

Consolidated Review of Evidence on Safety and Effectiveness of Osmotic Laxatives as Per Recommendations in Childhood Constipation

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ABSTRACT

Childhood Functional constipation is a common pediatric problem all over the world. The main goal of the treatment should be the disimpaction of the stools, followed by maintenance therapy to prevent reimpaction. A significant number of children are evaluated by pediatric gastroenterologists because of frequent relapses of symptoms. There are a wide variety of pharmacological options available in the treatment of functional constipation. Osmotic Laxatives are the most used intervention for treating functional constipation in children. But there is uncertainty on the safety and efficacy of osmotic laxatives for the recommended duration of therapy. We conducted a review of the evidence of osmotic laxatives usage for a minimum of 2 months and found that polyethylene glycol (PEG) was the most studied laxative for the recommended duration. Polyethylene glycol was associated with a significant increase in bowel frequency and treatment success compared to placebo or other laxatives. PEG use was associated with significantly fewer adverse effects like bloating, abdominal pain, pain in defecation, straining, and the need for rescue medication compared to lactulose. Conclusively PEG is the only laxative that is effective as well as safe for the recommended duration. PEG 3350 is the most widely studied form of Polyethylene glycol in children.

Keywords: Constipation; Osmotic laxatives; Children

Abbreviations: PEG: Polyethylene Glycol; PMF: Polyethylene Glycol Electrolyte Balance Solution; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition; ISPGHAN: Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition; AAFF: American Academy of Family Physicians; PEG+E: Polyethylene Glycol+Electrolytes; RCT: Randomized Control Trial; NICE: National Institute of Health and Care Excellence; GIT: Gastrointestinal Tract

INTRODUCTION

Childhood Functional constipation is a common pediatric problem all over the world, with prevalence ranging between 0.7 and 29.6% [1]. Functional constipation is mainly characterized by infrequent bowel movements, hard and large stools, painful defecation, fecal incontinence, and is often accompanied by abdominal pain [2]. The most common triggering event of functional constipation is avoiding defecation because of multiple reasons (unable to timely defecate during travel, social reasons like the problem with friends in school, socially inactive parents, etc.) Functional constipation is common in both sexes equally and there is no differentiation in terms of socioeconomic backgrounds, dietary practices, and cultural influences [1]. Functional constipation usually starts with a painful bowel movement, which leads to voluntary withholding of stools, which causes prolonged fecal stasis, and leads to stretching of the pain-sensitive anal canal, which in turn causes more painful defecation, and thus the cycle continues. Diagnosis of functional

constipation is usually done by Rome's 4 criteria. According to Rome 4 criteria, the child must have 2 or more of the following symptoms which include less than or equal to 2 defecations per week, at least 1 episode of fecal incontinence per week, excessive stool retention, painful bowel movements, large fecal mass in the rectum, and large diameter stools [4]. These symptoms must occur at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome.

A significant number of children are evaluated by pediatric gastroenterologists because of frequent relapses of symptoms. 5 years follow-up study conducted in Italy by Staiano et al. [4] demonstrated that constipation persisted in 52% of the children even after a 12-week treatment period. [5] In another prospective longitudinal follow-up study by van Ginkel et al. [5], 418 children treated for constipation were followed for a period of 5 years and found that, 50% of the children who were treated successfully experienced at least one period of relapse [5]. The main goal of

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the treatment should be the disimpaction of the stools, followed by maintenance therapy to prevent reimpaction. Despite a wide variety of pharmacological options available in the treatment of functional constipation. They have limitations preventing them to use for a longer period (Table 1). Biofeedback training and physiotherapy interventions aimed at gaining better control over the pelvic floor muscles are thought to have a role in process of defaecation. But it is not routinely recommended in young children due to insufficient evidence, partly because of the heterogeneity between studies in children [6]. Emollients like Mineral oil have a risk of aspiration (lipid pneumonia) and should be avoided in infants and children mainly those who have dysphagia or vomiting. Also, mineral oil usually interferes with the absorption of fat-soluble vitamins [7]. The prolonged use of stimulant laxatives such as bisacodyl and Senna are usually recommended for temporary constipation as it causes abdominal cramps in long-term use, and it is found ineffective in severe constipation. Also, Melanosis coli occurs in patients with long-term use of stimulant laxatives [8]. Bulk laxatives like methylcellulose, calcium polycarbophil, and psyllium may cause delayed gastricking time, acute allergic reactions, cough, and asthma [9]. Peg is the polymer that is biologically inert and highly soluble in water which causes its absorption through the Gastrointestinal tract negligible. As it is a neural polymer without any charge, it does not affect the shift of other solutes through GIT. These effects, make PEG a potent laxative [8]. Finally, osmotic Laxatives, are the most used intervention for treating functional constipation in children [10].

LITERATURE REVIEW

Recommendations

Osmotic laxatives are the first line of choice recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [11], Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN) [12], NICE [13], and American Academy of Family Physicians [AAFP] [14]. ESPGHAN recommends the use of osmotic laxatives for a minimum period of 2 months as maintenance therapy. ISPGHAN recommends a minimum period of 6 months before starting to taper the dose to prevent the risk of relapse which is very common in the short-term use of laxatives [12]. Even though osmotic laxatives are considered the first line of treatment; the duration of treatment is still an uncertainty for pediatricians mainly due to multiple reasons. A thorough literature search is conducted to

address the gaps in clinical practice and the objective of this review is to provide a detailed summary of evidence as recommended for use of laxatives in children with constipation.

Methods

Medical literature published in PubMed, and Cochrane library, in English from inception till 2020 were included in this review. Articles were screened for the following keywords, constipation AND osmotic laxatives AND children. Only literature published in the English language is considered for this review

Inclusion and exclusion criteria: We included both clinical and observational studies on the use of osmotic laxatives for treating functional constipation. We included studies conducted in children aged 2-18 years who were suffering from functional constipation and were prescribed osmotic laxatives for a minimum of 2 months. Studies determining either the safety of osmotic laxatives or efficacy of osmotic laxatives or both were included. We excluded studies that show the effect of osmotic laxatives on Organic diseases like Hirschsprung's disease and anorectal malformations, retentive fecal incontinence, and children with mental handicaps or psychiatric diseases. There was no minimum length of follow-up required for inclusion, and no maximum loss to follow-up (Figure 1).

RESULTS

The initial database search yielded 816 articles including both clinical studies and review articles on the management of functional constipation. On the evaluation of full-text copies of the research papers, 19 studies with 1784 patients were found to meet the inclusion criteria, while the rest were rejected. Not availability of full text articles, studies where laxatives were used for less than 2 months, the combination of laxatives, Use of laxatives for different indications apart from functional constipation. Use of treatment options other than osmotic laxatives was excluded. A summary of included studies was presented in Table 2 [15-31].

Two RCTs comparing PEG with placebo, three RCTs comparing PEG with lactulose, two RCTs comparing PEG with liquid paraffin, two RCTs comparing liquid paraffin with lactulose, one RCT comparing PEG with magnesium hydroxide, one RCT comparing PEG with PEG+E, one RCT comparing fiber mixture with lactulose, two open labelled studies using PEG+E and PEG alone, 5 observational studies using PEG alone were included in this review. (Supplementary Tables 1 and 2).

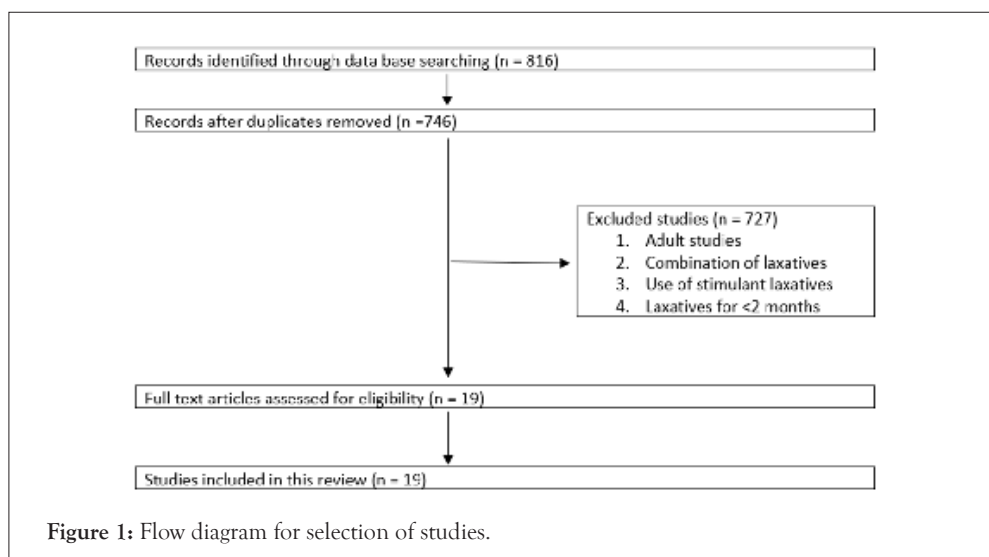


Table 1: Available options for treating functional constipation.

Treatment options	Limitations
Biofeedback training	Insufficient evidence in young children [6].
Emollients	Possible risk of aspiration they interfere with the absorption of fat-soluble vitamins [7].
Stimulant laxatives	Causes abdominal cramps Melanosis coli [8].
Bulk laxatives	Causes delayed gastric emptying time, acute allergic reactions, cough, and asthma [9].

Table 2: Summary of included studies.

Author	Treatment	Comparator	Duration	Results
Voskuil, et al. [15]	PEG 3350	Lactulose	8 weeks	Higher treatment success-PEG 56% vs lactulose 29% (p=0.02)
Rafati, et al. [16]	PEG 3350	Liquid paraffin	4 months	Higher treatment success-PEG 95% vs liquid paraffin 87% (p=0.087)
Modin et al. [17]	PEG 3350	Placebo	24 weeks	Higher treatment success-PEG 67% vs placebo 36% (significant)
Gomes, et al. [18]	PEG 4000	magnesium hydroxide	6 months	Higher PEG acceptance-91.6% vs mg (0h)2-33.3%
Kokke, et al. [19]	Fiber mixture	Lactulose	8 weeks	Higher stool consistency in lactulose-4/week vs fiber mixture 3.6/week (P=0.01)
Farahmand, et al. [20]	Liquid paraffin	Lactulose	8 weeks	Higher treatment success in liquid paraffin 85% vs lactulose 29% (P<0.001)
Dupont, et al. [21]	PEG 4000	Lactulose	3 months	Lower number of hard stools in PEG 4000-6% vs lactulose -28% (P=0.008)
Jarzebicka, et al. [22]	PEG 3350	Lactulose	12 weeks	Higher no of stools/week in PEG 3350-7.9 vs lactulose-5.7 (P=0.008) Lower side effects in PEG 3350-15 vs lactulose 23 (P=0.02)
Karami, et al. [23]	PEG	Liquid paraffin	2 weeks to 12 months	Similar stool consistency in PEG-4.7 vs liquid paraffin-4.5
Corazziari, et al. [24]	PMF-100	Placebo	12 weeks	Lower number of hard stools in PEG-4% vs placebo 27% (p<0.001)
Llerena, et al. [25]	PEG+E	PEG	12 weeks	Similar stools/week in both PEG+E-5.4/week vs 4.6/week
Urganci, et al. [26]	Liquid paraffin	Lactulose	8 weeks	Higher stool consistency in liquid paraffin-2.29 vs 2.21 (P>0.05)
Gondo, et al. [27]	PEG 3350+E	None	12 weeks	The higher number of stools/week after 12 weeks-5.18/week (P<0.001)
Hardikar, et al. [28]	PEG 3350	None	12 weeks	The higher number of stools/week after 12 weeks-7.1/week (P<0.001)
Pashankar, et al. [29]	PEG 3350	None	>3 months	Long-term peg therapy is safe and well accepted by children.
Pashankar, et al. [30]	PEG 3350	None	8 weeks	The higher number of stools/week after 12 weeks-16.9/week (P<0.001)
Pashankar, et al. [30]	PEG 3350	None	>3 months	The higher number of stools/week after 12 weeks-9.9/week (P<0.001)
Dupont, et al. [31]	PEG 4000	None	3 months	The higher number of stools/week after 3 months-9/week (P<0.001)
Bae, et al. [7]	PEG 4000	None	6 months	PEG 4000 is safe for long-term use with minimal side effects

Treatment outcomes: Bowel frequency per week was the main outcome assessed in this review. Some studies also assessed the percentage of children with treatment success, stool consistency, faecal incontinence, abdominal pain, PEG acceptance, use of rescue medication and additional laxatives, pain during defecation, encopresis frequency, Straining, stool retention, a large volume of stools and hard stools before and after the treatment.

Polyethylene glycol is evidently the most used treatment option for maintenance therapy which was confirmed by randomized control trials, open labeled studies, and observational studies. A Randomized Placebo controlled study carried out in Denmark with 102 children treated with either PEG or placebo for 24 weeks found that treatment success was significantly higher in the PEG group (67%) than in the placebo group (36%) at the end of the treatment. Weekly stool frequency also increased significantly in PEG treated group compared to baseline. They also found that 4% in the PEG group switched to rescue medication compared to 57% in the placebo group ($P < 0.001$) [17]. A randomized, multicenter study conducted in Poland, comparing polyethylene glycol with lactulose has shown that, after 12 weeks of treatment side effects like bloating, nausea and abdominal pain were significantly more in the lactulose group at 4 weeks ($P = 0.04$) and at 12 weeks ($P = 0.02$). Significant Improvement in bowel movements per week was seen in the PEG group after 4 weeks of therapy which was consistent even after 12 weeks of therapy. Bowel movements per week were significantly higher in the PEG group after 12 weeks of therapy compared to lactulose ($p = 0.008$) [22]. Similarly in another randomized double-blind trial carried out in the Netherlands with 100 children with functional constipation, PEG or lactulose were given for 8 weeks. Even though defecation frequency and encopresis improved in both groups, improvement is higher in the PEG group (7/week) than in the lactulose (6/week) group. Moreover, treatment success was significantly higher in the PEG group (56%) compared to lactulose group (29%) ($p = 0.02$). Patients in the PEG group have less abdominal pain, straining, and pain at defecation than children using lactulose [15]. Similar results were seen when PEG is compared with liquid paraffin and magnesium hydroxide.

In an open-labeled randomized study carried out in Iran, 160 children with pediatric functional constipation were treated with PEG or liquid paraffin for 4 months. Patients using PEG 3350 had more success rate i.e., of 95% compared with the patients in the paraffin group i.e., 87%. Defecation frequency increased significantly in both groups from baseline although the improvement was higher in PEG (8.7/week) compared to lactulose (7.5/week). Adverse events like nausea, vomiting, flatulence, abdominal pain, and dehydration, occurred more frequently in patients using liquid paraffin compared with PEG 3350 ($p < 0.05$) [16]. Lactulose was also compared with liquid paraffin in a few studies which shows that the long term effect is better in liquid paraffin compared to lactulose. In an open label randomized study carried out in Iran, 247 children with functional constipation were treated with either liquid paraffin or lactulose for 8 weeks. They found that defecation frequency was significantly more in the liquid paraffin group (13.1/week) compared to the lactulose group (8.1/week) ($p < 0.001$). Encopresis frequency and treatment success are also significantly more in the liquid paraffin group compared to the lactulose group. ($p < 0.001$). Significantly more adverse events were reported in the lactulose group including vomiting, bloating and abdominal cramping [20].

The results were similar in non-comparative studies. In an

open labeled nonrandomized study carried out in Australia, 78 constipated children were treated with PEG for 12 weeks. The bowel movements significantly increased from 1.4/week to 7.1/week ($p < 0.001$). Abdominal pain and pain on defecation improved significantly ($p < 0.0001$). Serious adverse events were found unrelated to the study drug [28]. Finally in an observational study, with 74 children treated with PEG for at least 3 months (mean duration of treatment is 8.4 months, bowel frequency was improved from 2.9/week to 9.9/week ($p < 0.001$). stool consistency, painful defecation, blood in stools, stool withholding, and fecal impaction all improved after PEG therapy ($p < 0.001$). There are no major clinical adverse effects observed [30].

DISCUSSION

The most common type of constipation is functional constipation which accounts for 90%-95% of all constipation cases [32]. Osmotic laxatives are first line treatment options recommended for functional constipation [17,18]. In this review, we report the results of studies that used osmotic laxatives for treating functional constipation for at least 2 months as recommended by ESPGHAN. Studies that are included in this review article include compared PEG-based laxatives, including PEG+E, and non-PEG laxatives such as lactulose, milk of magnesia, liquid paraffin, and fibr 0065 mixture. 19 articles met the inclusion criteria and were included in this review.

Polyethylene glycol was associated with a significant increase in bowel frequency and treatment success compared to placebo or other laxatives. The use of lactulose for a minimum of 2 months resulted in significantly more adverse effects like bloating, abdominal pain, pain in defecation, straining and the need for rescue medication. Previously a meta-analysis was published which says PEG is superior to placebo, lactulose, and milk of magnesium for treating childhood constipation [33-35]. Another review article assessed the use of PEG for the management of functional constipation including 58 clinical studies, however they included both adult and pediatric studies, and they did not differentiate the long-term use of PEG from short term use studies [36]. However, the studies included in this previous meta-analysis included the use of laxatives for a minimum of 6 days also.

Many pediatricians are oblivious of the need for long term use of laxatives and much concerned about long-term safety. Firstly, compliance of child is an important cause as parents are worried about possible side effects and drug dependence. Secondly, pediatricians are also concerned that osmotic laxatives may cause bloating abdominal pain, cramps, and gastrointestinal problems and have dependency effects. Many pediatricians also believe that the efficacy of osmotic laxatives is decreased over time. This present review included only studies with osmotic laxatives which are used for more than 2 months. Treatment duration ranged from a minimum of 2 months to 12 months. Weekly stool frequency was higher in the PEG group in most studies compared with placebo, lactulose, magnesium hydroxide and liquid paraffin. PEG is more acceptable than other laxatives. Safety profile reported in 15 studies found that side effects are less observed in the PEG group compared to other laxatives. The most common adverse effects reported are abdominal pain, bloating, flatulence, and vomiting.

The first limitation of our study is that there is a heterogeneity in the type of PEG used in different studies PEG (PEG 3350, PEG 4000, PMF, PEG). Secondly the follow-up time were different ranging from 4 weeks after treatment to 24 weeks. The dose of laxatives

therapy was different in different studies. The main strength of this review is that we have evaluated the use of laxatives for more than 2 months as recommended by guidelines which gave a clear picture of the long-term safety and efficacy of osmotic laxatives. Secondly, this was an extensive review of studies exclusive to children.

In our review there appears to be a consensus amongst the studies that treatment with PEG is more effective than other osmotic laxatives for long term therapy with better tolerability.

CONCLUSION

Children suffering from functional constipation required a minimum of 2-month treatment with osmotic laxatives to prevent remission. This review article clearly determines the safety and effectiveness of osmotic laxatives based on the recommended duration of treatment. Among various osmotic laxatives, Polyethylene glycol was the most used osmotic laxative for a minimum period of 2 months. Results demonstrated that the use of polyethylene glycol was associated with a significant increase in bowel frequency and treatment success compared to placebo or other laxatives. There were very few reported adverse effects compared to other laxatives. There is an urgent call for action from both clinician and parents' perspectives to adhere to recommended duration of therapy to improve treatment outcomes in childhood constipation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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