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REVIEW

Efficacy and Patient Tolerability of Split-Dose Sodium Picosulfate/Magnesium Citrate (SPMC) Oral Solution Compared to the Polyethylene Glycol (PEG) Solution for Bowel Preparation in Outpatient Colonoscopy: An Evidence-Based Review

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Background: Colonoscopy is the gold standard exam for evaluation of colonic abnormalities and for screening and surveillance for colorectal cancer. However, the efficacy of colonoscopy is dependent on the quality of the pre-colonoscopy bowel preparation. Polyethylene glycol (PEG) and sodium picosulfate/magnesium citrate (SPMC) have emerged as two of the most commonly used bowel preparation agents. We conducted an evidence-based review of current evidence to further investigate the efficacy and patient tolerability of split-dose SPMC oral solution compared to PEG solution for colonoscopy bowel preparation.

Methods: A systematic search was performed using Pubmed (MEDLINE), Web of Science, EMBASE, and Cochran Central Register of Controlled Trials databases. All studies on split-dose bowel preparation with SPMC and PEG were reviewed. Relevant studies regarding colonoscopy and bowel preparations were also included. Randomized controlled trials were prioritized due to the high quality of evidence.

Results: Eight randomized controlled trials were included. Split-dose SPMC and PEG were associated with similar results for adequacy of bowel preparation. Split-dose SPMC was associated with increased patient tolerability and compliance.

Conclusion: Split-dose SPMC and PEG are both adequate and safe for bowel preparation for outpatient colonoscopy, with split-dose SPMC being more tolerable for patients. Additional RCTs comparing these and other bowel preparation solutions are necessary to further investigate quality of bowel preparation, patient preference, and cost-effectiveness of the various options.

Keywords: colonoscopy, bowel, polyethylene, glycol, sodium, picosulfate, magnesium, citrate, PEG, SPMC, tolerability, adenoma

Introduction

Colonoscopy remains the gold standard exam for the investigation of colonic mucosal abnormalities and is an integral part of colorectal cancer screening and surveillance programs. However, the efficacy of colonoscopy in the detection of high-risk lesions is greatly dependent on the quality of the pre-colonoscopy bowel preparation[1,5] and, even in emergency procedures, adequate and thorough bowel preparation can improve patient safety and outcomes.[6–14] There are various factors,

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such as patient medical comorbidities, tolerance and compliance, and cost burden of preparations which are important considerations in selecting an agent. Polyethylene glycol (PEG) and sodium picosulfate/magnesium citrate (SPMC) have emerged as two of the most commonly used agents worldwide.

PEG is a non-absorbable, large polymer that remains in the gut lumen resulting in an osmotic lavage effect and can be osmotically balanced with non-fermentable electrolyte solutions.[15] While PEG has been the most commonly used bowel preparation agent, it requires the consumption of a large volume of liquid, resulting in poor patient tolerance and compliance. Thus, in recent years, studies have investigated other preparation agents in attempts to improve patient adherence and thus quality of preparation and adenoma detection rates.

SPMC is one such alternative preparation, which serves as a purgative laxative and is generally made up of two components: Sodium Picosulfate, a prodrug metabolized by the colonic flora into its active metabolite which stimulates peristalsis and increases bowel movement frequency, and magnesium oxide and citric acid, which react to create magnesium citrate, which induces catharsis and leads to increased fluid retention within the colon via its osmotic effect.[15,16] The SPMC bowel preparation reduces effective volume of the colon-cleansing solutions to 2-liters (2-L) from the standard 4-liters (4-L) of the PEG solution,[16] which is thought to improve patient satisfaction and adherence, while still achieving a similar cleansing effect. Additionally, there is evidence that administration of the preparation agent in a split dose, ie, giving preparation in separate doses on the day prior or day of the procedure, is superior to administration in a single dose in terms of patient convenience, tolerance and palatability, improved quality of bowel preparation, and increased adenoma detection rate.[17,18]

This review was designed to summarize present evidence about the efficacy and tolerability of split-dose SPMC oral solution compared to PEG solution for colonoscopy.

Methods

Individualized systematic searches of PubMed (Medline), EMBASE, Web of Science, and Cochrane Library were acquired of available literature from inception through February 2020. The combinations of keywords used were:

((Cathartic) OR (Bowel Evacuants) OR (Purgatives) OR (Bowel Preparation) OR (Colon cleans*) OR (Bowel cleans*)) AND ((PEG-based) OR (PEG) OR (Polyethylene Glycol) OR (Macrogol) OR (Polyethylene Oxide) OR (Polyethyleneoxide) OR (Polyoxyethylene) OR (Polyglycol) OR (Carbowax)) AND ((SPMC) OR (picosulfate-magnesium) OR (picosulfate/magnesium) OR (picosulfate AND magnesium) OR (picosulfate sodium) OR (sodium picosulfate) OR (picoprep) OR (Picolax) OR (Picosulfol) OR (Laxoberal))

All relevant full-text articles in English, regardless of the year of publication, were included. From the initial search results, duplicates were extracted, and then the titles and abstracts of all potentially relevant studies were screened for eligibility. Two reviewers (AAMN, IBR) independently screened the titles and abstracts of all the articles according to the below-predefined eligibility and exclusion criteria, extracting relevant information, for ensuring relevance to the selected topic. Any differences were resolved by mutual agreement and in consultation with a third reviewer (DTHM). Additionally, we had scanned the reference lists of included studies and gray literature was searched.

Studies which didn't fulfil the eligibility criteria were excluded. All studies evaluating the quality of split-dose preparations of SPMC and PEG, patient tolerability, and patient compliance were included. We included only randomized controlled trials (RCTs) with full texts published, due to the better quality of evidence, that were published or presented as original research articles in the English language. Studies were excluded from this review according to the following criteria: use of alternative bowel preparation solutions (not SPMC or PEG solutions); use for an indication other than outpatient colonoscopy; not adults patients; patients with dietary restrictions; and/or not using split doses for bowel preparation. The detailed process of study selection is shown in Figure 1.

Literature Results

We retrieved a total of 132 records from the electronic literature search. A total of eight randomized controlled trials were included in the final analysis and were reviewed. The study characteristics and patient demographics of the included studies are summarized in Table 1. The quality of the bowel preparation was evaluated on one of three previously validated scoring systems: Four of the articles used the Ottawa Bowel Preparation Scale (OBPS), three of the articles used the Boston Bowel Prep Score (BBPS), and three of the articles used the

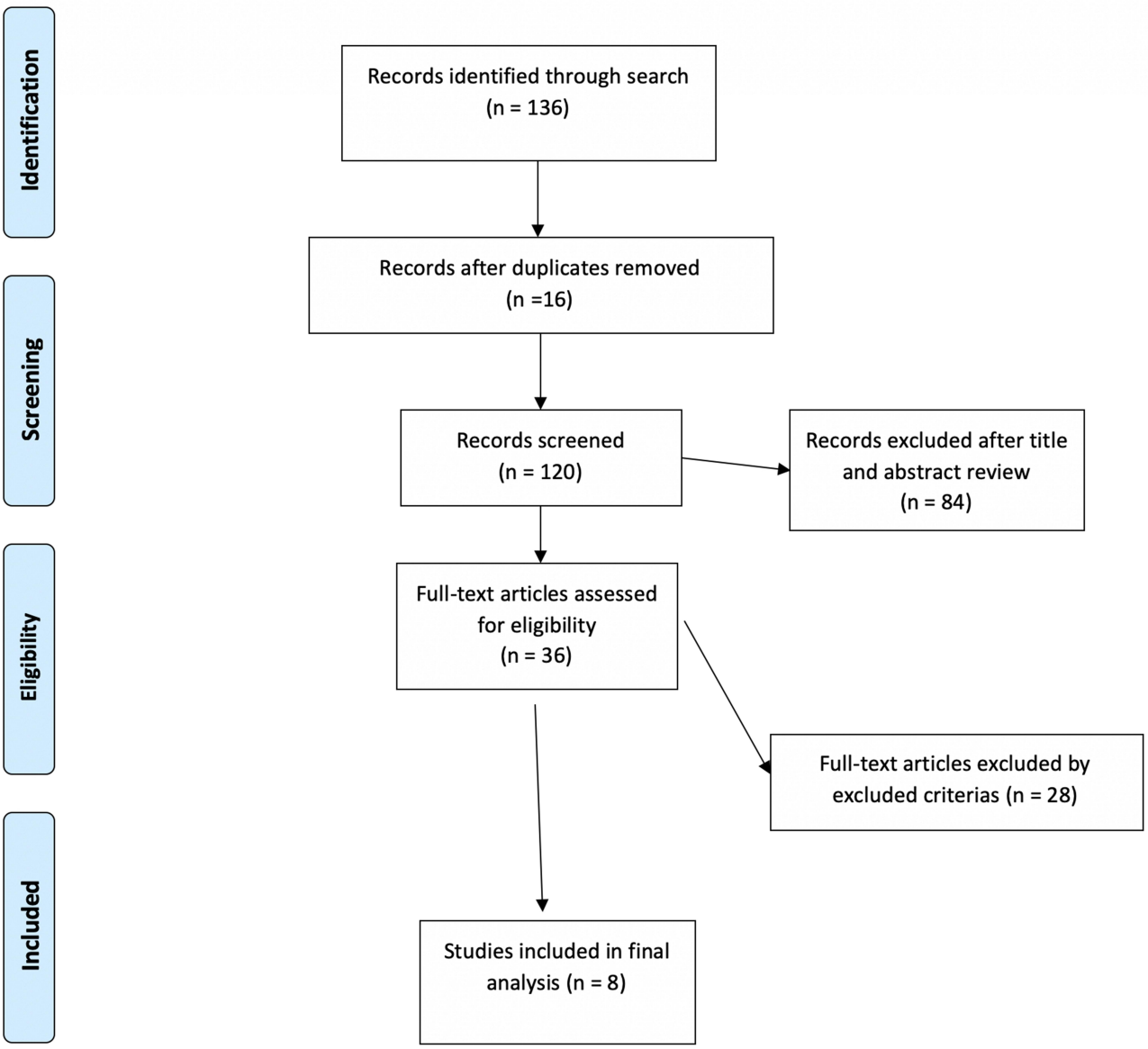

Figure 1 Flow chart for study selection.

Aronchick Score. The bowel preparation validated scoring systems used are summarized in Table 2.

Rostom et al[19] conducted a single-center randomized controlled trial in which 171 patients whom were scheduled for outpatient colonoscopy were randomized to either same-day or 2-day split-dose SPMC or PEG lavage. Bowel preparation quality was recorded in a blinded manner by the endoscopist using the OBPS prior to washing or suctioning. This group found that SPMC was inferior to PEG (P=0.019, mean OBPS: 4.14±2.64 vs 5.11±3.44). Additionally, they demonstrated that a 1-day split dose was inferior compared to a 2-day split-dose regimen (P<0.001, mean OBPS: 3.68±2.82 vs 5.69±3.06). Two-day split dosing also resulted in a better right colon cleanliness score compared to 1-day split dosing (right bowel, P<0.001, OBPS 1.27±0.11 vs 2.10±0.12).

Kojecky et al[20] conducted a randomized, endoscopist-blinded, multicenter study in which they evaluated the quality of bowel preparation, in a single or a split-dose preparation for 973 outpatients who received PEG, SPMC, or ethylene glycol/ascorbic acid (PEGA). Satisfactory bowel cleansing (Aronchick score 1+2) was observed more frequently when a split dose was used, irrespective of the solution type (P<0.006, PEG 90.1 vs 68.8%, PEGA 86.0 vs 71.6%, SPMC 84.3 vs 60.2%). In terms of patient tolerance, PEG was the worst tolerated (P<0.001), and SPMC was the best tolerated, followed by PEGA (P<0.006). It was also

Table 1 Characteristics of the Studies Included in the Review

Authors (Publication Year)	Study Design	N	Country	Gender (N)	Age Range	Solution Regimen	Score Bowel Preparation Quality	Results (Best Tolerability)
Rostom et al, 2019[19]	Prospective, randomized, single-center	141	Canada	PEG: 36 (female)/ SPMC: 34 (female)	PEG: 56.4/ SPMC: 57.6	Split-dose SPMC and PEG lavage into 1-day split or 2-day split	OBPS	-
Mathus-Viegen et al, 2018[21]	Noninferiority, randomized, single-center	341	Netherlands	PEG-Asc +B: 84 (female)/ SPMC: 88 (female)	PEG-Asc +B: 58.5/ SPMC: 55.5	SPMC and PEG-Asc+B split-dose	OBPS	SPMC
Seo et al, 2018[22]	Prospective, randomized, single-center	223	Germany	2-L-PEG/ Asc: 52 (male)/ SPMC: 65 (male)	2-L-PEG/ Asc: 56.1/ SPMC: 54.9	2-L-PEG/Asc and SPMC split-dose	Aronchick and OBPS	SPMC
Kojecky et al, 2017[20]	Prospective, randomized, multi-center	973	Czech Republic	-	-	PEG, SPMC and PEGA in a single or a split-dose	Aronchick	SPMC
Kim et al, 2015[26]	Prospective, randomized, multi-center	365	South Korea	SPMC/ bisacodyl: 94 (male)/ 4-L PEG: 100 (male)	SPMC/ bisacodyl: 53.5 (male)/ 4-L PEG: 53.8 (male)	Split preparation SPMC/ bisacodyl and conventional (4-L) split PEG	BBPS	SPMC/ bisacodyl
Yoo et al, 2015[23]	Prospective, randomized, single-center	200	South Korea	SPMC: 46 (male)/ PEG-Asc: 53 (male)	SPMC: 53.27/ PEG-Asc: 56.97	Split-dose methods of SPMC and PEG-Asc	BBPS and Aronchick	SPMC
Jeon et al, 2015[24]	Prospective, randomized, single-center	388	South Korea	2-L-PEG/ Asc: 108 (male)/ SPMC: 109 (male)	2-L-PEG/ Asc: 54.7/ SPMC: 53.6	2-L-PEG/Asc and three sachets of SPMC, both in split-dose	BBPS	Similar tolerability
Manes et al, 2013[25]	Prospective, randomized, multi-center	285	Italy	1-L-PEG +Asc: 85 (male)/ SPMC: 76 (male)	1-L-PEG +Asc: 57.8/ SPMC: 60.9	Split-dose methods of 1-L-PEG+Asc and one sachet of SPMC	BBPS	SPMC

Abbreviations: PEG, polyethylene glycol; SPMC, sodium picosulfate/magnesium citrate; PEG-Asc+B, polyethylene glycol + ascorbic acid + bisacodyl; 2-L-PEG/Asc, 2 liters polyethylene glycol + ascorbic acid; 1-L-PEG/Asc, 1 liter polyethylene glycol + ascorbic acid; OBPS, Ottawa Bowel Preparation Scale; BBPS, Boston Preparation Scale.

Table 2 Characteristics of Bowel Validated Scoring Systems

Scale Name	Score	Description	Characteristics
Aronchick Scale	1	Excellent: small volume of liquid; >95% of mucosa seen.	Total score range: Minimum 1 (excellent) to maximum 5 (inadequate). Score performed before washing or suctioning. No separate ratings for segments; global colon rating only.
	2	Good: clear liquid covering 525% of mucosa, but >90% of mucosa seen.	
	3	Fair: semisolid stool could not be suctioned or washed away, but >90% of mucosa seen.	
	4	Poor: semisolid stool could not be suctioned or washed away and <90% of mucosa seen.	
	5	Inadequate: repeat preparation/screening needed.	
Ottawa Bowel Preparation Scale (by Colon Segment)	0	Excellent: mucosal detail clearly visible, almost no stool residue; if fluid present, it is clear, almost no stool residue.	Total score (obtained by adding scores for each segment + total colon fluid score) range: Minimum 0 (excellent) to maximum 14 (inadequate). Scoring performed before washing or suctioning. Rates cleansing by colon segment: Right colon, mid-colon, and rectosigmoid colon.
	1	Good: some turbid fluid or stool residue, but mucosal detail still visible without need for washing/suctioning.	
	2	Fair: Some turbid fluid of stool residue obscuring mucosal detail; however, mucosal detail becomes visible with suctioning, washing not needed.	
	3	Poor: Stool present obscuring mucosal detail and contour; a reasonable view is obtained with suctioning and washing.	
	4	Inadequate: Solid stool obscuring mucosal detail and not cleared with washing and suctioning.	
Boston Bowel Preparation Scale (by Colon Segment)	0	Unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared.	Total score (obtained by adding scores for each segment) range: Minimum 0 (very poor) to maximum 9 (excellent). Scoring performed after washing or suctioning. Segments separately rated: Right colon (including cecum and ascending colon); transverse (includes hepatic and splenic flexures); and left colon (descending and sigmoid colon, and rectum).Threshold optimally is total score of ≥6 AND ≥2 per segment.
	1	Portion of mucosa of the colon segment seen, but other areas of segment not well seen because of staining, residual stool, and/or opaque liquid.	
	2	Minor amount of residual staining, small fragments of stool, and/or opaque liquid, but mucosa of colon segment is well seen.	
	3	Entire mucosa of colon segment well seen, with no residual staining, small fragments of stool, or opaque liquid.	

observed that tolerability did not correlate with the regimen or amount of the solution used.

Mathus-Viegen et al[21] recently conducted a non-inferiority randomized trial comparing PEG-electrolyte solution plus bisacodyl (PEG-sc + B) and SPMC with 2 liters ascorbic-acid-enriched. A total of 341 patients underwent colonoscopy, and those patients reported significantly fewer physical complaints and a higher completion rate with SPMC compared to PEG-Asc+B; in particular, patients receiving SPMC reported increased

ease of consumption and improved taste compared to the PEG-Asc+B preparation. In the event of a repeat colonoscopy, 59.7% of patients in the PEG-Asc+B compared to 93.6% of patients in the SPMC group confirmed that they would opt for the same preparation again. Additionally, in this study, researchers reported that the observed changes in hemodilution and changes in electrolytes, including bicarbonate and magnesium, were largely attributable to the preparation used but were not clinically significant. Thus, they concluded that SPMC was non-inferior to PEG-Asc+B in terms of quality of bowel preparation and showed in this study that the effects on blood electrolyte concentrations were clinically insignificant.

Seo et al[22] conducted a randomized, endoscopist-blinded, single center controlled trial comparing SPMC vs 2L-PEG/Asc in 223 outpatients undergoing colonoscopy. There was no significant difference in overall quality of bowel preparation on the OBPS between the two groups; however, when broken down by each individual segment of the bowel, there was a trend towards improved quality of preparation in the right colon in the SPMC group compared to the PEG/Asc group (OBPS scores; P=0.08, 1.55±0.66 vs 1.74±0.88). SPMC was also better tolerated than PEG/Asc based on ease of consumption and preference to receive the agents again in the future. The authors observed that total adverse events like nausea, abdominal pain, and abdominal bloating were significantly lower in SPMC group compared with the PEG/Asc group (P=0.031, 47.4 vs 62.4%).

Yoo et al,[23] in another randomized, single-center, observer-blinded study evaluated 200 prospectively enrolled outpatients who received a split-dose preparation of either SPMC or PEG-Asc low-volume bowel preparations for colonoscopy. This group demonstrated that PEG-Asc was similar to SPMC in terms of quality of bowel preparation (P=0.718, ≥6 BBPS: 80% vs 82%; adequate Aronchick grade: P=0.352, 93% vs 96%). He also observed that SPMC caused fewer gastrointestinal symptoms (ie, abdominal fullness and general abdominal discomfort). Patients in the SPMC group reported significantly better palatability than PEG–Asc (mean±SD, score 1/excellent–5/bad: 2.39±0.73 vs 3.06±0.93, P<0.001).

Jeon et al[24] conducted a endoscopist-blinded randomized, single-center, controlled trial comparing 2-L PEG-Asc vs SPMC on both intention-to-treat (ITT) analysis (total of 388 patients) and per protocol (PP) analysis (total of 356 patients.) No significant differences in preparation adequacy were observed in ITT and PP analyses when assessed with the BBPS (P>0.05). The polyp and adenoma detection rate (PDR and ADR) were greater than 60 and 40% in both groups, respectively (P>0.05). While patient compliance levels were higher in the 2-L PEG/Asc group compared to the SPMC group (P<0.001), patient satisfaction (ITT, P=0.014; PP, P=0.032) and palatability (ITT and PP, P<0.001) levels were higher in the SPMC group than in the 2-L PEG/Asc group. Despite this, ease of consumption and future intention to reuse if necessary were similar in both groups (P>0.05, ITT and PP).

Manes et al[25] conducted an endoscopist-blinded, multicenter randomized study assessing 285 outpatients undergoing colonoscopy. Patients were randomized to receive either SPMC or PEG-Asc. Then, depending on the time of their scheduled colonoscopy, they were divided into either same-day or split-dose preparation regimens. Patients with a procedure earlier than 12:00 pm were instructed to complete the preparation in one night, starting at 5:00 pm the day before the procedure. Patients with a procedure later than 12:00 pm were instructed to consume the preparation in a split-dose regimen; they started the first half at 5:00 pm and consumed the second half the morning of their scheduled procedure. It was shown that the mean BBPS score for both the entire colon (6.8±1.76 for SPMC group vs 6.6±1.7 for PEG-Asc group) and for the right colon (1.95±0.73 for SPMC group vs 1.96±0.71 for PEG-Asc group) were comparable between groups. In addition, 97.1% patients in the SPMC group and 84.8% in the PEG-Asc group reported no or mild discomfort (P<0.0003) and 97.883.4% expressed their willingness to repeat the preparation (P<0.0001). The palatability was better in the SPMC cohort and related symptoms occurred more frequently in the PEG-ASC cohort. Regardless of which preparation was used, the split regimen was associated with better cleansing compared with the same-day method (OR=3.39; 95% CI=1.1–10.4; P=0.03). Predictors of poor cleansing were comorbid medical conditions, discomfort during preparation, and incomplete consumption (<75%) of preparation.

Kim et al[26] conducted a randomized, multicenter, single-blinded, non-inferiority study comparing split-dose Conventional 4-L PEG versus split-dose SPMC/bisacodyl. A total of 365 patients were analyzed on intention-to-treat analysis; 18 in the PEG group and 28 patients in the SPMC did not complete the entire preparation, and thus 319 patients were evaluated in a per protocol (PP) analysis

(166 in the PEG cohort vs 153 in the SPMC cohort). This group observed that the total mean BBPS score was similar between the two groups in both the ITT (SPMC/bisacodyl: 7.3±1.6 vs Conventional 4-L PEG: 7.2±1.7; P=0.329) and PP (SPMC/bisacodyl: 7.3±1.6 vs Conventional 4-L PEG: 7.2±1.6; P=0.680) analysis. The mean visual analog scale (VAS), used to analyze compliance and satisfaction level, and Likert scale (LS) score, used to analyze ease of use, were higher in the SPMC group in both ITT (P<0.001, 7.58±1.94 vs 5.79±2.43) and PP analyses (P<0.001, 7.62±1.95 vs 5.92±2.35). The adverse event rate was lower in the SPMC group than in the PEG group (P<0.05). Thus, it was concluded that SPMC preparation was comparable to conventional PEG with respect to bowel preparation adequacy and superior with respect to compliance, satisfaction, and safety.

Discussion

This review assessed the efficacy and patient tolerability of split-dose SPMC vs PEG for outpatient colonoscopy. The use of SPMC split-dose preparations correlated with improved tolerability, fewer physical complaints from patients, and a higher adherence and completion rate in most cases. However, in terms of adequacy of bowel preparation, the split-dose SPMC and PEG preparations were similar in the majority of studies. Adequate bowel preparation is an integral part of adequate screening and surveillance in patients referred to colonoscopy. Poor bowel preparation may cause incomplete visualization of the colon, and may lead to missed lesions, procedure failure, prolonged procedure time (increasing both cecal intubation and withdrawal time), and an increased risk of complications.[27,28] The traditional PEG 3- or-4-L regimens are still widely used and are associated with excellent efficacy when well tolerated. However, some studies have demonstrated poor compliance because of the large volumes of these solutions.[29]

In a recent update from 2019, ESGE guidelines for bowel preparation for colonoscopy recommend the use of split-dose bowel preparation for elective colonoscopy (strong recommendation, and high-quality evidence).[30] Typically, the standard dose of a bowel preparation is split between the day before and the morning of the procedure. The second dose should be administered between 3–8 hours before the planned start of the colonoscopy procedure,[31] as patients must have completed the preparation a minimum of 2 hours before sedation to avoid potential aspiration.[32] The guidelines reference a meta-analysis involving 47 RCTs, including four different bowel preparation regimens (polyethylene glycol, sodium phosphate, picosulfate, or oral sulfate solutions) with a total of 13,478 patients, where it was shown that split-dose regimens, regardless of the type and dose of the cleansing agent, provided excellent or good colon cleansing more frequently than day-before bowel preparation (OR=2.51, 95% CI=1.86–3.39). This result was confirmed in sub-analyses restricted to PEG (OR=2.60, 95% CI=1.46–4.63), sodium phosphate (OR=9.34, 95% CI=2.12–41.11), and picosulfate (OR=3.54, 95% CI=1.95–6.45). Split dosing was also associated with a higher proportion of patients willing to repeat the preparation (OR=1.90, 95% CI=1.05–3.46).[33]

Similarly, ASGE guidelines for bowel preparation for colonoscopy[34] recommend split-dose regimens for all patients and/or same day preparations for afternoon colonoscopies with a portion of the preparation taken within 3–8 hours of the procedure, both to enhance colonic cleansing as well as improve patient tolerance (moderate quality of evidence). In these guidelines, experts recommend that bowel preparations be individualized by the prescribing provider for each patient based on efficacy, cost, safety, and tolerability considerations balanced with the patient's overall health, comorbid conditions, and preferences (high quality of evidence). Both PEG and SPMC are good options for bowel preparations. However, these guidelines recommend that the SPMC preparation should be used cautiously in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as ascorbic acid may provoke hemolysis in these patients. In a systematic review and meta-analysis comparing different regimens, including split-dose regimens of SPMC and PEG for colonoscopy preparation, Jin et al[35] analyzed a total of 25 RCTs and observed that no difference was found in polyp detection rate (RR=0.94; 95% CI=0.82–1.08, P=0.37; I^2=46%) nor adenoma detection rate (RR=0.88; 95% CI=0.74–1.05, P=0.16; I^2=37%). However, adverse events, such as nausea, vomiting, and bloating, were less frequent in the SPMC group (RR=0.78, 95% CI=0.66–0.93, P=0.004; I^2=88%). Additionally, a higher proportion of patients were likely to complete the SPMC regimen (RR=1.08; 95% CI=1.04–1.13, P<0.001; I^2=95%) and the percentage of patients who were willing to repeat an identical bowel preparation in the future was significantly higher in the SPMC group compared to the PEG group (RR=1.44; 95% CI=1.25–1.67, P<0.001; I^2=95%). In terms of colon cleansing, there was no significant difference between the two agents, although there was a trend in favor of the PEG solution (RR=0.93, 95% CI=0.86–1.01, P=0.07; I^2=87%).

Similarly, in a recent systematic review and meta-analysis, Rocha et al[7] analyzed 16 RCTs and compared SPMC and PEG before elective outpatient colonoscopy. The authors concluded that SPMC and PEG can be used for split preparations as there are no difference in bowel cleaning success, tolerability, and adverse events, but SPMC should be the preferred choice for day-before preparations because of its improved tolerability. There was no difference observed between the two preparations when comparing polyp or adenoma detection rates.

However, while these aforementioned studies saw no differences in adverse events, it should be noted that because of hyperosmolarity and magnesium content, solutions containing SPMC are contraindicated in patients with congestive heart disease, hypermagnesemia, rhabdomyolysis, gastrointestinal ulcerations, and severe impairment of renal function, which can lead to magnesium accumulation. In a retrospective study[36] using administrative data to research adults >65 years old, SPMC was associated with an increased risk of hospital admission due to hyponatremia when compared with PEG solution. Although occasionally not well tolerated given lower palatability and increased volume, PEG is considered generally safe for patients with pre-existing electrolyte imbalances and for patients who cannot tolerate a significant sodium load (for example those with renal failure, congestive heart failure, or advanced liver disease with ascites).[37]

Conclusion

Studies comparing split-dose SPMC and PEG for bowel preparation for outpatient colonoscopy demonstrate that both are effective in terms of satisfactory bowel cleansing when evaluated with the OBPS, BBPS, and/or the Aronchick scoring system. Furthermore, split-dose SPMC may be associated with improved patient tolerance, adherence rates, and less side-effects.

Ethical Statement

The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr. Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work. The authors report no other conflicts of interest.

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