

# Polyethylene Glycol 4000 for Treatment of Functional Constipation in Children

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## ABSTRACT

**Objectives:** The aim of the study was to evaluate the effectiveness and safety of 2 different polyethylene glycol (PEG) doses for the maintenance treatment of functional constipation in children.

**Methods:** Children with functional constipation according to the Rome III criteria were randomly assigned to receive PEG 4000 at a dose of either 0.7 g/kg (high-dose group; n=45) or 0.3 g/kg (low-dose group; n=47) for 6 weeks. Adjustment of the therapy was recommended in the event of <3 bowel movements (BM) per week or  $\geq 3$  BM per day. The primary outcome measure was treatment success, defined as  $\geq 3$  BM per week with no fecal soiling during the last week of the intervention.

**Results:** A total of 90 of 92 randomized children, with a mean age of  $3.7 \pm 2.1$  years, completed the study. In the analysis based on allocated treatment, treatment success was similar in both groups (relative risk 0.9, 95% confidence interval 0.78–1.03). Compared with the high-dose PEG group, the low-dose PEG group had an increased need for therapy adjustment of borderline significance (relative risk 2.0, 95% confidence interval 1.0–4.2), an increased risk of painful defecation, a lower number of stools per week, and lower parental satisfaction. Adverse events were similar in both groups.

**Conclusions:** To achieve treatment success, both tested doses of PEG were equally safe and effective in the treatment of children with functional constipation.

**Key Words:** constipation, macrogol, therapy

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Constipation is one of the most common complaints in children, with a prevalence ranging from 0.7% to 29.6% (1). It accounts for 3% of general pediatric consultations and 25% to 30% of pediatric gastroenterology visits (2). Approximately one-third of children continue to have constipation into adulthood despite treatment and follow-up (3). Up to 95% of pediatric patients with constipation have no underlying medical disease and are diagnosed as having functional constipation. The aim of treatment is to

establish normal frequency and consistency of stools, without fecal incontinence and rectal bleeding. The key management steps include education, disimpaction, maintenance therapy, and behavioral modification. For a long-term maintenance therapy, the commonly used laxatives include polyethylene glycol (PEG), lactulose, magnesium hydroxide, and mineral oil (4).

PEG is a mixture of nonabsorbable and nonmetabolizable polymers that bind water molecules through hydrogen bonds; this leads to an increase in water in the colonic content, which facilitates bowel movements (BM) and painless defecation (5,6). A Cochrane review of randomized clinical trials showed that PEG is superior to placebo, lactulose, milk of magnesia, and mineral oil in the management of childhood constipation (7), and thus, PEG presently is considered as the first-line treatment for maintenance therapy (4). The suggested dose of PEG in children ranges from 0.2 to 0.8 g · kg<sup>-1</sup> · day<sup>-1</sup> (6). There is a paucity of data regarding the most effective dose of PEG, and dose-finding studies in children are needed (8). The aim of this study was to evaluate the effectiveness and safety of 2 different PEG doses for the maintenance treatment of functional constipation in children.

## METHODS

### Study Design

We conducted a randomized open-label trial from June 2013 through November 2013 at the Department of Paediatrics of the Medical University of Warsaw. The trial was initiated by the investigators and conducted independently of any commercial entities. The protocol for this trial was registered at clinicaltrials.gov before the start of recruitment.

### Patients

Children 1 to 18 years of age with functional constipation defined according to the Rome III criteria (9,10) (ie, defecation frequency of <3 times per week and 1 or more of the following criteria: fecal incontinence >1 episodes per week, a large amount of stools that clog the toilet, painful defecation, withholding behavior, or abdominal or rectal fecal impaction on physical examination) for at least 2 months were eligible for study inclusion. Exclusion criteria included a diagnosis of irritable bowel syndrome, mental retardation, endocrine disease (eg, hypothyroidism), an organic cause of defecation disorders (eg, Hirschsprung disease, spinal anomalies, anorectal pathology, a history of gastrointestinal surgery), functional nonretentive fecal incontinence, or intake of medications influencing gastrointestinal motility.

### Intervention

Once the diagnosis of functional constipation was made, the child was assessed for eligibility, and written informed consent to participate in the study was obtained. For children with fecal

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impaction, an enema (once per day, for a maximum of 3 days) was recommended. Eligible children were randomly allocated to receive PEG 4000 (Forlax; IpsenPharma, Paris, France) at a dose of either 0.7 g/kg (high-dose group) or 0.3 g/kg (low-dose group), for 6 weeks, in sachets to be dissolved in fluid and consumed once daily. Before the intervention, parents received a diary in which they recorded information about each child's BM, any discomfort during defecation, and adverse effects of the treatment. During the study period, if <3 BM per week or >3 loose stools per day were observed, the dose of PEG was adjusted and/or an additional laxative was administered. Assessment of outcome measures was based on the diaries collected during the final visit. Compliance was assessed during telephone contacts every 2 weeks and at the final visit at week 6. All of the children of appropriate developmental status were instructed to sit on the toilet for 5 minutes after each meal (up to 3 times per day).

## Outcomes

The primary outcome measure was treatment success, defined as 3 or more BM per week with no fecal soiling during the last week of the intervention. The secondary outcome measures included the need for therapy adjustment (ie, the number of patients in need for laxatives during treatment and/or a change of the starting dose throughout the study period). Moreover, at week 6, the following additional outcome measures were assessed: the number of stools per week, painful defecation, abdominal pain, and fecal incontinence. Parental satisfaction with the treatment was assessed using a 10-cm visual-analog scale during the final visit. All adverse events were recorded, and their possible relation to the study product consumption was evaluated.

## Sample Size

The sample size was based on the treatment success outcome. On the basis of the data from the literature, it was assumed that the effectiveness of PEG at a dose of 0.3 g/kg in the pediatric population was assumed to be approximately 70% (11). For a clinically significant difference in effectiveness of 25% between the study groups, taking into account the error  $\beta = 20\%$  (80% power) and the error  $\alpha = 5\%$ , with random assignment to the groups in a ratio of 1:1 and assuming 20% withdrawals or losses, it was calculated that 84 children had to be included in the study. Sample size calculations were performed using StatsDirect Statistical Software (version 2.7.8 (2010-03-15)) (<http://www.statsdirect.com>; StatsDirect Ltd, Cheshire, UK).

## Randomization and Allocation Concealment

Block randomization, with a block size of 4, was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial. The list was concealed from the clinicians enrolling patients and assessing outcomes, as well as from the parents, until the end of the study.

## Statistical Methods

The relative risk (RR), mean difference (MD), and 95% confidence interval (CI) were calculated using StatsDirect. The difference between study groups was considered significant when the  $P$  value was <0.05 or when the 95% CI for RR did not include 1.0, or for MD, did not include 0 (equivalent to  $P < 0.05$ ). We report the results of analysis based on allocated treatment, that is, all of the participants in a trial for which outcome data were available were

analyzed according to the intervention to which they were assigned, whether or not they received it. We also report the results of per-protocol analysis, that is, the analysis of the participants who complied with the protocol.

## Ethics

The ethics committee of the Medical University of Warsaw approved the study protocol. Informed consent was obtained from at least 1 parent or guardian of each child included in the study.

## RESULTS

Of the 92 children who underwent randomization, 45 were assigned to the high-dose PEG group (0.7 g/kg) and 47 were assigned to the low-dose PEG group (0.3 g/kg). One child in the high-dose group and 1 child in the low-dose group discontinued the study and eventually were lost to follow-up. Of the 92 children, 90 (98%), with a mean age of  $3.7 \pm 2.1$  years, were included in the analysis (supplemental Fig. 1, <http://links.lww.com/MPG/A369>). The baseline demographic and clinical characteristics did not differ between groups (Table 1).

## Primary Outcome Measure

Treatment success was similar in the low-dose and the high-dose PEG groups (41/46 vs 43/44, respectively; RR 0.9, 95% CI 0.78–1.03). Per-protocol analysis, however, showed that the low-dose PEG group had a borderline reduced chance of treatment success compared with the high-dose PEG group (24/29 vs 36/36, respectively; RR 0.82, 95% CI 0.7–0.97).

## Secondary Outcome Measures

In the low-dose PEG group, the dose of PEG had to be increased in 17 children (maximum dose of 0.7 g/kg). Two of these children needed enemas because of a lack of stool for 3 days. In the high-dose PEG group, the dose of PEG had to be reduced in 3 children because of loose stools (minimum dose of 0.5 g/kg), increased in 4 children because of a lack of effect (maximum dose of 1.5 g/kg), and 1 child refused to take the PEG. In the latter case, lactulose was then administered. The need for therapy adjustment tended to be higher in the low-dose PEG group compared with the high-dose PEG group (17/46 vs 8/44, respectively; RR 2.0, 95% CI 1.0–4.2). Moreover, in the low-dose PEG group, more children had painful defecation at week 6 compared with the high-dose PEG group (11/46 vs 0/44, respectively; RR 22, 95% CI 1.3–362), lower number of stools per week ( $5.2 \pm 1.5$  vs  $6.5 \pm 1.1$ , respectively; MD 1.3, 95% CI 0.75–1.8) and lower parental satisfaction with the

TABLE 1. Baseline characteristics

	Low-dose PEG group (0.3 g/kg)	High-dose PEG group (0.7 g/kg)
No. patients	46	44
Male/female	26/20	20/24
Age, y	4.2 $\pm$ 2.5	3.1 $\pm$ 1.3
Age range (median), y	1–13 (7)	1.5–8 (5)
Duration of constipation, mo	6.3 $\pm$ 2.6	6.0 $\pm$ 2.7
Stool frequency, /wk	1.3 $\pm$ 0.7	1.4 $\pm$ 0.6
Fecal incontinence, n (%)	11 (24)	10 (22)
Pain during defecation, n (%)	14 (30)	12 (27)

PEG = polyethylene glycol. Plus-or-minus values are mean  $\pm$  SD.

treatment assessed using a 10-cm visual-analog scale ( $8.1 \pm 1.9$  vs  $9.4 \pm 1.1$ , respectively; MD 1.3 95% CI 0.65–1.9).

At week 6, both groups had a similar number of patients with abdominal pain, and a similar number of patients with fecal incontinence. Both doses were well tolerated, and the risk of adverse events was similar in both groups (Table 2). Per-protocol analysis of the secondary outcomes yielded similar results and levels of significance (Table 3).

## DISCUSSION

### Principal Findings

This randomized open-label trial showed that both doses of PEG 4000 were equally effective in the treatment of children with functional constipation. After a 6-week intervention, the study groups did not differ with regard to treatment success (3 or more BM with no episodes of soiling during the last week of the study), which was high in the high-dose and low-dose PEG groups (97% and 89%, respectively). The low-dose PEG group, however, showed a trend toward the dose adjustment and/or other laxatives, which could have contributed to the treatment success in that group when compared with the high-dose PEG group. Moreover, the low-dose PEG group had an increased risk of painful defecation compared with the high-dose PEG group, a reduced number of stools per week, and lower parental satisfaction with the treatment. At the end of the intervention, the study groups did not significantly differ with regard to the number of children with fecal incontinence episodes and the number of children with abdominal pain. Adverse events were comparable in both groups.

According to recently published North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines, a starting PEG dose of  $0.4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  is recommended and should be adjusted according to clinical response (4). The results of our study suggest that PEG at a dose of either 0.3 or 0.7 g/kg administered for 6 weeks was equally effective and well tolerated. No need for the dose adjustment in the majority of patients in the high-dose PEG group suggests that in clinical practice this dose can be considered as an appropriate initial dose, particularly in settings with limited resources for follow-up.

### Strengths and Limitations

The strength of this study lies in its design, with an appropriate method of randomization, adequate generation of the allocation sequence, and a low percentage of patients lost to follow-up.

These features minimize the risk of selection and attrition biases. Moreover, this trial included a homogeneous population of children with a diagnosis of functional constipation based on the well-recognized Rome III criteria, without any important chronic comorbidities that may have influenced the outcomes.

The major limitation of this study was the lack of blinding, which increases the risk of performance and detection bias. The trial was conducted in a reference center, so the results may not be applicable to subjects encountered in the primary care setting. The majority of the study participants were young children. Thus, the results of this trial cannot be easily extrapolated to older age groups. This was, however, a consecutive series of patients, which mirrors our clinical practice. Another limitation of this study was the relatively short-term follow-up. It has been postulated that studies concerning a chronic condition such as childhood constipation should consider long-term outcomes with respect to both efficacy and safety outcomes (5). Nevertheless, up to now, only 1 randomized trial performed in children lasted >3 months (12). Finally, a limitation was the reliance on self-reporting and the use of diaries to measure outcomes and to minimize recall bias. The validity of diary records is questioned. Well-known problems with paper diaries include poor adherence and retrospective or just-before-a-visit recording (13).

### Comparison With Previous Studies

Earlier, only 1 double-blind, multicenter, placebo-controlled trial assessed the efficacy of 3 different doses of PEG 3350 ( $0.2$ ,  $0.4$ , or  $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) in 103 children with idiopathic functional constipation (11). Compared with placebo, all doses resulted in significantly higher rates of treatment success, defined as  $\geq 3$  BM during the second week of treatment. No significant differences were, however, found in the rates of treatment success among the 3 PEG groups (77%, 74%, and 73%, respectively). A direct comparison of our findings with the results reported by Nurko et al is difficult. First, PEG 3350, rather than PEG 4000, was used by Nurko et al. Second, their study follow-up period was shorter (2 weeks). Third, in the study by Nurko et al., all of the children also received a behavioral modification intervention. Similar to our study, all of the children were instructed to sit on the toilet for 10 minutes twice after meals. In addition, Nurko et al included positive reinforcement using age-appropriate printed calendars and special stickers for days without episodes of fecal incontinence and others with BM. Fourth, unlike in our study, tailoring of the treatment dose was not allowed. Finally, the 2 studies differ in the definition of treatment success between the 2 studies. Some of the above-mentioned differences,

TABLE 2. Primary and secondary outcomes (all assessed at week 6 of the intervention)

	Low-dose PEG (0.3 g/kg) (n = 46)	High-dose PEG (0.7 g/kg) (n = 44)	RR or MD (95% CI)
Treatment success (%)	41 (89)	43 (97)	0.9 (0.78–1.03)
Need for therapy adjustment	17	8	2.0 (1.0–4.2)
No. stools per week	$5.2 \pm 1.5$	$6.5 \pm 1.1$	1.3 (0.75–1.8)
Painful defecation	11	0	22 (1.3–362)
Abdominal pain	11	4	2.6 (0.97–7.4)
Fecal incontinence	6	1	5.7 (0.96–35.6)
Parental satisfaction (VAS)	$8.1 \pm 1.9$	$9.4 \pm 1.1$	1.3 (0.65–1.9)
Adverse events	3	4	0.7 (0.2–2.7)
	Rash n = 2 Acute gastroenteritis n = 1	Refusal of PEG n = 1 Loose stools n = 3	

Analysis based on allocated treatment. CI = confidence interval; MD = mean difference; PEG = polyethylene glycol; RR = relative risk; VAS = visual-analog scale. Plus-or-minus values are mean  $\pm$  SD.

TABLE 3. Primary and secondary outcomes (all assessed at week 6 of the intervention)

	Low-dose PEG 0.3 g/kg (n = 29)	High-dose PEG 0.7 g/kg (n = 36)	RR of MD (95% CI)
Treatment success	24/29	36/36	0.82 (0.7–0.97)
No. stools/wk	5.2 ± 1.5	6.5 ± 1.1	1.3 (0.7–1.9)
Painful defecation	7	0	∞ (2.4–∞)
Abdominal pain	7	4	2.2 (0.7–6.4)
Fecal incontinence	2	0	∞ (0.7–∞)
Parental satisfaction (VAS)	8.5 ± 2.1	9.5 ± 1.1	1 (0.2–1.8)
Adverse events	3	0	∞ (1.01–∞)

Per-protocol analysis. CI = confidence interval; MD = mean difference; PEG = polyethylene glycol; RR = relative risk; VAS = visual-analog scale. Plus-or-minus values are mean ± SD.

particularly the longer duration of the intervention, can explain the higher treatment success in our study compared with the study by Nurko et al.

Another study evaluated the efficient daily dose of PEG 4000 in 4 age groups (14). Regardless of age, a daily dose of PEG 4000 of approximately  $0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  was found to be effective in >90% of children with constipation, which corresponds to the results of our study. Again, a direct comparison of our findings with the results of this study is difficult because of the differences in the methodology, the duration of the intervention, and the differences in the definition of the primary outcome.

## CONCLUSIONS

The results of our randomized open-label trial showed that both tested doses of PEG 4000 administered for 6 weeks were equally safe and effective in the treatment of children with functional constipation. The use of low-dose PEG was, however, associated with an increased need for the adjustment of the therapy, which could have contributed to the treatment success in that group.

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