Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study

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Objectives: To assess the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG+E) for the treatment of chronic constipation in children.

Design: Randomised, double blind, placebo controlled crossover trial, with two 2-week treatment periods separated by a 2-week placebo washout.

Setting: Six UK paediatric departments.

Participants: 51 children (29 girls, 22 boys) aged 24 months to 11 years with chronic constipation (lasting ≥ 3 months), defined as ≤ 2 complete bowel movements per week and one of the following: pain on defaecation on 25% of days; $\geq 25\%$ of bowel movements with straining; $\geq 25\%$ of bowel movements with hard/lumpy stools. 47 children completed the double blind treatment.

Main outcome measures: Number of complete defaecations per week (primary efficacy variable), total number of complete and incomplete defaecations per week, pain on defaecation, straining on defaecation, faecal incontinence, stool consistency, global assessment of treatment, adverse events and physical examination.

Results: The mean number of complete defaecations per week was significantly higher for children on PEG+E than on placebo (3.12 (SD 2.05) v 1.45 (SD 1.20), respectively; $p < 0.001$). Further significant differences in favour of PEG+E were observed for total number of defaecations per week ($p = 0.003$), pain on defaecation ($p = 0.041$), straining on defaecation ($p < 0.001$), stool consistency ($p < 0.001$) and percentage of hard stools ($p = 0.001$). Treatment related adverse events (all mild or moderate) occurred in similar numbers of children on PEG+E (41%) and placebo during treatment (45%).

Conclusions: PEG+E is significantly more effective than placebo, and appears to be safe and well tolerated in the treatment of chronic constipation in children.

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Constipation affects 5–10% of school aged children in the UK¹ and accounts for 3% of general paediatric consultations and 25% of consultations with paediatric gastroenterologists.² Chronic constipation can follow an inadequately managed acute problem.³

Measures to induce defaecation in chronically constipated children include regular use of laxatives, increased consumption of fruit and green fibre, ensuring that the child drinks adequate fluids, and encouraging the child to sit on the toilet three or four times a day after meals. Despite common practice, the evidence for the use of laxatives in children is poor; for example, in a recent Cochrane review,⁴ no randomised controlled trials of the use of stimulant laxatives were found in the literature.

Movico (Norgine, Uxbridge, UK) is formulated as a powder containing the osmotic agent polyethylene glycol (PEG) 3350 and electrolytes. When the powder is dissolved in the correct volume of water, the resulting solution is iso-osmolar with respect to colonic extracellular fluid and therefore does not draw fluid into the colon from the body. This distinct mode of action is in contrast to that of hypertonic inorganic laxatives (eg, magnesium hydroxide or sodium sulphate) and organic laxatives (eg, lactulose), and means that PEG resists the normal drying action of the bowel to remove water from the faecal mass. As a result, the faeces are hydrated and bulked, stimulating peristalsis.

The combination of PEG 3350 with electrolytes (PEG+E) has been shown to be effective for treating chronic constipation and faecal impaction in adults⁵ and faecal impaction in children.⁶

The present trial was conducted to assess the efficacy and safety of PEG+E in children with chronic constipation who were being managed in a specialist paediatric outpatient setting.

METHODS

This double blind, randomised, placebo controlled crossover trial was undertaken in six UK paediatric outpatient departments. The trial was approved by the London Multicentre Research Ethics Committee, and local ethics approval was also obtained at each hospital involved.

Participants

Boys and girls aged 24 months to 11 years were eligible for enrolment if they had had chronic constipation for at least 3 months. Chronic constipation was defined according to the Rome criteria as fewer than three complete bowel movements per week, and at least one of the following: pain on defaecation on at least 25% of days; at least 25% of bowel movements with straining; and at least 25% of bowel movements with hard or lumpy stools. All were defined with diaries and specific detailed history-taking.

Children were excluded from the study if they had current or previous faecal impaction decided by either physical examination or abdominal x ray (because it was thought easier in this initial study to define and analyse a homogeneous group), if

Abbreviations: ANOVA, analysis of variance; 95% CI, 95% confidence interval; ITT, intention to treat; PEG+E, polyethylene glycol 3350 plus electrolytes; PP, per protocol; SD, standard deviation

Figure 1 Participant flow in placebo controlled trial of PEG+E.

they had previous intestinal perforation or obstruction, paralytic ileus, toxic megacolon, Hirschsprung’s disease, severe inflammatory conditions of the intestinal tract, severe gastro-oesophageal reflux (in case of theoretical retrograde aspiration, although practically this was not likely to have been an issue), diabetes, or if they were currently receiving doses of stimulant laxatives considered by local observers to be at the higher end of their own dose spectrum (senna or sodium picosulphate) with no effect, having assessed to their clinical satisfaction

adequate compliance. In this regard it is unlikely that these exclusion criteria would bias the group towards a “mild” constipation group. Length of treatment programme with heterogeneous approach and therapy prior to inclusion was not considered relevant to severity of symptoms in view of the strict inclusion criteria.

After written informed consent had been obtained from the child’s parent or guardian, the child was enrolled in the study by the site investigator and the child’s doctor was informed.

Table 1 Dosing regimen for PEG+E or placebo sachets

Child’s age	Number of sachets per day				Diarrhoea	Loose stools
	Days 1–2	Days 3–4	Days 5–6	Days 7–8		
2–6 years	1	2 (taken together)	3 (2 morning, 1 evening)	4 (2 morning, 2 evening)	Decrease by 2 sachets or miss a day	Decrease by 1 sachet
7–11 years	2 (taken together)	2 (taken together)	5 (2 morning, 3 evening)	6 (3 morning, 3 evening)	Decrease by 2 sachets or miss a day	Decrease by 1 sachet

Table 2 Baseline demographics and clinical characteristics, safety population

	PEG+E/ placebo	Placebo/ PEG+E	Total
Patients, n	27	24	51
Aged 2–6 years	18 (67%)	17 (71%)	35 (69%)
Aged 7–11 years	9 (33%)	7 (29%)	16 (31%)
Male:female ratio, n (%)	13:14 (48%:52%)	9:15 (38%:63%)	22:29 (43%:57%)
Age (years)			
Mean (SD)	5.3 (2.4)	5.5 (2.9)	5.4 (2.6)
Range	2–9	2–11	2–11
Previous laxative use, n	25 (93%)	22 (92%)	47 (92%)

Treatment allocation

Eligible children entering the treatment phase were allocated to their randomised sequence group. The random sequence group was computer generated before the start of recruitment using a block size of four patients, and study medication was labelled accordingly. Random blocks (with numbers stored in sealed code-break envelopes) were sent to the investigator sites as required. As children were enrolled, sites allocated treatment supplies sequentially, starting with the lowest available number. Both the children (and their parents or guardians) and those administering treatment were blinded to the allocation schedule.

Treatment schedule and administration

All children entered a 1-week run-in period, during which they were able to continue any laxative treatment that they were already taking (with the exception of high doses of stimulant laxatives). After this week, they were randomised to receive either PEG+E or matching placebo for 2 weeks (period I), followed by a 2-week placebo washout period (period II) before they crossed over to receive the alternative treatment for another 2 weeks (period III).

Study medication (6.9 g powder per sachet) was dissolved in approximately 62.5 ml unchilled tap water before addition of flavouring, which was not considered necessary but was offered. The dosage of study medication depended on the child's age, those aged 24 months to 6 years receiving a lower dose than those aged 7–11 years. The dosage was adjusted over the first week of treatment in periods I and III and could be adjusted in the second week of each treatment period to determine a dose at which symptoms of constipation as defined by the Rome criteria noted above did not occur, and as shown in table 1.

Assessments

Scheduled assessments took place at the start of the baseline run-in period (visit 1), at the end of the run-in period and beginning of treatment period I (visit 2), at the end of

treatment period I (visit 3), at the start of treatment period III (visit 4) and at the end of treatment period III (visit 5).

Between each visit, the children or their parents or guardians maintained a daily diary recording the numbers of complete and incomplete defaecations, problems on defaecation (rectal pain, straining and abdominal pain), faecal incontinence (number of soiling), stool consistency and the number of sachets taken. In addition, the investigator made an overall assessment of the child's symptoms at the end of each treatment period. Safety was monitored by adverse events recording, physical examination findings, and weight changes theoretically secondary to fluid shifts and gastro-intestinal fluid loss, however unlikely.

The primary efficacy variable was the mean number of complete defaecations per week. Secondary efficacy variables included the total number of complete and incomplete defaecations per week, pain on defaecation, straining on defaecation, faecal incontinence, stool consistency, and a global assessment of treatment by the investigator and by the child or his or her parent or guardian.

Statistical analysis

A sample size of 50 children was planned to achieve 40 evaluable children, giving 90% power to detect a true treatment difference of 0.3 bowel movements per week using a two-tailed significance test at the 5% level. However, the dropout rate was higher than originally estimated, so the recruitment target was increased to 60 children.

Three populations were defined for statistical analysis. The safety population comprised all patients who received at least one dose of the randomised treatment during period I or period III. The intention-to-treat (ITT) population comprised all patients in the safety population who provided any on-treatment efficacy data relating to bowel movement. The per-protocol (PP) population comprised all patients from the ITT population who supplied bowel movement data for at least 7 days of period I and 7 days of period III, and had no major protocol violations.

The primary efficacy outcome (mean number of complete defaecations per week) was summarised for both the ITT and PP populations using an analysis of variance (ANOVA) appropriate for a two period crossover design. The treatment difference was estimated, and associated 95% confidence intervals (95% CI) were presented.

The secondary efficacy outcomes were summarised and analysed for the ITT population only. Results were analysed as for the primary efficacy outcome. The global assessment of each treatment was summarised, and treatment differences were analysed using the Mainland-Gart test. No analyses by age subgroup were performed.

RESULTS

Recruitment to the trial started in April 2002 and the last child completed in April 2003. Fifty eight children were enrolled in the study (fig 1) and 51 children were randomised to study

Table 3 Primary efficacy endpoint: number of complete defaecations per week

	PEG+E	Placebo*	Treatment difference	p Value (95% CI)
ITT population	n = 47	n = 48		
Mean (SD)	3.12 (2.050)	1.45 (1.202)	1.64	<0.001 (0.99 to 2.28)
Range	0.00–8.87	0.00–3.73		
PP population	n = 36	n = 36		
Mean (SD)	3.63 (1.980)	1.63 (1.229)	1.96	<0.001 (1.19 to 2.72)
Range	0.00–8.87	0.00–3.73		

*Data do not include washout period.
95% CI, 95% confidence interval; ITT, intention to treat; PP per protocol.

Table 4 Secondary efficacy outcomes, ITT population

	PEG+E (n = 47)	Placebo* (n = 47)	Treatment difference	p Value (95% CI)
Total number of defaecations	5.68 (2.771)†	4.10 (2.503)	1.58	0.003 (0.55 to 2.60)
Pain on defaecation‡	0.49 (0.727)	0.77 (0.863)	-0.28	0.041 (-0.52 to -0.01)
Straining on defaecation‡	0.72 (0.789)	1.37 (1.041)	-0.65	<0.001 (-0.97 to -0.33)
Stool consistency§	1.73 (0.497)	2.21 (0.556)	-0.48	<0.001 (-0.68 to -0.27)
Percentage hard stools	14.64 (26.041)	38.19 (39.508)	-23.55	<0.001
Abdominal pain on defaecation	0.67 (0.789)	0.79 (0.903)	-0.12	NS
Faecal incontinence	4.70 (6.344)	4.85 (7.863)	-0.15	NS

Data are means (SD). 95% CI, 95% confidence interval.

*Data do not include washout period; †n = 46; ‡scored as 0 = none, 1 = mild, 2 = moderate, 3 = severe; §scored as 1 = loose/watery, 2 = normal, 3 = hard.

treatment (27 to PEG+E/placebo, 24 to placebo/PEG+E). Overall, 13 of the 51 children (7/27 in the PEG+E/placebo group, 6/24 in the placebo/PEG+E group) recorded at least one deviation from the study protocol (one child recorded two protocol deviations). The main reason for deviation was non-compliance with the study medication (7/51 children), followed by failure to supply sufficient bowel movement data (4/51 children), and taking concomitant non-study laxative medication after randomisation (3/51 children).

Table 2 shows the baseline demographic data for the children. The mean age was 5.4 years, and there were more girls (29/51) than boys (22/51). Clinically significant abnormalities on physical examination (mainly associated with faecal loading but *not* impaction) were recorded for eight children (5/27 in the PEG+E/placebo group, 3/24 in the placebo/PEG+E group). Before randomisation, 47 children were taking other laxatives (most frequently lactulose).

Efficacy outcomes

Taking the combined results from periods I and III, the primary efficacy outcome (mean number of complete defaecations per week) was significantly higher when the children took PEG+E than when they took placebo in both the ITT and PP populations ($p < 0.001$; table 3), with a treatment difference of 1.64 (95% CI 0.99 to 2.28) and 1.96 (95% CI 1.19 to 2.72), respectively. The 2-week placebo washout period should be more than enough to eliminate any carryover effects, and allow combination of the results from periods I and III.

For the secondary outcomes (table 4), significant differences in favour of PEG+E were observed in the total number of defaecations per week ($p = 0.003$), pain on defaecation ($p = 0.041$), straining on defaecation ($p < 0.001$), stool consistency ($p < 0.001$) and percentage of "hard" stools ($p = 0.001$). There were no significant differences between PEG+E and placebo with respect to abdominal pain on defaecation ($p = 0.550$) and faecal incontinence ($p = 0.685$). A greater proportion of children had their treatment rated by the investigator as improved or much improved when they received PEG+E (83%) than when they received placebo (21%).

The mean effective dose of PEG 3350 used in this study was 0.6 g/kg/day in the 2–6-year-old age group and 0.7 g/kg/day in the 7–11-year-old age group.

Safety

Adverse events were reported for similar numbers of children on PEG+E (31/49, 63%) and placebo (28/49, 57%) during periods I and III. None of these events was serious, and most were judged by the investigator to be moderate or mild in severity. Twenty children (41%) on PEG+E and 22 children (45%) on placebo experienced 41 events and 45 events, respectively, that were judged by the investigator to be at least possibly related to the study treatment. Most of these treatment related events were gastro-intestinal disorders (particularly abdominal pain), which were reported for fewer children on

PEG+E (39%, 39 events) than on placebo (45%, 41 events). One child in the placebo/PEG+E group was withdrawn at week 3 because of abdominal pain, which was assessed by the investigator as being related to treatment, and in fact this child was taking placebo at the time of withdrawal. New clinically significant abnormalities on physical examination (mainly associated with faecal loading) were reported for 13 children (8/27 in the PEG+E/placebo group, 5/24 in the placebo/PEG+E group). When analysed for what these children were taking for the 2 weeks before the physical examination, 23 out of the 24 reports (95.8%) occurred when the child was taking placebo. Only one report of an abnormal abdominal examination occurred while the patient was on PEG+E.

Mean weight was similar before and after treatment, and no significant difference was found between the two groups for change in weight while on treatment ($p = 0.357$).

DISCUSSION

The findings of this multicentre study are that PEG 3350 plus electrolytes (PEG+E, Movicol) was safe and well tolerated, and significantly more effective than placebo in the treatment of chronic constipation in children. The number of complete defaecations per week (the primary efficacy measure) was significantly increased when children took PEG+E than when they took placebo, and the improvement was confirmed by other outcome variables, determined as secondary in this study but important in a clinical context, such as total number of defaecations per week, pain or straining on defaecation, and stool consistency. In respect of abnormal physical examination attributable to constipation when analysed for what the children had been taking for the 2 weeks before the physical examination, 23 out of the 24 reports (95.8%) occurred when the child was taking placebo. Only one report of an abnormal abdominal examination occurred while the patient was on PEG+E.

No significant safety issues arose, which is in keeping with the experience in other studies involving PEG 3350 in children.^{7–9}

Despite the addition of electrolytes to PEG 3350, no compliance issue affected efficacy, as shown by the observed improvement in outcome whether analysed on a per-protocol or an intention-to-treat basis. Flavouring was allowed but there was no report of any palatability issues, although this was not included in the analysis.

The only other published prospective randomised controlled study of a PEG plus electrolyte laxative (Transipeg: PEG 3350+sodium sulphate+electrolytes) in children with chronic functional constipation showed superior efficacy over lactulose; however, 20% of that study group required the addition of stimulant laxatives during the intervention period.¹⁰

One possible criticism of a crossover design in a clinical study is the possibility of carryover of effect from one period of the study to the following period. This possibility is reduced by incorporating a washout period between the two treatments. In

What is already known on this topic

- Current approaches to the management of chronic constipation in children include lifestyle changes and laxatives.
- The evidence base for the use of laxatives is poor, with few good quality randomised, placebo controlled trials of laxatives for chronic constipation in children.
- Polyethylene glycol 3350 plus electrolytes (PEG+E) is a new type of laxative that has already been used successfully in adults and is being assessed for use in children.

What this study adds

- This study provides further evidence that PEG+E is significantly more effective than placebo in the management of constipation in children aged 2–11 years.
- PEG+E has a similar side effect profile to that of placebo in these children.
- All data were analysed in a blinded fashion and no conflict of interest was present.

the present study, all of the children received placebo for 2 weeks before starting the second treatment. This is almost certainly more than enough to eliminate any carryover effect.

A further criticism of the crossover design is that it is suitable only for conditions in which the symptoms remain stable throughout the study. Because children with chronic constipation may have the problem for up to 5 years before seeking medical help,¹¹ although dramatic changes either way in the severity of symptoms over 4 weeks are certainly possible and do occur with appropriate holistic management they are not guaranteed, so a crossover design is valid.

In conclusion, polyethylene glycol 3350 plus electrolytes is significantly more effective than placebo in the treatment of chronic constipation in children, many of whom have tried a number of other laxatives previously, and it appears to be a relatively safe and well tolerated therapy.

CONTRIBUTORS

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