CHAPTER III

RESEARCH METHODOLOGY

Research questions

Primary research question

Is the effectiveness of polyethylene glycol different from milk of magnesia in improvement of functional constipation in infants and children aged 1-4 years ?

Secondary research questions

1. Are there any adverse effects of these 2 laxatives?
2. How are the patient compliance during taking these 2 laxatives ?

Research objectives

Primary objective

To compare the effectiveness between 2 laxatives, polyethylene glycol and milk of magnesia in improvement of functional constipation in infants and children aged 1-4 years.

Secondary objectives

1. To compare the adverse effects between these two laxatives.
2. To compare the patient compliance between these two laxatives.

Research hypothesis

Null hypothesis

The effectiveness of polyethylene glycol (PEG) does not differ from milk of magnesia (MOM) in improvement of functional constipation in infants and young children

Alternative hypothesis

The effectiveness of polyethylene glycol (PEG) differ from milk of magnesia (MOM) in improvement of functional constipation in infants and young children

Statistical hypothesis

The primary outcome in the study was the improvement rate, defined as the proportion of patients who had $\geq$3 bowel movements per week, $\leq$2 episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy.

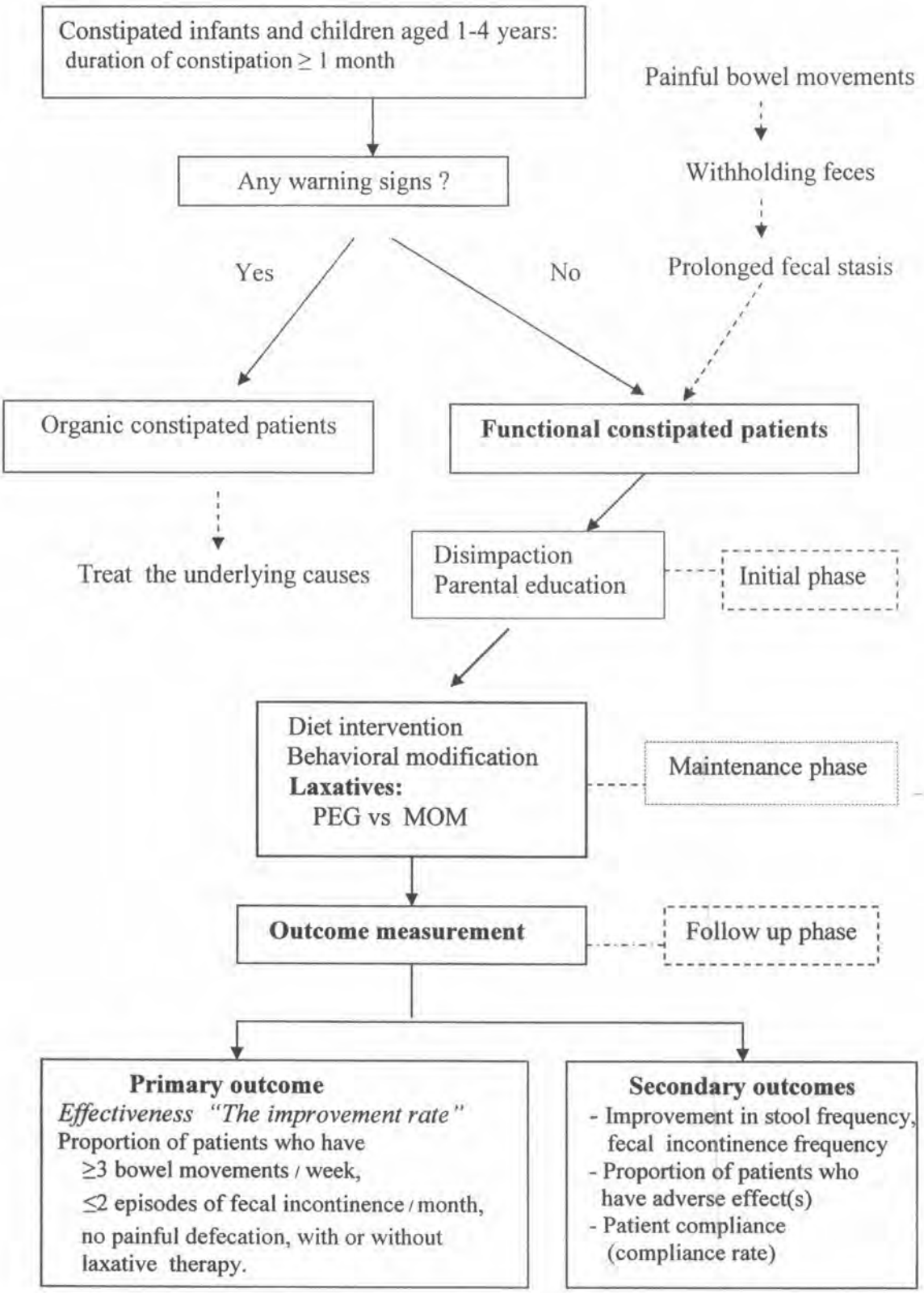
$$H_0 : \pi_1 - \pi_2 = 0$$

$$Ha : \pi_1 - \pi_2 \neq 0$$

π_1 = proportion of patients who have improvement with PEG treatment

π_2 = proportion of patients who have improvement with MOM treatment

Figure 1: Conceptual framework



Key words

Polyethylene glycol

Milk of magnesia

Functional constipation

Abbreviations

PEG—polyethylene glycol

MOM—milk of magnesia

Operational definition

Organic constipation was defined as constipation caused by any organic causes eg. anatomic abnormalities of the G.I. tract, metabolic disorders, endocrine disorders.

Warning signs for organic causes of constipation in infants and children are shown as below (4) .

Warning Signs for Organic Causes of Constipation in Infants and Children

Warning signs or symptoms	*Suggested diagnosis*
Passage of meconium more than 48 hours after delivery, small-caliber stools, failure to thrive, fever, bloody diarrhea, bilious vomiting, tight anal sphincter, and empty rectum with palpable abdominal fecal mass	Hirschsprung's disease
Abdominal distention, bilious vomiting, ileus	Pseudo-obstruction
Decrease in lower extremity reflexes or muscular tone, absence of anal wink, presence of pilonidal dimple or hair tuft	Spinal cord abnormalities: tethered cord, spinal cord tumor, myelomeningocele
Fatigue, cold intolerance, bradycardia, poor growth	Hypothyroidism
Polyuria, polydipsia	Diabetes insipidus
Diarrhea, rash, failure to thrive, fever, recurrent pneumonia	Cystic fibrosis
Diarrhea after wheat is introduced into diet	Gluten enteropathy
Abnormal position or appearance of anus on physical examination	Congenital anorectal malformations: imperforate anus, anal stenosis, anteriorly displaced anus

Fecal impaction was defined as a hard mass in the lower abdomen identified during physical examination, a dilated rectum filled with a large amount of stool found during rectal examination, or excessive stool in the colon identified by abdominal radiography (20).

Fecal incontinence was defined as the involuntary leakage of feces (33).

Improvement rate was the proportion of patients who had $\geq$3 bowel movements per week, $\leq$2 episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy.

Adverse effects were defined as any symptom of abdominal pain, abdominal discomfort, bloating, flatulence, nausea, vomiting and diarrhea during medication intervention.

Patient compliance (compliance rate) was assumed as the proportion of patients who could receive equal to or more than 80% of the prescribed medication throughout the study.

Research design

This was a randomized controlled trial.

Research methodology

Population and sample

Target population

Functional constipated infants and children aged 1-4 years

Sample

Functional constipated infants and children aged 1-4 years who attended at the pediatric outpatient clinic of Bhumibol Adulyadej Hospital from March 2008 to January 2009

Inclusion criteria and exclusion criteria

Inclusion criteria

The infants and children who met the diagnostic criteria for functional constipation (According to Rome III criteria for childhood functional gastrointestinal disorders (6).

Must include 1 month of at least 2 of the following characteristics.

1. Two or fewer defecations per week
2. At least 1 episode per week of incontinence after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Exclusion criteria

The infants and children with renal insufficiency that might have risk of magnesium overdose from milk of magnesia.

Sampling technique

All patients who met the inclusion criteria and their parent willing to participate in the study were included.

Sample size determination

The primary outcome measure was the improvement rate, defined as the proportion of patients who have $\geq$3 bowel movements per week, $\leq$2 episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy

From all of the literature reviews, there had been no any randomized controlled trial studied about the effectiveness of these two laxatives, PEG versus MOM in young infants and children aged less than 4 years.

Our data in treatment of constipated children aged 1-4 years at pediatric gastrointestinal special clinic in Bhumibol Adulyadej Hospital. There were 10 out of 28 (≈35%) constipated patients who had improvement after 4 weeks MOM treatment, and from our pilot study (12pt.) , 67% of PEG-treated children and 33% of MOM-treated children exhibited improvement.

Therefore, the sample size calculation was based on a desired ability to detect a difference in improvement rate of 30% between two study arms, that would have a clinical importance with a 2 side α of 0.05 and power of 0.8. We calculated the sample size using this formula for equal sample size group .

$$n = \frac{[\, Z_{\alpha/2}\sqrt{2p(1-p)} + Z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}\,]^2}{(p_1 - p_2)^2}$$

n = sample size in each group

- $p = p_1+p_2 / 2 = 0.50$
- p_1 (proportion of patients with improvement in PEG treatment group)
- p_2 (proportion of patients with improvement in MOM treatment group)
- $\alpha = 0.05$ (two-sided), $Z_{\alpha/2} = 1.96$
- $1-\beta = 0.80$, $Z_{\beta} = 0.842$

Where p_1 = expected proportion of improvement in PEG treatment group = 0.65

p_2 = proportion of improvement in MOM treatment group = 0.35

The number of sample in each group calculated from the above formula was 42. With the assumption that 10% dropout might occur, therefore, the adjusted sample size was 47 in each group.

Randomization

The randomization procedure consisted in a computer generated randomization list in mixed block sizes by a nonparticipated statistician.

Patients were randomized into PEG treatment group or MOM treatment group.

Allocation concealment

A blinded nurse dispensed either PEG or MOM according to the computer generated randomization list.

Treatment allocation was prepared in separated sealed, opaque sequentially numbered envelops.

Intervention

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 1 week to make sure that the parent can observe their child 's symptoms and fill in the parental record form. After this run in phase , the randomization into 2 treatment groups was started.

Details of the intervention, potential adverse effects and treatment of the adverse effects were explained to all parents before signing the consent form.

Treatment phase

Children received initially either PEG 0.5 g /kg/day (PEG4000 without electrolytes,10 g./sachet) or MOM 0.5 ml/kg/ day (Milk Of Magnesia suspension, 400 mg./5 ml) once daily. A sachet of PEG (10 g) was mixed in 5 oz of a beverage (such as juice, or water), making a solution of 5g /75 ml. 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 1 or 2 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 3 days such as ½ oz of PEG (maximal dose 1g/kg/day) or 0.5 ml/kg of MOM (maximal dose 3ml/kg/day). Parent were instructed to record a diary about each bowel movement listing, amount, consistency according to the Bristol stool form scale (35), episodes of

fecal incontinence, symptoms of painful defecation and any adverse effect such as diarrhea, defined as three or more watery stools per day, abdominal pain/discomfort, bloating/flatulence, nausea/vomiting and record the amount of medications that they gave to their children.

Follow-up

Patients were followed at the end of 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. After 4 weeks of treatment or the end of the study period, patients were followed and evaluated of 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.

Outcome measurement

Primary outcome

The improvement rate, defined as the proportion of patients who have $\geq$3 bowel movements per week, $\leq$2 episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy.

Secondary outcomes

1. Improvement in stool frequency, improvement in fecal incontinence frequency (episodes per week)
2. Adverse effect (proportion of patients who had any adverse effect)
3. Patient compliance (compliance rate or the proportion of patients who could receive equal to or more than 80% of the prescribed medication throughout the study)

Co-intervention

Every parents were received the counseling about the cause of functional constipation to reduce their conflicts, diet intervention and child's behavioral modification as toilet training , positive reinforcement in the same way before randomization and were informed that they should not give any other drugs or laxatives to their child and recorded their child's dietary intake during the study.

Contamination

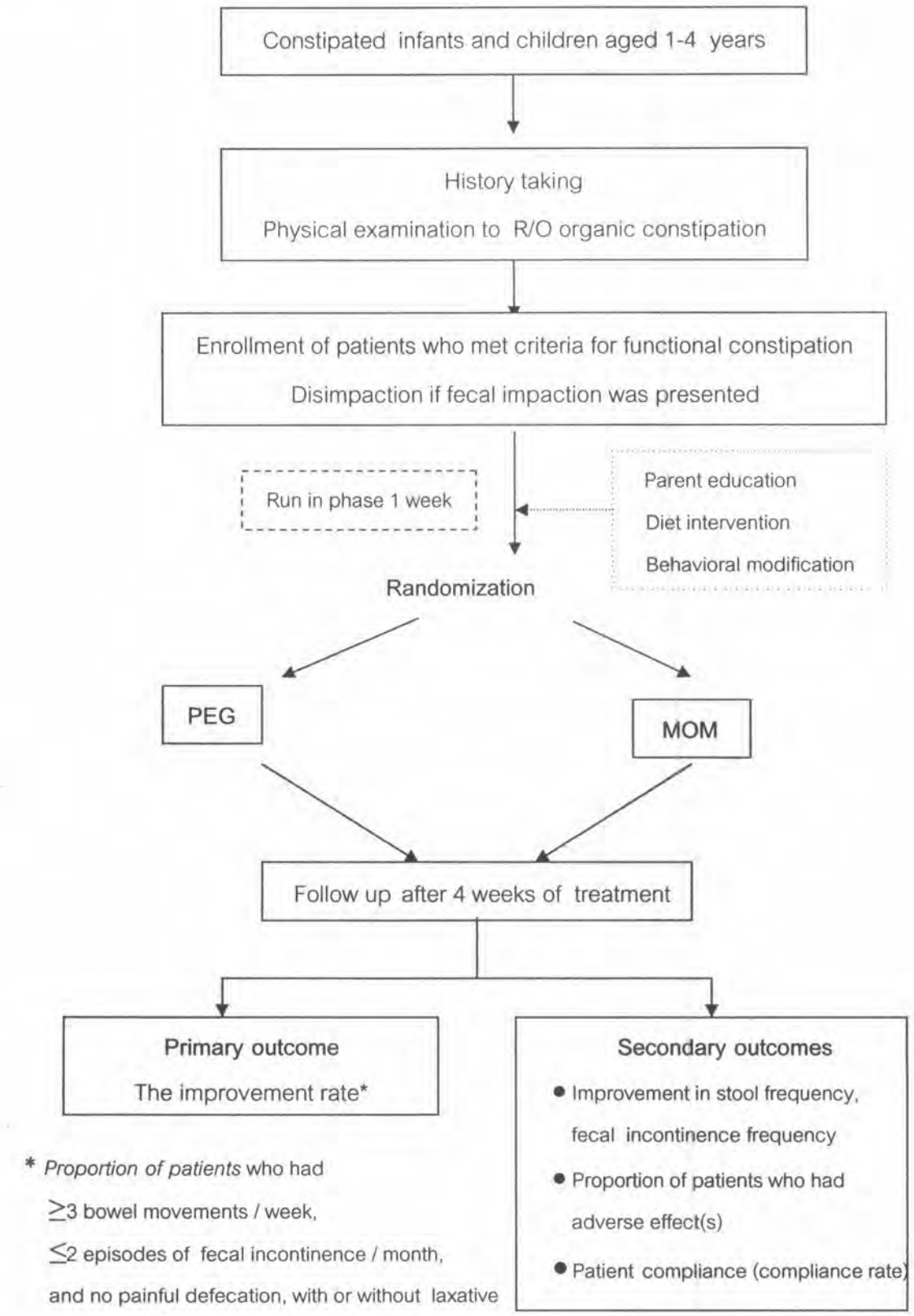
Parents were asked not to receive another laxative for their children except the prescribed medication during the study.

Compliance

The strategies to promote the compliance were the followings.

- Convincing the parent of the need
- Good relationship and supports
- Studied medications was simple and once daily dosage
- Diary record of medication use in the parental record form and checking amount of medication left at follow up date
- Positive reinforcement

Figure 2: Summarized flow diagram of the study



Data collection

1. *Parent 's consent form* (in Appendix A) The researcher asked the parent for permission and willing to participate in the study and signed in this consent form.

2. *The Constructed case record form* (in Appendix B) was generated for each patient to keep the clinical data, prepared in 2 separated sheets.

2.1. *Physician record form* The details consist of 3 parts.

Part I : Patient ' s baseline characteristics

The baseline characteristics included age, sex, body weight, criteria for enrollment, interviewed history (from parent about their child's bowel movement include history of functional constipation) and record of the physical examination before intervention.

Part II : Monitoring during treatment intervention .

The parents were questioned by telephone at the end of every week about any symptom(s) or adverse effect(s) during medical intervention to monitor the safety along the study period . The information were recorded in this part.

Part III : 4 week outpatient follow up visit

The follow up data after completed 4 week of study period included the details of child 's bowel movement, the adverse effect(s) after medication intervention and the compliance of medical use. The primary and secondary outcome data were recorded in this part.

2.2. *Parental record form* was prepared for 4 week parental diary record of their child's bowel movement. The data being recorded included stool frequency, stool consistency, episodes of fecal incontinence, symptoms or any adverse effects during treatment intervention and successful administration of the prescribed medication. Furthermore, diary record about food intake was also performed for helping the researcher to evaluate about dietary fiber intake during treatment intervention.

All of the data being measured are summarized in next page.

Table 2: Summary of measurements

Variables		Scale (coding)	Description of data
1. Baseline characteristics			
1.1. Demographic data			
	Age (years)	Continuous	Mean(SD) or Median,(Q_1,Q_3)
	sex	Nominal (0= male, 1= female)	Number, Percentage
	Body weight (kg.)	Continuous	Mean(SD) or Median,(Q_1,Q_3)
1.2. History of Functional constipation			
	Stool frequency (episodes per week)	Discrete	Median,(Q_1,Q_3)
	History of fecal incontinence	Nominal (0 = no, 1 = yes)	Number, Percentage
	Fecal incontinence frequency (episodes per week)	Discrete	Median,(Q_1,Q_3)
	Duration of constipation (weeks)	Continuous	Mean(SD) or Median,(Q_1,Q_3)
	History of previous laxative treatment	Nominal (0 = no,1 = yes)	Number, Percentage
	Duration of previous laxative treatment (weeks)	Continuous	Mean(SD) or Median,(Q_1 ,Q_3)
	Family history of functional constipation	Nominal (0 = no, 1 = yes)	Number, Percentage

Table 2: Summary of measurements (continued)

Variables		Scale (coding)	Description of data
2. Primary outcome variable			
	Improvement	Dichotomous (0 = No improvement 1 = Improvement)	Number, Percentage
3. Secondary outcome variables			
	Improvement in stool frequency (stool frequency: after – before medication intervention)	Continuous	Mean(SD) or Median,(Q_1,Q_3)
	Presence of adverse effect*	Dichotomous (0 = absent, 1 = present)	Number, Percentage
	Patient compliance	Dichotomous (0 = not compliance 1 = compliance**)	Number, Percentage

* Adverse effects: diarhea, abdominal pain / discomfort, bloating / flatulence, nausea / vomiting or others.

**Compliance: patient who could receive $\geq$ 80 % of the medication throughout the study.

Data analyses

1. *Baseline characteristics* were presented and analyzed by descriptive statistics.
2. *Primary outcome variable*

- As for categorical data.

• The proportion of the patients who improved after treatment (the improvement rate) was presented as percentage.

Comparison between 2 groups was done by chi square or Fisher' s exact test where appropiate with significance accepted at the 5% level.

The precision or the effect size was presented as the difference in proportion of patients with improvement amoung 2 groups and 95% confidence interval

3. *Secondary outcome variables* were assessed as both continuous and catechorical data.

- As for continuous data.

• The improvement in stool frequency, the improvement in fecal incontinence frequency, mean and standard deviation or median and Q_1,Q, where appropiate, were presented.

Comparison between 2 groups was done by Mann-Whitney U test with significance accepted at the 5% level.

- As for categorical data.

• The proportion of the patients who had any adverse effect

• The compliance rate (the proportion of patients who could receive $\geq$ 80 % of the medication).

The data was presented as percentage and the comparison between 2 groups was done by chi square or Fisher 's exact test, where appropriate, with significance accepted at the 5% level.

4. Binary logistic regression might be applied in order to detect variables prognostic factors for the primary outcome.

• The variables that might be included in the binary logistic regression were the duration of constipation, the duration of previous laxative treatment before enrollment, family history of functional constipation and the amount of dietary fiber intake during treatment intervention.

Statistical analyses were done following intention to treat principle. As a sensitivity analysis, the patients who were lost to follow up were included in further analysis as not improved.

Statistical analyses were done using SPSS software version 15 and STATA version 10 on Microsoft window XP platform.

Table 3: Summary of statistical analyses

Outcome	Type	Statistical test
Primary outcome		
Improvement rate	Categorical	Chi-square test or Fisher's exact test
Secondary outcomes		
Improvement in stool frequency	Discrete	Mann-Whitney U test
Proportion of patients with adverse effect	Categorical	Chi-square test or Fisher's exact test
Compliance rate	Categorical	Chi-square test or Fisher's exact test

Ethical considerations

The design was approved by the ethics committees of Bhumibol Adulyadej Hospital.

According to the equipoise principle, at present, insufficient data conclude that either medication polyethylene glycol or milk of magnesia is the superior laxative in treatmeat of functional constipation.

Safety profile

Regarding the safety of the new laxative, polyethylene glycol especially in infants and milk of magnesia ,based on the results of previous studies (4,10,15,24,25,30).

Oral powdered PEG 3350 at a maintenance dose of 0.78 g/kg/day is safe and effective for patients younger than 18 months. Dose and safety profiles were similar for those reported in older children . Also, there were no major clinical adverse effects in long term PEG therapy (25).

From a large scale dose determination study of PEG 4000 in the treatment of refractory functional constipated children for a 3-month period confirmed the wide safety margin of PEG 4000. The recommened daily dose of PEG 4000 in children aged 6 months to 15 years was approximately 0.50 g/kg/day whatever the age(30). The dosage range suggested by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) are 0.50-1 g/kg/day for PEG and 0.5-3 ml/kg/day for MOM (4).

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

Limitations

1. It was not possible to perform a blinded study because these 2 medications were administered to children in different ways.
2. Time limitation for long term follow up.

Disclosure

A grant for conducting this study was supported by Bhumibol Adulyadej Hospital Fund.

No conflict of interest