

Efficacy of Two Regimens for Colon Cleansing Using Polyethylene Glycol 4000: A Randomized Open Label Trial

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Aim: To compare effectiveness, safety and tolerance of two colon cleansing regimens using polyethylene glycol 4000 (PEG) in children.

Methods: Prospective, randomized, open clinical trial carried out in 129 children, 3 to 18 years old undergoing colonoscopy. Patients were randomized into two groups, 64 children received PEG with electrolyte (50 mL/kg) and oral bisacodyl (PEG+B group) or 65 other children received PEG with electrolyte (70 mL/kg) and glycerol enema (PEG+G group).

Results: Both regimens showed a good colon cleansing effectiveness with the percentage of successful cleansing being

93.8% for PEG+B regimen and 89.1% for PEG+G regimen ($P=0.51$). There was no statistically significant difference between the pre-regimen and post-regimen laboratory values. The rates of nausea (65.6% vs 31.3%; $P<0.001$) and bloating (50% vs 17.2%; $P<0.001$) of PEG+G group were significantly higher than that of PEG+B group.

Conclusion: Both regimens had good efficacy and safety for colon cleansing in children. The tolerance of PEG+B regimen was better.

Keywords: Bisacodyl, Bowel preparation, Colonoscopy, Glycerol enema.

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Appropriate bowel cleansing before colonoscopy for children requires consideration of the efficacy, safety, and tolerance of the regimen. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and American Society for Gastrointestinal Endoscopy (ASGE) recommend polyethylene glycol (PEG) with or without stimulant laxative (Bisacodyl) as the most common clean-out regimen for colon preparation in children [1,2]. Recent studies have shown that PEG alone (single or split dose) or difference in length of preparation (1-4 days) is good enough [3-7]. Hence, PEG plus bisacodyl (low-volume solution) may be considered as one of the many effective methods of colon cleansing. Glycerol suppositories, recommended for the treatment of constipation without any side-effects [8], can be added in the colon cleansing regimen in children. However, PEG 3350 and glycerol suppositories are not available in Vietnam, whereas glycerol enema and PEG 4000 are available in Vietnam. Besides, there have been studies showing the effectiveness and safety of regimen using PEG 4000 with electrolytes for colon cleansing in children [9].

In our hospital, we used PEG 4000 with electrolytes in

combination with glycerol enema before colonoscopy, which showed a dramatic improvement of cleansing effectiveness. However, in children this regimen requires drinking a large amount of fluid, limiting the compliance level and the efficacy. Therefore, this study was conducted in order to compare the effectiveness and safety of two colon cleansing regimens using PEG 4000 with electrolytes in combination with either oral bisacodyl or glycerol enema.

METHODS

This study was a prospective, randomized, open-label clinical trial, conducted in our hospital from October 1, 2016 to June 31, 2017. We enrolled consecutive children aged 3–18 years undergoing colonoscopy in our hospital. A written parental consent was obtained for all the enrolled patients in this study.

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We excluded children with; severe systemic disease that require parenteral nutrition, known chronic cardiovascular, liver, kidney, neurological or systemic diseases, known coagulopathy and/or thrombocytopenia with a decreased platelet function, known chronic granulocytopenia and/or immune deficiency, electrolyte

imbalance, and finally children with acute intestinal obstruction.

Patients' colonoscopy eligibility for enrollment selection was done at the outpatient department. A complete clinical physical examination was performed with the blood tests: hemoglobin, hematocrit, sodium, potassium, chloride, phosphorus, calcium, glucose, urea, creatinine, and alanine transaminase and aspartate transaminase. If all results were normal, the patient moved to next step.

Eight paper notes were prepared in a box, which contained four options for PEG+B regimen and another four options for PEG+G regimen. Then, selected patients were openly randomized to receive an option regimen in a box. When all paper notes in a box were selected, other 8 paper notes were prepared and the random selection process was repeatedly performed. The researchers recorded clinical symptoms and laboratory parameters before the beginning of the trial medication. The researchers, then prescribed, distributed a guide explaining to the patients' parents how to implement the regimen for CC, including diet, how to prepare drugs and PEG solution according to the selected regimen. Researchers also explained the possible side effects of drugs, instructed how to monitor and manage them initially when encountering these problems. The patient was then discharged home for the beginning of the selected regimen with a patient parental questionnaire reporting all clinical manifestations, side effects, therapeutic compliance and tolerance during the selected study regimen.

After applying the selected regimen, patients were monitored by researchers with a complete clinical physical examination, and patients or patients' parents were interviewed with the questionnaire during the selected regimen. The researchers recorded clinical manifestations, side effects, therapeutic compliance and tolerance of the used regimen, then the second blood tests were performed, as those before colonoscopy, and results recorded.

Colonoscopy was performed by an experienced pediatric endoscopist and evaluated with the Boston scale. Researchers recorded all endoscopic information, completed clinical research records, and requested a second physical examination, if any abnormalities occurred during colonoscopy.

All researchers and endoscopists were blind to the used regimens during monitoring visit before colonoscopy, during colonoscopy and in the post-colonoscopy period.

Colonic cleansing process: Both groups received a diet including snacks until 4 PM on the day before the colonoscopy. PEG+B regimen; after 4 PM on the day before

the colonoscopy, children received an oral bisacodyl tablet of 5 mg according to their bodyweight (Bisacodyl, fabrication: 1 tablet \leq 20 kg, 2 tablets 20-30 kg, and 3 tablets $>$ 30 kg) [2,3,9]. From 6 PM to 9 PM on the day before the colonoscopy, children were given PEG 4000 solution with electrolytes (Fortrans, fabrication), with a dose of 50 mL/kg of body weight with a maximum amount of two liters [9]. One Fortrans package contains 64g macrogol and is dissolved in one liter of water before drinking.

For PEG+G regimen, children were given PEG 4000 with a dose of 70 mL/kg of body weight with a maximum amount of 4 liters. Children had to drink half the dose of solution from 4 PM to 6 PM, take 2 hours off, and then drink the remaining half dose from 8 PM to 10 PM on the day before the colonoscopy [10]. Children received two glycerol 9g (Microlismi fabrication) by rectal enema. The first enema was done at 4 PM on the day before colonoscopy and the second one was done in the morning at 8 AM on the colonoscopy day.

Colon cleansing efficacy was evaluated by endoscopists according to the Boston Bowel Preparation Scale (BBPS) [11], consisting of a 4-point scoring system applied to each of the three broad regions of the colon: right colon, transverse colon, and left colon. Overall colon cleansing was scored by summing up the scores of each segment. The total score ranging from 0 to 9 was divided into 4 grades: excellent cleansing (total score, 8-9), good cleansing (total score, 6-7), poor cleansing (total score, 4-5) and inadequate cleansing (total score, 0-5). Successful colon cleansing was defined with a total score of at least 6.

Vital signs, physical examination, and blood tests were performed at the time of patient enrollment and after a colonoscopy that included hematological parameters, liver and kidney function test, sodium, potassium, chloride, calcium, phosphorus, glucose. Immediately before the procedure, each patient was asked about his or her experience by using a standardized questionnaire and answered about tolerability, acceptability and compliance. Tolerability assessment was based on the recording of the occurrence and severity of gastrointestinal symptoms such as nausea, bloating, abdominal pain and anal discomfort. We evaluated the acceptability of colon cleansing regimens by willingness to repeat with three grades: willingness to repeat, difficulty to repeat and no acceptance to repeat.

All participants were recorded completely using oral Bisacodyl 5 mg tablets as well as glycerol rectal enema 9g. Hence, treatment compliance was based on the volume of PEG; it was considered as excellent when the patient intake was $>$ 90% of prescribed volume of PEG, moderate between 50 to 90%, and poor $<$ 50%.

Statistical analysis: The statistical analyses were performed by using absolute and relative frequency tables and contingency tables. For categorical variables we used Chi-square test and Fisher exact test, and Student *t*-test for continuous variables. Differences in pre-post laboratory variables for each group were assessed using the Wilcoxon signed-ranks test. The statistical significance was set at $P < 0.05$. The analyses were conducted using SPSS version 20.0.

RESULTS

Our study had 136 patients who had an indication for colonoscopy, of which 129 were finally randomized to two groups: 65 patients received PEG+B regimen and 64 other patients received PEG+G regimen (**Fig.1**). However, one patient in PEG+B group did not complete intervention because this patient drank under 30% of PEG solution and passed solid stools before the procedure. This patient had delayed colonoscopy 1 day later with another colon cleansing regimen. There were no differences in gender and age between the two groups (**Table I**).

The total score was observed by 4 grades without statistically significant difference in two groups. The rates of PEG+G group and PEG+B group were 9.4% vs 15.6% in excellent cleansing; and 4.7% vs 1.6% in inadequate cleansing (**Table II**).

CC was also evaluated by each colonic segment and there was no significant difference in the efficacy of the

Table I Baseline Characteristics of Children Receiving Two Colon Cleansing Regimens (N=128)

Variable	PEG+B, (n=64)	PEG+G, (n=64)
Male sex	39 (60.9)	44 (68.8)
Age (y) ^a	5.80 (2.67)	5.67 (2.53)
Body mass index (kg/m ²) ^a	15.1 (2.18)	16.26 (2.94)
<i>Reason for colonoscopy^b</i>		
Bloody stools	62 (96.8)	59 (92.1)
Persistent diarrhea	1 (1.6)	3 (4.7)
Persistent abdominal pain	1 (1.6)	1 (1.6)
<i>Colonoscopy findings</i>		
Normal	10 (15.6)	9 (14.1)
Polyp	38 (59.4)	37 (57.8)
Anal fissure	15 (23.4)	13 (20.3)
Other	1 (1.6)	5 (7.8)

Values in no. (%) or ^amean (SD). Cleansing regimen – polyethylene glycol with electrolytes and oral bisacodyl (PEG+B) or glycerol enema (PEG+G). ^bOne child in PEG+G group underwent colonoscopy for anal mass.

two protocols in the different colonic segments. Mean BBPS score of PEG+G group and PEG+B group were similar (**Table II**).

Both regimens were equally efficient with a high rate of successful colon cleansing (95.3% of PEG+B regimen and 89.1% of PEG+G regimen) by per-protocol analysis or intention-to-treat analysis (93.8% vs. 89.1%; $P=0.51$). 128 patients underwent colonoscopy up to the cecum.

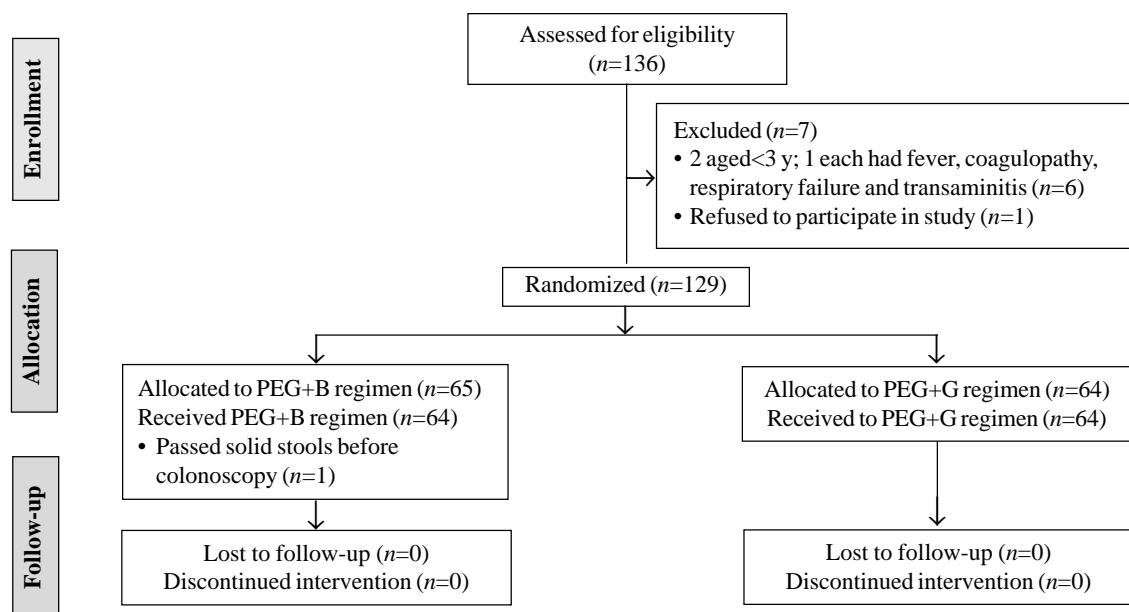


Fig. 1 Study flow chart.

Table II Efficacy of Two Colon Cleansing Regimens Among Children Undergoing Colonoscopy (N=128)

Variable	PEG+G (n=64)	PEG+B (n=64)
<i>Qualitative cleansing rating</i>		
Excellent (BBPS score: 8-9)	6 (9.4)	10 (15.6)
Good (BBPS score: 6-7)	51 (79.7)	51 (79.7)
Poor (BBPS score: 4-5)	4 (6.2)	2 (3.1)
Inadequate (BBPS score: 0-3)	3 (4.7)	1 (1.6)
Successful colon cleansing	57 (89.1)	61 (95.3)
<i>BBPS score per segment^a</i>		
Overall	6.1 (1.2)	6.4 (1.3)
Right colon	2.02 (0.4)	2.13 (0.4)
Transversal colon	2.05 (0.4)	2.16 (0.4)
Left colon	2.03 (0.4)	2.13 (0.45)

Values in no. (%) or ^amean (SD). All patients in both groups had cecal intubation. Polyethylene glycol with electrolytes and oral bisacodyl (PEG+B) or glycerol enema (PEG+G). BBPS-Boston bowel preparation scale. All $P>0.05$.

In this study, none of the enrolled children from both used regimens developed any severe side effects. The hemoglobin and hematocrit tended to decline in both the groups. Glucose level tended to decrease slightly in both groups; however, there were no children having hypoglycemia after implementing the regimen. There were 2 children with high blood glucose at 199.8 mg/dL and 176.4 mg/dL but without any clinical features. The rest of the laboratory indicators were normal.

The rates of nausea (65.6% vs 31.3%; $P<0.001$) and bloating (50% vs 17.2%; $P<0.001$) of PEG+G group were significantly higher than that of PEG+B group. However, the rate of vomiting (18.8% vs 10.9%) and abdominal pain (32.8 vs 27.9%) were not different between the both groups.

We found that 79.7% ($n=51$) of families and children had willingness to repeat the same colon cleansing regimen if needed in the PEG+B group. This rate was significantly higher compared to that of 35.9% ($n=23$) in the PEG+G group ($P<0.001$). The rate of excellent compliance (children with $\geq 90\%$ of fluid intake) in PEG+B group (62.5%), significantly higher than that in the PEG+G group (42.2%), ($P=0.03$).

DISCUSSION

Our study found that the two regimens were equally effective for colonic cleansing, with success rate of PEG+G group of 89.1% and PEG+B of 93.8%. Different reports in children report a successful rate of 72-95% [4-7,9,12,13]. The wide range of these results are related to the regimen used in research. Our study; thus, demonstrated similar efficacy of low-volume PEG 4000 solution with oral bisacodyl in colon preparation as the

other protocol (high-volume PEG 4000 or 3350, split-dose, length preparation) in children [4-7].

None of the children in this study developed any severe side effects with use of either regimen, compared to the study by Di Nardo, et al. [9] who reported a 10-year-old girl developing severe dehydration, and orthostatic hypotension, with use of PEG 4000 requiring intravenous fluid for 6 hours. There were no biochemical abnormalities due to these regimes, except the blood glucose levels slightly decreased in both groups but without any documented hypoglycemia. There were two children with hyperglycemia that could be resulted from the fact that we had instructed patients to take sugar 3 hours before endoscopy. These results were similar to other studies using PEG 3350 and PEG 4000 [9,13]. In contrast, another study showed the rate of hypokalemia was 24%, but without clinical manifestations, in electrolyte-free PEG-3350 regimen [4].

Among our patients, none presented with extra-intestinal symptoms such as seizures. However, digestive symptoms such as nausea and bloating after bowel preparation occurred significantly more commonly in the PEG+G group vs the PEG+B group. This could be related to the higher ingested fluid volume in the PEG+G regimen vs the PEG+B one. Likely, these symptoms are more common when patients need to drink more fluid. Such symptoms also affect the patient's ability to comply with the regimen [9]. However, there were no differences between the groups for vomiting and abdominal pain.

Our study showed the rate of children complying with $\geq 90\%$ of the fluid in PEG+G group (42.2%) was lower than the other group PEG+B (62.5%). Some recent studies presented the percentage of compliance in split-dose or low-volume solution or length of preparation was higher than full single dose [4-7,9]. The PEG+B group in our study had significantly higher acceptability in the willingness to repeat than PEG+G group, which was similar to a previous report. This result was also similar to another study on split-dose versus full single-dose regimen of PEG [6].

Limitation of our study was that the dose of PEG 4000 volume in two groups was different and made it difficult to compare the compliance. Other limitations of this study are the small sample size and done in only one centre. As a matter of fact, our results of Boston scores in both regimens were not as high as our expectation, around 6 points. Therefore, we hope to conduct a meta-analysis in future to find the optimal protocol for bowel preparation in Vietnamese children.

Both regimens used had a good colon cleansing efficacy in children, with a high safety by both clinical and

WHAT IS ALREADY KNOWN?

- Using PEG 4000 with electrolyte is effective and safe in CC in children.

WHAT THIS STUDY ADDS?

- Using either of PEG+B or PEG+G regimen was effective and safe for colon cleansing in children; however, the tolerance of PEG+B regimen was better.

biochemical indicators. The tolerance of PEG+B regimen was better.

Ethics clearance: Research Institute of Child Health of Vietnam National Children's Hospital; No. 113/QĐ-BVNTU, dated: September 16, 2016.

Contributors: HPT: concept and designed the study, analysed data and drafted the manuscript; TVH: collected the data and helped in data analysis; Ha NT: helped in data analysis; KN: helped in drafting the manuscript and methodological comments. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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