SYSTEMATIC REVIEW AND META-ANALYSIS

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Strategies to Improve Colonoscopy Preparation in Inflammatory Bowel Disease. A Systematic Review and Network Meta-analysis of Randomized Trials

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ABSTRACT

Background & Aims: Colonoscopy has a vital role in the diagnosis of inflammatory bowel disease (IBD), as well as in the estimation of disease severity, monitoring response to therapy, and surveillance for neoplasia. We performed a systematic review of randomised trials of various bowel preparations for colonoscopy in IBD.
Methods: We searched various electronic databases (PubMed, Embase, and CENTRAL) for studies reporting about the use of various strategies to improve colonoscopy preparation in IBD. We included only randomized clinical trials (RCTs). A network meta-analysis was done using a frequentist approach to compare the effectiveness of various bowel preparations. The risk of bias was assessed using Cochrane risk of bias tool 2.0. Other outcome parameters like compliance, tolerance, acceptance, and adverse effects were assessed qualitatively.
Results: Seven RCTs reporting about 960 patients were included. On comparison with 4 liter (L) of poliethylen glycol (PEG), oral sulfate solution (OR=1.1, 95%CI: 0.65-1.86); PEG2L/Ascorbate (OR=0.98, 95%CI: 0.65-1.48); PEG1L (OR=1, 95%CI: 0.55-1.81); PEG2L plus bisacodyl (OR=1.08, 95%CI: 0.71-1.65); PEG4L plus simethicone (OR=1, 95%CI: 0.67-1.50); PEG/ sodium picosulfate and magnesium citrate (SPMC) 1.5L (OR=0.99, 95%CI: 0.55-1.78); SPMC 2L (OR=1.09, 95%CI: 0.61-1.97) had similar effectiveness. Three RCTs reported compliance, five RCTs reported tolerance, two studies reported patient acceptance and five RCTs reported data on the willingness of patients to repeat the procedure in the future. Low-volume preparations had better compliance, tolerance, acceptance, and willingness to repeat. No difference in additional outcomes like change in disease activity after colonoscopy, procedure-related outcomes after colonoscopy like cecal intubation rate, and change in electrolyte levels were found.
Conclusion: Various bowel preparations had similar effectiveness in respect to colonoscopy preparation in IBD patients. Low-volume preparations have better compliance, tolerance, and acceptance. The systematic review was limited by a small number of included RCTs.

Key words: colonoscopy – inflammatory bowel disease – IBD – bowel cleansing – Crohn's disease – bowel preparation – ulcerative colitis.

Abbreviations: BBPS: Boston bowel preparation scale; BMI: body mass index; HCS: Harefield cleansing scale; IBD: inflammatory bowel disease; L: liter; OBPS: Ottawa bowel preparation scale; OSS: oral sulfate solution; PEG: polyethylene glycol; PEG2LASC: PEG with ascorbate 2 liters; RCT: randomised clinical trial; SPMC: sodium picosulfate and magnesium citrate.

INTRODUCTION

Colonoscopy is an important tool in the management of inflammatory bowel disease (IBD). It has an important role in the diagnosis, estimation of disease severity, monitoring response to therapy, surveillance for neoplasia, and making important treatment decisions [1-3]. Over last few decades, colonoscopy has undergone major advances in the form of image-enhanced endoscopy (like chromoendoscopy, narrow-band imaging, confocal laser endomicroscopy etc.) and is taking a leap with the incorporation of artificial intelligence (AI) with it. However, the true benefit of these advances is dependent on adequate visualization of the colonic mucosa during the procedure. Despite these technological advancements, the role of bowel preparation cannot be emphasized enough for a high-quality endoscopic evaluation [4-6].

Several studies have investigated factors that affect the adequacy of bowel preparation. Factors like cirrhosis, diabetes, parkinsonism, history of colorectal surgery, high body mass index (BMI), and male gender seem to adversely impact bowel preparation [5, 7, 8]. Several studies have evaluated different factors affecting bowel preparation in IBD patients but the data are conflicting. To obviate this problem, some strategies like prolonged low-fiber diet, intake of split-dose bowel preparation, and a shorter interval between completion of preparation and procedures (less than 5 hours) are useful [9-14]. The inflammation of the mucosa also seems to affect the adequacy of bowel preparation [15]. In a retrospective study, suboptimal bowel preparation was found to positively correlate with active disease [13].

European Society of Gastrointestinal Endoscopy (ESGE) recommended polyethylene glycol (PEG)-based regimen for bowel preparation in IBD patients [16]. However, as various preparations and adjuvants are being evaluated in these patients, the best strategy for adequate bowel preparation for colonoscopy is still evolving and there is lack of sufficient comparative data to reach a conclusion with certainty. Lack of adequate preparation in patients with IBD may have serious consequences including the need for repeat procedures, economic costs, risk of missing dysplasia/malignancy and inappropriate estimation of disease extent or activity [17, 18]. Therefore, we performed this systematic review to better inform the practices with respect to ensuring adequate colonoscopy preparation in patients with IBD.

METHODS

The present systematic review has been conducted in accordance with the PRISMA guidance for Network meta-analysis [19]. The review was registered at OSF registry (https://osf.io/3r2pc) .

Information Sources and Search Strategy

We searched electronic databases (Pubmed, Embase, and Cochrane central register of controlled trials that is CENTRAL) for relevant articles. The search was conducted directly in the relevant databases on 26th May, 2023. We combined the three terms 'Inflammatory bowel disease,' (or equivalent terms like ulcerative colitis and Crohn's Disease), 'colonoscopy,' and 'bowel preparation' with the operator AND. This search was done without any filter for the type of study or the language of publication. The complete search strategy is shown in Supplementary file, Table I.

Eligibility Criteria

We included all randomized clinical trials which reported on the use of different strategies to improve the quality of bowel preparation in the patients with IBD. The strategies to improve bowel preparation were not restricted and any intervention in any of the domains (pre-colonoscopy preparation strategies, colonoscopy preparations, educational interventions etc) were eligible for inclusion. The studies were included irrespective of the language of publication. We excluded reports that had a wrong study type (observational studies), not reporting original research (letters, comments, guidelines, editorials, or reviews), had a wrong population/indication (studies done in general population or where separate data for IBD was not available).

Study Selection

All titles identified through the database searches were combined. This was followed by removal of duplicates. The initial titles and abstract screening were done by two reviewers (A.C., S.K.) independently of each other. Subsequently, the assessment of the full text of eligible studies was done. All of these steps were performed by two reviewers (A.C., S.K.) independently. Any discrepancies were resolved after discussion with the senior author (V.S.). None of the steps were automated.

Data Extraction

Data from each of the eligible studies was extracted in a pre-designed format. We extracted information regarding publication details (author, journal, year), study design (type of RCT), study population (IBD or its type, age, gender, disease activity), intervention and control arms, definitions of primary and secondary outcomes (see below) and the results of these studies. Data was extracted independently by two reviewers (A.C., S.K.) and discrepancies resolved by consensus (V.S.).

Outcomes

The primary outcome was the effectiveness of various strategies in improving bowel preparation. This was typically measured as the number of participants having a good bowel preparation as defined by various scores. The definition of effectiveness was as per the definition provided in individual studies The secondary outcome measures included the safety of preparation, tolerance of the preparations, and willingness to undergo a repeat procedure.

Data Synthesis

We performed a frequentist network meta-analysis to combine the direct and indirect evidence for improving colonoscopy preparation. We performed an analysis using an intention-to -treat strategy. We used R-software with the package 'netmeta' for conducting this network meta-analysis. The summary odds ratio had 95% confidence interval (CI) were estimated and the treatments were ranked using performance score. Statistical significance was defined at a level of <0.05. Heterogeneity was assessed with the use of Q-statistic (within design) and heterogeneity statistic (I^2).

Qualitative assessment was made for other outcome parameters including tolerance of preparation, acceptance, willingness to repeat, haziness and bubbles, and adverse effects.

Risk of Bias

The risk of bias was assessed using Cochrane risk of bias tool 2.0 which assesses bias arising from five domains (randomization, deviation from planned intervention, missing outcomes, measuring the outcome and selective reporting. We planned to assess publication bias using a funnel plot and Egger test if more than 10 studies are available. The present systematic review was not funded from any source.

RESULTS

Screening and Study Selection

The electronic search of various databases yielded 2,024 titles. The titles were combined and duplicates removed. After duplicate removal, 1,574 titles were available for initial screening (title and abstract screening). Eventually, 1.549 titles were excluded after removal of abstract and title screening. Of the remaining 25 titles, 13 were removed after full text screening for lack of relevant information. Eventually 13 articles were assessed and 7 were included in the systematic review and network meta-analysis [20-26] while 6 were excluded due to various reasons (Supplementary file, Table II). For the purpose of analysis, the standard 4 litre (L) PEG was used as a reference standard. This was because of the obvious absence of a control (placebo) arm. Fig. 1 shows the PRISMA flow chart for the study selection and inclusion.

Network of Comparisons

In the seven RCTs included in the systematic review, 960 patients were randomised to 8 interventions. The interventions were PEG4L, PEG1L, oral sulfate solution (OSS), PEG2L with ascorbate (PEG2LASC), PEG2L with bisacodyl, PEG4L with simethicone, PEG with sodium picosulfate and magnesium citrate (SPMC). Fig. 2 indicates the network of all the included RCTs. In this network meta-analysis, the number of pairwise comparisons were 8 and the number of treatments were 8. Most RCTs were two-arm study except for one study by Garcia et al. [20], which was a three-armed RCT.

Included Studies

Table I shows the major characteristics of the included studies. Among the included RCTs, the first RCT was published in 1993 and the most recent one in 2023. Most studies had a total number of IBD patients between 100-200. One study by Garcia et al. [20] had less than 100 (n=92) IBD patients and one study by Manes et al. [21] had more than 200 (n=216) IBD patients. All RCTs were published in English in full-text form. The definition of effectivenessvaried across various studies. Four RCTs used the Boston bowel preparation scale (BBPS) to measure effectivenessof bowel preparation. The definition of adequate bowel preparation was based on a total BBPS score ≥6 with ≥2 score for each colonic segment. Two RCTs used the Ottawa bowel preparation scale (OBPS). OBPS score ≥2 for each colonic segment (right, transverse and left), and total score of ≤7 was considered successful preparation. One RCT used Harefield cleansing scale (HCS) as grade A or B. In one study, adequate bowel preparation was defined in ordinal scale by endoscopist's assessment (graded as excellent, adequate, poor, and unacceptable). In addition to efficacy, various other outcomes were assessed which vary according to the study. There are various definitions that have been used in different studies. These definitions used for other outcomes parameters are summarized in Supplementary file, Table III.

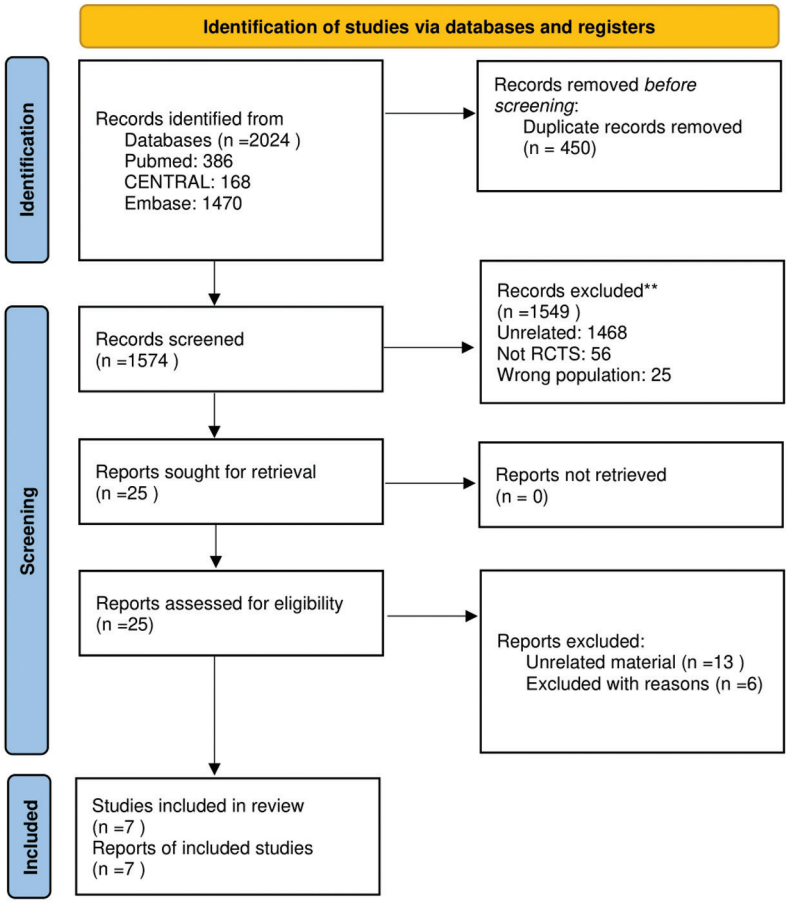

Fig. 1. PRISMA flowchart for study selection and inclusion process.

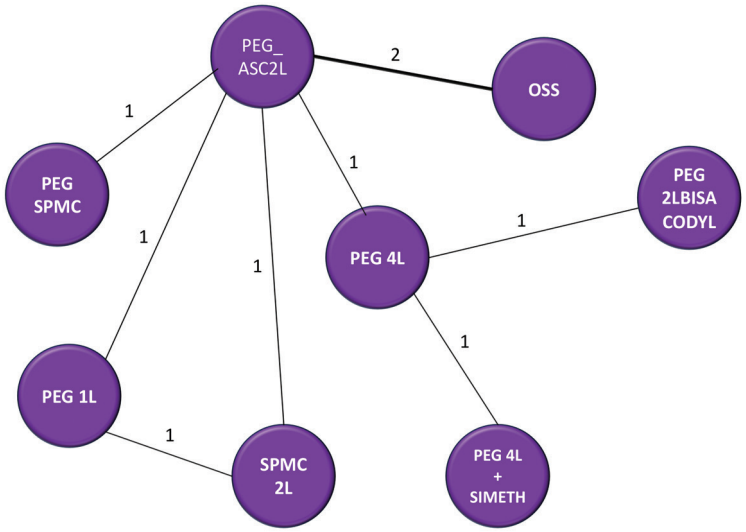

Fig. 2. The network plot depicting various randomised trials of colonoscopy preparation in inflammatory bowel disease. PEG4L: polyethylene glycol 4 liters; OSS: oral sulfate solution; PEG_ ASC2L: PEG with ascorbate 2L; PEG2LBISACODYL: PEG2L with Bisacodyl; PEG4L+SIMETH: PEG4L with simethicone; PEG with SPMC: sodium picosulfate and magnesium citrate.

Indications for colonoscopy have been mentioned in three studies. In the study by Manes et al. [21] mentioned indications for colonoscopy in the PEG-BIS group and PEG4L group were surveillance (52.8% and 34.3%, respectively), relapse of symptoms (24.5% and 35.2%, respectively), posttreatment response assessment (9.4% and 18.1%), severe recurrence (7.5% and 2.9%, respectively), for evaluation of possible complications (3.8% and 4.8%, respectively), and diagnosis (1.9% and 3.8%, respectively). (One patient in the 4-L PEG group underwent colonoscopy for some 'other' indication which is not detailed further). In the study by Kim et al. [22] indications were colorectal cancer surveillance and assessment of mucosal healing among IBD patients. In the study by Kim et al. [23] surveillance and monitoring of mucosal healing were mentioned as indications for colonoscopy among clinically inactive IBD patients. In other four studies, indications are not clearly mentioned.

Effectiveness Comparison

On comparison with PEG4L, OSS (OR=1.1, 95%CI: 0.65-1.86, p=0.7); PEGASC2L (OR=0.98, 95%CI: 0.65-1.48, p=0.93); PEG1L (OR=1, 95%CI: 0.55-1.81, p=0.99); PEG2L plus bisacodyl (OR=1.08, 95%CI: 0.71-1.65, p=0.69); PEG 4L

Table I. Important characteristics of included RCTs

Study	Year	Country	Centre	N_IBD	M/F	Mean (± SD) Age (years)	Regime	Groups	Efficacy definition
Lazzaroniet al [25]	1993	Italy	Single	105	63/42	35 (±13) vs 36 (±14)	Split dose	PEG4L+placebo vs PEG+ simethicone 120 mg	Endoscopist assessment of the degree of bowel cleansing: excellent, adequate, poor, or unacceptable
Manes et al [21]	2015	Italy	Multi-centre	216	126/90	52.4 (±15.3) vs 48.7 (±13.6)	Both	PEG2L plus bisacodyl vs PEG4L	OBPS
Kim et al [22]	2017	USA	Multi-centre	127	77/50	46.85 (± 14.04) vs 50.14 (± 13.06)	Both	PEG4L vs PEG2LASC	BBPS
Mohsen et al [26]	2021	Australia	Single	125	65/60	Mean age in IBD patients was 40.3 (± 14.7)	Split dose	PEG2LASC vs. PEG1L plus SPMC	OBPS
Kim et al [23]	2022	South Korea	Multicentre	110	73	41.9 (±14.9) vs 44.4 (±17.1)	Split dose	Oral sulfate tablets vs PEG2LASC	HCS
Garcia et al [20]	2023	Spain	Single	92	NA	51.76 vs 53.47 vs 50.09	Split dose	SPMC vs PEG1L vs PEG2L/ascorbate	BBPS
Lee et al [24]	2023	Korea	Multicentre	185	100/85	47.9 (±14.7) vs 48.9 (±15.0)	Split dose	Oral sulfate solution vs PEG2LASC	BBPS

BBPS: Boston bowel preparation scale; HCS: Harefield cleansing sale; OBPS: Ottawa bowel preparation scale. PEG: polyethylene glycol; PEG2LASC: PEG with ascorbate 2 liters; SPMC: sodium picosulfate and magnesium citrate.

plus simethicone (OR=1, 95%CI: 0.67-1.50, p=0.97); PEG/SPMC 1.5L (OR=0.99, 95%CI: 0.55- 1.78, p=0.99); SPMC 2L (OR=1.09, 95%CI: 0.61-1.97, p=0.7) had a similar odd of effectiveness in respect to bowel preparation (Table II). Fig. 3 provides the summary Forest Based on performance score, SPMC2L, PEG 2L plus bisacodyl, and OSS ranked among the top three most effective bowel preparations (p-score values provided in the Supplementary file, Table IV).

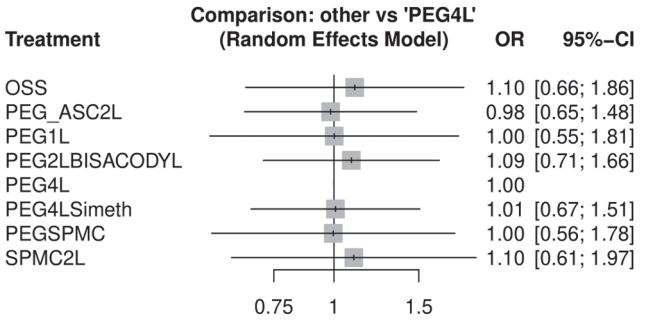

Fig. 3. Network forest plot comparing the effectiveness of various colonoscopy regimens in patients with inflammatory bowel disease. For abbreviations see Fig.1.

Assessment of Heterogeneity

Heterogeneity assessment was done that showed tau^2 = 0.0410 and within design heterogeneity Q=3.56, p=0.059, and I^2 = 71.9%) [0.0%; 93.7%].

Assessment of Other Outcome Measures

Different secondary outcome parameters were reported in different studies and their definitions were also different. In Supplementary file, Table III, the definitions used for secondary outcomes in the included studies are summarised. Table III summarises the findings for additional outcomes.

Compliance

Three RCTs reported compliance for the preparation. In the study by Manes et al. [21], PEG2L plus bisacodyl had significantly better compliance than PEG4L preparation. In the studies by Kim et al. [22], and Lee et al [24], no significant difference in compliance were found between the groups. Other RCTs did not report patient compliance among IBD patients. In one study, authors found compliance was not affected by disease activity [21].

Tolerance

Five RCTs reported tolerance of the preparation. In the study by Lazzaroni et al. [25] PEG4L with simethicone was better tolerated than PEG4L. In the study by Manes et al. [21] PEG2L with bisacodyl was better tolerated than its comparator PEG4L. In the study by Kim et al. [23] OSS was better tolerated than its comparator PEG2LASC, in terms of ease of ingestion and taste of the preparation. In the study by Garcia et al. [20] SPMC preparation was better tolerated than its comparators (PEG2LASC and PEG1L). One study did not report tolerance clearly [24]. Other 2 RCTs did not report tolerance in IBD patients.

Acceptance

Two studies reported patient acceptance [24, 25]. In the study by Lazzaroni et al [25], PEG4L with simethicone had better acceptance compared to its comparator PEG4L. In the study by Lee et al. [24] there was no significant difference in terms of patient acceptance between two groups. In the study by Manes et al. [21] acceptability was described to be significantly better in the PEG2L with bisacodyl group than in the PEG4L group. However, it lacks detailed description other than representation in a figure. Other 4 RCTs did not report data on the same in IBD patients.

Willingness to Repeat

Five RCTs reported data on willingness of patient to repeat the procedure in future using the same preparation. In the study by Manes et al. [21], better willingness was found in PEG2L plus bisacodyl group than PEG4L. In the study by Kim et al. [22], better willingness was found in PEG2LASC than PEG4L. In the study by Kim et al. [23], better willingness was found in OSS group than PEG2LASC. In the study by Garcia et al. [20], better willingness was found in SPMC2L group compared to PEG2L group and worse willingness was reported in PEG1L group compared to PEG2L group. In the study by Lee et al. [24] there was no difference.

Haziness and Bubbles

One RCT reported on haziness during endoscopic visualization [25] and no significant difference was found between the groups. Three RCTs reported on presence of bubbles during the procedure. In the study by Lazzaroni et al. [25] PEG4L with simethicone group was better than the comparator group.

Table II. Indirect and network comparisons of various bowel preparations

OSS	1.12 (0.81; 1.55)	.	.	.	.	.	.
1.12 (0.81; 1.55)	PEG_ASC2L	0.98 (0.64; 1.51)	.	0.98 (0.65; 1.48)	.	0.99 (0.65; 1.49)	0.89 (0.59; 1.36)
1.10 (0.65; 1.89)	0.98 (0.64; 1.51)	PEG1L	.	.	.	.	0.91 (0.60; 1.37)
1.02 (0.52; 1.99)	0.91 (0.50; 1.63)	0.92 (0.44; 1.91)	PEG2LBISACODYL	1.09 (0.71; 1.66)	.	.	.
1.10 (0.66; 1.86)	0.98 (0.65; 1.48)	1.00 (0.55; 1.81)	1.09 (0.71; 1.66)	PEG4L	0.99 (0.66; 1.49)	.	.
1.10 (0.57; 2.12)	0.98 (0.55; 1.74)	0.99 (0.48; 2.04)	1.08 (0.60; 1.93)	0.99 (0.66; 1.49)	PEG4LSimeth	.	.
1.11 (0.66; 1.87)	0.99 (0.65; 1.49)	1.00 (0.55; 1.82)	1.09 (0.53; 2.24)	1.00 (0.56; 1.80)	1.01 (0.50; 2.05)	PEGSPMC	.
1.00 (0.59; 1.70)	0.89 (0.59; 1.36)	0.91 (0.60; 1.37)	0.99 (0.48; 2.03)	0.91 (0.51; 1.63)	0.92 (0.45; 1.87)	0.91 (0.50; 1.63)	SPMC2L

For abbreviations see Fig. 2.

Table III. Summary of secondary outcome in various studies

Parameter	Study	Arm1	Arm2	Result	Comments
Compliance	Manes et al. [21]	PEG4L	PEG2L plus bysacoyl	95.3% PEG/BIS vs 66.7% PEG4L; Compliance is not affected by dose regime or disease activity	Better compliance in PEG with bisacodyl group compared to the PEG4L group
	Kim et al. [22]	PEG4L	PEG2LASC	94.6% PEG2LASC and 96.2% PEG4L group	No significant difference
	Lee et al. [24]	OSS	PEG2LASC	excellent, 91(99%), 90(97%); fair 1(1%), 2(2%); and poor 0, 1(1%) respectively	No significant difference
Tolerance	Lazzaroni et al. [25]	PEG4L	PEG4L plus simethicone	Good 40% vs 63% Fair 46% vs 26% Poor 14% vs 11%	PEG4L with simethicone was better tolerated than PEG4L
	Manes et al. [21]	PEG4L	PEG2L plus bisacodyl	Significantly higher number of patients in the PEG2L with bisacodyl group described no or mild discomfort from preparation intake compared to PEG4L group (88/106, 83% versus 47/105, 44.8%)	PEG plus bisacodyl was better tolerated than PEG4L in terms of less discomfort; Activity of disease did not seem to influence tolerability
	Kim et al. [23]	OSS	PEG2LASC	(See definition) VAS for ease of ingestion and taste 8.2 ± 1.6 vs 6.0 ± 2.2; and 7.0 ± 2.8 vs 5.4 ± 2.4, respectively.	Better tolerability reported in OSS group compared to PEG ascorbate 2L group
	Garcia et al. [20]	PEG1L	PEG2LASC vs SPMC2L	PEG1L, PEG2LASC, SPMC group: Tolerability: 9.59 (SD 1.42), 8.62 (SD 2.53), 9.93 (SD 0.35)	PEG2LASC and SPMC2L were better tolerated compared to PEG1L
Acceptance	Lazzaroni et al. [25]	PEG4L	PEG4L plus simethicone	Less malaise (44% vs 19%) and sleep disturbance (44% vs 19%) in PEG4L plus simethicone group	According to the authors, acceptability was better in PEG4L with simethicone group in terms of less malaise and sleep disturbance* (acceptability was not separately defined)
	Lee et al. [24]	OSS	PEG2LASC	ease of taking solution in a 4-point ordinal scale 1.5±0.7 and 1.6±0.8 respectively	No difference in acceptability between the two groups
	Manes et al. [21]	PEG4L	PEG2L plus bisacodyl	Data not available	Reportedly significantly better acceptance in PEG2L bisacodyl group
Willingness to repeat	Manes et al. [21]	PEG4L	PEG2L plus bisacodyl	94.3% 2L PEG and 61.9% 4L PEG	PEG2L with bisacodyl group had significantly better compared to PEG4L alone
	Kim et al. [22]	PEG4L	PEG2LASC	82.1% in PEG2LASC group vs 64.2% in PEG4L group	PEG2LASC was significantly better
	Kim et al. [23]	OSS	PEG2LASC	94.5% OST group and 75% in 2L PEG2LASC	OSS was significantly better than PEG2LASC
	Garcia et al. [20]	PEG1L	PEG2LASC vs. SPMC2L	PEG1L, PEG2LASC, SPMC2L group 42.4%, 78.5%, and 96.7%, respectively	PEG2LASC and SPMC2L were significantly better than PEG1L
	Lee et al. [24]	OSS	PEG2LASC	78 (85%) and 81 (87%) OSS and 2 L PEG2LASC group respectively	No significant difference
Haziness	Lazzaroni et el. [25]	PEG4L	PEG4L and simethicone	no/slight/moderate/very hazy 32/12/4/0 in placebo and 41/14/1/1 in simethicone group (p 0.341)	No significant difference
Bubbles	Lazzaroni et al. [25]	PEG4L	PEG4L and simethicone	no/minimal/moderate/severe bubbles in 37/4/6/1 in placebo and 44/12/1/0 in simethicone group	PEG4L with simethicone had significantly less bubbles than PEG4L group
	Manes et al. [21]	PEG4L	PEG2L plus bisacodyl	0-1 bubble score in 71.7% PEG with bisacodyl cases 36.2% PEG4L cases	Low bubble score was significantly higher in the PEG with bisacodyl group compared to PEG4L group
	Kim et al. [23]	OSS	PEG2LASC	Zero bubble score 94.5% in OST and 50% PEG2LASC	Zero bubble score was significantly higher in the OSS group compared to PEG2LASC group

For abbreviations see Table I.

In the study by Manes et al. [21], PEG4L with bisacodyl group was better than the comparator group. In the RCT by Kim et al. [23] OSS was significantly better than PEG2LASC group.

Adverse Events

The adverse effects reported in various RCTs are summarised in Supplementary file, Table V.

Additional outcomes

Two studies reported outcomes related to the procedure of colonoscopy [21, 22]. In one study, completion of colonoscopy, time to reach cecum and withdrawal time were not significantly different between two groups [21]. In the other study, cecal intubation rate and withdrawal time were not significantly different between the two compared groups [22].

Three studies reported change in disease activity after colonoscopy [22-24]. In one study [22], no significant difference in disease severity scores (SCCAI) were found within 1 month after colonoscopy compared to baseline scores, in either of the compared groups. Symptomatic relapse (defined as SCCAI ≥5) were found in 5.7% and 3.6% in PEG4L and PEG2LASC group, respectively, although the difference was not significant. The need for add-on therapy or dose escalation for relapse were also not significantly different. In another study [23], no significant difference in disease activity were noted at 1 week and 4 weeks after colonoscopy, between OSS and PEG2LASC preparation. In the other study [24], at 2-4 weeks of follow-up, there was no significant difference between the two compared groups in terms of change disease activity post-colonoscopy.

Three studies reported change in the electrolyte levels [23, 24, 26]. In one study [23], no significant difference in serum electrolyte levels were found between two compared groups. In the same study, there was numerically significant increase in serum blood urea nitrogen and creatinine levels, although all values were within normal range, thus, interpreted as clinically not meaningful. In another study [26] significant difference in post-preparation hypermagnesemia were found between two groups (mean increase of 0.11±0.106 mmol/L and 0.03±0.117 mmol/L in PEG2LASC and PEG with SPMC group, respectively, $p<0.0001$), although no clinically demonstrable concerns were described like cardiac arrhythmia, pulmonary edema, or heart failure. In the other study [24] , serum chloride level was found to be significantly different between the two compared groups (103.7±2.6 meq/L and 104.7±3.1 meq/L, respectively; $p=0.03$), although the values were within normal range. Supplementary file, Table VI depicts the summary of these additional outcomes.

Risk of Bias Assessment

Three studies analysed results using intention to treat analysis and 4 studies used per protocol analysis. Among these 7 RCTs, overall high risk of bias was identified in 5 studies and some concerns were found in 2 studies. Some concerns and high risk of bias in the randomization process was found in one and two RCTs, respectively. For the domains related to the deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported outcome, some concerns and high risk of bias was noted in 1 and 2; 0 and 0; 0 and 0; 1 and 5 RCTs respectively. Supplementary Figure 1 depicts the overall assessment of risk of bias.

DISCUSSION

In this systematic review and network meta-analysis, 7 RCTs were included and there were 9 comparator arms. Our findings suggest that there are no significant differences among various bowel preparations with respect to effectiveness of the bowel preparation among IBD patients. In addition, we note that there is a clear lack of uniformity in reporting information about various secondary outcome measures. Therefore, we are unable to derive a definite conclusion with respect to tolerability, acceptance, compliance, willingness to repeat of the various preparations used across the RCTs. However, a trend suggesting a lesser overall tolerance of PEG-based and higher-volume preparations is visible. In addition, we identify a lack of clinical trials in domains other than those involving bowel preparation (eg pre-preparation dietary changes or educational interventions).

Several studies have compared different bowel preparation solutions to each other outside the setting of IBD. In a systematic review and meta-analysis of 40 studies (n=13,064), which included both IBD and non-IBD patients, PEG with ascorbate and simethicone was found to be the best-performing preparation with respect to BBPS, and PEG with simethicone was best-performing preparation with respect to OBPS [27]. However, our meta-analysis did not show any difference in effectiveness among the preparations. Although in individual studies included in our meta-analysis, effectiveness of PEG2L with bisacodyl was found non-inferior to PEG4L; PEG2LASC had similar effectiveness to PEG4L; similar effectiveness of sulfate solution and PEG2LASC were shown in two RCTs; effectiveness of PEG2LASC was similar to PEG with SPMC; similar effectiveness was noted between PEG4L with and without simethicone. There can be several reasons behind this. Firstly, IBD has been shown to be linked to inadequate bowel preparation in studies, and endoscopic disease activity was also found to be related to suboptimal bowel preparation [15]. Secondly, the side effects of the preparation can be more pronounced in the IBD group, which might affect the acceptability of the preparation, ultimately affecting the efficacy. Thirdly, the number of studies may not be enough to answer the question.

In the recent meta-analysis, secondary outcomes were also analysed in the form of cecal intubation rate (CIR), cecal intubation time (CIT), adenoma detection rate (ADR) and polyp detection rate (PDR) as secondary outcome measure. OSS was found to be not well tolerated with significantly less willingness to repeat. This is likely due to the unpleasant taste and nausea occurring after taking the preparation. In this study, authors also found that high volume preparations are less well tolerated than low volume preparations [27].

Apart from the type of bowel preparation used, regimen also plays a valuable role in optimal bowel preparation. In a meta-analysis (2012), split-dose high volume PEG-based solutions were shown to have superior effectiveness than other preparations (OR=3.46, 95%CI: 2.45-4.89) [28]. In two subsequent meta-analyses of 11 and 14 RCTs, respectively, similar results in terms of efficacy, tolerability, and willingness to repeat the preparation were found between split-dose and same-day regimens [29, 30]. In one meta-analysis, high volume PEG-based split-dose regimen was found superior to split-dose low-volume regimens (OR=1.89, 95%CI: 1.01-3.46). In our systematic review, five studies used a split-dose regime, and two studies used both split-dose and same-day regimens. In

one study [21] the split dose group was found to have better colon cleansing than the standard regimen (total colon score 6.64±2.71 vs 4.04±2.48, p<0.0001). No significant difference was found in the other study [22]. Thus, due to the lack of enough studies, we avoided a quantitative synthesis to compare split versus same-day preparation in IBD.

Previous studies have also shown better tolerability and acceptance with low-volume preparations. In our study, results from the included RCTs also describe similar findings. Previous studies have also reported that low-volume PEG plus ascorbate preparations have less acceptance due to increased side effects like nausea and vomiting, though not severe enough to compromise the effectiveness of the preparation. Adverse events of the preparations described in included RCTs tend to show lesser side effects with low-volume preparations (e.g., lower vomiting in PEG2LASC than PEG4L). More nausea and vomiting were reported with PEG2LASC preparation compared to OSS. More abdominal pain was reported in PEG-SPMC compared to PEG2LASC. This is a valuable finding from our study as low-volume preparations have better acceptance and tolerability, and selected preparations like OSS and PEG ascorbate preparations may have fewer side effects, though the effectiveness is similar. Most of the IBD patient population undergo colonoscopies multiple times in their lifetimes for several indications, including screening for colorectal cancer. There lies the importance of a more acceptable and well-tolerated preparation that offers similar effectiveness of bowel cleansing.

There are some limitations to our study. Firstly, the number of included RCTs was small. Secondly, several domains remained unaddressed, including the preparation volume and type of preparation (split dose vs continuous). Thirdly, there is non-uniformity in reporting various secondary outcome domains. While these domains may not be as important to the endoscopist as the efficacy of preparation, they are relevant to the patient like taste, acceptance, compliance etc. We did not analyze the type of preparation regime separately, i.e., split dose, continuous or both. Of course, there is little literature on the need for adequate preparation on intrepretatability of colonoscopy using artificial intelligence [31]. Lastly, there is high risk of bias in some studies in different domains that reduces the quality of evidence generated from the meta-analysis.

The strength of our study consists of being the first to evaluate systematically the effectiveness of bowel preparation in randomized trials in IBD patients. Despite the underlying heterogeneity of preparations and definitions of outcomes, the systematic review study clearly identifies that the tolerance and acceptance of bowel preparation may be related, in part, to the amount of preparation. Our results also identify the lacunae in published literature: lack of uniformity in defining outcomes and lack of RCTs in specific domains like education interventions. These should be addressed in future studies.

CONCLUSIONS

Based on our systematic review and meta-analysis on the effectiveness of various bowel preparations in IBD patients, there is no difference in the effectiveness of one preparation over the other. However, small volume preparations are better tolerated and accepted by the patients. In IBD, where patients require multiple colonoscopies during their lifetime, small-volume preparations may be preferred. There is a need for more studies and better reporting of adverse events of various preparations.

Conflicts of interest: None to declare.

Author' contributions: V.S., S.K., A.C. conceived and designed the study. V.S. searched the literature. A.C. and S.K. screened and selected the studies. V.S. and A.P. analysed the data. A.C., S.K and V.S. validated the results. A.C. drafted the manuscript. V.S., U.D. and S.S. critically revised the manuscript. All authors read and approved the final version of the manuscript.

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