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Polyethylene Glycols with or without Electrolytes for Constipation in Children: A Network Meta-Analysis

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Abstract

Background: Polyethylene glycol laxatives are the cornerstone of the management of constipation in children. They are available with and without electrolytes.

Aims: The aims of this network meta-analysis (NMA) were to assess the relative efficacy, safety and tolerability of polyethylene glycol with (PEG+E) or without electrolytes (PEG) in the management of constipation in children.

Methods: A systematic review and NMA was undertaken to identify and analyse all published randomised controlled clinical trials of polyethylene glycol in children with constipation. Text word searches were carried out using MEDLINE, MEDLINE in Progress, EMBASE, Cochrane Database and Systematic Reviews databases covering inception to April 2015. The primary efficacy analysis was the mean number of bowel movements per week. Secondary endpoints assessed safety, tolerability and compliance.

Results: 15 studies (involving 1,384 patients) were included in the NMA. PEG and PEG+E are both more effective than placebo, increasing the mean number of bowel movements per week by 2.3 (95% CrI 0.3, 4.4) and 2.2 (95% CrI 0.1, 4.7) respectively. Direct comparison of PEG+E with PEG identified no differences in efficacy, safety, or tolerability, with the exception of one study demonstrating better tolerability with PEG. Compared to PEG+E, PEG was easier to take, with a trend towards improved compliance.

Conclusion: This NMA provides no evidence to support the clinical utility of added electrolytes to polyethylene glycol in the management of constipation in children. PEG alone is as effective as PEG+E and both therapies are well tolerated. This analysis supports the ongoing use of polyethylene glycol as a first-line treatment of constipation in children. Formulations without electrolytes should be considered first to optimize patient acceptability and adherence.

Keywords: Constipation; Macrogol; Polyethylene glycol; Electrolytes

Introduction

Constipation, defined as difficulty or pain on defecation, is a common problem in children which can be challenging to manage. Constipation most commonly first appears amongst toddlers (ages 2 to 4 years) [1] but can also occur in babies often when weaning on to solids [2] and affects up to a third of children [3]. In children, constipation usually occurs without evidence of an underlying disease (functional constipation) and is often the result of stool retention associated with toilet training, changes in diet or routine, stressful events, illness or withholding [4]. Constipation can be a chronic problem in children, sometimes resulting in significant physical morbidity and psychosocial distress [5].

The management of constipation in children involves education, establishing a regular toileting routine, behavioural modification, the treatment of faecal impaction and laxative maintenance therapy [2,6]. There are multiple laxatives that are safe to use in children, however polyethylene glycol based laxatives have become one of the mainstay of therapy as they are effective, well tolerated and easy to administer [7].

Polyethylene glycol is available as either 3,350 or 4,000 g/mol, with or without electrolytes [8]. Polyethylene glycol softens the stool and relieves constipation by essentially holding the water it is ingested with and not via drawing water into the lumen from the body. This retained water softens hardened stools and increases the stool volume which encourages natural peristaltic reflexes [9].

Several meta-analysis [10,11] and a Cochrane systematic review [12] have assessed the efficacy of polyethylene glycols for constipation in children. The Cochrane review suggested that polyethylene glycols are more effective than placebo, lactulose, liquid paraffin and magnesium hydroxide, however the authors recommended caution due to issues associated with heterogeneity and risk of bias [12]. The most recent meta-analysis concluded that polyethylene glycols are an effective therapy for constipation, but were not significantly more effective than other laxatives [11]. These reviews did not distinguish between the different polyethylene glycol formulations and the clinical utility off added electrolytes was not assessed.

A key to the successful management of constipation in children is for the child to be able to take an adequate dose and comply with the regimen. The inclusion of electrolytes can affect the palatability of polyethylene glycol, which on its own is essentially tasteless. What is

not known is whether the added electrolytes augments, reduces or has little impact on the clinical effectiveness of polyethylene glycol in the management of constipation in children.

Objectives

The objectives of this systematic review and network meta-analysis (NMA) were to assess the relative efficacy, safety and tolerability of polyethylene glycol with or without electrolytes in the management of constipation in children. The primary efficacy end point was the mean number of bowel movements per week.

Methods

Search methodology

Text word searches were carried out using EMBASE, MEDLINE, MEDLINE in Progress and the Cochrane Database and Systematic Reviews databases covering inception to April 2015. Search terms were (constipation) AND (PEG OR polyethylene OR macrogol OR movicol OR idrolax OR miralax OR transipeg OR forlax OR colyte OR golytely OR isocolan OR nulytely) NOT colonoscopy. Only published randomised controlled trials comparing oral polyethylene glycol with placebo or a comparator laxative in children with constipation were included in this analysis. A separate analysis of data in adults using the same methodology was conducted in parallel and has been published elsewhere [13]. The diagnosis of constipation was based on the Rome I, II or III diagnostic criteria, clinical symptoms or the clinician's opinion. Bibliographies of all identified relevant studies and reviews were used to perform a recursive search. Only papers published in English were included in the analysis.

Data extraction

Two independent reviewers followed a four-step process for data collection. First, titles and abstracts of the identified citations were assessed according to the research objectives. Next, potentially relevant articles were screened as full texts. For the studies that met the selection criteria one reviewer extracted relevant data using a standardised database and the accuracy of the extracted data was confirmed by a second reviewer. Both reviewers then determined if the study met the inclusion criteria and was to be included in the analysis. Disagreements were resolved by consensus involving two additional reviewers.

The following data were extracted: author; publication year, title; journal; patient population (adult or paediatric); study design; definition of constipation; patient age; characteristics; exclusion/inclusion criteria; mean duration of constipation prior to study intervention; intent to treat population (ITT); comparability of treatment groups; subanalysis based on age; study duration; study medications, dose and duration of treatment. To standardise the assessment of efficacy, a single objective outcome, the mean number of bowel movements per week (mean plus standard deviation [SD] or standard error [SE]) was used. Where available the assessment after a 2-week treatment period was used, otherwise the value at the end of treatment was used. If means were not reported, medians and interquartile ranges were used. Data was normalised to mean number of bowel movements per week. To assess secondary endpoints: Laboratory data, vital signs, tolerability data and measures of compliance were collected.

The risk of bias was assessed as per the recommendations published in the Cochrane Handbook for Systematic Reviews of Interventions [14].

Data analysis

Studies were grouped according to whether the polyethylene glycol had added electrolytes (PEG+E) or not (PEG) and then according to the comparator (placebo or different active controls).

The statistical methods used for the NMA have been previously published [13]. For all comparisons where there was more than one study available, standard meta-analysis was performed using a Bayesian fixed effects and a Bayesian random effects models. All the available data were combined using a NMA with a Bayesian random effects model fitted to assess the relative effectiveness of PEG and PEG +E [15]. In this analysis, for each simulation the result for active treatment was compared with control. If the mean stool frequency for active treatment was greater than the mean stool frequency for control, this was regarded as active being better than control, for that simulation. Across all simulations the percentage of simulations where active is greater than control was obtained and is reported as a percentage, 'probability best'. If the two treatments are equivalent, the 'probability best' is 50%, while if the active treatment is always superior to the control the probability best is 100%.

Sensitivity analysis was performed by repeating the analysis using only high quality studies with a low risk of bias.

Results

Literature search

Literature searches identified 1,612 potentially relevant abstracts which were reduced to 1,484 after removal of duplicates. 29 publications underwent full-text review and 15 studies were included in the final analysis (Figure 1) [16-30].

Study characteristics

Of the 15 qualifying studies, 9 studies were with PEG; 1 versus placebo and 6 versus other osmotic laxatives and 2 versus stool softeners; 5 studies were with PEG+E, 1 versus placebo, 3 versus other osmotic laxatives and 1 versus bulk forming laxatives; and 1 study made a direct comparison between PEG and PEG+E. Table 1 provides an overview of the individual studies.

1,384 patients were randomised to receive polyethylene glycol with or without electrolytes or control (placebo or active controls). Five of the 15 studies were assessed as having a low risk of bias [14] (Table 2 and Figure 2).

Patients were predominantly experiencing chronic functional constipation [16-23,25-30] with the exception of one study being amongst patients with spina bifida with chronic neurogenic constipation [24]. Overall there was approximately equal proportion of male and female patients with the average patient age ranging from 2.0 to 11.3 years.

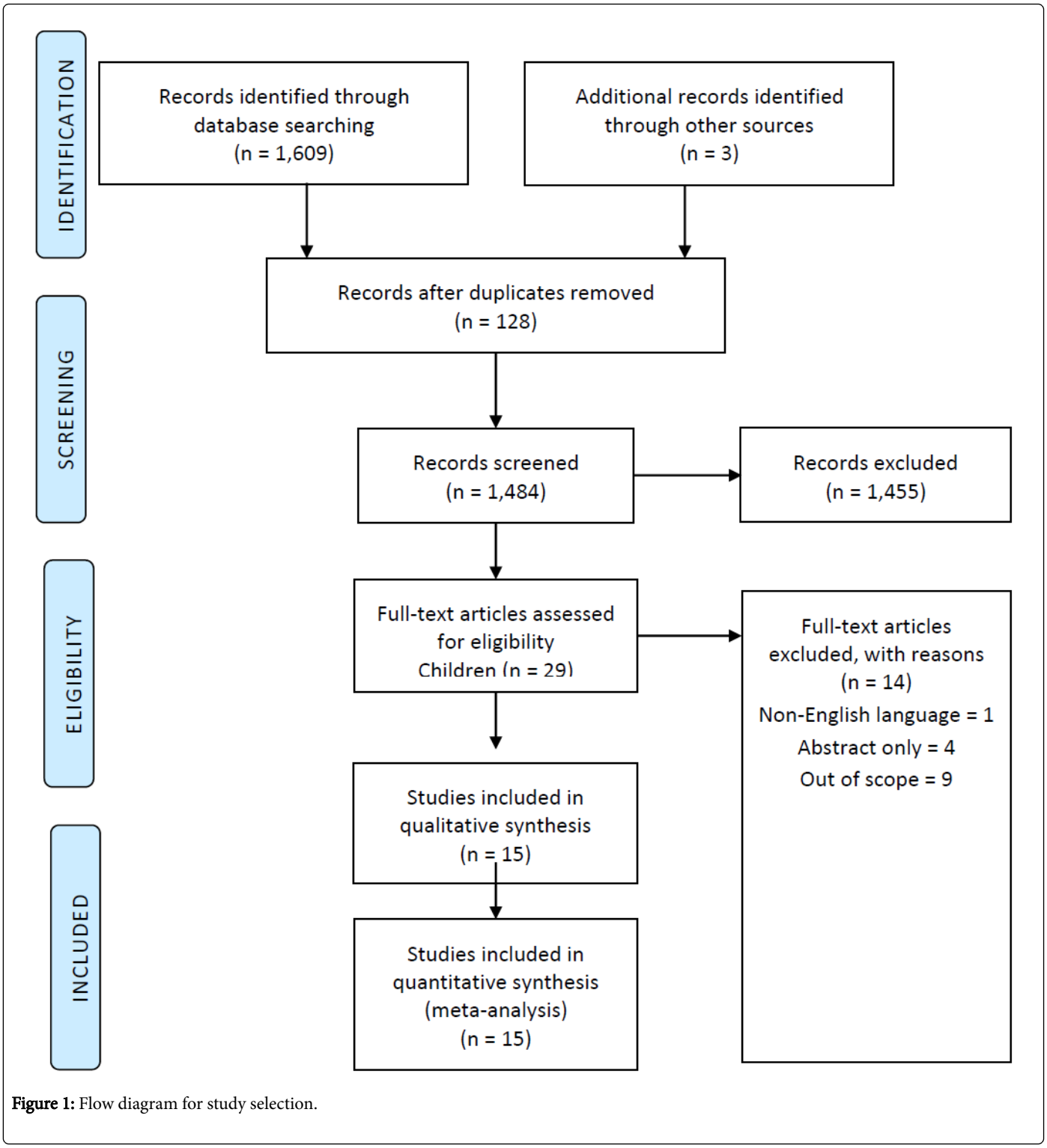

Figure 1: Flow diagram for study selection.

Network meta-analysis

Figure 3 shows the network formed by the different treatments used to manage constipation in this NMA. Across the 15 studies there were 19 connections between the different treatments. Table 2 summarizes the mean number of bowel movements per week for all individual studies.

Table 3 summarizes the results for the standard meta-analysis for direct evidence (Bayesian random effects pairwise meta-analysis). None of these direct comparisons yielded statistically significant differences between the either of the polyethylene glycols and their comparators.

Study	Total (N)	Length of study	Constipation type	Baseline stool frequency mean (SD)	Age mean (SD) years	Gender (% male)	Study groups comparable	Polyethylene glycol formulation and daily dose	Polyethylene glycol (N)	Comparator and daily dose	Comparator (N)
Candy et al. [16]	53	12 weeks	Chronic functional	Not specified	5.7 (2.6)	67%	Comparable	PEG3350+E 6.9-41.4 g	27	Lactulose 5.0-30.0 g	26
Dupont et al. [17]	96	3 months	Chronic functional	P: 0.86 (0-1) C: 1 (0.5-1)	Median: P: 2.3 C: 2.15	P: 43% C: 64%	Comparable	PEG4000 4-8 g	51	Lactulose 3.3-6.6 g	45
Gomes et al. [18]	38	6 months	Chronic functional	P: 2.0 (1.6) C: 1.3 (0.8)	P: 4.4 (2.8) C: 5.1 (3.1)	P: 58.8% C: 61.9%	Comparable	PEG4000 0.5-1.5 g/kg	17	Magnesium hydroxide 1-3 mL/kg	21
Karami [19]	103	2-4 months	Chronic functional	P: 2.7 (1.4) C: 3.0 (1.5)	4.0 (2.3)	51.5%	Comparable	PEG 1.6 g/kg/day	48	Liquid paraffin 2 cc/kg	55
Nurko et al. [20]	103	2 weeks	Chronic functional	1.6 (0.8)	8.5 (3.1)	67.0%	Comparable	PEG3350 L=0.2 g/kg M=0.4 g/kg H=0.8 g/kg	L=26 M=27 H=26	Placebo	24
Quitadamo et al. [21]	100	2 months	Chronic functional	P: 2.1 (1) C: 2.4 (1)	6.5 (2.7)	38%	Comparable	PEG3350+E 0.5 g	50	Mixture of acacia & psyllium fibre plus fructose 16.8 g	50
Rafati et al. [22]	158	4 months	Chronic functional	P: 1.6 (0.8) C: 1.4 (0.5)	P: 4.4 (2.0) C: 4.2 (2.0)	P: 51.3% C: 55.1%	Comparable	PEG3350 1.0-1.5 g/kg	80	Liquid paraffin 1.0-1.5 mL/kg	78
Ratanamongkol et al. [23]	89	4 weeks	Chronic functional	Median (Q1,Q3): P: 3 (2,4) C: 3 (2,5)	P: 2.6 (0.8) C: 2.6 (1.0)	P: 33% C: 49%	Comparable	PEG4000 0.5 g/kg	46	Magnesium hydroxide 0.5 mL/kg	43
Rendeli et al. [24]	64	6 months	Chronic neurogenic constipation	<3/week P: 93% C: 91%	7.8 (5.3)	59.3%	Comparable	PEG4000+E 0.5 g/kg	30	Lactulose 1.5 g/kg	34
Saneian et al. [25]	90	6 months	Chronic functional	P: 1.3 (1.2) C1: 1.4 (2.4) C2: 1.5 (1.4)	P: 3.3 (1.5) C1 3.1 (1.1) C2: 3.2 (1.4)	Not specified	Comparable	PEG 1-3 cc/kg	30	C1: Magnesium hydroxide 1-3 cc/kg C2: Lactulose 1-3 cc/kg	C1: 30 C2: 30
Savino et al. [26]	91	28 days	Chronic functional	Not specified	P:5.6 (3.3) C: 5.5 (3.0)	P: 57.1% C: 44.9%	Comparable	PEG3350+E 6.9-27.6 g	42	PEG4000 0.7 g/kg	49
Thomson et al. [27]	49	2 x 2 weeks	Chronic functional	Not specified	5.4 (2.6)	43.1%	Crossover design	PEG3350+E 6.9-41.4 g	47	Placebo	48

Treepongkaruna et al. [28]	87	4 weeks	Chronic functional	P: 4.4 (1.8) C: 4.9 (2.1)	2.0 (0.5)	P: 59.1% C: 54.6%	Comparable	PEG4000 8 g	43	Lactulose 3.3 g	44
Voskuijl et al. [29]	91	8 weeks	Chronic functional	P: 2.6 (3.3) C: 2.8 (3.1)	P:6.52 (3.2) C: 6.5 (3.4)	P: 54% C: 56%	Comparable	PEG3350+E 2.95-5.9 g	46	Lactulose 6-12 g	45
Wang et al. [30]	216	2 weeks	Functional	P: 2 C: 2	P: 11.3 (2.8) C: 11.2 (2.8)	P: 41.0% C: 42.3%	Comparable	PEG4000 20 g	105	Lactulose 10 g for 3 days 6.7 g for 11 days	111
P=Polyethylene Glycol Group, C=Comparator group, H=High Dose, M=Medium dose, L=Low dose.											

Table 1: Summary of the fifteen included studies.

Study	Assessment time	Stools per week (number of patients)						
		PEG+E	PEG	Placebo	Other osmotic laxatives	Stool softeners	Bulk forming	Low risk of bias
Thomson et al. [27]	2 weeks	3.1 (N=47)		1.5 (N=48)				Yes
Candy et al. [16]	12 weeks	9.4 (N=27)			5.9 (N=26)			Yes
Rendeli et al. [24]	6 months	5.1 (N=30)			2.9 (N=34)			No
Voskuijl et al. [29]	8 weeks	7.1 (N=46)			6.4 (N=45)			No
Quitadamo et al. [21]	2 weeks	4.8 (N=50)					4.3 (N=50)	No
Nurko et al. [20]	2 weeks		L: 4.5 (N=26) M: 3.4 (N=27) H: 5.9 (N=26)	2.1 (N=24)				Yes
Dupont et al. [17] (Babies)	84 days		8.5 (N=10)		11.5 (N=12)			No
Dupont et al. [17] (Toddlers)	84 days		7.0 (N=41)		6.0 (N=33)			No
Gomes et al. [18]	6 months		5.8 (N=17)		4.9 (N=21)			No
Ratanamongkol et al. [23]	4 weeks		6.0 (N=46)		5.0 (N=43)			No
Saneian et al. [25]	1 month		4.9 (N=30)		C1: 4.7 (N=30) C2: 6.0 (N=30)			No
Treepongkaruna et al. [28]	2 weeks		7.5 (N=43)		5.4 (N=44)			Yes
Wang et al. [30]	2 weeks		7.0 (N=105)		6.0 (N=111)			Yes
Karami [19]	1 month		4.7 (N=48)			4.5 (N=55)		No
Rafati et al. [22]	2 weeks		6.1 (N=80)			5.1 (N=78)		No
Savino et al. [26]	28 days	7.8 (n=49)	9.2 (N=42)					No
PEG=Polyethylene Glycol alone, without electrolytes; PEG+E=Polyethylene Glycol with electrolytes; H=High dose; M=Medium dose; L=Low dose.								

Table 2: Individual study results included in the network meta-analysis.

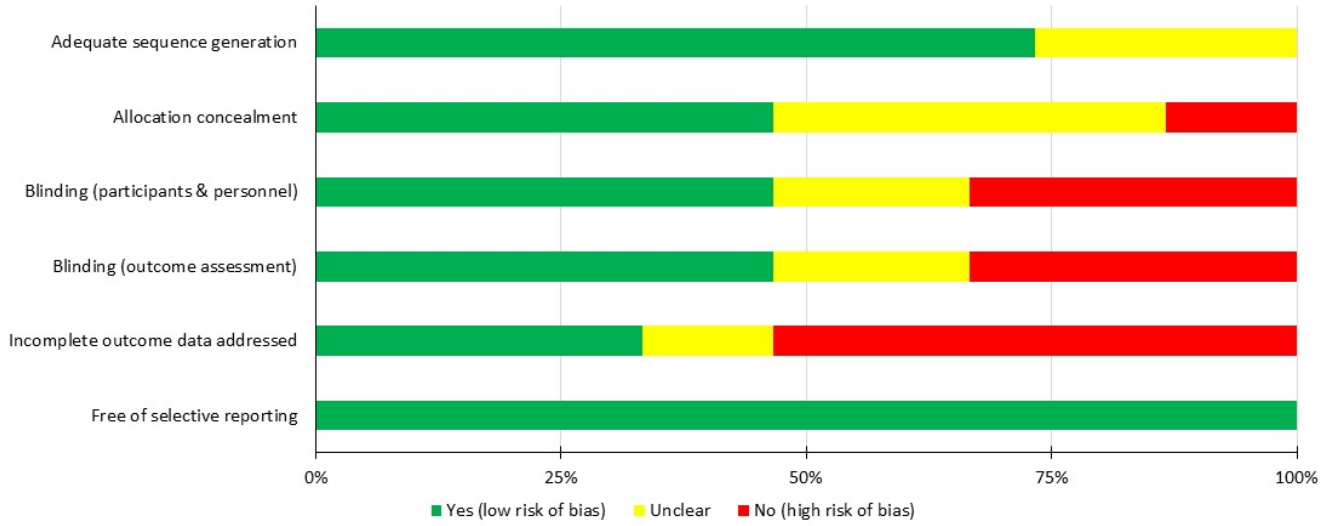

Figure 2: Risk of bias.

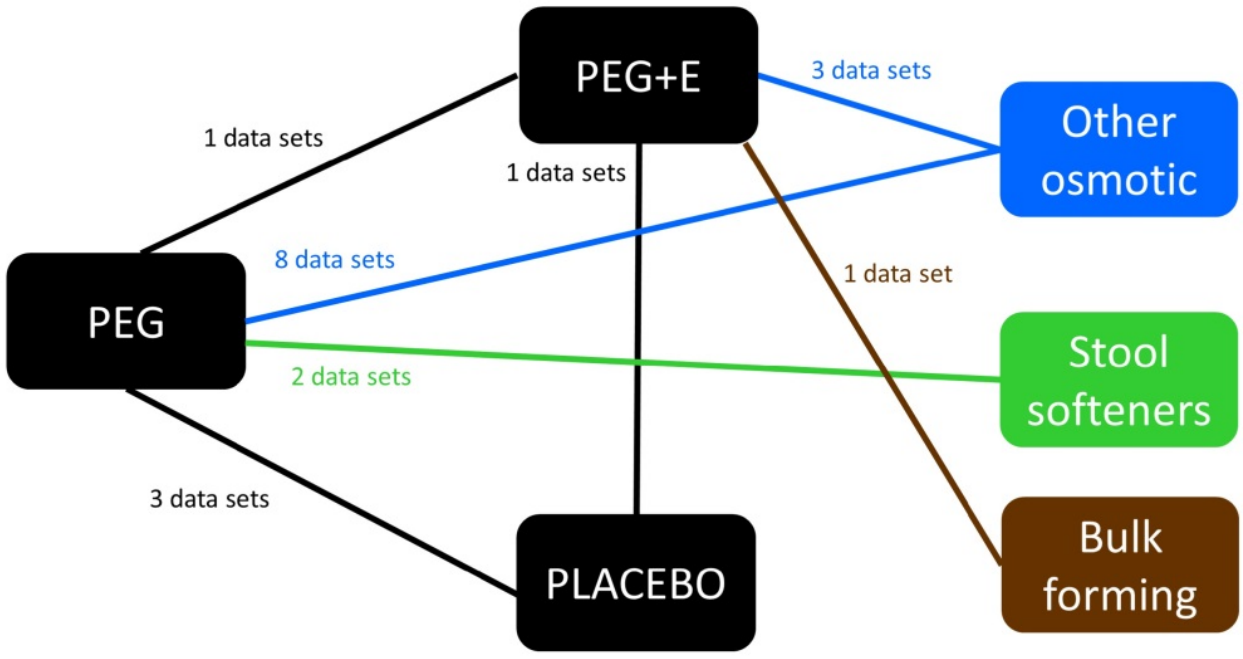

Figure 3: Network diagram, constipation treatments and direct comparisons included in the analyses (PEG=Polyethylene glycol alone, without electrolytes; PEG+E=Polyethylene glycol with electrolytes).

Comparison	Difference in mean stool frequency (direct)	Lower credible limit (direct)	Upper credible limit (direct)	Tau-sq: between study heterogeneity for direct MA	Number of data sets for direct MA	Difference in mean stool frequency (NMA)	Lower credible limit (NMA)	Upper credible limit (NMA)	Probability active treatment is better than comparator in NMA*
PEG vs. Placebo	2.1	-3.7	6.9	2.09	3	2.3	0.3	4.4	98.8%

PEG+E vs. Placebo						2.2	0.1	4.7	97.7%
PEG+E vs. PEG						-0.1	-1.8	1.9	44.9%
PEG vs. Other osmotic	0.6	-0.9	1.9	0.91	8	0.8	-0.5	2.0	90.9%
PEG+E vs. Other osmotic	2.0	-4.1	8.2	2.29	3	0.7	-1.1	2.7	79.6%
PEG vs. Stool softener	0.7	-3.1	4.8	1.64	2	0.6	-1.4	3.3	73.1%
PEG+E vs. Stool softener						0.5	-2.1	3.6	65.9%
PEG vs. Bulk forming						0.6	-3.0	4.0	65.1%
PEG+E vs. Bulk forming						0.5	-2.6	3.6	64.3%
PEG=Polyethylene Glycol alone, without electrolytes. PEG+E=Polyethylene Glycol with electrolytes. NMA=Network Meta-Analysis, MA=Meta-Analysis *Note a probability of 50% equates to no difference between the two therapies.									

Table 3: Results for the direct head-to-head random effects meta-analysis and network meta-analysis.

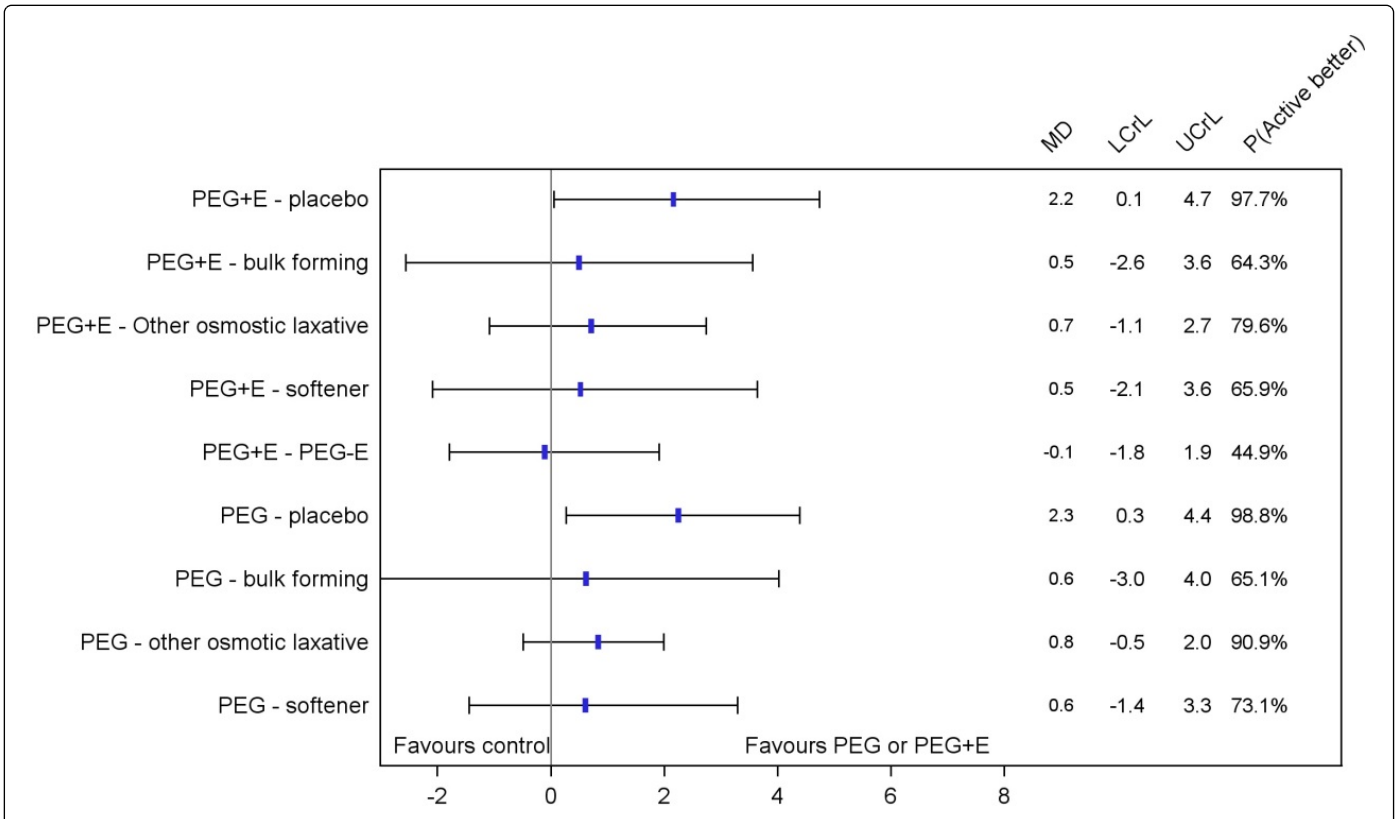

Figure 4: Pairwise comparisons for PEG and PEG+E from the network meta-analysis (The control group for the direct comparison between PEG+E and PEG is PEG without electrolytes. PEG=Polyethylene glycol alone, without electrolytes; PEG+E=Polyethylene glycol with electrolytes; MD=Difference in mean stool frequency; LCrL=Lower credible limit).

With the inclusion of more data, as accommodated by the NMA, both PEG and PEG+E were found to be significantly more effective than placebo, increasing the mean number of bowel movements per week by 2.3 and 2.2 respectively. Comparisons with the different active controls favoured the polyethylene glycols, but were not statistically significant. The addition of electrolytes did not enhance the efficacy of polyethylene glycol as illustrated by the direct comparison between PEG and PEG+E (Table 3 and Figure 4).

Safety and tolerability

Fourteen of the 15 studies provided evidence on tolerability of polyethylene glycol and five studies provided safety data (laboratory results and/or vital signs), 2 for PEG+E [16,24] and 3 for PEG [17,20,30] (Table 4). No clinically relevant changes in laboratory measures were reported for either PEG or PEG+E. Polyethylene glycol with or without added electrolytes were well tolerated and generally better tolerated than other active constipation therapies (lactulose [16,17,25,29] liquid paraffin [22] and magnesium hydroxide [23,25]). Treatment-related side effects were predominantly gastrointestinal, including abdominal pain, diarrhoea and nausea. The only head-to-head clinical trial of PEG and PEG+E found that PEG was better tolerated than PEG+E with a lower incidence of nausea [26]. Serious treatment-related adverse events were uncommon as were discontinuations due to adverse events.

Study	Type of polyethylene glycol	Comparator	Safety signals (Laboratory data, vital signs)	Tolerability (Adverse events)
Candy et al. [16]	PEG3350+E	Lactulose	No clinically significant abnormal values were observed in urine and plasma electrolytes.	Adverse events were less common with PEG+E than lactulose (64% vs 83%). Most events were GI and transient.
Dupont et al. [17]	PEG4000	Lactulose	No treatment-related changes in whole blood measurements. No changes in blood electrolytes, total protein, serum albumin, iron, folates and vitamins A and D.	6 treatment-related adverse events, all non-serious, diarrhoea (5 episodes in 2 patients in both treatment groups) and anorexia (1 patient in the lactulose group). GI tolerance; less flatulence and vomiting with PEG. No differences in other GI adverse events.
Gomes et al. [18]	PEG4000	Magnesium hydroxide	NA	PEG was better accepted than magnesium hydroxide, where treatment was interrupted in 43% of patients due to persistent refusal or vomiting.
Karami [19]	PEG	Liquid paraffin	NA	NA
Nurko et al. [20]	PEG3350	Placebo	No electrolyte abnormalities. No differences in laboratory measurements between PEG and placebo.	Adverse events occurred in similar frequency to placebo. No differences in the type of non-GI-related adverse events, most common being headache. Higher incidence of GI events for PEG (dose-related adverse events; flatulence, abdominal pain, nausea and diarrhoea). 2 serious adverse events (impaction with PEG 0.2 g/kg group) resulted in hospitalisation.
Quitadamo et al. [21]	PEG3350+E	Mixture of acacia & psyllium fibre plus fructose	NA	Transient diarrhoea was the only clinically significant adverse event.
Rafati et al. [22]	PEG3350	Liquid paraffin	NA	All adverse events (nausea, vomiting, flatulence, abdominal pain and dehydration), other than diarrhoea, occurred less frequently with PEG than liquid paraffin ($p<0.05$). Most common adverse event with PEG was nausea, incidence 4.5%.
Ratanamongkol et al. [23]	PEG4000	Magnesium hydroxide	NA	No difference in the overall incidence of adverse events between both treatments ($p=0.245$). Diarrhoea was less common with PEG (4.3% vs 28%, $p=0.002$). Mild, transient abdominal pain/discomfort, bloating/flatulence and nausea/vomiting were reported.
Rendeli et al. [24]	PEG4000+E	Lactulose	No treatment-related changes in full blood count, serum concentrations of sodium, potassium, calcium, phosphorus, creatinine, glucose, transaminases and alkaline phosphatases and BUN.	No significant differences in adverse events between the two treatments. Common adverse events were flatulence, abdominal pain, hard stools, bad palatability, diarrhoea and nausea. No serious adverse events.
Saneian et al. [25]	PEG	Magnesium hydroxide and Lactulose	NA	PEG was associated with a lower incidence of adverse events than the comparators. Lower incidence of abdominal pain versus both comparators ($p=0.001$), bloating versus lactulose ($p<0.001$) and diarrhoea versus magnesium hydroxide ($p=0.024$).
Savino et al. [26]	PEG3350+E	PEG4000	NA	PEG was better tolerated than PEG+E, with respect to nausea ($p=0.003$). 1 patient interrupted PEG therapy for 2 days due to diarrhoea and vomiting. 1 patient discontinued PEG+E due to abdominal pain.
Thomson et al. [27]	PEG3350+E	Placebo	NA	Incidence of adverse events was similar between PEG+E and placebo (63% vs 57%). Most treatment-related adverse events were GI, most

				commonly abdominal pain, which was less frequent with PEG+E than placebo (39% vs 45%).
Treepongkarun a et al. [28]	PEG4000	Lactulose	NA	Incidence of adverse events was similar for both treatments. Most events were mild and none were severe. 3 cases of diarrhoea with PEG were possibly or probably drug-related. 2 adverse events led to discontinuation of PEG, 1 case of vomiting and diarrhoea and 1 case of fever and vomiting associated with sinusitis.
Voskuijl et al. [29]	PEG3350+E	Lactulose	NA	PEG+E was associated with fewer adverse events compared to lactulose, but more reports of bad palatability. 1 patient on PEG+E withdrew due to bad palatability. No serious or significant adverse events.
Wang et al. [30]	PEG4000	Lactulose	No changes in serum concentrations of sodium, potassium, calcium or glucose. No changes in full blood counts, renal and liver function.	No significant adverse events. 1 case of diarrhoea (treatment discontinued) and 1 case of abdominal pain with PEG.
NA=No applicable data reported. GI=Gastrointestinal				

Table 4: Safety and tolerability of polyethylene glycol.

Compliance, willingness to continue therapy

Only four studies assessed patient compliance or willingness to continue laxative therapy. Of most relevance is the direct comparison of PEG and PEG+E. In this study more children had no difficulties taking PEG than PEG+E (96% vs. 52%, p<0.001). This ease of use benefit was associated with a trend towards improved compliance with PEG (98% vs. 88%, p=0.062) [26]. Two studies demonstrated better patient acceptance and compliance of PEG versus magnesium hydroxide [18,23]. One study demonstrated better compliance with PEG+E than a bulk forming agent (p=0.002) [21].

Discussion

This NMA provides no evidence for the addition of electrolytes to polyethylene glycol in the management of constipation in children. The added electrolytes does not improve the efficacy, safety or tolerability of polyethylene glycol, but it may reduce compliance.

The benefits of a NMA is that it allows the use of all the available data to address the clinical questions at hand, where standard meta-analysis may have insufficient direct comparisons to interrogate the issue. This is the case with determining the efficacy of polyethylene glycol versus placebo. Two previous meta-analyses have failed to address this important clinical issue [10,11]. However, this NMA demonstrated that both PEG and PEG+E are more efficacious than placebo increasing the number of bowel movements per week by 2.3 and 2.2 respectively. These results are consistent with the Cochrane review where polyethylene glycol with or without electrolytes increased the mean number of bowel movements per week by 2.61 relative to placebo [12].

Both PEG and PEG+E were well tolerated and overall better tolerated than other laxatives such as lactulose. The most common treatment-related side effects were gastrointestinal, which were generally mild and transient in nature. The only head-to-head comparison of PEG and PEG+E, found PEG to be better tolerated with a lower incidence of nausea [26]. No safety signals were identified that would suggest a safety benefit for the added electrolytes in the management of constipation.

Polyethylene glycol alone is tasteless and, when dissolved, colourless. In paediatric practice, it can be masked by dissolving in a drink of the child's choice. The addition of electrolytes alters the palatability of polyethylene glycol for some children making it more difficult to administer. This was demonstrated in the only direct clinical comparison of PEG and PEG+E. The taste of PEG was rated as superior than PEG+E (p<0.001) with almost all (96%) children having no difficulties with taking PEG compared to approximately half taking PEG+E (p<0.001). This study also indicated that improved palatability has the potential to enhance compliance [26]. Better patient acceptability was also demonstrated for PEG versus magnesium hydroxide [18,23] and in a long-term trial versus previous laxative therapy [31].

Limitations

Study heterogeneity is a potential limitation for this NMA. There was a wide range of paediatric populations, from infants to adolescents and the assessment period varied between 2 weeks and 6 months. To reduce the impact of heterogeneity stool frequency was assessed at 2 weeks where the data was available, which was the case in 40% (six) of the studies, Even though the dose of polyethylene glycol varied between studies, over half (eight) of the studies used a dose 0.4 to 0.7 mg/kg/day, with the most common mean daily dose being 0.5 mg/kg/day. Similarly, the age of enrolled patients varied across the studies, however 60% (nine) of the studies were conducted amongst patients with a mean age ranging between 4 and 9 years, with a further 4 studies being conducted amongst patients aged less than 4 years old. Ten of the studies had a high risk of bias. When these studies were excluded in the sensitivity analysis, the results remained essentially unchanged, but they were no longer statistically significant.

Conclusion

This NMA demonstrated that polyethylene glycol with and without electrolytes are effective, well tolerated treatments for constipation in children from the age of 6 months. The addition of electrolytes does not appear to provide any clinical benefits over polyethylene glycol alone. There is no enhancement of efficacy, safety or tolerability. As polyethylene glycol alone is tasteless, it is easier to administer to

children and its enhanced patient acceptability has the potential to improve adherence. This analysis supports the ongoing use of polyethylene glycol as a first-line treatment of constipation in children. Formulations without electrolytes should be considered first to aid administration and compliance.

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