

Original article

Polyethylene glycol 4000 without electrolytes versus milk of magnesia for the treatment of functional constipation in infants and young children: a randomized controlled trial

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Background: Functional constipation is a common pediatric problem. Polyethylene glycol and milk of magnesia are osmotic agents used to treat constipation. There were few studies comparing the two laxatives for the treatment of functional constipation in infants and young children.

Objective: To compare two laxatives, polyethylene glycol 4000 without electrolytes (PEG) and milk of magnesia (MOM), by evaluating the effectiveness, adverse effects, and patient compliance.

Materials and methods: A randomized controlled trial was performed in 94 patients aged one-four years who attended at the pediatric outpatient clinic of Bhumibol Adulyadej Hospital and met the Rome III criteria for functional constipation receiving either PEG or MOM for four weeks. The primary outcome evaluation was the improvement rate. The secondary outcomes included the improvement of stool frequency, adverse effects, and compliance rate.

Results: Eighty-nine patients completed the study, including 46 in the PEG group and 43 in the MOM group. Baseline characteristics of age, body weight, sex, initial stool frequency, and duration of constipation were similar between groups. At the four week follow-up visit, 91% of PEG-treated patients and 65% of the MOM-treated patients exhibited improvement ($p=0.003$). Patients in the PEG group had greater increase of stool frequency after treatment than patients in the MOM group. Overall, adverse effects were mild, transient and not different among groups, but there was more diarrhoea in MOM treated patients. No serious adverse effects were observed. Compliance rates were 89% for PEG and 72% for MOM ($p=0.041$).

Conclusion: PEG was more effective and had greater patient compliance than MOM for the management of functional constipation in infants and children aged one-four years.

Keywords: Functional constipation, milk of magnesia, polyethylene glycol.

Constipation, defined as a delay or difficulty in defecation, is a common pediatric problem. It occurs in approximately 3% of general pediatric outpatient visits and 25% of pediatric gastroenterology consultations [1]. Chronic constipation is a source of anxiety for parents who worry about a symptom of a

serious disease. The most common cause is functional constipation without objective evidence of a pathological condition. It is most commonly caused by painful bowel movements with resultant voluntary withholding of feces by a child who wants to avoid unpleasant defecation [2]. Withholding feces can lead to prolonged fecal stasis in the colon, with reabsorption of fluids and an increase in the size and consistency of stools. The passage of large, hard stools to stretch the anus may frighten the child, resulting in a fearful determination to avoid all defecation. Such retentive

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behavior becomes an automatic reaction. As the rectal wall stretches, fecal soiling or incontinence may occur, angering parents and frightening the child [3].

Maintenance therapy consists of dietary interventions, behavioral modification, and laxatives [2]. Dietary changes consist of an increased intake of dietary fiber such as vegetables, fruits and other absorbable or nonabsorbable carbohydrates that soften stools. The goal of treatment is to promote daily, soft and painless stools preventing re-accumulation of feces [4].

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, 2006) recommends the laxatives as the maintenance therapy of childhood constipation. These are lubricants such as mineral oil or osmotic agents, including magnesium hydroxide (MOM), lactulose, sorbitol and polyethylene glycol (PEG). Despite the availability of different laxatives, few studies compared the efficacy or adverse effects of such different laxatives in children [5-9].

Polyethylene glycol (PEG) without electrolytes is a new type of osmotic laxative that has already been used successfully in adults. It appears to be superior to other osmotic agents in palatability and acceptance by children [5, 6, 10-16]. Preliminary clinical data suggest that administration of PEG to infants is effective without adverse effects noted [17].

Many studies have investigated the efficacy of polyethylene glycol (PEG) in management of childhood constipation [5, 6, 8-10, 12, 14, 15, 17-23]. The studies show that PEG increased stool frequency and reduced fecal incontinence episodes, and some studies reported adverse effects.

Four randomized controlled trial [6-8, 18] were conducted to compare PEG and lactulose in the treatment of childhood constipation. It was found that patients in the PEG group had more stool frequency after treatment than patients in the lactulose group. In a couple of studies [5, 9], Loening-Baucke et al. compared PEG and MOM in constipated children aged more than four years, and showed similar effectiveness of PEG and MOM in the long-term treatment of children with constipation and fecal incontinence [5, 9]. However, they used different inclusion criteria and criteria for successful outcomes in the two studies. For this reason, the studies using PEG could not be quantitatively compared in the treatment of childhood constipation.

This study was designed to compare polyethylene glycol without electrolytes (PEG4000) with milk of magnesia (MOM) by evaluating the effectiveness, adverse effects, and patient compliance. To evaluate the treatment response to osmotic laxatives, children younger than four years (infants and preschool children) were selected for this study. This aged group is better than older aged group, because they may have not yet been affected by colon inertia or chronic colon dilatation due to prolong stasis of feces. Moreover, because the prognosis is better if the treatment is started earlier [21, 24]. Comparison of the two laxatives in this age group has not been reported up to date.

Materials and methods

Patients

All infants and children aged one-four years, who attended at the pediatric outpatient clinic of Bhumibol Adulyadej Hospital for treatment of functional constipation between March 2008 and January 2009, were eligible for this study. Inclusion criteria were the patients who met the diagnostic Rome III criteria for functional constipation [25], including one month of at least two of the following characteristics: 1) two or fewer defecations per week, at least one episode per week of incontinence after the acquisition of toileting skills, 2) history of excessive stool retention, 3) history of painful or hard bowel movements, 4) presence of a large fecal mass in the rectum, and 5) history of large-diameter stools that may obstruct the toilet. Infants and children with renal insufficiency were excluded because they may have risk of magnesium overdose from milk of magnesia. Details of the intervention, potential adverse effects, and treatment of the adverse effects were explained to all parents before signing the consent form. This study was approved by Ethics Committee of Bhumibol Adulyadej Hospital.

Randomization

The randomization procedure consisted in a computer-generated randomization list in mix block sizes by a nonparticipating statistician. A blinded nurse dispensed either PEG or MOM according to the randomization list. Treatment allocation was prepared in separated sealed, opaque sequentially numbered envelopes.

Run-in, treatment, and follow-up phase

Run-in phase. The history taking was obtained from the parent of the constipated patient by a well-trained pediatrician. It included the age at the time of onset of constipation, the frequency of defecation and fecal incontinence (smears, small bowel movements, or large bowel movements in underpants) per week, size, and stool consistency. The history of excessive stool retention, painful or hard bowel movements and the history of large-diameter stools that may obstruct the toilet were obtained. Presence of retentive behavior, abdominal pain or discomfort, were recorded. Other recorded baseline characteristics were symptoms of bloating, nausea, vomiting, flatulence, and painful defecation. The past history of any laxative used was also recorded. Every patient was examined to rule out organic causes of constipation. Emphasis was on the presence of the "Warnings signs". If organic cause were suggested in any patient, they were excluded. Physical examination also included searching for abdominal mass and/or large fecal mass in the rectum. Patients who had fecal impaction received one phosphate enema daily for three days before receiving the first treatment. At initial visit, the parent received counseling about the cause of functional constipation to reduce anxiety, diet intervention, and behavioral modification of the child. They were instructed how to observe their child's symptoms, bowel movements, adverse effects, and how to record these in the parental record form. This run-in phase was used for one week to make sure that the parent could observe their child's symptoms and fill in the parental record form. After this run-in phase, the randomization into two treatment groups was started.

Treatment phase. Children received initially either PEG 0.5g/kg/day (PEG400 without electrolytes, 10g/sachet) or MOM 0.5mL/kg/day (milk of magnesia suspension, 400mg/5mL) once daily. A sachet of PEG (10 g) was mixed in 5 ounce (oz) of a beverage (such as juice, or water), making a solution of 5g/75mL. MOM could be mixed into juice or milkshakes, or chocolate and other flavorings. Parents were provided with written instructions regarding how to adjust the dosage of medication and children were treated with the minimal effective dosage of PEG or MOM, allowing for a daily stool and preventing painful defecation and fecal incontinence. Written instructions informed the aim of treatments being one or two stools

of soft consistency (Bristol type: 4-6) each day. Parents were asked to increase the dosage if stools were still too hard (Bristol type: 1-3) or not frequent enough and to decrease the dosage if the stools were watery (Bristol type 7) or too numerous. They were also instructed to make only small changes every three days such as 1 oz of PEG (maximal does 1 g/kg/day) or MOM (maximal does 3 mL/kg/day). Parent were instructed to record a diary about each bowel movement listing, amount, consistency according to the Bristol stool form scale [26], episodes of fecal incontinence, symptoms of painful defecation. They were also asked to record any adverse effect such as diarrhea, defined as three or more watery stools per day, abdominal pain/discomfort, bloating/flatulence, or nausea/vomiting and the amount of medications they gave to their children.

Follow-up. Patients were followed at the end of the 2nd week after initiation of treatment at the pediatric outpatient clinic for evaluation of symptoms and checked whether their parent understood and could record the parental form properly. Four weeks after treatment or the end of the study period, patients evaluated the treatment results as outcomes of the study. If any patients were unable to visit for follow-up, data were obtained by telephone with parents. Data from parent's verbal reports were accepted.

Safety profiles

For monitoring during treatment, parents were questioned by telephone every week with respect to diarrhea, ease of passage of stools, cramps, flatus, or any other adverse effects.

Primary outcome

The primary outcome measure was the improvement rate, defined as the proportion of patients who had $\geq$ three bowel movements per week, $\leq$ two episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy. Comparison between two groups was done by Chi square or Fisher's exact test.

Secondary outcomes

Other outcome studies were: 1) improvement in stool frequency per week; 2) the proportion of the patients who had any adverse effects; and 3) the compliance rate, defined as the proportion of patients who received more than 80% of the medication.

Statistical analyses

It was estimated that a total sample of 94 patients would be adequate to show a difference of at least 30% improvement rate at four weeks using PEG in comparison with MOM, with a two-tailed alpha level of 0.05 and a power of 80%. Statistical analysis was done following the intention-to-treat principle. Also, the patients who were lost to follow-up were included in the analysis. Values are expressed as mean (SD), median (Q_1 , Q_3) and n (%). Comparisons between the two treatment groups were performed using Student's t-test or non-parametric Mann-Whitney U-test according to the distribution of values, and χ^2 tests. A p-value of <0.05 was considered statistically significant. Statistical analyses were done using SPSS software (version 16 and STATA version 10).

Results

Initial patient characteristics

Ninety-nine patients and their parents were asked to participate and enter the one-week run-in phase of

our study. After the run-in phase, five patients were excluded because their parents declined to participate. Therefore, 94 patients were enrolled in the study.

The 47 patients were randomly allocated into the PEG group and 47 into the MOM group. The run-in, enrollment, and completion phase of the study protocol is shown in **Fig. 1**.

Eighty nine patients completed the study. Five patients, one from the PEG group was ill due to acute bronchitis and four from the MOM group were lost to follow-up.

Demographic data of study patients are summarized in **Table 1**. Patients in both groups were comparable in the demographic data and initial patient characteristics.

Median total Rome III criteria for enrolling the patients were four criteria in both groups. The distribution of each criterion is shown in **Table 2**. All study patients had a history of painful defecation as shown as Rome criteria IV of everyone in both groups.

Initial physical examinations of the study patients are summarized in **Table 3**.

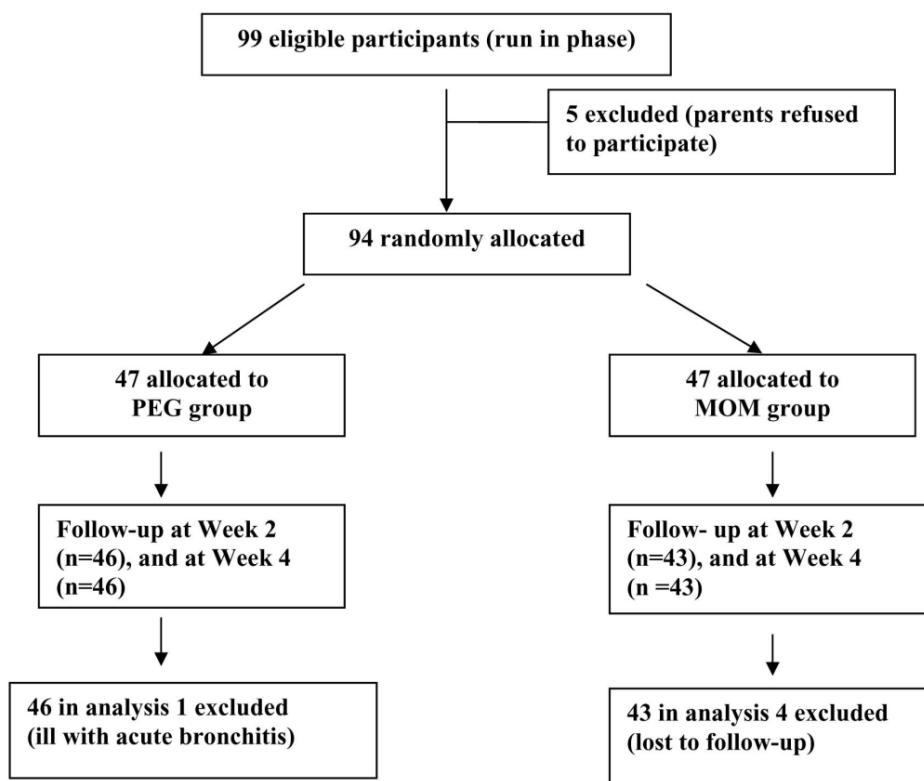


Fig. 1 Flow-chart of participants through the run-in, enrollment and completion phases of the study protocol.

Table 1. Baseline characteristics of study patients.

Characteristics	PEG (n = 46) Mean (SD)	MOM (n = 43) Mean (SD)
Age (year)	2.58 (0.84)	2.58 (1.01)
Body weight (kg)	12.85 (2.61)	13.20 (3.08)
	Median (Q ₁ , Q ₃)	Median (Q ₁ , Q ₃)
Stool frequency, episodes/week	3 (2, 4)	3 (2, 5)
Duration of constipation (week)	52 (24, 69)	52 (20, 104)
	N (%)	N (%)
Sex, male	15 (33)	21 (49)
Previous treatment with laxatives	6 (13)	4 (9.3)
Family history of functional constipation	29 (63)	23 (53)

Table 2. Rome III criteria of study patients.

Criteria	PEG (n = 46) Number (%)	MOM (n = 43) Number (%)
Criteria I		
Stool frequency ≤ 2 episode/week	21 (46)	20 (47)
Criteria II		
Fecal incontinence frequency ≥ 1 episode/week	1 (2.2)	1 (2.3)
Criteria III		
History of excessive stool retention	45 (98)	39 (91)
Criteria IV		
History of painful or hard bowel movement	46 (100)	43 (100)
Criteria V		
Presence of abdominal and/or rectal fecal mass	36 (78)	29 (67)
Criteria VI		
History of large-diameter stools that may obstruct the toilet	26 (57)	27 (63)
	Median (Q ₁ , Q ₃)	Median (Q ₁ , Q ₃)
Total number of Rome III criteria met	4 (3, 5)	4 (3, 4)

Table 3. Initial physical examination of the study patients.

Physical examination	PEG (n = 46) Number (%)	MOM (n = 43) Number (%)
Normal	16 (35.0)	20 (47.0)
Abnormal	30 (65.0)	23 (53.0)
Distend abdomen	1 (2.2)	1 (2.3)
Fecal mass	2 (4.3)	3 (7.0)
Anal fissure	17 (37.0)	7 (16.0)
Perianal skin tag	6 (13.0)	6 (14.0)
Anal fissure and perianal skin tag	4 (8.7)	6 (14.0)

Primary outcome analyses

The patients in the PEG group had significantly higher improvement four weeks after treatment, compared with the patients in the MOM group (improvement rate 91% vs. 65%, $p = 0.003$). Moreover, two weeks after treatment, when the patients came for follow-up at the middle point of the study, the improvement in the PEG groups were also significantly higher than in the MOM groups (63% vs. 42%, $p=0.045$).

Two patients in the PEG group still had a stool frequency of less than three episodes/week and two other patients still had painful defecation with bleeding from anal fissure. In the MOM group, four patients still had stool frequency of less than three episodes/week and 11 patients still had painful defecation four weeks after treatment.

The treatment effect as primary outcome, showed the difference in proportion of patients with improvement between the two groups four weeks after treatment. It was 26% (95%CI: 9.8%, 43%). The calculated number needed to treat was four.

A further analysis of primary outcome included patients who were lost to follow-up at the end of the study. The patients in the PEG group still had more improvement than the patients in the MOM group four weeks after treatment (89% vs. 60%, $p=0.001$).

The amount of dietary fiber intake during treatment in both groups might affect outcome. It was recorded on the daily dietary charts by parents. All data were analyzed using information from the Table of nutritive values of Thai foods, Division of Nutrition, Ministry of Public Health [27]. As for duration of constipation, duration of previous laxative treatment before treatment and the family history of functional constipation, the amount of daily dietary fiber intake during treatment in both groups were not significantly

different (2.70 vs. 2.64 gm/day, $p=0.82$).

Secondary outcome analyses

The initial frequency of bowel movements per week was higher than expected level in both groups. However, every study patient met two or more Rome III criteria for diagnosis of functional constipation. Therefore, there was no need to have a stool frequency ≤ 2 episodes/week as criteria I in every case.

The stool frequency at the initial four week follow-up visit, and the difference (or improvement) in stool frequency are shown in **Table 4**. Interestingly, the patients in the PEG group had more improvement in stool frequency after completing four weeks of treatment, compared with patients in the MOM group ($p= 0.04$).

There were only two patients with fecal incontinence (one in PEG, another in MOM group). We expected a low incidence (about 2%) in our patients with age <four years, but both patients exhibited improvement, as fecal incontinence frequency became less than one episode /week four weeks after treatment.

Adverse effects

During the four-week study period, no serious adverse events were observed in either group. Overall adverse effects in both groups were not significantly different ($p=0.245$). The symptoms of adverse effects as observed were abdominal pain/discomfort, bloating/flatulence and nausea/vomiting. All were mild and transient, but patients in the MOM group had more diarrhea than those in the PEG group (28% vs. 4.3%, $p=0.002$). The diarrheal episodes were resolved by reducing the dosages. No patient was withdrawn from the study due to adverse effects.

Table 4. Improvement in stool frequency.

Stool frequency (episodes/week)	PEG (n = 46) Median (Q ₁ , Q ₃)	MOM (n = 43) Median (Q ₁ , Q ₃)	Mann Whitney test	
			Z	P
Initial visit	3 (2, 4)	3 (2, 5)	-1.44	0.15
Four weeks follow-up visit	6 (4.75, 7)	5 (4, 7)	-0.79	0.43
Improvement ^a	3 (1, 4)	2 (0, 3)	-2.07	0.04

^aImprovement in stool frequency = Stool frequency: “after” - “before” medication.

Compliance

The patients in the PEG group had a better compliance rate than patients in the MOM group (89% vs. 72%, $p=0.041$). Parents of patients who received MOM recorded that their children did not like the taste of MOM, even if it was mixed with juice. The patients who were counted as non-compliance received <80% of the medication. No patient in either group continued to refuse medications.

The adverse effects and the compliance rate recorded by parents is summarized in **Table 5**.

Treatment doses

The median PEG treatment dose at the four-week follow-up evaluation was 0.5g/kg body weight daily (Q_1 : 0.4; Q_3 : 0.6). The median PEG doses were similar for patients who had and had not experienced improvement ($p=0.75$).

The median MOM treatment dose at the four-week follow-up evaluation was 0.6 mL/kg body weight daily (Q_1 : 0.5; Q_3 : 0.7). The median MOM doses were also similar for patients who had not experienced improvement ($p=0.88$).

Patients in the PEG group had significantly more weight gain than those in the MOM group (0.63 vs. 0.18 kg, $p=0.006$) at four-week follow-up.

Discussion

Constipation is a common pediatric problem in childhood. Most cases are associated by painful defecation and classified as functional constipation. Although constipation is quite common, there are very few studies comparing different laxatives in children [5-9]. The present study is the first randomized controlled trial in which all eligible patients were enrolled using newly-defined Rome III criteria for infants and children aged from one to four years with

functional constipation [25]. This is also the first study that compared the two laxatives, PEG and MOM, in this young age group. Our study obtained the improvement ratio by four week treatment as well as the increase of stool frequency. In general, the improvement cannot be represented by the increased stool frequency alone. We must consider the stool consistency and child's symptoms such as pain or other difficulty on defecation. In this study, we used the Bristol stool form scale [35] for evaluation of the stool consistency. Moreover, we specifically designed a parental record forms, Using this forms, parents could record the daily details of their child's bowel movement and symptoms during the intervention period. It provided a valid and reliable method of assessing the outcomes of this study, thus avoiding bias. A blinded study could not be performed because the two medications were administered to children in different ways.

In this study, we evaluated the short-term outcomes at four weeks in term of improvement, stool frequency, adverse effects, and the compliance rate. All baseline characteristics of both groups were balanced in age, body weight, sex, duration of constipation before treatment, family history of constipation and previous laxative treatment. During the treatment intervention, the amount of dietary fiber intake was analyzed using the dietary records of every patient. We found that our study patients, in both groups, had low daily dietary fiber intake and this was not significantly different between both groups.

As shown in **Table 4**, our results demonstrated more improvement in the PEG, compared to the MOM treatment at four weeks. The effect size was approximately 26% as the difference in proportion of patients with improvement between the two groups four weeks after treatment. Assuming that the

Table 5. Adverse effects and compliance rate.

Variable	PEG(n = 46) Number (%)	MOM (n = 43) Number (%)	χ^2_1	P-value
Any adverse effect	20 (44.0)	24 (56.0)	1.353	0.245
Diarrhea	2 (4.3)	12 (28.0)	9.306	0.002
Abdominal pain/discomfort	9 (20.0)	14 (33.0)	1.958	0.162
Bloating/ flatulence	13 (28.0)	13 (30.0)	0.042	0.838
Nausea/vomiting	4 (8.7)	9 (21.0)	2.667	0.102
Compliance rate^e	41 (89.0)	31 (72.0)	4.175	0.041

^edefined as the proportion of patients who received $\leq 80\%$ of the medication throughout the study.

calculated number needed to treat is 4, similar effects were still preserved when performed sensitivity analysis as the intention to treat basis.

The difference in the effectiveness of treatment between the two medications could also be observed at two weeks follow-up visit in our study. We found that patients in the PEG group had more improvement than the MOM group at this time. The treatment response was earlier than expected. This may be due to the younger aged group of our study patients compared with previous reports [5, 9]. Since older patients have a longer duration of constipation and more stasis in the colon, they might have more difficult treatment. Similar to previous studies [5-9], PEG and MOM were not associated with any serious adverse effects. Some adverse events (such as abdominal pain/discomfort and bloating/flatulence) were often observed by parents of children in both groups. All these symptoms were mild and transient, and thus there were few complaints from the parents. Diarrhea occurred more frequently in the MOM group than in the PEG group. These symptoms resolved by reducing the dosage.

Compliance with taking PEG was superior (89%), compared with MOM-treated patients (72%). This finding was similar to the study by Loening-Baucke et al. [9]. The PEG 4000 has a good taste with orange-grapefruit flavor, and can be mixed in fruit juice. On the other hand, MOM does not have good palatability, and its taste cannot be hidden even when it is mixed with some foods. The compliance of patients is very important in successful treatment of constipation, especially in long-term treatment.

Conclusion

PEG had more effectiveness and better patient compliance than MOM for the management of functional constipation in infants and children aged from one to four years. Pediatricians and general practitioners will have a new choice of medication for treatment of functional constipation in infant and children.

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Abbreviations

PEG: polyethylene glycol

MOM: milk of magnesia

Bristol Stool Scale: a medical aid designed to classify the form of human stools into seven types as follows:

Type 1: Separate hard lumps, like nuts (hard to pass);

Type 2: Sausage-shaped, but lumpy;

Type 3: Like a sausage but with cracks on its surface;

Type 4: Like a sausage or snake, smooth and soft;

Type 5: Soft blobs with clear cut edges (passed easily);

Type 6: Fluffy pieces with ragged edges, a mushy stool;

Type 7: Entirely liquid.

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