REVIEW ARTICLE



Effectiveness and safety of polyethylene-glycol-4000 versus sodium picosulphate plus magnesium oxide and citric acid for bowel cleansing before colonoscopy in children: A systematic review with meta-analysis

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Abstract

Colonoscopy is performed for diagnostic and therapeutic purposes. The quality of colonoscopy depends on adequate bowel cleansing. However, there is no standardized protocol for bowel preparation in children. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to estimate the effectiveness, safety, and tolerability profile of polyethylene glycol (PEG) compared with those of sodium picosulfate magnesium citrate (SPMC) in children. The primary sources of the reviewed studies were Scopus, PubMed, and Cochrane Library. The databases were systematically searched for RCTs comparing PEG 4000 to SPMC as a bowel cleansing solution. Six studies were included. The analysis showed that both PEG and SPMC are effective for bowel cleansing, while a split-dose regimen may be preferable to a day-before one. There were no differences between the two groups regarding adverse events (AEs) such as abdominal pain, nausea, vomiting, bloating, and anal discomfort. Additionally, preparation with SPMC was preferred in terms of

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acceptability and compliance. Still, the need to place a nasogastric tube was significantly lower in the SPMC group compared to the PEG group and in the split dose regimen compared to the day before. In conclusion, PEG and SPMC are equally effective in obtaining an adequate bowel cleansing with a comparable AE rate; moreover, split-dose administration may be preferable to day-before one in terms of effective bowel cleansing. However, SPMC preparation is more acceptable seems to result in higher compliance, and to reduce the use of a nasogastric tube, that we encounter daily in clinical practice, is perceived as a stressful experience for children and their families.

KEYWORDS

bowel preparation, endoscopy, pediatric

1 | INTRODUCTION

Colonoscopy is commonly performed in adults and children for diagnostic and therapeutic purposes. In pediatrics, it is indicated in chronic abdominal pain/ diarrhea, rectal bleeding, and weight loss or failure to thrive.^{2,3} It is often used to diagnose and monitor inflammatory bowel disease (IBD), with terminal ileum (TI) intubation and routine biopsy of gastrointestinal mucosa crucial even in the absence of visible abnormalities.4 Quality colonoscopy depends on effective bowel cleansing. However, about one-third of pediatric colonoscopies suffer from inadequate preparation, with 20%-30% of cases having incomplete procedures due to suboptimal cleansing. Inadequate preparation reduces diagnostic accuracy, prolongs procedural time, increases adverse events (AEs), necessitates rescheduling, and raises costs.⁶ There is no standardized preparation protocol for children, as methods must consider age, size, and clinical condition.^{7,8} While several adult trials support the use of polyethylene glycol (PEG) low-volume preparations, few randomized studies exist for pediatric populations.9

PEG, a high molecular weight (4000 Da) nonabsorbable macrogol polymer in a dilute electrolyte solution, acts as a bowel cleanser through osmotic effects. Despite being recommended for both adult and pediatric colon preparation, 10,11 PEG's large fluid volume can reduce tolerability in children. Recent pediatric meta-analyses show better acceptability for split-dose PEG (two separate doses, usually one the evening before and one the morning of the procedure) compared to the day-before dose (in a single dose the day before the procedure), 12 though its effectiveness and safety warrant further research. Sodium picosulfate magnesium citrate (SPMC), a low-volume cleanser, combines stimulant laxative sodium picosulfate (PICO) and hyperosmotic magnesium citrate to enhance luminal water.8 Two randomized controlled trial (RCTs) and a recent meta-analysis suggest that SPMC is as effective as PEG but better tolerated. 13,14 Additionally. a pediatric RCT found split-dose SPMC superior to the

What is Known

- Colonoscopy is an important examination and depends on adequate bowel preparation.
- There are no standardized protocols for children, but polyethylene glycol (PEG) and sodium picosulfate magnesium citrate (SPMC) are the most commonly used in pediatrics, with different administration regimens (day-before and split-dose).

What is New

- PEG and SPMC are equally effective for bowel cleansing; moreover, split-dose administration may be preferable to day-before in terms of effective bowel cleansing.
- SPMC preparation is more tolerated by patients, has higher compliance, and avoids the use of a nasogastric tube.

day-before regimen for both cleansing success and acceptability. While split-dose regimens outperform single-dose ones in adults 16,17 and in meta-analyses, a comprehensive meta-analysis for pediatric bowel preparation before colonoscopy is still lacking. We conducted a systematic review and meta-analysis of RCTs to evaluate PEG's effectiveness, safety, and tolerability compared with SPMC for bowel preparation before pediatric colonoscopy.

2 | MATERIALS AND METHODS

2.1 Study design

We performed a systematic review of the literature and a pooled analysis of the proportions of RCTs according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.¹⁹

2.2 | Review question

The review question was formulated according to the PICO scheme (P: patients, I: intervention, C: comparison, O: outcomes) as follows:

Among children who undergo elective colonoscopy (P), when using the day-before or split dose preparation with either PEG (I) or SPMC (C), is there any superiority in terms of efficacy as primary outcome (O) and as secondary outcomes, we evaluated AEs, tolerability, acceptability, and compliance.

2.3 Data source and search strategy

The primary sources of the reviewed studies were Scopus, PubMed, and Cochrane Library. The databases were systematically searched for RCTs comparing PEG 4000 to SPMC as a bowel cleansing solution. The search was launched using Medical Subject Headings (MeSH) terms combined with the Boolean operators ("AND," "OR") as follows: "(Bowel preparation) AND (colonoscopy) AND ((randomized controlled trial) OR (RCT) OR (randomized trial)) AND (children)." Database searches were supplemented with literature searches of reference lists from potentially eligible articles by two reviewers (S. F. and M. P.) to find additional studies. The period included in our search was from January 1, 2000 to June 11, 2023.

2.4 | Eligibility criteria

Inclusion criteria were as follows: (1) RCT on PEG 4000 or SPMC; (2) studies published in 2000 or later; (3) studies reporting data on efficacy, AEs, tolerability, acceptability, and compliance after bowel preparation for elective colonoscopy in children.

Exclusion criteria were as follows: (1) studies on animal experiments; (2) conference reports, case reports, editorial materials, letters, protocols, meta-analyses, and reviews; (3) studies with full text unavailable; (4) studies with incomplete or missing essential data; (5) non-English studies; (6) adult patients.

2.5 Outcomes measurement and data synthesis

The primary outcome was the efficacy of bowel preparation according to validated scales (Aronchick, Boston Bowel Preparation, and Ottawa Bowel Preparation Scales) as reported by studies. Secondary outcomes included AEs (abdominal pain, nausea, vomiting, bloating, anal discomfort), acceptability (ease of take assessed through questionnaires), nasogastric tube use after the failure of the oral route, and compliance

(amount of solution intake). Study-level variables included publication year, geographic source, design, study size, type of analysis (intention to treat or per protocol), quality, and bowel preparation modality (daybefore vs. split-dose). Patient-level variables included age, sex, race, body mass index (BMI), colonoscopy indication, and diagnosis at colonoscopy.

After duplicate removal, titles and abstracts were screened (identification), followed by a full-text screening of eligible papers (screening). The reference lists were also screened for missing papers (forward search) in a third round (eligibility). Eligible papers were included based on inclusion criteria (inclusion). Two authors (M. P. and S. F.) independently conducted the search rounds, resolving discordances by consensus with a third senior author (L. R.).

2.6 Risk of bias

Methodological quality and risk of bias for each study were assessed using the revised tool to determine the risk of bias in randomized trials (RoB2 tool).²⁰

2.7 | Statistical analysis

Continuous variables were analyzed using the weighted mean difference and 95% confidence interval (CI). Categorical variables were assessed with the odds ratio (OR) and 95% CI. Variables reported as median and range or interquartile range were converted to mean and standard deviation following Hozo et al.²¹ Pooled relative risk and pooled risk difference were calculated using random-effects models. The I2 statistic was used to gauge heterogeneity, with values of 40% or lower considered trivial and 75% or higher as considerable. Publication bias was examined with the Egger test; a p-value < 0.05 indicated significant smallsize study effects. If fewer than 10 studies were included, results for heterogeneity and publication bias were deemed unreliable. A conventional p < 0.05 was considered statistically significant. Statistical analysis was performed using Jamovi v 2.5 (The Jamovi Project, Sydney, Australia).

3 | RESULTS

The electronic database search identified 106 studies. After duplicate removal and exclusion based on publication date, 53 studies remained. Forty studies were excluded after screening titles and abstracts, and seven were excluded after full-text review. Finally, six papers 13-15,22-24 were included in the analysis. The search strategy is summarized in Figure 1.



Two solutions were compared: PEG as high-volume preparation (PEG 4000-ELS)^{13,14,22-24} and SPMC.^{13–15,23} Both were used in day-before and split-dose regimens. PEG was administered in the day-before regimen in five studies^{13,14,22-24} and split-dose in two studies.^{22,24} SPMC was given in the day-before regimen in three studies^{14,15,23} and split-dose in two studies.^{13,15} All RCTs assessed commercially available products at full dosage.

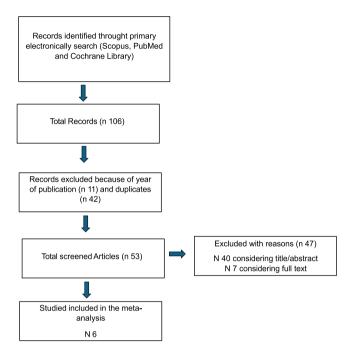


FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the search process.

The comparisons analyzed were PEG versus SPMC and split-dose versus day-before regimen. Three RCTs compared PEG 4000 L to SPMC. 13,14,23 Two trials compared PEG split-dose with the day-before regimen, 22,24 and one compared SPMC split-dose with the day-before regimen. 15 One trial compared the PEG day-before regimen to the SPMC split-dose regimen. 13 Studies with the same protocols and outcomes were included in the meta-analysis.

3.1 | Outcome

3.1.1 Patients and demographics

Table 1 summarizes the characteristics of the patients (n = 965) in the six included studies, which included 451 patients (46.7%) who received PEG^{13,14,22-24} and 514 patients (53.3%) who received SPMC. 13-15,23 The PEG group had 163 females and 288 males (36.1% and 63.9%), while the SPMC group had 232 females and 282 males (45.1% and 54.9%). The mean age ranged from 8.5 to 14.5 years in the PEG group and from 12.1 to 13.9 years in the SPMC group. The population was diverse, including patients from various continents. Bowel cleanliness was assessed using the Aronchick scale 25 in one study,24 the Ottawa Bowel Preparation Scale (OBPS) 26 in one study, 13 and the Boston Bowel Preparation Scale (BBPS) ²⁷ in four studies. ^{14,15,22,23} Adequate bowel preparation was defined as a total BBPS score ≥6 with all colon segment scores ≥2, a total OBPS < 5 with all colon segment OBPSS scores <2, or a total Aronchick

TABLE 1 Characteristics of the studies included in the meta-analysis.

Study	Country and year	Arms	No. of patients	Age	Sex (M/F)	BMI or weight* (kg)
Turner et al.	Canada 2009	PEG-ELS DB	40	12.3 ± 3.1	25/15	18.1 ± 3.2
		PMC DB	43	12.6 ± 3.1	29/14	20.1 ± 4.7
Di Nardo et al.	Italy 2014	PEG-ELS DB	72	12.9 ± 4.6	42/30	20.2 ± 4.1
		PMC Split	72	12.2 ± 4.7	36/36	20 ± 3.7
Sriphongphankul et al.	Thailand 2019	PEG-ELS DB	22	9.8 ± 4.3	11/11	22.25 ± 4.75*
		PEG-ELS Split	23	8.5 ± 4.5	12/11	22 ± 6
Szaflarska-Poplawska et al.	Poland 2019	PEG-ELS DB	43	14.5 ± 2.2	22/21	56.2*
		PMC DB	39	13.9 ± 2.7	16/13	51.7*
Tripathi et al.	India 2020	PEG-ELS DB	86	11.3 ± 4.92	64/22	34.98 ± 16.53
		PEG-ELS Split	93	11.7 ± 4.75	66/27	37.76 ± 17.99*
Di Nardo et al.	Italy 2023	PMC DB	180	12.1 ± 4.4	193/77	20.6 ± 4.2
		PMC Split	180	12.5 ± 3.3	98/82	20.4 ± 4.1

Abbreviations: BMI, body mass index; DB, day before; ELS, electrolyte lavage solution; F, female; M, male; PEG, polyethylene glycol; PMC, picosulphate plus magnesium oxide and citric acid.

^{*}Stands for weight.

scale <2. Data from the four studies using the BBPS score were pooled.

3.2 | Efficacy of bowel preparation

Among patients receiving a day-before dose, bowel preparation was adequate in 120 of the 137 patients (87.6%) in the PEG group and 248 of the 291 patients (85.2%) in the SPMC group (p = 0.51). For those on a split dose, 22 of the 23 PEG patients (95.7%) and 176 of the 180 SPMC (97.8%) patients had adequate preparation (p = 0.53). Comparing PEG and SPMC groups overall, bowel preparation was adequate in 142 of the 160 PEG patients (88.8%) and 424 of the 471 SPMC patients (90%) (p = 0.64). The split dose had significantly higher bowel cleansing success than the day-before dose (p < 0.001).

3.3 | AEs

Abdominal pain rate was recorded in all six included studies. Eighty-two cases were recorded among 335 patients receiving PEG in a day-before dose (24.5%), while eight cases were reported among 116 patients receiving the split dose (6.9%). In the SPMC group, 51 cases were recorded among 291 patients in the day-before dose group (17.5%), while 71 cases were recorded among 223 patients receiving the split dose (31.8%).

There were no differences in abdominal pain rates between the PEG and SPMC groups (p = 0.16). However, in the day-before dose subgroup, there was a significantly higher rate of abdominal pain in the PEG group compared to SPMC (p = 0.03). In the split dose, the abdominal pain rate was significantly lower in the PEG group (p < 0.01).

Nausea rate was recorded in four studies. 13,14,23,24 Eighty cases were recorded among 169 patients receiving PEG on the day-before dose (4.7%), while zero cases were recorded among 39 patients receiving SPMC (p < 0.01). For split-dose, 39 out of 93 (41.9%) in the PEG groups and 15 out of 43 (34.9%) in the SPMC group reported nausea (p = 0.43).

Comparing the PEG and SPMC groups, nausea was recorded in 119 out of 162 patients (73.5%) in the PEG group and 15 out of 82 patients (18.3%) in the SPMC group (p < 0.01). There were no significant differences between the day-before and split-dose groups.

The vomiting rate could not be pooled due to incomplete data. The bloating rate was recorded in five studies. ^{14,15,22,24} Seventy-three cases were recorded among 220 patients (33.2%) receiving PEG on the daybefore dose, while 42 cases were recorded among 152 patients (27.6%) receiving SPMC (p = 0.25). For split-dose, 10 out of 116 (8.6%) in the PEG groups and 61 out of 223 (27.3%) in the SPMC group reported bloating

(p < 0.01). Comparing the PEG and SPMC groups, bloating was recorded in 83 out of 336 patients (24.7%) in the PEG group and 103 out of 375 patients (27.5%) in the SPMC group (p = 0.40). There were no significant differences between the day-before and split-dose groups. Anal discomfort rate was recorded in five studies. 13-15,22,23 Sixteen cases were recorded among 177 patients (9%) receiving PEG on the day-before dose, while 20 were recorded among 191 (10.5%) patients receiving SPMC (p = 0.64). For split-dose, three out of 23 (13%) in the PEG group and 19 out of 223 (8.5%) in the SPMC group reported anal discomfort (p = 0.47). Comparing PEG and SPMC groups, anal discomfort was recorded in 19 out of 200 (9.5%) patients in the PEG group and 39 out of 414 (9.4%) in the SPMC group (p = 0.98). There were no significant differences between the day-before and split-dose groups.

3.4 | Acceptability

Acceptability of the solutions and regimens, evaluated as easy or challenging to take, was recorded in five of the six included studies. ^{13–15,22,23} One study was excluded for reporting erroneous data (the number of patients in the results did not match the number of enrolled patients). ²⁴

High acceptability was noted in 53 out of 177 patients (30%) receiving PEG the day before, compared to 240 out of 291 patients (82.5%) receiving SPMC the day before (p < 0.01). For split-dose, high acceptability was recorded in 20 out of 23 patients (87%) in the PEG groups and 207 out of 223 (92.8%) in the SPMC group (p = 0.32). Comparing PEG and SPMC, a higher acceptability rate was recorded in the SPMC group (p < 0.01). Comparing day-before and split-dose administrations, acceptability was significantly higher in the split dose (p < 0.01). In patients who received a split dose, 22 out of 116 (19%) in the PEG groups and one out of 223 (0.4%) in the SPMC group needed the nasogastric tube. The statistical analysis showed a lower rate of nasogastric tube use in the SPMC group (p < 0.01). Comparing PEG and SPMC groups, the nasogastric tube was used in 97 out of 336 patients (28.9%) in the PEG group and 9 out of 475 patients (1.9%) in the SPMC group, showing a significantly lower rate in the SPMC group (p < 0.01). Comparing day-before and split-dose administrations, nasogastric tube use was significantly less frequent in the split-dose group (Figure 2).

3.5 | Compliance

The compliance rate was recorded in all the six included studies. ^{13–15,22–24} In five studies, compliance was measured as the amount of solution (less or more than 75%) taken by the patient. ^{13–15,22,23} One study ²⁴ measured compliance by the percentage of patients'

Use of nasogastric tube in intestinal preparations

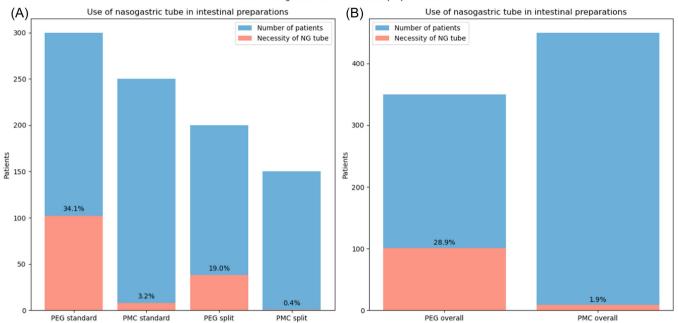


FIGURE 2 Use of the nasogastric tube in intestinal preparations. (A) The nasogastric tube was required in 34.1% of PEG standard cases, 3.2% of plus magnesium oxide and citric acid (PMC) standard cases, 19% of PEG split cases, and 0.4% of PMC split cases. A significantly lower rate of nasogastric tube utilization was noted in the PMC cohort (p < 0.01), both in standard and split administration modes. (B) Necessity of nasogastric tube insertion among all patients who underwent PEG and PMC, without differentiating the administration mode. In the PEG group, the nasogastric tube was required in 28.9% of cases, while in the PMC group, it was needed in 1.9% of cases, with a statistically significant difference favoring the PMC group (p < 0.01). PEG, polyethylene glycol; PMC, picosulphate plus magnesium oxide and citric acid.

intolerance to drinking. Two hundred and seventeen compliance cases were recorded among the 263 patients (82.5%) who received PEG on the day-before dose, while 274 out of the 291 patients (94.2%) received SPMC in the day-before dose (p < 0.01). In patients who received the split dose, compliance was recorded in 104 out of 116 patients (89.7%) in the PEG groups and 202 out of 223 patients (90.6%) in the SPMC group (p = 0.79).

Comparing PEG and SPMC, a higher compliance rate was recorded in the SPMC group (p < 0.01). There were no significant differences between the groups when comparing day-before and split-dose regimens.

3.6 Meta-analysis

From the included studies, four^{14,22–24} were analyzed for meta-analysis, comparing two protocols: PEG day before versus PEG split and PEG day before versus SPMC day before.

3.6.1 | PEG day-before versus PEG split-dose

Two studies^{22,24} compared these regimens. One hundred and eight patients received PEG day before, and

116 received PEG split. Successful bowel cleansing occurred in 53 patients (49%) with PEG day before versus 93 (80%) with PEG split (OR 1.48, 95% CI 0.86-2.08, p < 0.001). Abdominal pain was reported in 13 (13.8%) and eight (6.9%) patients, respectively (OR 0.8, 95% CI -0.13 to 1.74, p < 0.09). Nausea and vomiting occurred in 67 (62%) and 48 (41.4%) patients, respectively (OR 0.83, 95% CI 0.29–1.36, p < 0.002). Bloating was documented in 19 and 10 (17.6% and 8.6%) patients (OR 1.03, 95% CI 0.08–1.98, p < 0.08). The nasogastric tube was needed in 30 and 22 (27.8% and 19%) patients (OR 0.81, 95% CI -0.13 to 1.74, p < 0.09). Compliance was achieved in 93 and 104 patients (86% and 89.6%) (OR 0.34, 95% CI -0.72 to 1.4, p < 0.53). Anal discomfort was reported in one study (two vs. three patients) (see Figure 3).

3.6.2 | PEG day-before versus SPMC daybefore

Two studies 14,23 compared these regimens. One hundred and fifteen patients received PEG day before, and 111 received SPMC day before. Successful bowel cleansing was achieved in 104 patients (90%) with PEG day before versus 99 (89.2%) with SPMC day before (OR -0.14, 95% CI 0.99-0.71, p < 0.75). Abdominal pain occurred in 15 (13%) and 38 (34.2%)

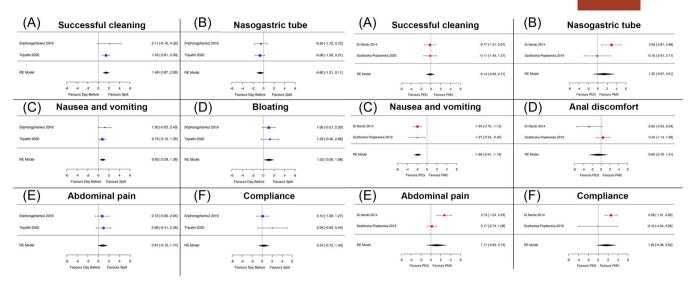


FIGURE 3 Meta-analysis of studies assessing the effectiveness of PEG day before versus PEG split overall cleansing success p < 0.001 (A), nasogastric tube p = 0.095 (B), nausea and vomiting p = 0.002 (C), bloathing p = 0.033 (D), abdominal pain p = 0.09 (E), compliance p = 0.531 (F). Meta-analysis of studies assessing the effectiveness of PEG day before versus PMC day before overall cleansing success p = 0.748 (A), nasogastric tube p = 0.26 (B), nausea and vomiting p < 0.001 (C), anal discomfort p = 0.579 (D), abdominal pain p = 0.251 (B), compliance p = 0.111 (E). PEG, polyethylene glycol; PMC, plus magnesium oxide and citric acid.

patients, respectively (OR 1.17, 95% CI -0.825 to 3.15, p < 0.251). Nausea and vomiting were reported in 50 (43.5%) and 12 (10.8%) patients, respectively (OR -1.89, 95% CI: -2.6 to -1.18, p < 0.001). Anal discomfort was documented in nine and four (7.8% and 3.6%) patients (OR -0.6, 95% CI -2.7 to 1.5, p < 0.58). The nasogastric tube was required in 16 and 2 (13.9% and 1.8%) patients (OR 0.81, 95% CI -0.13 to 1.74, p < 0.09). Compliance was achieved in 89 and 108 patients (77.4% and 97.3%) (OR 1.63, 95% CI -0.38 to 3.63, p < 0.11). Bloating was reported in one study (33 vs. 5 patients) (see Figure 3).

4 | DISCUSSION

There is no standardized protocol for bowel preparation before colonoscopy in children. An ideal bowel preparation is efficacious, safe, palatable, and minimally disruptive. While no current regimen meets all criteria, several safe and efficacious 1-day regimens are used. In the last decade, PEG without electrolytes has gained popularity in the United States. More recently, SPMC formulations have gained traction worldwide. Data suggest that both regimens are equally efficacious, but SPMC is more accepted and tolerable. This systematic review and meta-analysis aimed to summarize evidence regarding PEG and SPMC and split-dose or daybefore regimens for pediatric colonoscopy preparation. We found both PEG and SPMC equally effective for bowel cleansing, consistent with European

Society of Gastrointestinal Endoscopy (ESGE) guidelines for adults. 10 At the same time, we found that split-dose administration was preferable to day-before regimens, consistent with a recent meta-analysis of 47 RCTs on adult bowel preparation, which concluded that split-dose regimens yield the highest quality colon cleansing. 17 The ESGE guidelines recommend split dosing of bowel preparation is recommended because it significantly improves the percentage of patients with satisfactory colon cleanliness, significantly increases patient compliance, and substantially decreases nausea. 10 We found higher acceptability for SPMC and splitdose regimens. Compliance was higher for SPMC, with no differences in administration regimens, aligning with a meta-analysis of 25 RCTs comparing PEG and SPMC in adults that concluded that SPMC, with better tolerability and less frequent AEs, demonstrated noninferior bowel cleansing efficacy compared to PEG. 18 SPMC also had a significantly lower need for nasogastric tubes than PEG and lower with split-dose regimens. Nasogastric tube necessity was 28.9% for PEG cases and 1.9% for SPMC cases (p < 0.01). There is limited data in the adult literature on this finding because nasogastric tube administration for bowel preparation is generally not required in the adult population. In the pediatric setting, this finding can be considered a significant result related to the apprehension of the children undergoing repeated colonoscopies and their families, who perceive the nasogastric tube as an invasive treatment.



This study has limitations, including the limited number of studies in the comparative analysis and the inability to assess other confounding factors and the use of different scales used to determine the effect of bowel preparation. Despite several adult trials showing the benefit of PEG low-volume preparations, few randomized studies exist for the pediatric population.9 The main strength is that this is the first pediatric-focused systematic review and meta-analysis on bowel preparation before colonoscopy. We included studies from various countries (Italy, India, Canada, Thailand, and Poland), possibly extending the results' global validity. We also compared different administration regimens, providing valuable support for clinical practice. In conclusion, PEG and SPMC are equally effective for bowel cleansing with comparable AE rates. Splitdose administration may be more effective than daybefore regimens. SPMC is more acceptable, seems to result in higher compliance, and to reduce the need for a nasogastric tube, that we encounter daily in clinical practice, can be stressful for children and their families.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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