Polyethylene Glycol *vs.* Lactulose in Infants and Children with Functional Constipation

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SUMMARY

In this randomized, multicentric trial, patients with functional constipation received either polyethylene glycol (PEG) or lactulose for 12 weeks and were subsequently followed for 4 weeks. The primary outcome variables were the number of defecations per week after 12 weeks of treatment, and improvement in stool consistency of at least 2 points in the Bristol scale. Bowel movements ≥3 per week and stool consistency ≥2 (Bristol scale) were considered as successful treatment. Investigators enrolled 102 patients with mean (SD) age of 3.62 (1.42) years, out of which 88 completed the study. The mean (SD) number of defecations per week was more in PEG group as compared to the lactulose group (7.9 (0.6) *vs* 5.7 (0.5), *P*=0.008). Both groups had similar frequency of painful defecation, stool retention, large volume of stools, and hard stools. There were more patients with side effects of bloating and abdominal pain in the lactulose group (23 *vs* 15, *P*=0.02). The authors concluded that PEG 3350 is more effective and causes fewer side effects compared to lactulose in the treatment of constipation in infants and children.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: This was an open-label, multi-site randomized controlled trial (RCT) – conducted in three teaching hospitals in Poland – comparing polyethylene glycol (PEG) against lactulose in infants and children with functional constipation [1]. ***Table* I** summarizes the trial details.

Critical appraisal: Overall, this study [1] can be considered to have a moderate risk of methodological bias. This is based on critical appraisal using the Cochrane Risk of Bias tool [2]. The baseline characteristics of participants in both arms of the trial were similar in terms of age distribution, gender, body weight, duration of constipation, nature of prior treatment received, severity of functional constipation (described by defecation frequency, type of stools, stool consistency) and clinical examination findings.

The random sequence was generated using a software program, and participants were randomized in blocks of four, stratified by the study site. Allocation concealment was achieved by the random sequence being available at a central site and investigators having to request for finding the allocation of each participant. However, there was no blinding of the participants or family members reporting outcomes, or the investigators collecting the data. Only the personnel conducting statistical analysis were blinded. This raises the risk of bias, even though many of the parent-reported outcomes were made as objective as possible. Baseline data were reported for all the 102 children included in the study. However, those who dropped out within the first four weeks were excluded from all subsequent analyses. Per protocol and modified intention-to-treat analysis were undertaken on the remaining participants.

One issue that raises the risk of bias in this study [1] is that although the two primary and several secondary outcomes were to be determined after 12 weeks treatment (at 12 and 16 weeks after enrolment), the data do not show all the outcomes at these two time points. Instead, many outcomes were reported after four weeks of therapy, which was not the original plan. This creates an element of selective outcome reporting. Further, it is surprising that the authors did not examine treatment adherence and patient/parent satisfaction – outcomes that are highly relevant in functional constipation.

The investigators declared no conflicts of interest [1]. However, the publication does not report the source of funding except that PEG was provided by a local

TABLE I SUMMARY OF THE TRIAL COMPARING LACTULOSE AND PEG FOR CONSTIPATION IN INFANTS AND CHILDREN

Criteria	*Comments*
Research question	Although a research question (in PICO format) was not explicitly framed, the study appears to be designed to evaluate safety and efficacy (Outcomes) of polyethylene glycol (PEG) 3350 (Intervention) versus lactulose (Comparison) in infants and young children with functional constipation (Population/Problem).
Inclusion criteria	Children (6 mo to 6 y) with functional constipation (newly as well as previously diagnosed). Standard criteria were used to define the condition.
Exclusion criteria	Children with organic cause(s) of constipation *viz* structural gastrointestinal tract anomaly, previous gastrointestinal surgery, syndrome of intestinal bacterial overgrowth and history of intolerance to PEG or lactulose or PEG. However, it is unclear whether every eligible child was screened for each of these exclusion criteria prior to enrolment.
Intervention and Comparison groups	Prior to enrolment, eligible children underwent fecal dis-impaction if required. They were then randomized. The Intervention group was prescribed PEG 3350 (dosage 5 g/d for those <8 kg, 10 g/d for 8-12 kg, 15 g/d for 12-20 kg, and 20 g/d for those >20 kg). The Comparison group was prescribed lactulose in the dose of 2 mL/kg/d. Both groups received the medication in two divided doses. The preparation was administered orally for 12 weeks. Children in both groups also received dietary advice. In children who did not improve at the end of 4 weeks therapy with PEG, provision was made to increase the dose. Those who did not improve with lactulose were switched to PEG. Children who achieved therapeutic success at the end of 12 weeks underwent dose reduction.
Follow-up protocol	Enrolled children were evaluated clinically at the end of 4 and 12 weeks therapy, and telephonically at the end of 16 weeks (from enrolment); *i.e.,* 4 weeks after the end of treatment.
Outcomes	*Primary*: (*i*) Frequency of stool passage per week, after completing 12 weeks therapy; (*ii*) Improvement in consistency of stool by at least 2 types in the Bristol scale, after 12 weeks therapy; and (*iii*) A composite score of the above outcomes characterized as good (≥3 stools/ week and improvement in stool consistency by 2 types) after 12 weeks therapy. *Secondary:* (*i*) Adverse events (total number, abdominal pain, nausea or vomiting, diarrhea, bloating or flatulence, anal irritation); and (*ii*) Other symptoms *viz* number of painful defecations, hard or large stools passed, and conscious avoidance of defecation.
Sample size	*A priori* sample size calculation required 102 participants assuming a 30% difference in effect size for treatment success (term not defined) between PEG (60% efficacy) and lactulose (30% efficacy), with beta error 20%, alpha error unspecified, and a 20% drop-out rate. This sample size was achieved at enrolment.
Data analysis	Per protocol analysis was performed at the end of 12 weeks and 16 weeks (as specified). Additional data at the end of 4 weeks treatment were also reported. Intention-to-treat (ITT) analysis was performed counting only those children who had at least one follow-up visit.
Summary of results	Although the investigators presented data at the end of 4 weeks treatment, 12 weeks treatment and 16 weeks treatment, only the latter two were originally planned. These are summarized in ***Table* II**. This shows that statistically significant differences (in favor of PEG) were observed for only three outcomes *viz* defecation frequency, presence of any adverse event, and frequency of bloating and flatulence.

manufacturing company. However, the trial registry (ClinicalTrials.gov) shows that the trial was registered with the title "Efficacy of Dicopeg Junior in comparison with lactulose for the treatment of functional constipation in children aged 6 months to 6 years" [3] suggesting that the trial could have been a sponsored study. Selective reporting of outcomes rather than reporting the outcomes (at the time points) decided *a priori* further creates doubt about the bias-free nature of the study.

This perspective is further strengthened when we consider the (rather limited) scientific rationale for undertaking this study. The evidence-based clinical practice guidelines published in February 2014 jointly by the European and North American Pediatric Gastroenterology Societies (ESPGHAN and NASPGHAN) recommended PEG (with or without electrolytes) as the treatment of choice for functional constipation [4]. This was based on data from five clinical

TABLE II SUMMARY OF RESULTS AS PER THE PROTOCOL (PEG *VERSUS* LACTULOSE)

Outcome	*At the end of 12 weeks*	*At the end of 16 weeks*
No. of stools per week; mean (SD)	7.9 (0.6) *vs* 5.7 (0.5)*	Not reported
Improvement in stool consistency by 2 types	Not reported	Not reported
Good clinical outcome	43/44 *vs* 35/39	39/44 *vs* 32/39
Any adverse event	15/44 *vs* 23/39*	Not reported
Abdominal pain	6/44 *vs* 12/39	Not reported
Diarrhea	1/44 *vs* 0/39	Not reported
Nausea or vomiting	1/44 *vs* 1/39	Not reported
Bloating or flatulence	11/44 *vs* 20/39*	Not reported
Anal irritation	5/44 *vs* 2/39	Not reported
Other symptoms		
Painful defecation	2/44 *vs* 2/39	Not reported
Large volume of stool	13/44 *vs* 12/39	Not reported
Hard stool	3/44 *vs* 5/39	Not reported
Retention of stool	3/44 *vs* 4/39	Not reported
Fecal incontinence	Not reported	Not reported
Stool consistency	Not reported	Not reported

**Statistically significant difference.*

trials and systematic reviews available at that time. In contrast, the study [1] start date is shown as February 2016 in the trial registry [3], *i.e*., two years after the publication of the guidelines. In August 2016, a Cochrane review also confirmed the superiority of PEG over lactulose in children and adolescents with functional constipation [5]. This review of six trials reported that children receiving PEG had greater defecation frequency, less requirement of additional laxatives, and comparable adverse events. However, there was considerable heterogeneity among the studies in terms of the definitions used, inclusion criteria, age of enrolled participants, type and/or dose of interventions, outcomes studied, and follow-up duration.

Could there be another rationale for initiating this study [1]? The authors emphasized that previous trials comparing PEG versus lactulose either did not use PEG 3350 or included only children older than two years. In fact, the stated aim of this study was to compare the two therapies in children including those younger than 2 years [1]. However, two observations refute this. First, one of the six trials published before this study [1] did include children as young as 6 months and also used PEG 3350 as an intervention [6]. Three other trials also included children younger than two years, although two used PEG 4000 [7,8] and one did not specify the type of PEG [9]. The second observation that weakens the authors' claim is that they enrolled only 15 children younger than 2 years, suggesting that this age group was not the primary focus.

What is the difference between PEG 4000 and PEG 3350? The numbers refer to the average molecular weight of the product. PEG is liquid when the molecular weight is less than 1000, and have a waxy consistency above this weight [10]. Both PEG 4000 and PEG 3350 have strong osmotic activity across the mucus membrane of the small intestine. There is limited data comparing PEG 4000 against PEG 3350 in children. One non-inferiority trial examined PEG 3350 with electrolytes versus PEG 4000 without electrolytes in children aged 6 months to 16 years. However, the *a priori* non-inferiority criteria were not met; although, efficacy after one year and frequency of adverse events appeared similar with both agents [11].

This trial [1] and other similar studies raise the issue of the optimal duration of follow-up for determination of treatment success (or otherwise). This study had a limited four-week follow-up after completion of the treatment course. Similarly, 5 of the 6 trials in the Cochrane review [5] had short follow-up durations ranging from 4 to 12 weeks. Only one trial [9] mentioned a follow-up duration of 4-6 months.

What can we conclude from this study? PEG 3350 was superior to lactulose for only three outcomes *viz* defecation frequency, presence of any adverse event, and frequency of bloating and flatulence. The mean difference in defecation frequency at the end of 12 weeks treatment works out to 2.20 (95% CI 1.96, 2.44) per week. However, since the target defecation frequency was thrice per week, one wonders whether frequencies as high as 8 per week with PEG (compared to 6 with lactulose) are really very different in clinical terms. The second outcome of adverse event frequency raises an interesting issue. For both PEG and lactulose groups, the number of children with adverse events at week 4 was higher than at week 12. This pattern is present for almost each of the individual adverse events. This makes it difficult to properly interpret the relative safety advantage of PEG over lactulose, emphasized by the authors.

Extendibility: What is the clinical relevance of this study in the Indian context? In a review on constipation, Poddar summarized the evidence in favor of PEG (compared to lactulose) [12]. He additionally highlighted that long-term use of lactulose alters the gut microbial flora, reducing its efficacy. The review also emphasized that oral laxative needs to be continued for several months (perhaps years) for optimal effectiveness; and early/rapid cessation of

therapy is the most frequent reason for recurrence of symptoms. These latter aspects are lacking in most trials. Moreover, the Indian guidelines already recommend PEG for treatment of childhood constipation for children over 1 year of age [13].

Conclusion: This RCT showed superiority of PEG over lactulose for some clinically relevant outcomes. However, some methodological issues and risk of bias reduce the confidence in the reported results.

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Pediatric Gastroenterologist's Viewpoint

The present study by Jarzebicka, *et al*. [1] has compared the clinical efficacy and side effects of polyethylene glycol 3350 (PEG 3350) and lactulose for the treatment of functional constipation in infants and children, and concluded that PEG 3350 is more effective and causes fewer side effects than lactulose. The salient feature of this study is the inclusion of infants between ages of 6 and 12 months.

In recent years, we have seen increasing incidence of functional constipation in infancy too. As utility and safety of PEG in infants was not well established before, it is being prescribed only in selected cases or when lactulose is no longer beneficial. Laxatives like senna and bisacodyl are contraindicated in infants.

A meta-analysis of five randomized controlled trials comprising of 519 children (<18 years of age) documented that PEG is more effective than lactulose with equal tolerability and fewer side effects [2]. A recent Cochrane review included 25 studies with a total of 2310 children that compared ten different agents to either placebo (inactive medications) or each other; the pooled analysis suggested that PEG preparations may be superior to placebo, lactulose and milk of magnesia for childhood constipation [3]. The additional advantage with PEG is that with long-term use, lactulose loses its

efficacy due to change in gut flora but PEG does not. Now with the current evidence provided by authors of this study, it would further promote usage of PEG in infants with constipation.

However, I would add a word of caution for our fellow pediatricians – to first rule out organic causes of constipation in infants, before prescribing laxatives.

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