Bowel Preparations for Colonoscopy: An RCT

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WHAT’S KNOWN ON THIS SUBJECT: Available bowel preparation solutions for colonoscopy continue to represent a challenge for children and their families due to poor taste, high volume, and dietary restrictions with subsequent poor compliance and need to place nasogastric tube for administration.

WHAT THIS STUDY ADDS: Low-volume polyethylene glycol (PEG) preparations and sodium picosulphate plus magnesium oxide and citric acid (NaPico+MgCit) are noninferior to PEG 4000 with simethicon for bowel preparation before colonoscopy in children. Given its higher tolerability and acceptability profile, NaPico+MgCit should be preferred in children.

KEY WORDS colonoscopy, colon cleansing, children

ABBREVIATIONS BBPS—Boston Bowel Preparation scale
CI—confidence interval
NaPico+MgCit—sodium picosulphate plus magnesium oxide and citric acid
PEG—polyethylene glycol
PEG-Asc—polyethylene glycol 3350 with ascorbic acid
PEG-CS—polyethylene glycol 4000 with citrates
PEG-ELS—polyethylene glycol 4000 with simethicon

METHODS: This randomized, investigator-blinded, noninferiority trial enrolled all children aged 2 to 18 years undergoing elective colonoscopy in a referral center for pediatric gastroenterology. Patients were randomly assigned to receive polyethylene glycol (PEG) 4000 with simethicon (PEG-ELS group) or PEG-4000 with citrates and simethicone plus bisacodyl (PEG-CS+Bisacodyl group), or PEG 3350 with ascorbic acid (PEG-Asc group), or sodium picosulfate plus magnesium oxide and citric acid (NaPico+MgCit group). Bowel cleansing was evaluated according to the Boston Bowel Preparation Scale. The primary end point was overall colon cleansing. Tolerability, acceptability, and compliance were also evaluated.

RESULTS: Two hundred ninety-nine patients were randomly allocated to the 4 groups. In the per-protocol analysis, PEG-CS+Bisacodyl, PEG-Asc, and NaPico+MgCit were noninferior to PEG-ELS in bowel-cleansing efficacy of both the whole colon (P = .910) and colonic segments. No serious adverse events occurred in any group. Rates of tolerability, acceptability, and compliance were significantly higher in the NaPico+MgCit group.

CONCLUSIONS: Low-volume PEG preparations (PEG-CS+Bisacodyl, PEG-Asc) and NaPico+MgCit are noninferior to PEG-ELS in children, representing an attractive alternative to high-volume regimens in clinical practice. Because of the higher tolerability and acceptability profile, NaPico+MgCit would appear as the most suitable regimen for bowel preparation in children.

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Colonoscopy is an established diagnostic and therapeutic tool in a variety of gastrointestinal tract conditions affecting children and adolescents. For example, it is crucial for establishing the diagnosis of inflammatory bowel disease and provides definitive therapeutic options in patients with colonic polyps or lower gastrointestinal bleeding.\(^1\) The success of colonoscopy relies on multiple factors, and bowel preparation is among the most important of these. Inadequate bowel cleansing may have negative consequences for the examination, including incomplete visualization of the colon, missed detection of lesions, lower procedural safety, prolonged procedure time, and reduced interval time for procedural safety, prolonged procedure time, and reduced interval time for follow-up with significant economic impact.\(^2\) Up to 20% to 30% of incomplete colonoscopies are due to inadequate bowel cleansing, often attributed to the significant discomfort associated with the various preparation regimens.\(^3\)–\(^5\)

The ideal preparation should be of low volume, palatable, and successful in complete colon cleansing. Additionally, it should not be associated with adverse events including no significant fluid or electrolyte abnormalities or effects on histology findings. Despite the availability of various bowel preparations, the ideal preparation regimen for pediatric colonoscopy remains elusive, and only few well-controlled studies in pediatric population have been published.\(^6\)–\(^7\) Available preparations continue to represent a challenge for children and their families because of poor taste, large volume, and dietary restrictions with subsequent poor compliance and need to place nasogastric tube for the administration of intestinal lavage solution.\(^6\)

The primary aim of this investigator-blinded, randomized, controlled trial was to compare the efficacy of four methods of bowel cleansing before colonoscopy in children. Secondary aims were to compare safety, tolerability and acceptance of these four bowel cleansing solutions.

**METHODS**

**Study Design**

This is a single center, randomized, observer-blind, parallel group study conducted in Italy. The study design was defined according to the international recognized guidelines for clinical studies (www.clinicaltrials.gov, Identifier NCT01711437) and was approved by the local ethics committee. Written consent from young patients and informed consent from the legal guardian and patients aged >14 years were obtained.

**Participants**

Eligible participants were all children aged 2 to 18 years undergoing elective colonoscopy in our institution. Exclusion criteria were (1) requirement for urgent colonoscopy, (2) bowel obstruction, (3) known or suspected hypersensitivity to the active or other ingredients, (4) clinically significant electrolyte imbalance, (5) previous intestinal resection, and (6) known metabolic, renal, or cardiac disease.

The study took place in the Pediatric Gastroenterology Unit of the University of Rome, Sapienza in Rome, Italy, from January 2011 to February 2013. This unit is an academic tertiary referral center for pediatric IBD and for gastrointestinal endoscopy.

**Interventions**

Group A patients received a polyethylene glycol 4000 (PEG) solution with simethicone (PEG-ELS; Selg Esse, Promefarm, Italy) starting at 4 PM the day before colonoscopy at a dose of 100 mL/Kg (maximum 4 L). The patients were instructed to drink all the solution in ~4 to 6 hours.

Group B patients received a combination of PEG 4000 with citrates and bisacodyl (PEG-CS+Bisacodyl). PEG-CS is a new sulfate-free iso-osmotic formulation of PEG 4000 with citrates and simethicone (Lovol-esse; Promefarm, Milan, Italy) available as powder to be dissolved in 2 L of water.

Subjects allocated to this study group were instructed to take 1 to 4 (based on the weight and on the constipation questionnaire) bisacodyl 5-mg tablets (Lovoldyl, Promefarm, Milan, Italy) at 4 PM, followed 2 to 3 hours later by 50 mL/Kg (maximum 2 L) of PEG-CS solution. Patients were instructed to drink all the solution in ~2 to 3 hours.

Stool appearance was assessed by the children and their parents with the Bristol stool form chart.\(^8\) Stool type 1 or 2 was considered consistent with constipation.

Because bisacodyl could not be administered in a crushed tablet form per manufacturer’s recommendations, we decided to use the following dosage: 1 tablet in children ≤20 kg, 2 tablets for children between 20 and 30 kg, and 3 tablets for children ≥30 kg. In children with constipation, dosages were increased as follows: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 3 tablets in children ≥30 kg, respectively.

Group C patients received a PEG 3350 hyperosmotic solution with ascorbic acid (PEG-Asc; Moviprep, Norgine Ltd, Harefield, United Kingdom) starting at 4 PM the day before the colonoscopy at a dose of 50 mL/kg (maximum 2 L) with 25 mL/kg additional clear fluid (maximum 1 L) after completing solution intake according to the instruction of the manufacturing company. The patients were instructed to drink all the solution in ~2 to 3 hours.

Group D patients received 2 oral doses of sodium picosulfate plus magnesium oxide and citric acid (NaPico+MgCit; Picoprep, Ferring Italia, Milan, Italy), each diluted in 150 mL of water, at 4 PM and 5 hours later in the evening before the colonoscopy (on quarter sachet for children <6 years, a half sachet for children 6 to 12 years, and 1 sachet for children >12 years). Intake of at least 40 to 50 mL/Kg (maximum 2 L) of clear fluids (cold tea, sports drink, etc) was recommended after each dose. The age-adjusted dosage was dictated by the instructions of the manufacturing company:

- Subjects aged 2 to 8 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.
- Subjects aged 9 to 12 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.
- Subjects aged 13 to 18 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.

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Written consent from young patients and informed consent from the legal guardian and patients aged >14 years were obtained.

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Subjects allocated to this study group were instructed to take 1 to 4 (based on the weight and on the constipation questionnaire) bisacodyl 5-mg tablets (Lovoldyl, Promefarm, Milan, Italy) at 4 PM, followed 2 to 3 hours later by 50 mL/Kg (maximum 2 L) of PEG-CS solution. Patients were instructed to drink all the solution in ~2 to 3 hours.

Stool appearance was assessed by the children and their parents with the Bristol stool form chart. Stool type 1 or 2 was considered consistent with constipation.

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- Subjects aged 2 to 6 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.
- Subjects aged 7 to 12 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.
- Subjects aged 13 to 18 years: 2 tablets in children ≤20 kg, 3 tablets in children between 20 and 30 kg, and 4 tablets in children ≥30 kg.

Exclusion criteria were (1) requirement for urgent colonoscopy, (2) bowel obstruction, (3) known or suspected hypersensitivity to the active or other ingredients, (4) clinically significant electrolyte imbalance, (5) previous intestinal resection, and (6) known metabolic, renal, or cardiac disease.

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company. No solid food intake was allowed during the 24 hours before the examination according to the instructions of the manufacturing company.

In all 4 groups, a nasogastric tube was inserted if the child failed to drink the prescribed amount of cleanout preparation within the first hour.

The preparations were dispensed by a nurse who carefully explained how the products should be taken, emphasizing the importance of complete intake of the solution to ensure a safe and effective procedure. Moreover, each patient was provided with dietary instructions: low residue diet for 3 days before colonoscopy. During and after bowel preparation, solid food was not allowed. Clear liquid could be taken until 2 hours before the procedure. All patients enrolled in this study were scheduled for colonoscopy procedure. All patients enrolled in this study could be taken until 2 hours before the procedure. Moreover, each patient was provided with dietary instructions: low residue diet for 3 days before colonoscopy. During and after bowel preparation, solid food was not allowed. Clear liquid could be taken until 2 hours before the procedure. All patients enrolled in this study were scheduled for colonoscopy procedure.

The primary efficacy variable, excellent and good cleansing were considered "successful" and poor or inadequate as "failure." Before study initiation, the 3 endoscopists (GDN, SO, and SC) performed a calibration exercise on 20 colonoscopies using the scoring system adopted in this study (BBPS) to reach a satisfactory level of concordance among the physicians involved in the assessment of the degree of bowel cleansing.

All examinations were performed with a pediatric colonoscope (EVIS EXERA II video colonoscope PCF-Q180I, Olympus, Hamburg, Germany) under general anesthesia (in patients <10 years of age, undergoing both upper and lower endoscopy or with poor clinical conditions) or with moderate intravenous sedation (ie, midazolam 0.1 mg/kg intravenously, maximum dosage 5 mg).

**Evaluation of Bowel Preparations**

**Efficacy**

Preparation efficacy was evaluated by the blinded endoscopist according to the Boston Bowel Preparation Scale (BBPS) consisting of a 4-point scoring system applied to each of the 3 broad regions of the colon: right colon, transverse colon, and left colon (see Table 1 for details). In addition, overall cleansing of the colon was scored by summing up the scores of each segment. For the study, the total score ranging from 0 to 9 was divided into 4 classes: excellent cleansing (total score 8–9), good cleansing (total score 6–7), poor cleansing (total score 4–5), and inadequate cleansing (total score 0–3). For the primary efficacy variable, excellent and good cleansing were considered "successful" and poor or inadequate as "failure." Before study initiation, the 3 endoscopists (GDN, SO, and SC) performed a calibration exercise on 20 colonoscopies using the scoring system adopted in this study (BBPS) to reach a satisfactory level of concordance among the physicians involved in the assessment of the degree of bowel cleansing.

**Safety**

Vital signs, complete physical examination, and blood tests were performed at the time of patient enrollment and on the day of colonoscopy and included liver and kidney function test, potassium, magnesium, sodium, chlorides, and calcium. Adverse events were assessed on the day of colonoscopy by direct questioning and telephone interview 48 to 96 hours after colonoscopy. All new symptoms were considered to be treatment related and are included in the analysis. Any symptom that manifested after treatment (except those expected and included in the evaluation of gastrointestinal tolerability) and exacerbations of preexisting symptoms were assumed to be related to the bowel preparation regimen.

**Tolerability, Acceptability, and Compliance**

On the morning of colonoscopy, immediately before the procedure, a nurse questioned each patient about his or her experience by using a standardized questionnaire. Patients were asked about tolerability, need for nasogastric tube insertion, acceptability, and compliance. The endoscopist was not allowed to take part in the questioning or to supervise the questionnaire before colonoscopy.

Tolerability assessment was based on the recording of occurrence and severity of gastrointestinal symptoms such as nausea, bloating, abdominal, pain/cramps, and anal discomfort. A 5-point scale (1 = severely distressing, 2 = distressing, 3 = bothersome, 4 = mild, and 5 = none) was used to score the tolerability. The need for nasogastric tube insertion was also assessed.

The easiness of taking or swallowing the solution was graded according to the following scale: very severe distress = 4, severe distress = 3, moderate distress = 2, mild distress = 1, no distress = 0.

Willingness to repeat the same type of bowel preparation if necessary was also evaluated.

Compliance was scored on a 3-point scale according to the percentage of solution consumed (excellent: intake of the whole solution, good: intake of at least 75% of the solution, poor: intake of <75%).

**Study End Points**

The primary efficacy end point was the overall colon cleansing defined as the rate of “successful” cleansing (excellent and good scores in the BBPS, ie, ≥6 points).
Secondary end points included (1) the rate of adverse events, (2) the rate of specific symptoms associated to colonic lavage solutions, (3) the rate of children who declared that the intake of the solution was easy, (4) the rate of children who declared that they would be willing to repeat the same preparation regimen if needed, and (5) the rate of children taking an amount of solution $\geq$75%.

**Randomization and Blinding**
A randomized computer-generated list in blocks of 6 was prepared by a biostatistician, and eligible children were allocated to receive 1 of the 4 bowel preparations, stratified by 3 age groups: 2 to 7 years, 8 to 13 years, and 14 to 18 years. Opaque, sealed, and signed envelopes were prepared and numbered to ensure sequential allocation. Treatment was assigned by a clinic nurse using the next numbered envelope, opened only after written consent was obtained. The cleanout regimen was dispensed directly to the family.

The study was observer blind: the endoscopists were not allowed to perform any activities associated with study preparation before and after colonoscopy and had to avoid any discussion with the patients and the staff, which could disclose the type of bowel preparation.

**Statistical Analysis**
The sample size was calculated with the assumption of noninferiority between high-volume and low-volume regimen. Efficacy rate of high-volume regimens was assumed to be 80%. In addition, a difference of $\geq$20% of efficacy (ie, rate of successful bowel cleansing) between the high-volume and each of the low-volume regimens was assumed to be clinically relevant. To maintain the hypothesis, 5% type I error ($\alpha$), and 80% power ($1 - \beta$), the required sample size was estimated to be 70 patients per each arm.

The statistical analysis was performed by using absolute and relative frequency tables and contingency tables. The univariate analysis was conducted by using $\chi^2$ test for categorical variables and Student’s test for continuous ones. Differ- ences in pre–post laboratory variables for each group were assessed using the Wilcoxon signed-ranks test. Both intention-to- treat and per protocol analysis were provided. The noninferiority study was limited to the primary end point, whereas for tolerability, safety, and acceptance, superiority of the new treatment over the reference standard was analyzed. Because of the lack of data on the possible improvement in tolerability and acceptance in both adult and pediatric populations, it was necessary to base our sample size evaluation only in the primary end point.

The statistical significance was set at $P < .05$. The analysis was conducted by using SPSS, version 19.0.

**RESULTS**
Figure 1 shows the patients study flow. Of the 299 randomized patients 11 were excluded from the per protocol analysis (colonoscopy not performed in 8, randomized despite not meeting eligibility criteria 1, insufficient compliance 2). The 8 patients did not perform colonoscopy for reasons related to the hospital organization of the clinical activity and not related to the doctor choice or to patient refusal of the bowel solution. Two patients were excluded from the analysis because they added to the prescribed preparation a PEG-based laxative in the week before colonoscopy as commonly used in our institution before the study.

There was no difference in the incidence of dehydration between the 4 study arms, as judged by vital signs and clinical need for intravenous fluids. Only 1 clinical adverse event occurred in a 10-year-old girl of the PEG-ELS group who required intravenous fluid for 6 hours because of lethargy and dehydration (dryness of the oral mucosa and orthostatic hypotension) with serum electrolyte and glucose serum levels within the normal range.

No statistically significant difference between the pre- and posttreatment laboratory values of kidney, liver function, and serum electrolytes was found (Table 4).

Table 4 presents the data on patient tolerance for the bowel preparations. The rate of patients with none of the
specific symptoms associated with bowel lavage solutions was significantly higher in the NaPico+MgCit group (80.6%; 95% CI: 70.2–88.5) compared with PEG-ELS (45.8%; 95% CI: 34.6–57.4), PEG-CS+Bisacodyl (51.4%; 95% CI: 39.9–62.8), and PEG-Asc (50%; 95% CI: 38.6–61.4; P < .001).

Nausea, bloating, and abdominal pain were the most commonly reported symptoms and were significantly lower in the NaPico+MgCit group compared with PEG-ELS, PEG-CS+Bisacodyl, and PEG-Asc (P < .001; Table 5).

Anal irritation was significantly higher in the PEG-ELS group (8.3%; 95% CI: 3.4–16.5) compared with the PEG-CS+Bisacodyl (1.4%; 95% CI: 0.01–6.7), PEG-Asc (1.4%; 95% CI: 0.01–6.7), and NaPico+MgCit (0%; P < .001).

The percentage of children needing nasogastric tube placement for the infusion of the bowel-cleansing solution was significantly lower in the NaPico+MgCit group (1.4%) compared with PEG-ELS (20.8%), PEG-CS+Bisacodyl (2.8%), and PEG-Asc (5.6%; P < .001).

**Acceptability and Compliance**

The rate of children who stated that the intake of the solution was easy was significantly higher in the NaPico+MgCit (91.7%; 95% CI: 83.5–96.6) compared with PEG-ELS (34.7%; 95% CI: 24.4–46.2), PEG-CS+Bisacodyl (81.9%; 95% CI: 70.3–93.2), and PEG-Asc (61.1%; 95% CI: 49.5–71.8; P < .001).

The rate of children who declared that they would be willing to repeat the same

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**TABLE 2** Demographic Characteristics of the Study Groups at Per Protocol Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PEG-ELS (n = 72)</th>
<th>PEG-CS+Bisacodyl (n = 72)</th>
<th>PEG-Asc (n = 72)</th>
<th>NaPico+MgCit (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (58.3)</td>
<td>46 (63.9)</td>
<td>45 (59.7)</td>
<td>36 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (41.7)</td>
<td>26 (36.1)</td>
<td>29 (40.3)</td>
<td>36 (50)</td>
</tr>
<tr>
<td>Age (y) mean (SD)</td>
<td>12.9 (4.6)</td>
<td>12.3 (4.2)</td>
<td>13 (4.5)</td>
<td>12.4 (4.7)</td>
</tr>
<tr>
<td>2–7 y, n (%)</td>
<td>11 (15.3)</td>
<td>10 (13.9)</td>
<td>11 (15.3)</td>
<td>13 (18.1)</td>
</tr>
<tr>
<td>8–13 y, n (%)</td>
<td>20 (27.8)</td>
<td>33 (45.8)</td>
<td>20 (27.8)</td>
<td>25 (34.7)</td>
</tr>
<tr>
<td>14–18 y, n (%)</td>
<td>41 (56.9)</td>
<td>29 (40.3)</td>
<td>39 (56.9)</td>
<td>34 (47.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70 (97.2)</td>
<td>70 (97.2)</td>
<td>70 (97.2)</td>
<td>70 (97.2)</td>
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<td>Black</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>BMI (SD), kg/m²</td>
<td>20.2 (4.1)</td>
<td>20.3 (4.1)</td>
<td>20.6 (4.4)</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>Indication for colonoscopy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected IBD</td>
<td>7 (9.7)</td>
<td>8 (11.1)</td>
<td>8 (11.1)</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Bloody stools</td>
<td>13 (18.1)</td>
<td>19 (26.4)</td>
<td>21 (29.2)</td>
<td>17 (23.8)</td>
</tr>
<tr>
<td>Known IBD evaluation</td>
<td>46 (63.9)</td>
<td>35 (48.9)</td>
<td>38 (52.8)</td>
<td>40 (55.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (4.2)</td>
<td>4 (5.6)</td>
<td>2 (2.8)</td>
<td>5 (6.9)</td>
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<tr>
<td>Other</td>
<td>3 (4.2)</td>
<td>6 (8.3)</td>
<td>3 (4.2)</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Constipation before bowel cleanout, n (%)</td>
<td>5 (6.9)</td>
<td>4 (5.6)</td>
<td>7 (9.7)</td>
<td>6 (8.3)</td>
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<tr>
<td>Diagnosis at colonoscopy, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>45 (62.5)</td>
<td>35 (48.9)</td>
<td>42 (58.3)</td>
<td>36 (50)</td>
</tr>
<tr>
<td>Colitis (IBD)</td>
<td>23 (31.9)</td>
<td>24 (33.3)</td>
<td>24 (33.3)</td>
<td>24 (33.3)</td>
</tr>
<tr>
<td>Polyp</td>
<td>1 (1.4)</td>
<td>10 (13.9)</td>
<td>2 (2.8)</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.2)</td>
<td>3 (4.2)</td>
<td>4 (5.6)</td>
<td>7 (9.7)</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease.
preparation regimen if needed was significantly higher in the NaPico+MgCit (94.4%; 95% CI: 87.1–98.2) compared with PEG-ELS (34.7%; 95% CI: 24.4–46.2), PEG-CS+bisacodyl (79.2%; 95% CI: 68.7–87.4), and PEG-Asc (66.7%; 95% CI: 55.2–76.8; P < .001).

The rate of children taking an amount of solution ≥75% was significantly higher in the NaPico+MgCit (95.8%; 95% CI: 89.0–98.9) compared with PEG-ELS (63.9%; 95% CI: 52.3–74.3), PEG-CS+bisacodyl (88.9%; 95% CI: 80.0–94.7), and PEG-Asc (80.6%; 95% CI: 70.2–88.5; P < .001).

Theophylline and caffeine are also eliminated predominantly through the kidneys and liver, and thus in-patient administration through nasogastric tube is often required.7 In pediatric clinical trials, PEG-ELS has been more effective than active laxatives, including bisacodyl, senna, and magnesium citrate,6 also showing a cleansing effectiveness similar to that of NaPico+MgCit but with more adverse events.11

In contrast to adults, in whom low-volume PEG solutions represent an important alternative to standard volume formulations,12,13 there are no pediatric data on the use of low-volume PEG solutions.7

Our results showed, for the first time in children, that the tested low-volume PEG regimens (PEG-CS+bisacodyl, PEG-Asc) and NaPico+MgCit were noninferior to standard high volume solution (PEG-ELS) in bowel-cleansing efficacy. The high efficacy rate could be due to several factors. First, nurses expended much time to explain, especially among outpatient, how to take the bowel preparations and how important it is to take them as directed for a good colonoscopy outcome. Second, all colonoscopies were performed close to the end of the bowel preparation (before 11 am). This is a factor that is well known to positively influence efficacy rate.14

Our data also confirmed both adult and pediatric data on the safety of NaPico+MgCit compared with PEG-ELS11,15–17 and, for the first time in a pediatric population, with 2 low-volume PEG solutions (PEG-CS+bisacodyl and PEG-Asc). Indeed, in our series there was no statistically significant difference in the incidence of dehydration or in pre- and posttreatment laboratory values of kidney and liver function and serum

**DISCUSSION**

Since the withdrawal of oral sodium phosphate from the US market, PEG-ELS is among the most commonly used agents for colonoscopy preparation in children, particularly in Europe. However, children do not tolerate well the large volume and salty taste of these solutions, and thus in-patient administration through nasogastric tube is often required.7 In pediatric clinical trials, PEG-ELS has been more effective than active laxatives, including bisacodyl, senna, and magnesium citrate,6 also showing a cleansing effectiveness similar to that of NaPico+MgCit but with more adverse events.11

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**TABLE 3** Efficacy Outcomes Analysis at Per Protocol and Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PEG-ELS</th>
<th>PEG-CS+Bisacodyl</th>
<th>PEG-Asc</th>
<th>NaPico+MgCit</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol population</td>
<td>n = 72</td>
<td>n = 72</td>
<td>n = 72</td>
<td>n = 72</td>
<td></td>
</tr>
<tr>
<td>Qualitative preparation rating</td>
<td>NSb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>30 (41.7)</td>
<td>31 (43.1)</td>
<td>29 (40.3)</td>
<td>31 (43.1)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>36 (50)</td>
<td>32 (44.4)</td>
<td>31 (43.1)</td>
<td>34 (47.2)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>6 (8.3)</td>
<td>8 (11.1)</td>
<td>10 (15.9)</td>
<td>6 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Successful bowel cleansing, n (%)</td>
<td>66 (91.7)</td>
<td>63 (87.5)</td>
<td>60 (83.3)</td>
<td>65 (90.3)</td>
<td>NSc</td>
</tr>
</tbody>
</table>

**NS**, nonsignificant.

* P = 0.10, χ² test.

* P = 0.43, χ² test.

* PEG-ELS versus PEG-CS: right, P = 5; transverse, P = 9; left, P = 4. PEG-ELS versus PEG-Asc: right, P = 3; transverse, P = 4; left, P = 1. PEG-ELS versus NaPico+MgCit: right, P = 9; transverse, P = 3; left, P = 5. Student’s t test in all cases.

* PEG-ELS versus PEG-CS (P = 4); PEG-ELS versus PEG-Asc (P = 6); PEG-ELS versus NaPico+MgCit (P = 4).

* P = 0.39, χ² test.

* P = 0.4, χ² test.

**TABLE 4** Mean Changes in Laboratory Values

<table>
<thead>
<tr>
<th>Laboratory Variable</th>
<th>PEG-ELS, Mean (SD)</th>
<th>P*</th>
<th>PEG-CS+Bisacodyl, Mean (SD)</th>
<th>P*</th>
<th>PEG-Asc, Mean (SD)</th>
<th>P*</th>
<th>NaPico+MgCit, Mean (SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>0.03 (5.10)</td>
<td>0.98</td>
<td>4.13 (19.98)</td>
<td>0.58</td>
<td>4.14 (19.97)</td>
<td>0.58</td>
<td>4.83 (23.25)</td>
<td>.742</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>-0.06 (0.60)</td>
<td>-0.05 (0.58)</td>
<td>-0.02 (0.58)</td>
<td>-0.04 (0.58)</td>
<td>-0.04 (0.58)</td>
<td>-0.04 (0.58)</td>
<td>-0.16 (0.54)</td>
<td>.120</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>0.26 (1.11)</td>
<td>0.20</td>
<td>0.45 (5.47)</td>
<td>0.47</td>
<td>0.46 (5.50)</td>
<td>0.46</td>
<td>0.48 (5.50)</td>
<td>.088</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.05 (0.13)</td>
<td>0.05</td>
<td>0.01 (0.13)</td>
<td>0.05</td>
<td>0.02 (0.14)</td>
<td>0.02</td>
<td>0.01 (0.13)</td>
<td>.549</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>0.22 (0.27)</td>
<td>0.25</td>
<td>0.03 (0.30)</td>
<td>0.47</td>
<td>0.02 (0.28)</td>
<td>0.47</td>
<td>-0.04 (0.27)</td>
<td>.103</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>0.09 (0.39)</td>
<td>0.07</td>
<td>0.08 (0.39)</td>
<td>0.04</td>
<td>0.07 (0.40)</td>
<td>0.17</td>
<td>0.12 (0.37)</td>
<td>.076</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.00 (0.36)</td>
<td>0.00</td>
<td>0.02 (0.32)</td>
<td>0.00</td>
<td>0.02 (0.32)</td>
<td>0.00</td>
<td>0.05 (0.36)</td>
<td>.244</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-0.78 (15.01)</td>
<td>-0.78</td>
<td>0.06 (14.54)</td>
<td>0.48</td>
<td>-1.25 (16.78)</td>
<td>.807</td>
<td>0.54 (12.70)</td>
<td>.590</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>-0.84 (12.84)</td>
<td>-0.84</td>
<td>-0.31 (12.40)</td>
<td>-0.79</td>
<td>-0.07 (12.50)</td>
<td>-0.94</td>
<td>-2.79 (10.48)</td>
<td>.058</td>
</tr>
<tr>
<td>γ-GT (U/L)</td>
<td>0.80 (7.88)</td>
<td>0.80</td>
<td>0.87 (9.67)</td>
<td>0.53</td>
<td>1.29 (10.14)</td>
<td>2.39</td>
<td>-1.04 (0.47)</td>
<td>.669</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; GT, glutamyl transpeptidase.

* Test of significant change from screening to examination visit.
electrolytes in the 4 study groups. There was only 1 clinical adverse event in a 10-year-old girl from the PEG-ELS group who required intravenous fluid.

The clinical relevance of our study is also related with the different tolerability and acceptability profile of the four bowel-cleansing solutions. Indeed, our data showed that NaPico+MgCit appeared to be noninferior to the other solutions but better tolerated and accepted than both the standard high-volume preparation and the 2 low-volume PEG solutions. In our opinion, the higher tolerability and acceptability of NaPico+MgCit accounts, at least partially, for the noninferior efficacy of this regimen compared with the standard 4-L PEG preparation. In contrast, the 4-L PEG presented with an opposite ratio between efficacy and compliance.

Meta-analyses in adult patients have shown that the use of a split-dose of PEG for bowel preparation significantly improved the number of satisfactory bowel preparations, increased patient compliance, and decreased nausea compared with the full-dose PEG.18 We did not use this approach because in our unit, colonoscopy was performed early in the morning, which made it impossible to use this bowel preparation method. We acknowledge that this could also be a promising approach in children, and future studies are warranted to test this hypothesis.

The main limitations of the present analysis are the single-center design; however, the assessment of the efficacy was performed by 3 endoscopists blinded to the method of the preparation, which makes our results less prone to performance bias. Second, the majority of patients had suspected or known inflammatory bowel disease as an indication for the colonoscopy; this is mainly related to the setting of the study and could potentially limit the generalizability of the results. Third, the bowel cleansing was performed in both outpatient and inpatient settings; however, most of the procedures were performed on outpatients (~95%), ensuring the generalizability of the study results. Fourth, because of the lack of comparative studies, we adopted a 3-day period of low-residue diet before colonoscopy, irrespectively of the regimen adopted. We cannot exclude that a shorter period would have similarly decreased the mean level of bowel cleansing in all the groups.

CONCLUSIONS
In conclusion, our study shows for the first time in children that low-volume PEG preparations (PEG-CS+Bisacodyl and PEG-Asc) and NaPico+MgCit are non-inferior to PEG-ELS for bowel preparation before colonoscopy in children. NaPico+MgCit also appear to be better tolerated, representing a promising regimen for bowel preparation in children.

ACKNOWLEDGMENTS
We thank Alessandra Persi and Debora Panattoni for undertaking the important role of dispensing the products and explaining how they should be taken.

REFERENCES


TABLE 5 Secondary End Points at Per Protocol Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PEG-ELS</th>
<th>PEG-CS+Bisacodyl</th>
<th>PEG-Asc</th>
<th>NaPico+MgCit</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of any of the following</td>
<td>33 (45.8)</td>
<td>37 (51.4)</td>
<td>38 (50)</td>
<td>58 (80.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (52.8)</td>
<td>28 (38.9)</td>
<td>29 (40.3)</td>
<td>10 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>bloating</td>
<td>33 (45.8)</td>
<td>16 (22.2)</td>
<td>23 (31.9)</td>
<td>5 (6.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>22 (30.6)</td>
<td>6 (8.3)</td>
<td>12 (16.7)</td>
<td>2 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>anal discomfort</td>
<td>6 (8.3)</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>.010</td>
</tr>
<tr>
<td>need for nasogastric tube</td>
<td>15 (20.8)</td>
<td>2 (2.8)</td>
<td>4 (5.6)</td>
<td>1 (1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>acceptability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ease of taking: no distress, n (%)</td>
<td>25 (34.7)</td>
<td>59 (81.9)</td>
<td>44 (61.1)</td>
<td>66 (91.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>willingness to repeat, n (%)</td>
<td>25 (34.7)</td>
<td>57 (79.2)</td>
<td>48 (66.7)</td>
<td>68 (94.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>compliance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amount of solution intake ≥75%,</td>
<td>46 (63.9)</td>
<td>64 (88.9)</td>
<td>58 (80.6)</td>
<td>69 (95.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* χ² test.
Bowel Preparations for Colonoscopy: An RCT
Giovanni Di Nardo, Marina Aloi, Salvatore Cucchiara, Cristiano Spada, Cesare Hassan, Fortunata Civitelli, Federica Nuti, Chiara Ziparo, Andrea Pession, Mario Lima, Giuseppe La Torre and Salvatore Oliva
Pediatrics; originally published online July 7, 2014;
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