI, confidence interval.

and decreased serum sodium levels in up to 21.2% of patients⁴⁵ with one report of severe hyponatremia (119 mmol/L).⁵⁵ Schulz *et al.* reported hyperkalemia (6.2 and 8.5 mmol/L, respectively) in two young patients, which resolved without sequelae.

In the 1L-PEGA group, AEs were reported in 11 of 12 studies, occurring in 13.2–43.4% of patients. In the NER1006 studies,^{58,60,61} higher rates of temporary decrease in renal function and hypernatremia (median +4.0 mmol/L from baseline) were reported, compared to other ultra-low volume fluids included in these review.

For NaP, AEs were reported in two of the four included studies, occurring in 44.3–72.2% of the patients. The type of reported AEs was similar to those reported above. Additionally, an increase in serum inorganic phosphorus levels (from a median of 3.5 mEq/L at baseline to 6.3 mEq/L at the day of colonoscopy) was noted.⁷²

Adverse events were reported in all OSS studies and occurred over a range of 18.5–77.4% of the patients.

Laboratory abnormalities included a temporary decrease in renal function.⁶¹ Other electrolyte changes were not considered as clinically significant.^{61,69}

Heterogeneity

Heterogeneity was considerable for all bowel preparation fluid studies and could only partially be explained by the prespecified subgroups (additive use and differences in dosing schedule). In subgroup analyses based on type of bowel preparation scale, I^2 remained substantial (BBPS I^2 91%, OBPS I^2 96%, data not shown). No changes in the pooled effect size nor in the extent of heterogeneity were observed in sensitivity analysis (Fig. S7). Influence analysis, including Baujat and GOSH plots, identified possible outliers^{55,58,68,74} (Figs S7–S9). Excluding these outliers in the meta-analyses did not, however, change the pooled effect sizes significantly but reduced the CI. For SPMC, the CI changed from 67.6–81.4 to 73.2–76.0. For 1L-PEGA,

Table 2 Subgroup analyses for sodium picosulfate with magnesium citrate and 1 L polyethylene glycol with ascorbate

Subgroup analysis (category)	No. of studies	Adequately prepared (%; 95% CI)	<i>I</i> ² (%)
All studies	43		
SPMC	19	75.15 (67.63–81.41)	96
1L-PEGA	10	82.94 (74.39–90.08)	94
OSS	3	92.06 (79.67–97.17)	86
NaP	2	81.91 (36.75–97.24)	98
SPMC			
With additives	5	85.77 (74.05–92.71)	96
Without additives	14	71.18 (62.37–78.63)	79
Same day	1	86.79 (53.13–97.44)	NA
Day before	6	52.71 (36.52–68.36)	91
Split-dose	9	77.96 (68.40–85.25)	93
Liquid diet	3	78.68 (59.84–90.14)	98
Low-residue diet	6	80.42 (66.45–89.50)	92
Combined	9	69.75 (57.46–79.74)	96
1L-PEGA			
With additives	7	80.04 (75.46–83.95)	91
Without additives (NER1006)	3	80.72 (76.59–84.27)	97
Same day	6	88.69 (79.48–94.07)	84
Day before	1	58.40 (22.30–87.29)	NA
Split-dose	4	80.75 (65.10–90.42)	94
Liquid diet	5	78.56 (61.44–89.39)	93
Low-residue diet	1	89.50 (69.89–96.90)	NA
Combined	4	86.82 (71.13–94.62)	94

1L-PEGA, 1 L polyethylene glycol with ascorbate; CI, confidence interval; NA, not applicable; NaP, sodium phosphate solution; OSS, oral sulfate solution; SPMC, sodium picosulfate with magnesium citrate.

after removing the outliers,^{58,68} the pooled percentage changed non-significantly from 82.9% (95% CI 74.4–90.1; *I*² = 94%) to 77.0% (95% CI 75.7–78.1; *I*² = 94%).

Risk of bias

Funnel plots showed no evidence for publication bias (Fig. S11a–d). The overall risk of bias was low in 58.1%, intermediate in 23.3%, and high in 16.3% of the included studies (Fig. 7, Fig. S12). The pooled outcome did not change significantly for any of the fluids when excluding the studies classified as high risk of bias,^{36,46,52,63,67,72,74} but for the 1L-PEGA group, a drop from 83.0% (95% CI 74.4–90.1) to 75.3% (95% CI 73.0–77.3) was found.

DISCUSSION

THIS SYSTEMATIC REVIEW and meta-analysis show that ultra-low volume (≤1 L) bowel preparation with SPMC, 1L-PEGA, NaP, or OSS, was adequate in 75.2%, 82.9%, 81.9%, and 92.1%, of patients, respectively. While ESGE guidelines on bowel preparation and CRC screening recommend an adequate bowel cleansing rate in at least 90% of procedures,¹ the majority of these ultra-low volume bowel preparation fluids, with the exception of OSS, do not meet this quality standard as defined by the ESGE in our analysis. It should be noted that only a low number of studies investigating NaP (*n* = 4) and OSS (*n* = 4) were included, which likely mirrors their limited use in daily clinical practice. The preference for SPMC and 1L-PEGA in various international guidelines is motivated by potential

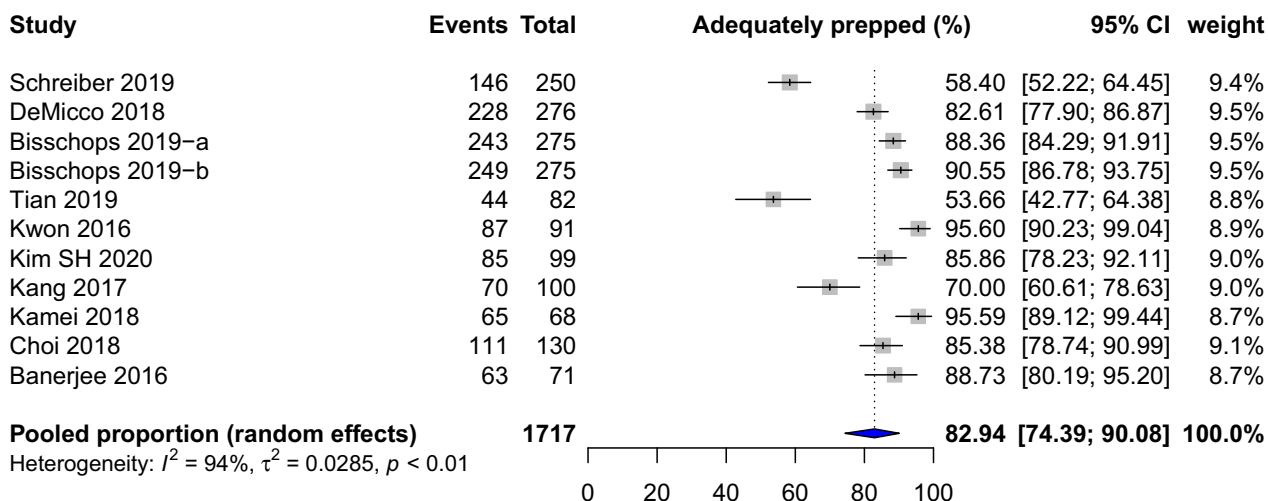


Figure 3 Pooled efficacy for 1 L polyethylene glycol with ascorbate (PEGA).

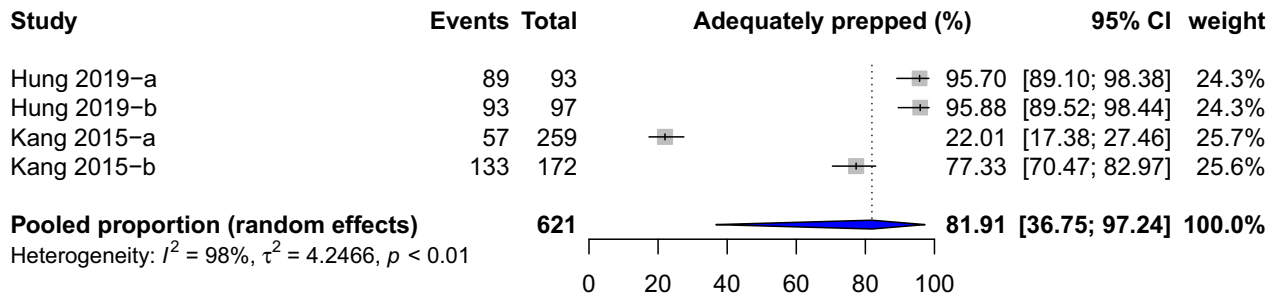


Figure 4 Pooled efficacy for sodium phosphate solution (NaP). CI, confidence interval.

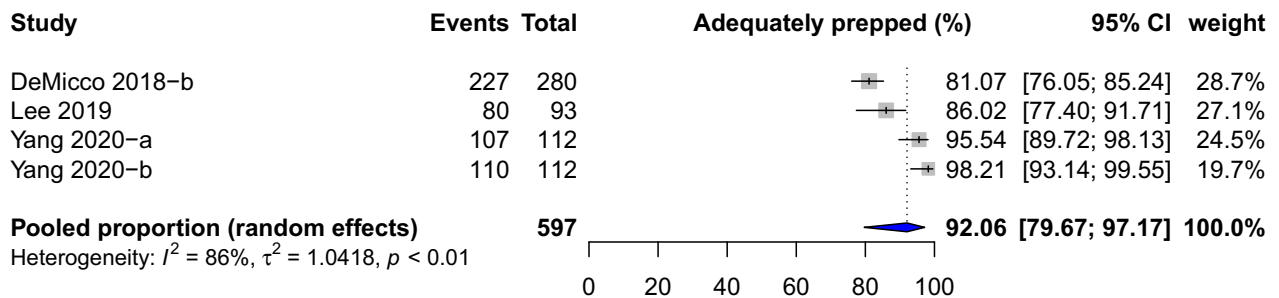


Figure 5 Pooled efficacy for oral sulfate solution (OSS). CI, confidence interval.

side-effects that have been reported with use of NaP and OSS.^{1,2,8}

Evidence on the efficacy of low-volume fluids is contradictory.⁷⁷ Some meta-analyses comparing high-volume (>3 L) PEG with lower-volume fluids (≤ 2 L) have demonstrated a lower efficacy of low-volume fluids,^{78,79} whereas others have suggested non-inferiority when comparing these two different volume fluids.^{14,80–82} An explanation of the suboptimal efficacy results in our meta-analysis may well be that we limited our analysis to ≤ 1 L (ultra-low volume) fluids, while others classify a volume of ≤ 2 L already as low-volume. High- or intermediate volume laxatives such as 4L-PEG or 2L-PEGA have a well-established efficacy profile.¹ Therefore, when 2 L preps are included in the same group as the ultra-low-volume fluids, this may improve the overall efficacy results of the low-volume group and give the wrong impression that all low-volume fluids are equally effective or non-inferior to the high-volume counterpart. Another explanation may be that day-before dosing generally performed worse than split-dose protocols in our analysis. This has also been reported in other meta-analyses^{78,80} and might at least partly explain why the pooled efficacy we found is lower than expected as in the included studies both split-dose and day-before dosing was used. It is recommended that a colonoscopy procedure should take place within 2–5 h after finishing bowel

preparation to make sure that the colon is most optimally prepped,¹ thereby reducing the risk that neoplastic lesions will be missed due to bowel contamination.^{83,84} Furthermore, it is questionable whether split dosing is feasible with ultra-low volume fluids, especially in isotonic fluids, or that same-day dosing should be standard. Split dosing may lower the purging effect of the first dose, thereby reducing the final laxative effect of the hypertonic second dose. In our dosing-stratified analyses, the pooled efficacy of same-day and split dosing were close to the recommended 90%. Further studies on ultra-low volume fluids should focus on the efficacy of dosing on the day of colonoscopy, as in this way ultra-low volume bowel preparation fluids might still be a viable option for bowel cleansing.

The ultra-low volume laxatives presented here may offer a solution for patients having difficulties with drinking high volumes. Additionally, the optimized patient perception as compared to high-volume fluids likely will increase the willingness of patients to repeat colonoscopy and decreases the number of patients avoiding colonoscopy.^{11,80,81} Spadaccini *et al.*⁸⁰ performed a meta-analysis including 17 RCTs ($n = 7582$) in which they showed that the compliance rate, tolerability, and willingness to repeat taking the same preparation were all in favor of low-volume (< 2 L) preparations. Nevertheless, lowering the volume of bowel preparation fluids does not release patients from drinking large

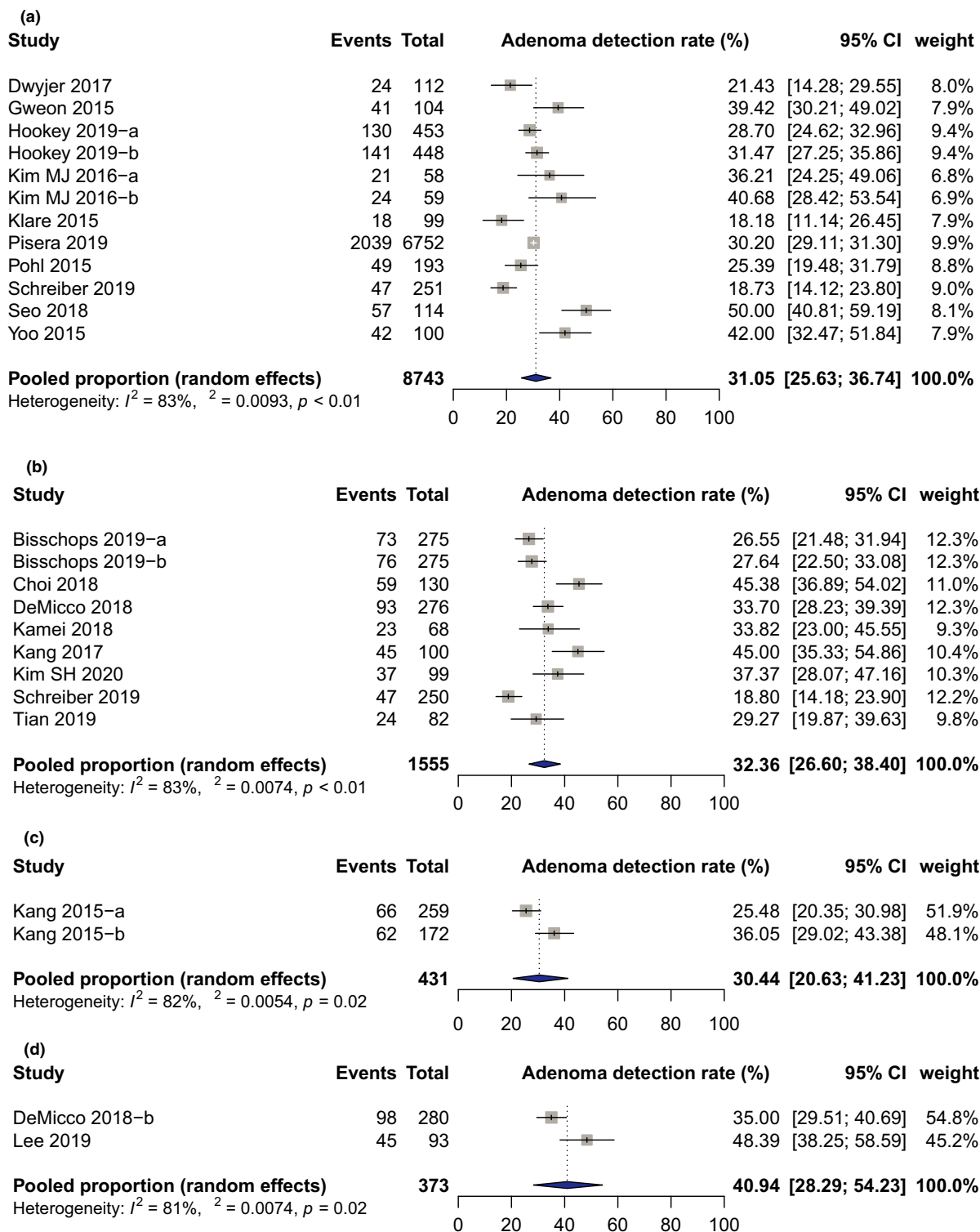


Figure 6 Forrest plots for pooled adenoma detection rate for fluid studies. (a) Sodium picosulfate with magnesium citrate (SPMC), (b) 1 L polyethylene glycol with ascorbate (PEGA), (c) sodium phosphate solution (NaP), (d) oral sulfate solution (OSS). CI, confidence interval.

volumes. The stimulant and hyperosmotic pharmacologic mechanism of action that draws water into the gut lumen makes taking extra fluids necessary in addition to the laxatives. Thus, patients should be instructed to maintain hydration to compensate for the large fecal effluent of 2.5 L–3 L.⁸⁵ For the 300 mL prep SPMC for example, this means drinking at least 2 L of fluid, which is the same as is recommended in addition to 2L-PEGA.

High-volume bowel preparation fluids such as 4L-PEG may anyhow be preferable in patients with a high risk of dehydration-related complications, such as acute kidney injury, or fluid shifts. The iso-osmotic nature of the PEG electrolyte solution minimizes fluid shifts and thereby reduces the risk of electrolyte disturbances. These electrolyte disturbances such as transient hypermagnesemia for SPMC, hypo- or hyponatremia for 1L-PEGA, and hyperphosphatemia for NaP have been reported in this systematic review, as well as in other publications.⁸⁶ No serious AEs were reported in our included studies, but there are case reports that report on fatal hyponatremia and hypermagnesemia.^{87,88} The rare risk of acute phosphate nephropathy caused by tubular calcium depositions due to NaP use has resulted in a warning by the United States Food and Drug Administration to consider alternative bowel preparations instead of NaP.⁸⁹ Therefore, hyperosmotic ≤ 1 L laxatives may be less suitable for elderly or patients with renal dysfunction.^{1,3,6}

Nonetheless, it is debatable whether the above-mentioned electrolyte changes are clinically relevant for the majority of

patients.^{90,91} In a retrospective study of 2.8 million participants, 30- and 90-day hospitalizations for electrolyte changes were $<0.1\%$ in patients who used several low-volume bowel preparations, which was not significantly different from patients using high-volume alternatives.⁹² However, the severe AEs that occur only rarely, are often reported in post-marketing surveillance data in case-series or retrospective studies. For some of the more recently developed bowel preparation fluids, such as NER1006, these data are still limited. Additionally, study populations of included studies in this meta-analysis mostly comprised healthy adult patients, excluding patients at risk for AEs or unable to drink larger volumes. This should be taken into account when deciding on the most suitable laxative for a particular patient.

Bowel preparation quality can be improved in several ways. On the one hand, lowering the volume of bowel preparation fluids may reduce non-compliance rates in patients.⁸⁰ On the other hand, diet restrictions may influence the experienced burden of bowel preparation significantly. Compared to a clear liquid diet (CLD), low-residue diets (LRD) are better tolerated.^{93–95} Two meta-analyses compared LRD to CLD in studies with similar bowel preparation solutions in both arms and found an equal bowel cleansing efficacy but better tolerability with a higher willingness to repeat for LRD.^{94,95} Furthermore, too many rules and restrictions for patients can be overwhelming and may undermine understanding the importance of adequate cleansing.⁹⁶ Enhanced patient education has been shown

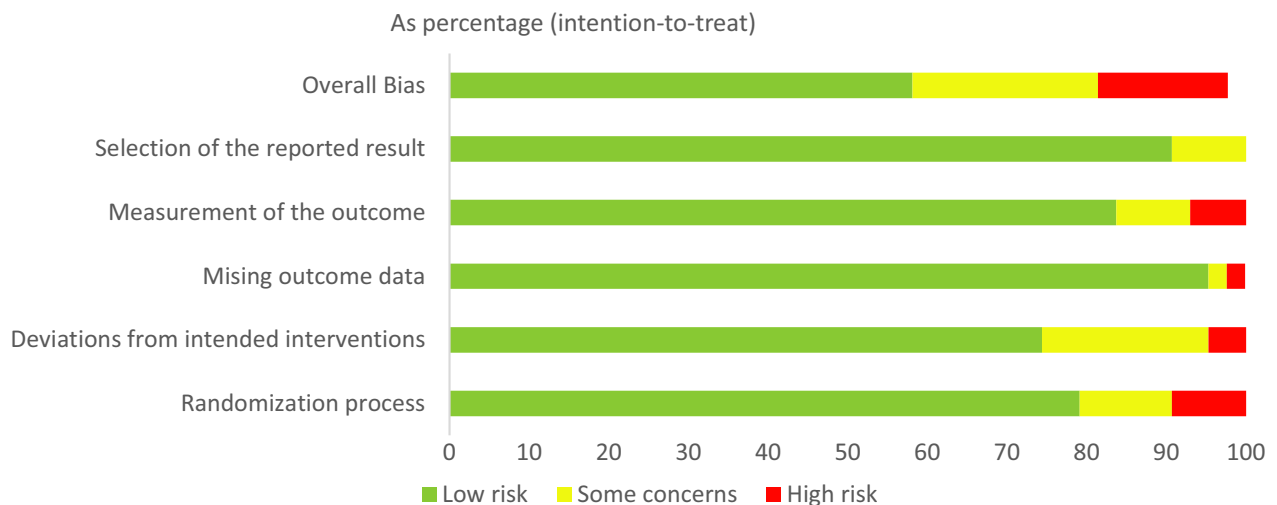


Figure 7 Summary of risk of bias for fluid studies (Cochrane RoB2 tool). The Cochrane RoB2 tool assesses the risk of bias across five domains, including randomization process, protocol deviations, missing data, outcome measurement, and selection of the reported result. The overall risk of bias is determined by the highest risk within the subdomains. This figure summarizes the risk of bias within all included studies, as percentage of the total number of studies.

to improve colonoscopy preparation,⁹⁷ for example using visual aids or mobile apps in addition to regular counseling.^{97–99} Two meta-analyses concluded that enhanced instructions benefit bowel preparation quality and ADR,^{100,101} although another meta-analysis acknowledging these benefits, pointed to a possible risk of publication bias.¹⁰²

An interesting and possibly useful development may be the use of bowel cleansing devices. Using mechanical bowel cleansing before or during colonoscopy is proposed as an alternative to oral laxatives in selected patient groups.^{103–107} Preprocedural devices work through retrograde bowel lavage using pressurized water one hour before colonoscopy,^{108–110} while intraprocedural devices can be used during colonoscopy providing water-pressured cleansing.^{107,111–113} Feasibility studies have shown a clear potential, with adequate bowel preparation achieved in 97.9–100% and 68.8–91.1% of patients in whom intraprocedural devices^{107,111–113} or preprocedural devices,^{108–110} respectively, were used. Nonetheless, the use of intraprocedural devices adds significantly to the total procedure time, and preprocedural devices require a specialized nurse to operate the system. The associated costs may prohibit ubiquitous use, but the application of these bowel cleansing devices could be of interest in patients with risk factors for inadequate preparation, in whom a repeat endoscopic procedure often is indicated. Additionally, these devices could reduce admission time for inpatients.

Strengths and limitations

The strengths of our meta-analysis are the large number of patients included ($n = 13,222$) and the robustness of the results in the extensive sensitivity analysis. Moreover, we only included studies in which bowel preparation fluids with a volume of ≤ 1 L were included. Currently, 2L-PEGA is widely prescribed and recommended,¹ but some patients still have difficulty with this volume. This makes ≤ 1 L fluids a welcome innovation.

The large heterogeneity in our meta-analysis inevitably limits interpretation of the results. This is illustrated by the reduced efficacy of 1L-PEGA after removing outliers and studies with a high risk of bias. Pooling the proportion of adequately prepped patients might have introduced heterogeneity in our results, besides the existing heterogeneity due to different study locations (Asia, Europe), dietary instructions, dosing regimens, and use of additives. Through subgroup and extensive sensitivity analyses, the influence of this heterogeneity could be minimized, and this further endorsed the robustness of our results. Although we could not take into account individual patients' risk factors for

poor bowel preparation, such as high age, body mass index, history of poor preparation, constipation, or history of neurological disorders,^{9,17,114} the RCTs in this meta-analysis frequently did not include patients who, for example, had serious systemic illnesses or used tricyclic antidepressants. While the use of different bowel preparation scales across studies is a drawback for performing a meta-analysis, our approach is not different from other published meta-analyses.^{80,115} The trend that a large proportion of published studies are non-inferiority trials and underpowered to detect superiority, and the great variety of comparative arms led us to only pool the efficacy of the ultra-low volume fluids without the comparative high-volume arms of the included studies. This enabled us to select more studies, giving a more precise direction to the pooled effect.

CONCLUSION

LARGE SCALE USE of ultra-low volume bowel preparation is limited by an overall efficacy of these ≤ 1 L fluids below the 90% ESGE quality target. Therefore, their use might mainly be considered in selected patient populations with no risk factors for dehydration-related complications or inadequate preparation, as well as for patients having difficulty drinking large volumes.

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CONFLICT OF INTEREST

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NONE.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 Subgroup analysis based on additive use, sodium picosulfate/magnesium citrate (SPMC).

Figure S2 Subgroup analysis based on dosing schedule, sodium picosulfate/magnesium citrate (SPMC).

Figure S3 Subgroup analysis based on diet, sodium picosulfate/magnesium citrate (SPMC).

Figure S4 Pooled efficacy 1 L PEG with ascorbate (PEGA), additives subgroups.

Figure S5 Pooled efficacy of 1 L PEG with ascorbate (PEGA), dosing subgroups.

Figure S6 Pooled efficacy of 1 L PEG with ascorbate (PEGA), diet subgroups.

Figure S7 Leave-1-out analyses for pooled efficacy and heterogeneity.

Figure S8 Influence analyses and Baujat-plots for identifying outliers.

Figure S9 Graphic display of study heterogeneity (GOSH) plot analysis for identifying outliers, sodium picosulfate with magnesium citrate (SPMC).

Figure S10 Graphic display of study heterogeneity (GOSH) plot analysis for identifying outliers, 1 L PEG with ascorbate.

Figure S11 Funnel plots of percentage adequately prepped patients per fluid.

Figure S12 Traffic light plot for individual risk of bias of included studies, Cochrane RoB2 tool.

Appendix S1 Background information bowel preparation fluids.

Appendix S2 Search strategy 17 April 2020.

Appendix S3 Subgroup and heterogeneity analyses (figures).