Efficacy and Complications of Polyethylene Glycols for Treatment of Constipation in Children

A Meta-Analysis

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Abstract: Constipation is a common childhood complaint. In 90% to 95% of children, constipation is functional, which means that there is no objective evidence of an underlying pathological condition. Polyethylene glycol (PEG or macrogol) solution is an osmotic laxative agent that is absorbed in only trace amounts from the gastrointestinal tract and routinely used to treat chronic constipation in adults. Here, we report the results of a meta-analysis of PEG-based laxatives compared with lactulose, milk of magnesia (magnesium hydroxide), oral liquid paraffin (mineral oil), or acacia fiber, psyllium fiber, and fructose in children.

This meta-analysis was conducted in accordance with PRISMA guidelines and involved searches of MEDLINE, Cochrane, EMBASE, and Google Scholar databases up to February 10, 2014, using the keywords (Constipation OR Functional Constipation OR Fecal Impaction) AND (Children) AND (Polyethylene Glycol OR Laxative). Primary efficacy outcomes included a number of stool passages/wk and percentage of patients who reported satisfactory stool consistency. Secondary safety outcomes included diarrhea, abdominal pain, nausea or vomiting, pain or straining at defecation, bloating or flatulence, hard stool consistency, poor palatability, and rectal bleeding.

We identified 231 articles, 27 of which were suitable for full-text review and 10 of which were used in the meta-analysis. Patients who were treated with PEG experienced more successful disimpaction compared with those treated with non-PEG laxatives. Treatment-related adverse events were acceptable and generally well tolerated. PEG-based laxatives are effective and safe for chronic constipation and for resolving fecal impaction in children. Children's acceptance of PEG-based laxatives appears to be better than non-PEG laxatives.

Optimal dosages, routes of administration, and PEG regimens should be determined in future randomized controlled studies and meta-analyses.

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Abbreviations: PEG = polyethylene glycol.

INTRODUCTION

Constipation in children usually is functional (ie, constipation appears without objective evidence of an underlying pathological condition) and typically presents as the result of stool retention that may be associated with factors such as toilet training, changes in diet, stress, illness, or withholding.[1] Other uncommon causes of constipation may include neurological conditions (eg, cerebral palsy, mental retardation, or spinal cord problems), hypothyroidism, cystic fibrosis, abnormal development of the bowel (eg, Hirschsprung disease), and side effects of medications (eg, antacids, antidepressants, anticonvulsants, chemotherapy medications, or narcotic pain medications).[1–3] Treatment of functional constipation involves disimpaction using oral or rectal medication. Polyethylene glycol (PEG) is effective and well tolerated, but alternatives including lactulose, milk of magnesia (magnesium hydroxide), and oral liquid paraffin (mineral oil) are available.[4] After disimpaction, patients may require a maintenance program for months or even years because relapse of functional constipation is common. Maintenance medications include mineral oil, lactulose, milk of magnesia, PEG powder, and sorbitol.

Some researchers have suggested that the education of the family and, when possible, the child is instrumental in resolving functional constipation.[3] They suggested that behavioral education improved response to treatment, but biofeedback training did not appear to be effective. Because cow's milk may promote constipation in some children, clinicians may consider a treatment of removing milk from the patient's diet, and adding fiber to the patient's diet may help relieve constipation. Despite these interventions, only 50% to 70% of children with functional constipation demonstrated long-term improvement.

The Canadian Pediatric Society published management goals for treating constipation and suggested that the priorities were to produce soft, painless stools and to prevent the reaccumulation of feces by means of education, behavioral modification, daily administration of stool softeners, and dietary modification.[5] Fecal disimpaction may be necessary at the outset of treatment. After the impacted stool had been removed, the focus of the treatment should be on preventing recurrence with the use of laxatives. The Canadian group also suggested that medications were more effective than behavioral change alone in the treatment of constipation.[5] In 2009, a group from The Netherlands published a systematic review of laxative treatments for childhood constipation.[6] Based on 26

studies that met their inclusion criteria, they identified the relative paucity of well-designed trials for laxatives in children and the resultant difficulty in establishing first-line therapy (eg, the lack of placebo controls in published studies).[6]

Previous work published by the Cochrane Collaboration was based on an analysis of 18 randomized controlled trials (RCTs) and noted the efficacy of PEG compared with placebo, lactulose, and milk of magnesia but decried the high risk of bias in published studies and called for additional investigations of both the quality of published studies and further evaluation of long-term use of PEG to treat childhood constipation.[4] Similarly, researchers from the UK National Health Service identified 7 studies that examined PEG versus lactulose, milk of magnesia, or placebo.[7] The study duration ranged from 2 weeks to 12 months and demonstrated the efficacy of PEG, but the authors noted that differences in study design prevented a useful meta-analysis and called for an improved, evidence-based approach rather than empirical treatment.[7] Another group of researchers examined 10 articles and 1 abstract regarding PEG for disimpaction and

maintenance therapy in children and concluded that low-dose PEG (exact dosages undefined) was safe and effective but called for further studies to optimize dosages of PEG.[8] A report published in 2004 examined 4 published studies and determined that PEG 3350 held promise for the treatment of childhood constipation but, like the other studies just mentioned, called for more evidence-based information.[9] In this meta-analysis, we searched for articles that reported the use of PEG for the treatment of constipation in children and then summarized the findings regarding efficacy and safety of PEG formulations.

MATERIALS AND METHODS

Search Strategy and Inclusion Criteria

This meta-analysis was conducted in accordance with PRISMA guidelines.[10] The authors searched the MEDLINE, Cochrane, EMBASE, and Google Scholar databases up to February 10, 2014, using the following keywords: (Constipation
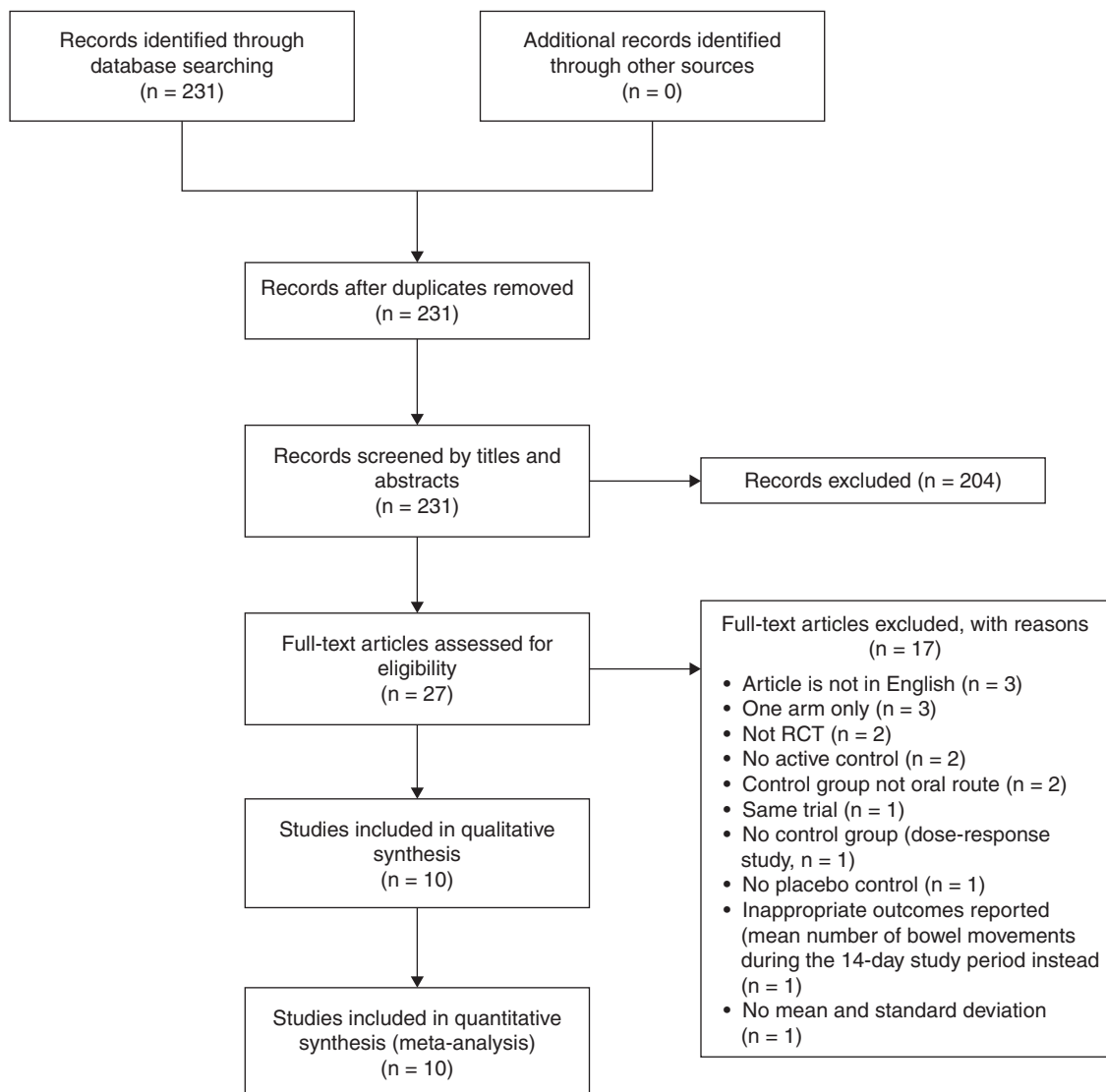

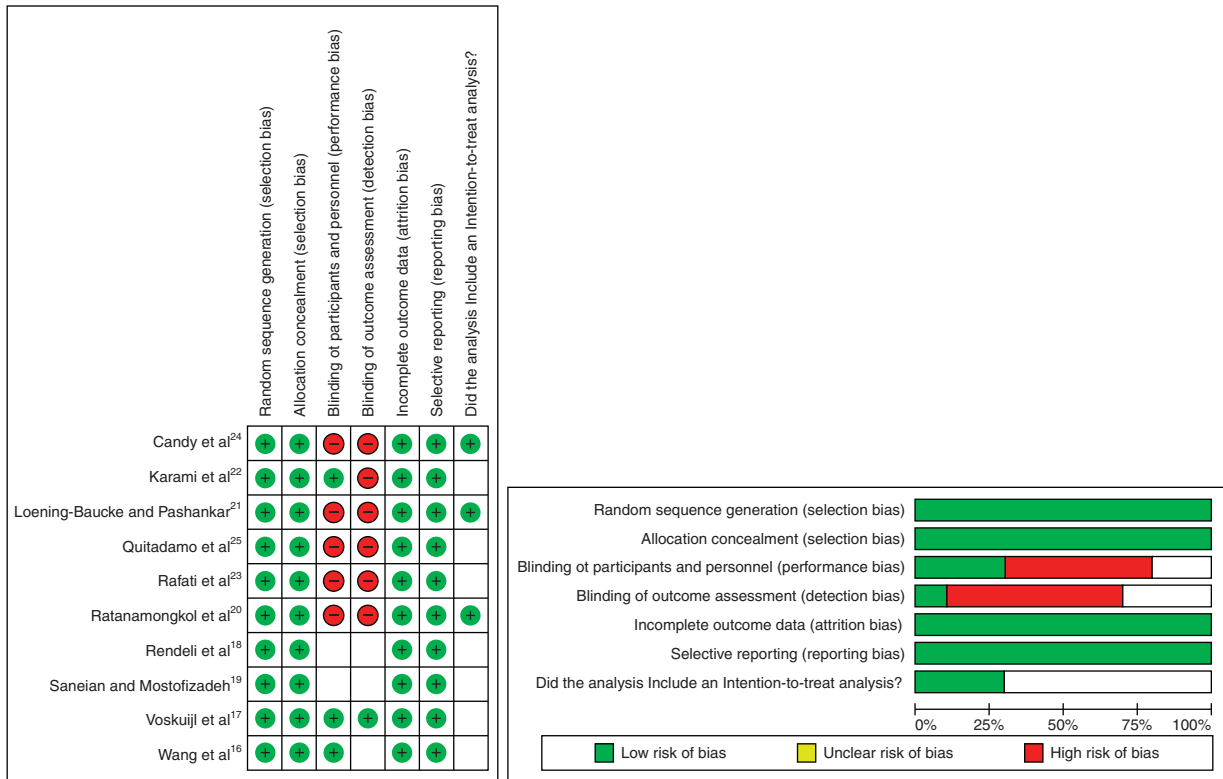**FIGURE 1.** PRISMA[10] flowchart for selection of trials.

FIGURE 2. Quality assessment for the risk of bias for each study included in this meta-analysis.

OR Functional Constipation OR Fecal Impaction) AND (Children) AND (Polyethylene Glycol OR Laxative). Inclusion criteria involved the following: RCTs or comparative prospective studies, children with constipation (chronic constipation, functional constipation, or fecal impaction), and quantitative outcomes (eg, stool frequency, timing of fecal disimpaction, stool consistency, frequency of bowel movements, fecal incontinence, and abdominal pain).

Exclusion Criteria

Exclusion criteria included the following: single-arm prospective studies, retrospective studies, cohort studies, cross-sectional studies, case-control studies, case series, case reports, comments, editorials, letters, proceedings, personal communications, involvement of adult patients, and quality of life or satisfaction as the primary outcome.

Study Selection and Data Extraction

Studies were identified according to the search strategy by 2 independent reviewers. When there was uncertainty regarding eligibility, a third reviewer was consulted.

The following information was extracted from the studies that met the inclusion criteria: the name of the first author and year of publication, study design, comparison group, number and type of subjects, demographic data (age and sex), regimen of medications (dose, frequency, route of administration, and duration), and length of follow-up.

Data extraction was performed by 2 independent reviewers, and a third reviewer was consulted when any uncertainties arose. Then we hand-searched the reference lists of relevant retrieved studies.

Study name	Comparison	Std Diff in Mean Changes	Lower Limit	Upper Limit	Z-Value	P-Value	Relative weight
Rendeli et al[18]	PEG vs non-PEG laxatives	0.19	−0.22	0.60	0.90	0.370	14.5
Saneian and Mostofizadeh[19]	PEG vs non-PEG laxatives	−0.18	−0.66	0.31	−0.72	0.474	14.0
Ratanamongkol et al[20]	PEG vs non-PEG laxatives	2.09	−1.57	2.60	7.91	0.000	13.7
Loening-Baucke and Pashankar[21]	PEG vs non-PEG laxatives	−0.39	−0.94	0.16	−1.40	0.161	14.8
Karami et al[22]	PEG vs non-PEG laxatives	0.30	−0.07	0.67	1.57	0.117	15.2
Rafati et al[23]	PEG vs non-PEG laxatives	0.36	−0.04	0.67	2.23	0.026	14.3
Quitadamo et al[25]	PEG+E vs non-PEG laxatives	0.31	−0.12	0.75	1.40	0.161	
Combined		0.38	−0.11	0.87	1.51	0.130	

Heterogeneity test: $Q = 55.70$, $df = 6$, $P < 0.001$, $I^2 = 89.23\%$
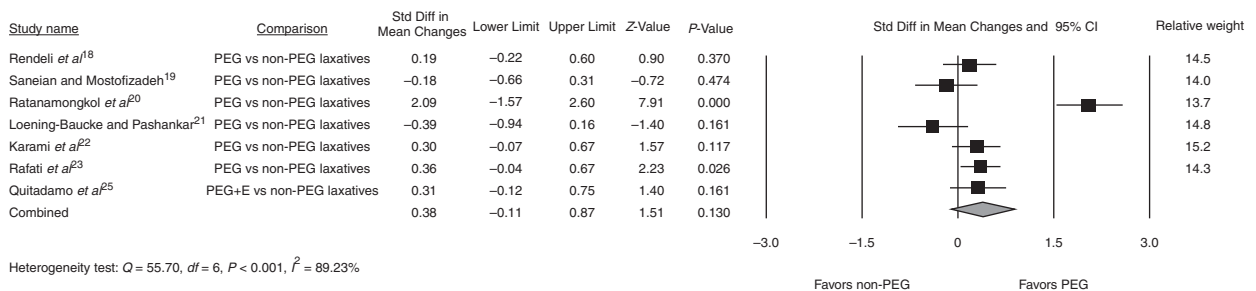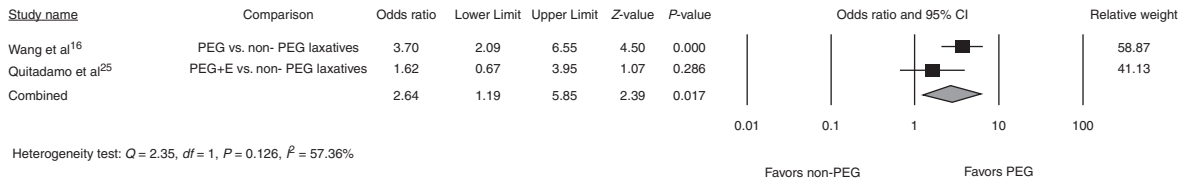
FIGURE 3. Meta-analysis for the weekly stool frequency of children with constipation–difference between PEG treatment and use of non-PEG laxatives. PEG = polyethylene glycol, Std diff = standardized differences.
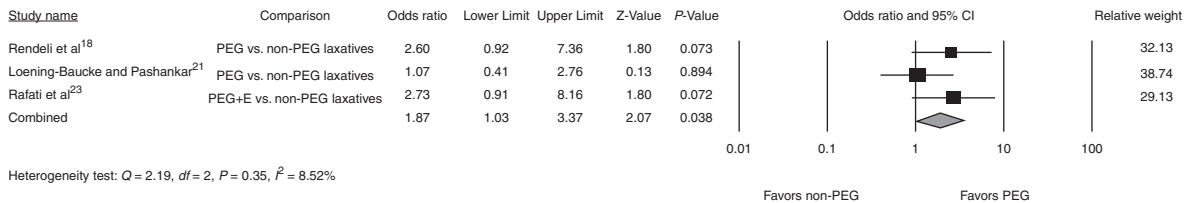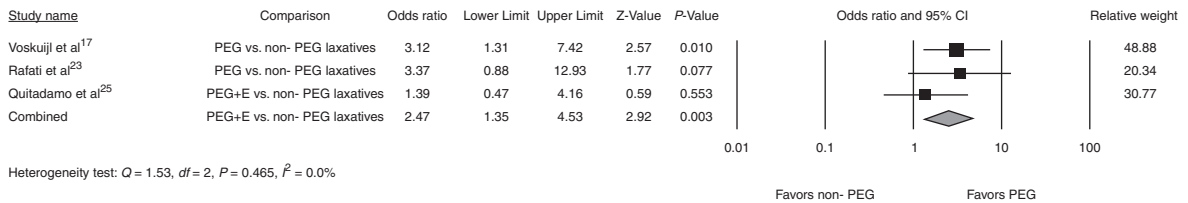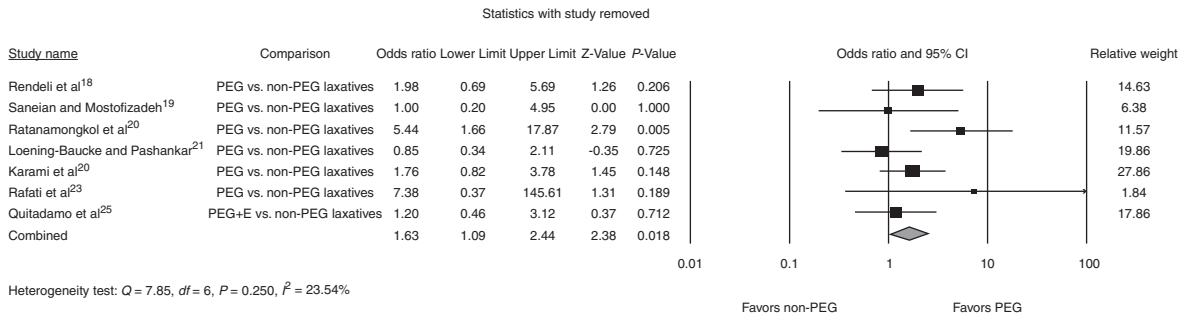
A

Study name	Comparison	Odds ratio	Lower Limit	Upper Limit	Z-value	P-value	Odds ratio and 95% CI	Relative weight
Wang et al[16]	PEG vs. non- PEG laxatives	3.70	2.09	6.55	4.50	0.000		58.87
Quitadamo et al[25]	PEG+E vs. non- PEG laxatives	1.62	0.67	3.95	1.07	0.286		41.13
Combined		2.64	1.19	5.85	2.39	0.017		

Heterogeneity test: Q = 2.35, df = 1, P = 0.126, I² = 57.36%

Favors non-PEG   Favors PEG

B

Statistics with study removed

Study name	Comparison	Odds ratio	Lower Limit	Upper Limit	Z-Value	P-Value	Odds ratio and 95% CI	Relative weight
Rendeli et al[18]	PEG vs. non-PEG laxatives	1.98	0.69	5.69	1.26	0.206		14.63
Saneian and Mostofizadeh[19]	PEG vs. non-PEG laxatives	1.00	0.20	4.95	0.00	1.000		6.38
Ratanamongkol et al[20]	PEG vs. non-PEG laxatives	5.44	1.66	17.87	2.79	0.005		11.57
Loening-Baucke and Pashankar[21]	PEG vs. non-PEG laxatives	0.85	0.34	2.11	-0.35	0.725		19.86
Karami et al[20]	PEG vs. non-PEG laxatives	1.76	0.82	3.78	1.45	0.148		27.86
Rafati et al[23]	PEG vs. non-PEG laxatives	7.38	0.37	145.61	1.31	0.189		1.84
Quitadamo et al[25]	PEG+E vs. non-PEG laxatives	1.20	0.46	3.12	0.37	0.712		17.86
Combined		1.63	1.09	2.44	2.38	0.018		

Heterogeneity test: Q = 7.85, df = 6, P = 0.250, I² = 23.54%

Favors non-PEG   Favors PEG

Study name	Comparison	Odds ratio	Lower Limit	Upper Limit	Z-Value	P-Value	Odds ratio and 95% CI	Relative weight
Voskuijl et al[17]	PEG vs. non- PEG laxatives	3.12	1.31	7.42	2.57	0.010		48.88
Rafati et al[23]	PEG vs. non- PEG laxatives	3.37	0.88	12.93	1.77	0.077		20.34
Quitadamo et al[25]	PEG+E vs. non- PEG laxatives	1.39	0.47	4.16	0.59	0.553		30.77
Combined	PEG+E vs. non- PEG laxatives	2.47	1.35	4.53	2.92	0.003		

Heterogeneity test: Q = 1.53, df = 2, P = 0.465, I² = 0.0%

Favors non- PEG   Favors PEG

Study name	Comparison	Odds ratio	Lower Limit	Upper Limit	Z-Value	P-Value	Odds ratio and 95% CI	Relative weight
Rendeli et al[18]	PEG vs. non-PEG laxatives	2.60	0.92	7.36	1.80	0.073		32.13
Loening-Baucke and Pashankar[21]	PEG vs. non-PEG laxatives	1.07	0.41	2.76	0.13	0.894		38.74
Rafati et al[23]	PEG+E vs. non-PEG laxatives	2.73	0.91	8.16	1.80	0.072		29.13
Combined		1.87	1.03	3.37	2.07	0.038		

Heterogeneity test: Q = 2.19, df = 2, P = 0.35, I² = 8.52%

Favors non-PEG   Favors PEG

FIGURE 4. Meta-analysis for the successful disimpaction of children with constipation–difference between PEG treatment and non-PEG laxatives at (A) 2 weeks, (B) 4 weeks, (C) 8 weeks, and (D) 12 weeks after treatment. PEG = polyethylene glycol.
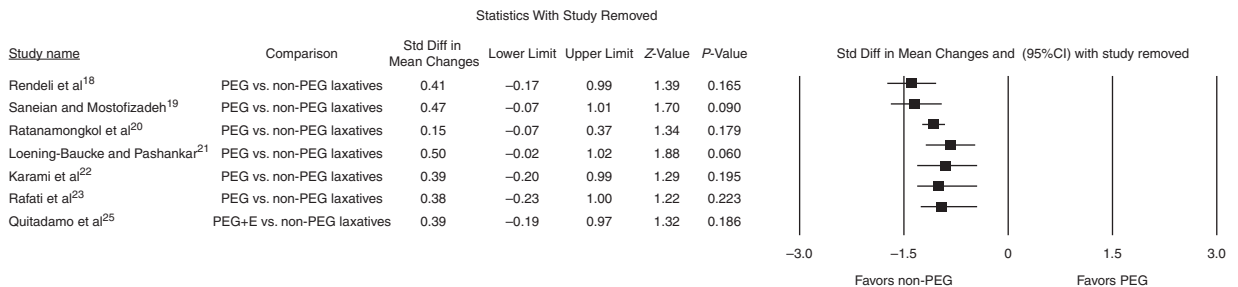
Statistics With Study Removed

Study name	Comparison	Std Diff in Mean Changes	Lower Limit	Upper Limit	Z-Value	P-Value	Std Diff in Mean Changes and (95%CI) with study removed
Rendeli et al[18]	PEG vs. non-PEG laxatives	0.41	-0.17	0.99	1.39	0.165	
Saneian and Mostofizadeh[19]	PEG vs. non-PEG laxatives	0.47	-0.07	1.01	1.70	0.090	
Ratanamongkol et al[20]	PEG vs. non-PEG laxatives	0.15	-0.07	0.37	1.34	0.179	
Loening-Baucke and Pashankar[21]	PEG vs. non-PEG laxatives	0.50	-0.02	1.02	1.88	0.060	
Karami et al[22]	PEG vs. non-PEG laxatives	0.39	-0.20	0.99	1.29	0.195	
Rafati et al[23]	PEG vs. non-PEG laxatives	0.38	-0.23	1.00	1.22	0.223	
Quitadamo et al[25]	PEG+E vs. non-PEG laxatives	0.39	-0.19	0.97	1.32	0.186	

Favors non-PEG   Favors PEG

FIGURE 5. Sensitivity analysis for treatment effects on weekly stool frequency by the leave-one-out approach. Std diff = standardized differences.

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

Reference	Study Type	Type of Patients	Intervention Group	Dose	Frequency	Duration	Number of Cases	Mean Age, y	Sex, Male %	Mean Weekly Stool Frequency Before	Mean Weekly Stool Frequency After	Successful Disimpaction at Week 4, %
Wang et al[16]	RCT	Children with constipation	PEG 4000	20 g	Once/d	2 wk	105	11.29	41.0	Median, 2	Median, 7	NA
			Lactulose	10 g (for first 3 d); 6.7 g for the following 11 d	Once/d	2 wk	111	11.2	42.3	Median, 2	Median, 6	NA
Voskuijl et al[17]	RCT	Children with constipation	PEG 3350	2.95 g	6 mo–6 y, 1 sachet/d; >6 y, 2 sachet/d	8 wk	50*	6.5	54.0	2.59	7.12	NA
			Lactulose	6.0 g	NA	8 wk	50†	6.5	56.0	2.75	6.43	NA
Rendeli et al[18]	RCT	Children with chronic neurogenic constipation	PEG 4000	0.5 g/kg/d	NA	6 mo	30	7.1	60.0	2.1	5.1	41
Saneian and Mostofi-zadeh[19]	RCT	Functional constipation in children	Lactulose	1.5 g/kg/d	NA	6 mo	34	8.6	58.8	2.2	2.9	26
			PEG	1 cm³/kg/d	NA	1 mo	25	3.26	0.0	1.33	Change, 3.56	90
			Magnesium hydroxide	1 cm³/kg/d	NA	1 mo	25	3.11	0.0	1.37	Change, 4.67	97
			Lactose	1 cm³/kg/d	NA	1 mo	25	3.19	0.0	1.53	Change, 3.16	83
Ratana-mongkol et al[20]	RCT	Functional constipation in infants and young children	PEG 4000	0.5 g/kg/d	Once/d	4 wk	46	2.58	33.0	Median, 3	Median, 6	91
Loening-Baucke and Pashan-kar[21]	RCT	Children with chronic constipation and fecal incontinence	Milk of magnesia suspension	0.5 mL/kg/d	Once/d	4 wk	43	2.58	49.0	Median, 3	Median, 2	65
			PEG 3350	0.7 g/kg/d	Once/d	12 mo	39‡	8	79.0	3.5	6.8	49
Karami et al[22]	RCT	Functionally constipated children	Milk of magnesia	2 mL/kg	Once/d	12 mo	40§	8.2	85.0	3.5	8.2	55
			PEG	1 cm³/kg	Twice/d	1 mo	58	4.1	51.5	2.7	4.7	68

(Continued)

TABLE 1. (Continued)

Reference	Study Type	Type of Patients	Intervention Group	Dose	Frequency	Duration	Number of Cases	Mean Age, y	Sex, Male %	Mean Weekly Stool Frequency Before	Mean Weekly Stool Frequency After	Successful Disimpaction at Week 4, %
Rafati et al[23]	RCT	Functional constipation	Paraffin	1 cm³/kg	Twice/d	1 mo	55	4.1	0.0	3	4.5	54.7
			PEG 3350	1.0–1.5 g/kg/d	Once/d	4 mo	80	4.1	51.3	1.6	8.7	100
Candy et al[24]	RCT	Fecal impaction	Paraffin	1.0–1.5 mL/kg/d	Once/d	4 wk	78	4.2	55.1	1.4	7.5	96.2
			PEG 3350+E	13.8 g	2–6 y: once for first day, twice for days 2–3, 3 times for 4–5 d, and 4 times for 6–7 d; 7–11 y: twice for first day, 3 times for second day, 4 times for third day, 5 times for fourth day, and 6 times for 5–7 d	12 wk	28¶	5.8	61.0	NA	9.4	NA
Quitadamo et al[25]	RCT	Chronic functional constipation in childhood	Lactulose	10 g	NA	12 wk	30**	5.6	73.0	NA	5.9	NA
			PEG+E	0.5 g/kg	Once/d	8 wk	50††	6.7	38.0	2.1	5.8	72.9
			AFPFF	16.8 g	Once/d	8 wk	50‡‡	6.5	38.0	2.43	5.6	69.2

AFPFF = acacia fiber, psyllium fiber, and fructose, NA = not available, PEG = polyethylene glycol, PEG+E = PEG plus electrolytes, RCT = randomized controlled trial.
*n = 46 for evaluating weekly stool frequency.
†n = 45 for evaluating weekly stool frequency.
‡n = 34 for evaluating weekly stool frequency.
§n = 21 for evaluating weekly stool frequency.
¶n = 27 for evaluating weekly stool frequency.
**n = 26 for evaluating weekly stool frequency.
††n = 47 for evaluating weekly stool frequency.
‡‡n = 36 for evaluating weekly stool frequency.

Quality Assessment

We used the Delphi list to perform a quality assessment of the included studies.[11] Again, the quality assessment was performed by 2 independent reviewers who consulted a third reviewer regarding any uncertainties.

Outcome Measures

Primary and secondary efficacy outcomes were the number of stool passage/wk and the percentage of patients who reported satisfactory stool consistency, respectively. The safety outcomes included diarrhea, abdominal pain, nausea or vomiting, pain at defecation, straining at defecation, bloating or flatulence, hard stool consistency, poor palatability, and rectal bleeding.

Statistical Analysis

The standardized differences in mean changes with 95% confidence intervals (CIs) were calculated for the weekly stool frequency for children treated with PEG compared with those treated with non-PEG laxatives. The odds ratio (OR) with 95% CI was calculated for the proportion of successful disimpactions among children treated with PEG compared with those treated with non-PEG laxatives. Heterogeneity among the studies was assessed by calculating the Cochran Q and the I^2 statistic. For the Q statistic, $P < 0.10$ was considered to indicate statistically significant heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability caused by heterogeneity. Heterogeneity determined using the I^2 statistic was defined as follows: 0% to 24% = no heterogeneity, 25% to 49% = moderate heterogeneity, 50% to 74% = large heterogeneity, and 75% to 100% = extreme heterogeneity. If heterogeneity existed between studies (a Q statistic with $P < 0.1$[12] or an I^2 statistic $>50\%$[13]), we performed the random effects model (DerSimonian–Laird method),[14] otherwise the fixed-effects model was recommended (Mantel–Haenszel method). Combined standardized differences in mean change or ORs were calculated, and a 2-sided P value <0.05 was considered to indicate statistical significance. Sensitivity analysis was performed for both primary and secondary outcomes based on the leave-one-out approach. Publication bias was assessed by constructing funnel plots for both primary and secondary outcomes and was quantitatively detected by Egger test.[15] The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and $P > 0.10$ in Egger test. All statistical analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search

After initially identifying 231 articles, we excluded 204 articles, leaving 27 studies for full-text review. After full-text review, we excluded 17 studies for the reasons mentioned in Figure 1. Finally, our study included 10 articles.[16–25]

Quality Assessment

Figure 2 shows the risk of bias for each study included in this meta-analysis. Clearly, the 2 largest sources of bias in these studies involve blinding of the outcome assessment (detection bias) and blinding of participants and personnel (performance bias).

Study Characteristics

Table 1 summarizes the basic characteristics of the studies included in this meta-analysis. Among the 10 RCTs included,[16–25] 8 RCTs compared the effects of PEG and non-PEG laxatives, and 2 RCTs compared the effects of PEG plus electrolytes (PEG+E) and non-PEG laxatives. A total of 1052 children with constipation were enrolled in the 10 RCTs, including 511 who were treated with PEG or PEG+E and 541 who were treated with non-PEG laxatives. The total number of patients in each of the studies ranged from 58 to 216. The mean weekly stool frequency after treatment ranged from 4.7 to 9.4 times/wk and 2.9 to 8.2 times/wk for children treated with PEG or PEG+E and those treated with non-PEG laxatives, respectively. The proportions of successful disimpaction at 4 weeks after treatment ranged from 41% to 100% and 26% to 96% for children treated with PEG or PEG+E and those treated with non-PEG laxatives, respectively.

Primary Efficacy Outcome: Weekly Stool Frequency

Among the 10 RCTs, 3 did not provide sufficient information regarding the weekly stool frequency before and after treatment[16,18] and were excluded from our meta-analysis. For the 7 RCTs included in the meta-analysis, we found extreme heterogeneity among the studies after we pooled the data ($Q = 55.70$, $df = 6$, $P < 0.001$, $I^2 = 89.23\%$). Therefore, we used a random effects model for the analysis. The results indicated that the mean change in weekly stool frequency did not differ significantly between children treated with PEG and those treated with non-PEG laxatives (combined standardized differences in mean change = 0.38, 95% CI −0.11 to 0.87, $P = 0.130$) (Figure 3).

Secondary Efficacy Outcome: Successful Disimpaction

To identify the proportion of successful disimpactions, we evaluated 4 time points after treatment: 2 weeks (2 RCTs), 4 weeks (7 RCTs), 8 weeks (3 RCTs), and 12 weeks (3 RCTs). The combined OR indicated that the proportions of successful disimpactions were significantly higher in children treated with PEG compared with those treated with non-PEG laxatives at week 2 (combined OR = 2.64, 95% CI 1.19–5.85, $P = 0.017$) (Figure 4A), week 4 (combined OR = 1.63, 95% CI 1.09–2.44, $P = 0.018$) (Figure 4B), week 8 (combined OR = 2.47, 95% CI 1.35–4.53, $P = 0.003$) (Figure 4C), and week 12 (combined OR = 1.87, 95% CI 1.03–3.37, $P = 0.038$) (Figure 4D) after treatment.

Additional Safety Outcomes

A total of 7 RCTs reported adverse events, including diarrhea, abdominal pain, nausea or vomiting, pain at defecation, straining at defecation, bloating or flatulence, hard stool consistency, bad palatability, and rectal bleeding. The summary of adverse events of study patients is shown in Table 2.

Sensitivity Analysis

The results of the sensitivity analyses, in which the studies were omitted one-by-one, are summarized in Figure 5 for the weekly stool frequency and successful disimpaction, respectively.

TABLE 2. Summary of Adverse Events of Study Patients

Reference	Intervention Group	Number of Cases	Overall	Diarrhea	Abdominal Pain	Nausea/ Vomiting	Pain at Defecation	Straining at Defecation	Bloating/ Flatulence	Hard Stool Consistency	Bad Palat- ability	Rectal Bleeding
									Adverse Events, %			
Wang et al[16]	PEG 4000	105	2	1	1							
	Lactulose	111	0	0	0							
Voskuijl et al[17]	PEG 3350	50		31	35	15	26	35	53	30	34	
	Lactulose	50		28	56	22	47	56	80	40	10	
Rendeli et al[18]	PEG 4000	30		18	45	11			50	30	27	
	Lactulose	34		17	50	13			60	40	20	
Saneian and Mostofiza- deh[19]	PEG	25		0	7	0			7			
	Magnesium hydroxide	25		17	57	0			3			
Ratanamongkol et al[20]	Lactose	25		3	47	3			57			
	PEG 4000	46	44	4.3	20	8.7			28			
	Milk of mag- nesia sus- pension	43	56	28	33	21			30			
Candy et al[24]	PEG 3350+E	28	83									
	Lactulose	30	64									
Quitadamo et al[25]	PEG+E	50			12.8	4.3	8.5		21.7			2.1
	AFPFF	50			14	2.3	18.6		19			4.7

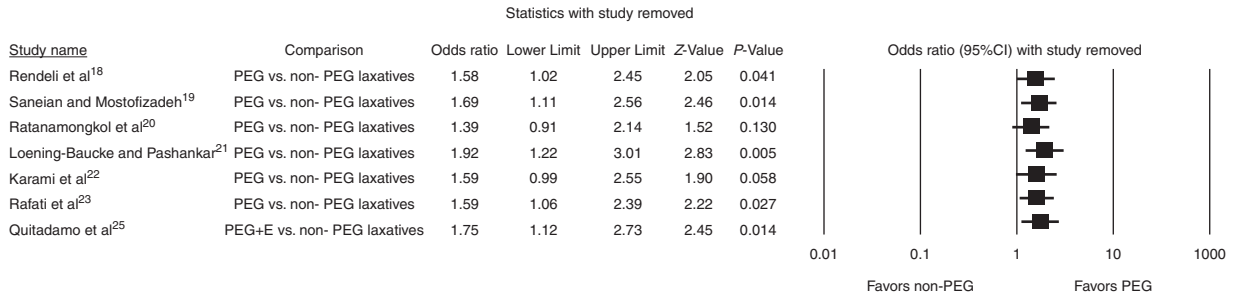AFPFF = acacia fiber, psyllium fiber, and fructose, PEG = polyethylene glycol, PEG+E = PEG plus electrolytes.

Statistics with study removed

Study name	Comparison	Odds ratio	Lower Limit	Upper Limit	Z-Value	P-Value
Rendeli et al[18]	PEG vs. non- PEG laxatives	1.58	1.02	2.45	2.05	0.041
Saneian and Mostofizadeh[19]	PEG vs. non- PEG laxatives	1.69	1.11	2.56	2.46	0.014
Ratanamongkol et al[20]	PEG vs. non- PEG laxatives	1.39	0.91	2.14	1.52	0.130
Loening-Baucke and Pashankar[21]	PEG vs. non- PEG laxatives	1.92	1.22	3.01	2.83	0.005
Karami et al[22]	PEG vs. non- PEG laxatives	1.59	0.99	2.55	1.90	0.058
Rafati et al[23]	PEG vs. non- PEG laxatives	1.59	1.06	2.39	2.22	0.027
Quitadamo et al[25]	PEG+E vs. non- PEG laxatives	1.75	1.12	2.73	2.45	0.014

Odds ratio (95%CI) with study removed

0.01   0.1   1   10   1000

Favors non-PEG   Favors PEG

FIGURE 6. Sensitivity analysis for treatment effects on successful disimpaction (4 weeks after treatment) by the leave-one-out approach.

Regarding the weekly stool frequency (Figure 5), the direction and magnitude of the pooled standardized differences in mean change did not vary substantially with the removal of any study, which indicates good reliability on this meta-analysis.

However, regarding the successful disimpaction at 4 weeks after treatment (Figure 6), the removal of the studies by Ratanamongkol et al[20] or Karami et al[22] caused the pooled OR to become nonsignificant. This finding suggested that the pooled estimates of the meta-analysis of successful disimpaction at 4 weeks after treatment may be influenced by some individual studies.

Publication Bias

Regarding the weekly stool frequency, the funnel plot for publication bias demonstrated evidence of symmetry

A

Funnel plot of standard error by std diff in mean changes
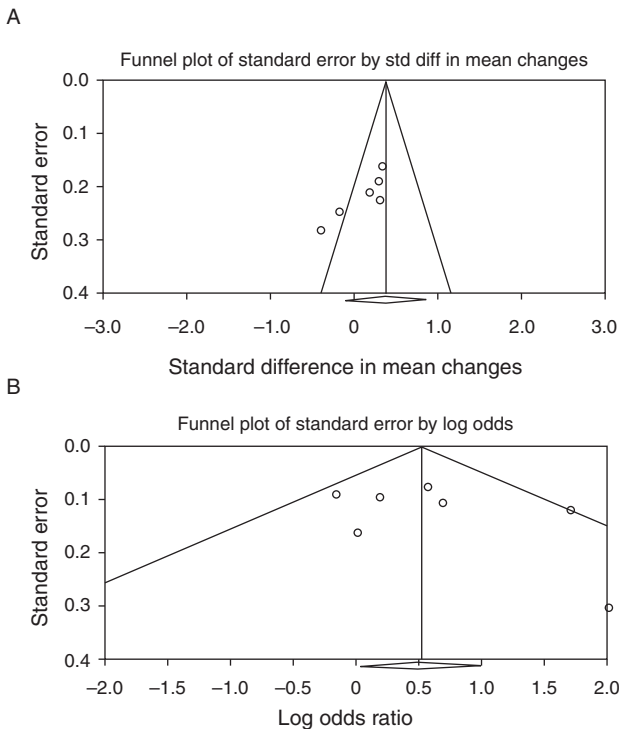
B

Funnel plot of standard error by log odds

FIGURE 7. Funnel plot for evaluating publication bias regarding (A) the weekly stool frequency and (B) successful disimpaction. White circles represent observed studies, and white rhombuses represent observed combined effect size. Std diff = standard difference.

(Figure 7A). Egger test of the intercept also indicated no significant evidence of publication bias ($t = 0.230$, $df = 5$, $P = 0.414$) (Figure 7A).

Moreover, regarding successful disimpaction at 4 weeks after treatment, the funnel plot for publication bias also demonstrated evidence of symmetry (Figure 7B). Egger test of the intercept also indicated no significant evidence of publication bias ($t = 0.898$, $df = 5$, $P = 0.205$) (Figure 7B).

DISCUSSION

Functional constipation occurs in 90% to 95% of children. PEG is an osmotic laxative agent that is absorbed in only trace amounts from the gastrointestinal tract and routinely used to treat chronic constipation in adults. In this meta-analysis, we report the results of studies that compared PEG-based laxatives, including PEG+E, and non-PEG laxatives such as lactulose, milk of magnesia, oral mineral oil, or acacia fiber, psyllium fiber, and fructose (AFPFF) in children. Ten published RCTs initially met the inclusion criteria, but 3 did not provide sufficient information regarding the weekly stool frequency as primary efficacy outcome before and after treatment and were excluded from the meta-analysis.

Previous pooled analyses[1,6] and a Cochrane systematic review[4] suggested that PEG preparations may be superior to placebo, lactulose, and milk of magnesia for treating childhood constipation. However, the results should be interpreted with caution because the overall quality of the evidence for the primary outcome (number of stools/wk) was low or missing because of sparse data, inconsistency among studies (heterogeneity), and a high risk of bias in the studies.

The results of this meta-analysis indicated that the mean change in weekly stool frequency did not differ significantly between children treated with PEG and those treated with non-PEG laxatives ($P = 0.130$). However, the combined OR indicated that the proportions of the successful disimpaction were significantly higher in children treated with PEG compared with those treated with non-PEG laxatives at weeks 2, 4, 8, and 12 ($P < 0.038$ for all measurements).

Adverse events reported in the 7 studies that were evaluated during our meta-analysis included diarrhea, abdominal pain, nausea or vomiting, pain at defecation, straining at defecation, bloating or flatulence, hard stool consistency, bad palatability, and rectal bleeding (Table 2).

The limitations of our study include the typical obstacles for meta-analyses,[10] particularly the heterogeneity in subjects (children of different ages and eligibility criteria that defined constipation), different types of PEG administered (PEG 4000, PEG 3350, PEG, PEG

3350+E, and PEG+E), and different control arms (lactulose, magnesium hydroxide, milk of magnesia suspension, liquid paraffin, or AFPFF).

Importantly, the optimal dosage, route, and regimen for PEG administration should be identified in future randomized controlled studies and meta-analyses. The length of follow-up was reported only in 2 of the studies we identified.[17,21] Longer follow-up may be required to identify late side effects.

CONCLUSION

PEG-based laxatives are effective and safe for chronic constipation and for resolving fecal impaction in children. Further research will help physicians use PEG-based laxatives in the safest and most effective manner possible.

REFERENCES

1. Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gasterenterol Nutr*. 2006;43:e1–e13.

2. Sullivan PB. Hirschprung's disease. *Arch Dis Child*. 1996;74:5–7.

3. Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. *Am Fam Physician*. 2006;73:469–477.

4. Gordon M, Naidoo K, Akobeng AK, et al. Osmotic and stimulant laxatives for the management of childhood constipation. *Cochrane Database Syst Rev*. 2012;7:CD009118.

5. Rowan-Legg A, Canadian Paediatric Society, Community Paediatrics Committee. Managing functional constipation in children. *Paediatr Child Health*. 2011;16:661–665.

6. Pijpers MA, Tabbers MM, Benninga MA, et al. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. *Arch Dis Child*. 2009;94:117–131.

7. Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. *Arch Dis Child*. 2009;94:156–160.

8. Arora R, Srinivasan R. Is polyethylene glycol safe and effective for chronic constipation in children? *Arch Dis Child*. 2005;90:643–646.

9. Kinservik MA, Friedhoff MM. The efficacy and safety of polyethylene glycol 3350 in the treatment of constipation in children. *Pediatr Nurs*. 2004;30:232–237.

10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.

11. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51:1235–1241.

12. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127:820–826.

13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.

15. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.

16. Wang Y, Wang B, Jiang X, et al. Polyethylene glycol 4000 treatment for children with constipation: a randomized comparative multicenter study. *Exp Ther Med*. 2012;3:853–856.

17. Voskuijl W, de Lorijn F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut*. 2004;53:1590–1594.

18. Rendeli C, Ausili E, Tabacco F, et al. Polyethylene glycol 4000 vs. lactulose for the treatment of neurogenic constipation in myelomeningocele children: a randomized-controlled clinical trial. *Aliment Pharmacol Ther*. 2006;23:1259–1265.

19. Saneian H, Mostofizadeh N. Comparing the efficacy of polyethylene glycol (PEG), magnesium hydroxide and lactulose in treatment of functional constipation in children. *J Res Med Sci*. 2013;17: S145–S149.

20. Ratanamongkol P, Lertmaharit S, Jongpiputvanich S. Polyethylene glycol 4000 without electrolytes versus milk of magnesia for the treatment of functional constipation in infants and young children: a randomized controlled trial. *Asian Biomedicine*. 2009;3:391–399.

21. Loening-Baucke V, Pashankar DS. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. *Pediatrics*. 2006;118:528–535.

22. Karami H, Khademloo M, Niari P. Polyethylene glycol versus paraffin for the treatment of childhood functional constipation. *Iran J Pediatr*. 2009;19:255–261.

23. Rafati MR, Karami H, Salehifar E, et al. Clinical efficacy and safety of polyethylene glycol 3350 versus liquid paraffin in the treatment of pediatric functional constipation. *Daru*. 2011;19:154–158.

24. Candy DC, Edwards D, Geraint M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. *J Pediatr Gastroenterol Nutr*. 2006;43:65–70.

25. Quitadamo P, Coccorullo P, Giannetti E, et al. A randomized, prospective, comparison study of a mixture of acacia fiber, psyllium fiber, and fructose vs polyethylene glycol 3350 with electrolytes for the treatment of chronic functional constipation in childhood. *J Pediatr*. 2012;161:710–715.