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Comparison of Polyethylene Glycol 3350+Electrolytes vs. Polyethylene Glycol 4000 for Fecal Disimpaction in Pediatric Functional Constipation: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Purpose: Polyethylene glycol (PEG) is recommended as the first-line laxative for fecal disimpaction in pediatric functional constipation. PEG 3350+electrolyte (E) and PEG 4000 are the most commonly available formulations. PEG 3350+E and PEG 4000 have hypothesized benefits of lower risk of electrolyte imbalance and better palatability, respectively. However, a head-to-head comparison of these two formulations for fecal disimpaction remains lacking. This study aimed to compare the efficacy, tolerability, and acceptability of PEG 3350+E vs. PEG 4000 for fecal disimpaction in pediatric functional constipation.

Methods: This double-blind, randomized controlled intention-to-treat trial included pediatric patients with functional constipation (as per ROME IV) and fecal impaction. Patients with organic constipation, h/o prior to gastrointestinal surgery, and those who were already receiving PEG/lactulose were excluded. Computer-generated block randomization was performed. Colorless liquid formulations of study medication were provided by investigator (JBK) as per treatment allocation in identical opaque bottles @1.5 gm/kg/dayx6 days or until fecal impaction resolution (passage of clear liquid stool), whichever is earlier.

Results: One hundred patients were randomized in a 1:1 ratio (50 patients in each arm). Efficacy of PEG 3350+E vs. PEG 4000 was similar (84% vs. 86%; p=0.9). Similarly, no significant differences were noted in the adverse event rates between two groups. Abdominal discomfort and vomiting were the most common adverse effects. PEG 4000 showed better palatability than PEG 3350+E (p=0.044). However, there was no significant difference in the compliance rate.

Conclusion: PEG 3350+E and PEG 4000 showed similar efficacies for fecal disimpaction, with minor side effects. PEG 4000 had better palatability; however, both were well tolerated by children.

Keywords: Constipation; Fecal impaction; Pediatrics; Polyethylene glycols

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INTRODUCTION

Functional constipation is one of the most common and often distressing gastrointestinal disorders in the pediatric age group, with a reported global prevalence of 14.4% [1]. Up to 30% to 75% of the patients present with fecal impaction [2,3], which, if left untreated, can lead to symptoms such as abdominal pain, nausea, vomiting, and even retentive fecal incontinence (encopresis). Fecal disimpaction is the first and most important step in the management of these children. Maintenance therapy becomes ineffective or may even worsen symptoms if started directly, thus skipping the initial disimpaction phase [4,5].

Polyethylene glycol (PEG), an osmotic laxative, has been recommended as the first-line pharmacotherapy for the treatment of fecal impaction and maintenance phase in pediatric functional constipation [4]. The two commonly available formulations are PEG 3350 with electrolytes (PEG 3350+E) and PEG 4000 without electrolytes (PEG 4000). Since fecal disimpaction requires the intake of a large amount of laxatives, taste could become a major issue for acceptability in pediatric patients, which in turn determines the success of disimpaction. Likewise, a higher purge rate during disimpaction could increase the risk of adverse effects such as electrolyte imbalance.

Because of the added electrolytes, PEG 3350+E preparations are hypothesized to have a lower risk of electrolyte imbalance but a saltier taste, which might lead to palatability issues. Conversely, PEG 4000 formulations might have the advantage of a better palatability profile because of the absence of salts but with a probable risk of electrolyte imbalance [6,7]. According to a meta-analysis of adult studies on constipation, the incorporation of electrolytes into PEG does not offer any clinical advantage over plain PEG [8]. A double-blind randomized controlled trial (RCT) found that PEG 3350+E and PEG 4000 were equally efficacious and safe for long-term maintenance therapy in children with functional constipation. However, this study did not report the tolerability or acceptability data for PEG formulations [9]. Savino et al. [10] reported that PEG 4000 is equally effective but has a better patient acceptance rate than PEG 3350. However, this study also focused on maintenance therapy, with only 14 of 96 recruited patients receiving disimpaction. Hence, pediatric trials comparing PEG 3350+E with PEG 4000 on a head-to-head basis, exclusively for the treatment of the most essential and crucial step in pediatric functional constipation management, that is, fecal disimpaction, are lacking. Therefore, the current study aimed to compare the efficacy, tolerability, and acceptability of PEG 3350+E and PEG 4000 for fecal disimpaction in pediatric patients with functional constipation.

MATERIALS AND METHODS

This single-center, double-blind, randomized controlled parallel-group intention-to-treat trial was conducted from April 2024 to November 2024 in the Pediatric Gastroenterology Division of the Department of Pediatrics at the Institute of Medical Sciences and SUM Hospital, Bhubaneswar, a tertiary care referral center and teaching institute in eastern India, after obtaining clearance from the Institutional Ethical Committee (IEC/IMS. SH/SOA/2024/683). The trial is registered with the Clinical Trial Registry of India [ctri.nic.in (CTRI/2024/03/063855)]. This study adhered to the ethical guidelines established by the Helsinki Declaration of 1975, revised in 2008.

Subjects aging between 1 and 16 years visiting the outpatient department with a diagnosis of functional constipation according to the ROME IV criteria with fecal impaction were included after obtaining written informed consent from their parents. Fecal impaction was defined as the fulfillment of any one of the following three criteria: (i) palpable fecolith on physical examination, (ii) dilated rectum filled with large hard stool on digital rectal examination, and (ii) fecal-loaded bowel on abdominal radiography. We did not routinely perform a digital rectal examination because of parental anxiety and difficulty in performing it in children due to a lack of cooperation. As a protocol, it was conducted only in selected patients who complained of bleeding per rectum along with h/o constipation with a suspicion of rectal polyps or had h/o fecal soiling with a suspicion of non-retentive fecal incontinence. Hence, if no fecoliths were found on physical examination, an abdominal radiograph was performed to look for fecal impaction. We excluded patients with diagnosed/suspected organic constipation, that is, those with an underlying cause such as neurological disorders (cerebral palsy/neural tube defects/motor neuron diseases), Hirschsprung disease/anorectal malformations, endocrine or metabolic disorders (hypothyroidism/celiac disease/diabetes mellitus), failure to thrive, or intake of drugs known to cause constipation. Patients with prior gastrointestinal surgery or suspected gastrointestinal obstruction/motility disorders were also excluded. Patients who had a history of allergic reactions to PEG formulations, chronic kidney disease/h/o acute kidney injury in the past 3 months, were taking PEG or any other laxatives (lactulose/stimulants) at the time of enrolment, or had taken any of these medications within 1 month before enrolment were also excluded.

Randomization

To ascertain balanced treatment allocation across different ages, the participants were stratified into three age groups (1–5, 6–11, and 12–16 years). Separate computer-generated randomization lists in six blocks were generated by a non-departmental colleague (who was not part of the research team) for each age group. The included subjects were randomly assigned to group A, receiving PEF 3550+E, or group B, receiving PEG 4000, at a 1:1 ratio. The list was kept by one of the investigators (JBK), and other research personnel did not have access to it. Sequentially numbered, opaque, sealed envelopes were used to ensure allocation concealment.

Intervention

As per treatment allocation, subjects were administered either PEG 3350+E or PEG 4000 at 1.5 gm/kg/day for 6 consecutive days or until resolution of fecal impaction, whichever is earlier. All disimpaction procedures were performed in an inpatient manner after admission. Liquid formulations of both medications were prepared according to a dilution protocol of 10 g of PEG dissolved in 75 mL water. The calculated dose of PEG was diluted in an appropriate amount of water and administered either orally or by a nasogastric tube (in the case of young children who were not accepting oral administration) as a single dose to be finished over 1–2 hours. The study medications were clear, colorless liquids provided in opaque bottles with identical packaging and labeling. Fecal impaction resolution was defined as the passage of clear liquid stool with no palpable fecoliths.

The caregivers of all the participants were educated on how to prepare and administer medications by a single skilled nurse familiar with the protocol. After the initial demonstration, 90% of them could deliver the medication independently; the remaining 10% required two to three times repetitions of the nursing staff demonstration. Caregivers were instructed to look for stool color and consistency to determine the effectiveness of

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disimpaction. They were also requested to report any tolerability problems such as repeated vomiting (>3 times) or abdominal discomfort (bloating/pain) experienced by the child during disimpaction. The team members involved in clinical care closely monitored the participants to detect dehydration during the process. To identify electrolyte imbalance, serum sodium and potassium levels were measured at baseline and after the completion of the intervention. Participants of age >5 years were asked to report their perception of taste for the drug used as one among the following three- "good," "not good, not bad," or "bad" to evaluate palatability. To assess compliance, the percentage of medication consumed from the prescribed amount was recorded for each participant. After disimpaction, participants were discharged on the same PEG formulation that they had received for disimpaction at 0.8 gm/kg/day for 3 months with necessary counseling.

Initial screening of the referred patients, followed by enrolment of eligible subjects in the trial, was performed by a single investigator (KP). JBK performed treatment allocation and drug dispersal for the enrolled subjects according to the randomization sequence list. Apart from JBK, the research team members, nursing staff, and participants were blinded to the treatment allocation. JBK was not involved in the initial screening for eligibility or recruitment of study subjects, clinical management, data collection, or data analysis. Unblinding was performed only after the final data analysis.

Outcome

The primary outcome was defined as the proportion of patients achieving fecal disimpaction in each arm. Secondary outcomes were as follows: (i) total number of days required to achieve fecal disimpaction; (ii) cumulative dose of PEG required for fecal disimpaction; (iii) proportion of subjects with side effects; (iv) palatability profile (good/not good not bad/bad), as reported by participants of aged >5 years; (iv) proportion of subjects compliant with treatment (>80% of the prescribed drug) in each arm.

Data collection

Baseline data were collected using a predesigned proforma regarding age, sex, anthropometry, duration of constipation, number of bowel movements per week, bristle stool grade, any painful defecation or fecal incontinence, and the modality for diagnosing fecal impaction (palpable fecolith/digital rectal examination/abdominal radiography). Data regarding efficacy included the number of patients completing the treatment and achieving successful disimpaction, the cumulative dose of PEG, and the total number of days required for successful disimpaction. For the tolerability and palatability profile, information was gathered from each arm about adverse events (>3 episodes of vomiting, abdominal discomfort [bloating/pain], or electrolyte imbalance) and palatability as reported by participants >5 years of age and number of subjects having good treatment compliance (>80% of the prescribed drug), respectively. The terms palatability and acceptability are used interchangeably to further describe the results and discussion of this study.

Sample size

Using a two-sided test, it was calculated that a minimum sample size of 50 in each arm would be required to elicit a 25% difference in the proportion of subjects having successful disimpaction between the two treatment groups at 80% power and a error of 0.05 with the assumption that 90% of the participants receiving PEG 3350+E would achieve successful fecal disimpaction.

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Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Co.). Continuous data were expressed as mean±standard deviation and categorical data as frequency (percentage). The independent sample *t*-test was used to compare continuous data between the two arms, whereas the chi-square and Fisher's exact tests were used to compare categorical data. Statistical significance was set at $p<0.05$.

RESULTS

During the study period, 224 pediatric patients with constipation were screened for eligibility, 100 of whom were enrolled in the trial (intention-to-treat population) and randomized into treatment groups (50 in each group). Two patients in the PEG 3350+E arm and one in the PEG 4000 arm discontinued treatment because of persistent vomiting and abdominal distension. The remaining study participants completed the treatment protocol as allocated (depicted in the Consort diagram in **Fig. 1**). However, because this was an intention-to-treat analysis, all randomized subjects were included in the final analysis.

Among 100 participants, 56% were male, and the mean age was 8.7±4.1 years. The cohort had a mean duration constipation of 7.3±3.7 months with 3.2±2.0 stools/week. Of these, 89% and 74%, respectively, complained of having hard stool (Bristle grade 1 or 2) and painful defecation with straining, whereas 56% had no abdominal pain. Fecal incontinence was reported in 26% of the enrolled patients. Diagnosis of fecal impaction was made by palpable fecoliths in 65%, abdominal radiography in 30%, and digital-rectal examination in 5%.
No significant differences were observed in the demography, duration/symptomatology of constipation, or diagnostic modality of fecal impaction between the two treatment arms (**Table 1**). Seven patients required nasogastric tube insertion (three with PEG 3350+E and four with PEG 4000) for drug administration; all of them were aged between 1 and 2 years.

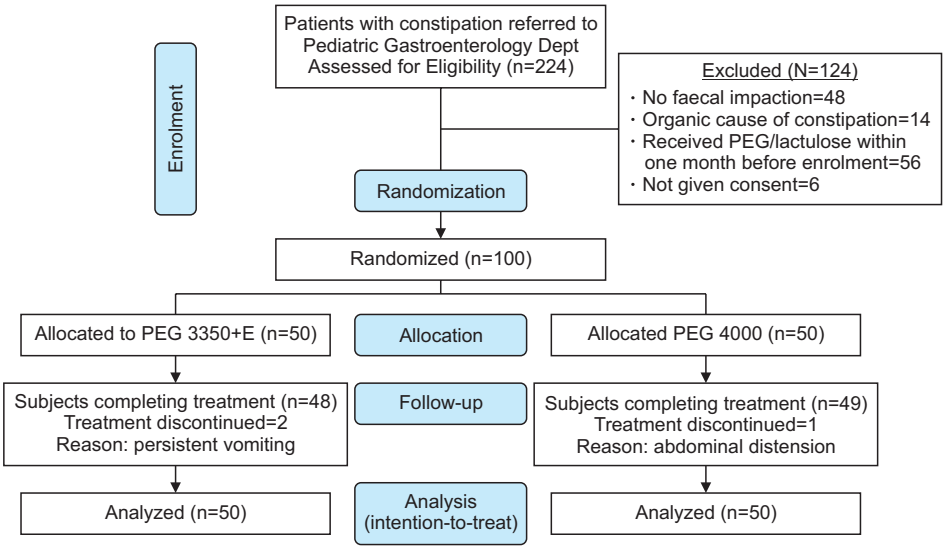

Fig. 1. Consort diagram for the randomized controlled trial.
PEG: polyethylene glycol.

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Table 1. Comparison of demographic and clinical parameters between the two treatment arms

Parameters	PEG 3350+ electrolytes (n=50)	PEG 4000 (n=50)	*p*-value
Age (y)	8.8±4.0	8.8±4.3	0.97
Age-stratified distribution of participants (y)			
1–5	16 (32.0)	17 (34.0)	0.912
6–11	17 (34.0)	15 (30.0)	
12–16	17 (34.0)	18 (36.0)	
Male	26 (52.0)	30 (60.0)	0.546
Weight (kg)	31.4±11.8	28.7±14.9	0.785
Length/height (cm)	131.6±24.4	130.2±26.2	0.941
Duration of constipation (mo)	8.2±3.4	7.2±4.0	0.195
Number of bowel movements/week	3.0±2.3	3.5±1.7	0.205
Proportion of subjects with h/o hard stool (Bristle grade 1 or 2)	44 (88.0)	45 (90.0)	1.000
Proportion of subjects with h/o painful defecation	39 (78.0)	35 (70.0)	0.495
Proportion of subjects with h/o retentive fecal incontinence	12 (24.0)	14 (28.0)	0.820
Proportion of subjects with h/o abdominal pain	25 (50.0)	31 (62.0)	0.314
Fecal impaction diagnosis modality			
Palpable fecolith	31 (62.0)	34 (68.0)	0.675
X-ray abdomen	16 (32.0)	14 (28.0)	0.828
Digital rectal examination	3 (6.0)	2 (4.0)	1.000

Values are presented as number (%) or mean±standard deviation.
PEG: polyethylene glycol.

Efficacy for disimpaction

Successful fecal disimpaction was achieved in 42 patients (84.0%) in the PEG 3350+E arm and 43 patients (86.0%) in the PEG 4000 arm, and there was no statistically significant difference between the two (p=0.9). Subjects in the PEG 3350+E arm required a mean cumulative PEG dose of 6.5±2.1 gm/kg and 4.3±1.3 days for disimpaction compared to 6.2±2.2 gm/kg and 4.1±1.4 days in the PEG 4000 arms (p=0.553 & p=0.581 respectively) (**Table 2**, **Fig. 2A**).

Tolerability profile

A total of 63 adverse events were observed in 26 patients among the whole cohort. The most commonly reported adverse effect was abdominal discomfort (33%), followed by vomiting

Table 2. Comparison of the efficacy, tolerability, and acceptability of PEG 3350+ electrolytes vs. PEG 4000 for fecal disimpaction in pediatric functional constipation

Parameters	PEG 3350+ electrolytes (n=50)	PEG 4000 (n=50)	*p*-value
Subjects completing treatment protocol	48 (96.0)	49 (98.0)	1.00
Efficacy for disimpaction			
Successful fecal disimpaction	42 (84.0)	43 (86.0)	0.9
Cumulative dose of PEG required for fecal disimpaction (gm/kg)	6.5±2.1	6.2±2.2	0.553
Number of days required for successful fecal disimpaction	4.3±1.3	4.1±1.4	0.581
Tolerability profile (proportion of subjects with adverse events)			
>3 episodes of vomiting	12 (24.0)	13 (26.0)	1.000
Abdominal discomfort	15 (30.0)	18 (36.0)	0.671
Dehydration	0 (0.0)	0 (0.0)	1.000
Dyselectrolaemia	2 (4.0)	3 (6.0)	1.000
Acceptability profile			
Palatability as reported by participants >5 years of age	(n=34)	(n=33)	
Good	0 (0.0)	0 (0.0)	0.044
Not good not bad	15 (44.1)	23 (69.6)	
Bad	19 (55.9)	10 (30.3)	
Subjects with good treatment compliance (taken >80% of the prescribed dose)	44 (88.0)	46 (92.0)	0.314

Values are presented as number (%) or mean±standard deviation.
PEG: polyethylene glycol.

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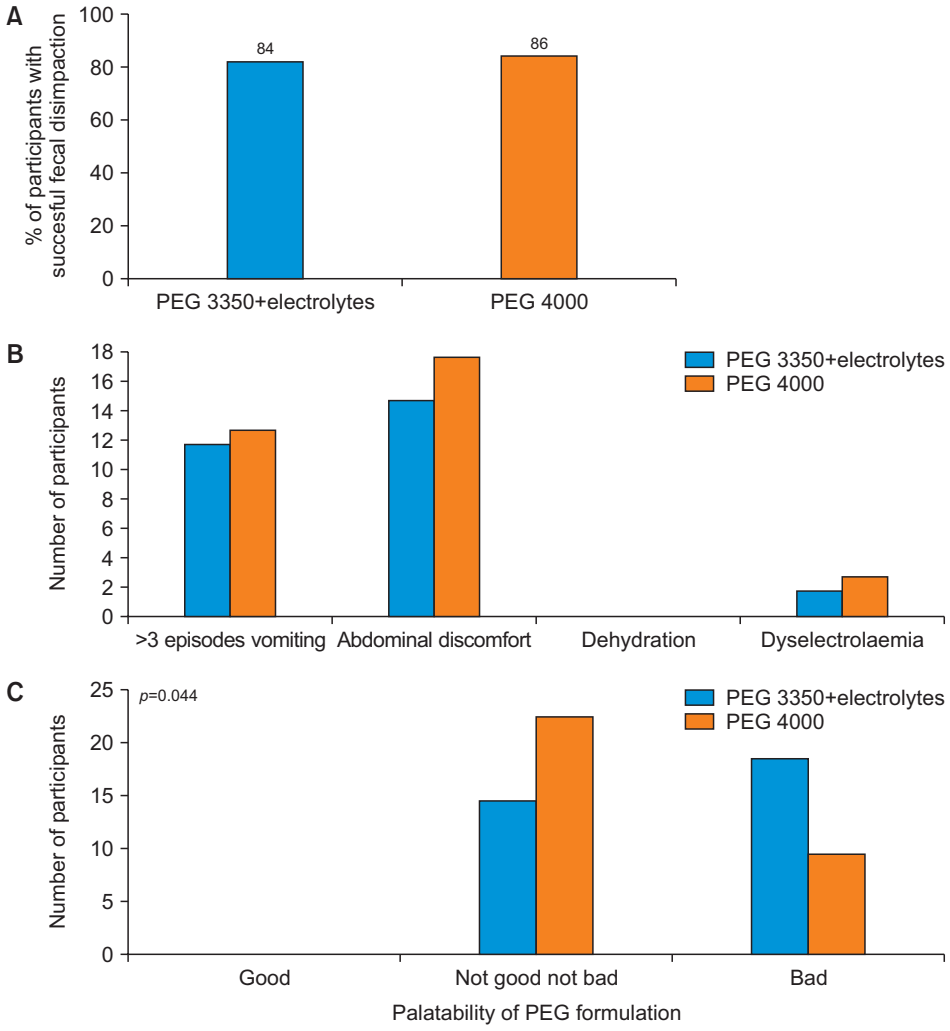

Fig. 2. Comparison between PEG 3350+ electrolytes and PEG 4000 for fecal disimpaction in pediatric functional constipation with respect to (A) efficacy (% of participants with successful fecal disimpaction); (B) adverse effects; (C) palatability.
PEG: polyethylene glycol.

(25%). In the PEG 3350+E arm, 24% had >3 episodes of vomiting, and 30% complained of abdominal discomfort, and 26% and 36% in the PEG 4000 arm had similar complaints, respectively. Two patients in the PEG 3350+E arm and one in the PEG 4000 arm discontinued treatment because of persistent vomiting and abdominal distension, respectively. Electrolyte imbalance in the form of mild hypokalemia was noted in 4% and 6% of patients in the PEG 3350+E and PEG 4000 arms, respectively. None of the patients in either arm developed dehydration during the disimpaction. No statistically significant difference was found in any of the side effects between the two groups (**Table 2**, **Fig. 2B**).

Palatability profile

Information regarding palatability was collected only from subjects aged >5 years (34 in the PEG 3350+E and 33 in the PEG 4000 arm). None of the participants in either group reported that the taste of the formulations was "good." In the PEG 3350+E arm, 55.9% (19/34) reported the taste as "bad'' and 44.1% (15/34) as "not good, not bad." Conversely, only 30.3% (10/33) of the PEG 4000 arm described the taste as "bad," the remaining 69.7% (23/33)

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reported it as "not good, not bad." The difference in the palatability profiles of the two formulations was statistically significant (p=0.044) (**Table 2**, **Fig. 2C**).

Compliance with the treatment was slightly higher in the PEG 4000 group (46/50 [92.0%]) in comparison to the PEG 3350+E group [44/50 (80.0%)]. However, this difference was not statistically significant (p=0.314).

DISCUSSION

Constipation accounts for approximately 3% of pediatric outpatient visits and 25% of referrals to pediatric gastroenterologists. In 90% of cases, no organic cause is found; hence, labelled as functional constipation [1,2]. Fecal impaction is observed in 30% to 75% of these patients, the impact of which extends beyond the physical symptoms to include psychological and social challenges for families, as it often disrupts daily life and may lead to emotional distress for both children and caregivers [2,3]. Fecal disimpaction is the first and most crucial step in the management of these children, without which maintenance therapy remains ineffective or might even paradoxically worsen symptoms due to overflow incontinence [4,5]. PEG is the recommended first-line therapeutic agent for the treatment of pediatric functional constipation. This nonabsorbable polymer functions as an osmotic laxative because it produces an osmotic gradient in the intestinal lumen that causes fluid retention, resulting in stool softening and painless defecation. The most commonly used formulations are PEG 3350, with a molecular weight between 3,200 and 3,700 g/moL, and PEG 4000, with an approximate molecular weight of 4,000 g/moL [7]. Both have been shown to be effective and safe for pediatric constipation management in multiple RCTs (vs. an active comparator lactulose/milk of magnesia) as maintenance therapy [4,11,12]. However, scant literature is available on other aspects, such as the palatability and acceptability of these PEG formulations. Moreover, there is a dearth of pediatric studies comparing these formulations exclusively for fecal disimpaction.

Fecal disimpaction requires the administration of large amounts of these medications. Hence, taste/palatability determines the acceptance rate among the pediatric population and, ultimately, the success of the treatment. Likewise, disimpaction might pose a risk of electrolyte imbalance owing to the high purge rate. Therefore, while comparing PEG formulations for the treatment of fecal impaction, apart from their efficacy, we also have to consider tolerability (safety or side effect profile) and acceptability. In this double-blind RCT, we conducted a head-to-head comparison between the two most commonly available and used PEG formulations in India (PEG 3350+E and PEG 4000) regarding their efficacy, tolerability, and patient acceptability for resolving fecal impaction in pediatric patients with functional constipation.

The present study demonstrated good and comparable efficacies of PEG 3350+E and PEG 4000 for a successful disimpaction (84% and 86%, respectively). This is consistent with previous studies [13-15]. Savino et al. [10] reported 86% and 100% successful disimpactions with PEG 3350+E and PEG 4000, respectively; however, their study targeted primarily the comparison for maintenance treatment, with only 14 of the 96 recruited patients receiving fecal disimpaction treatment (seven in each arm). In a retrospective study, Boles et al. [13] from the United States compared PEG 3350+E vs. PEG 3350 for fecal disimpaction and found similar efficacies for both (87% vs. 86%). Shatnawi et al. [14] also documented

a 100% successful fecal disimpaction rate with PEG 4000 by day 6 in their RCT of PEG 4000 and lactulose in a cohort of 65 children. However, the latter two studies did not clearly define how the endpoint (successful disimpaction) was evaluated. In contrast to these studies, a lower success rate of only 68% was noted by Bekkali et al. [16] in their RCT comparing PEG 3350+E to enema for fecal impaction. This discrepancy could be because, in their study, the end-point, that is, resolution of fecal impaction, was determined by repeat abdominal radiography/digital rectal examination, whereas we assessed it clinically as the passage of clear liquid stool and resolution of fecoliths, if any, at baseline. **Table 3** summarizes the outcomes of all previously published studies in which either PEG 3350+E or PEG 4000 was compared with other laxatives for pediatric fecal disimpaction.

Because PEG 3350+E contains additional electrolytes, it has been perceived to be more effective in avoiding electrolyte imbalance. However, a network meta-analysis published in 2016, including 19 RCTs on adult patients (12 provided data on safety/adverse events), did not find any significant difference in adverse events between the PEG+E and PEG groups. Hence, the authors concluded that there was no discernible advantage to the inclusion of electrolytes in PEG over plain PEG [8]. Two pediatric studies (by Salvino et al. [10] and Bekkali et al. [9])

Table 3. Summary of previously published studies on fecal disimpaction in pediatric functional constipation comparing PEG 3350+E or PEG 4000 with another laxative enema

Author, country (year)	Study design	Study population	Treatment arms & intervention	Outcome	Adverse events
Candy et al. [18] USA, 2006	Randomized controlled trial Initial disimpaction with PEG 3350+E followed by a comparison between PEG 3350+E vs. Lactulose as maintenance therapy	2–11 years with functional constipation with fecal impaction	PEG 3350+E for disimpaction: (n=63) Dosing was age-based and in an escalating manner	Fecal disimpaction rate: 92%	Gastrointestinal (abdominal pain/nausea/vomiting): 39 (62%)
Bekkali et al. [16] Netherlands, 2009	Open-label randomized controlled trial Enema vs. PEG 3350+E	4–16 years with fecal impaction (diagnosed by digital rectal examination)	Enema arm (n=46): (dioctyl sulfosuccinate sodium; once daily for 6 consecutive days (<6 y: 60 mL >6 y: 120 mL) PEG 3350+E arm (n=44): 1.5 gm/kg/day for 6 consecutive days	Fecal disimpaction rate Enema: 80% PEG 3350+E: 68% (No significant difference, p=0.28)	Abdominal pain for >30 mins Enema: 7 PEG 3350+E: 3
Savino et al. [10] Italy, 2012	Double-blind randomized controlled trial PEG 3350+Electrolytes vs. PEG 4000 for fecal disimpaction and maintenance therapy	2–16 years age with functional constipation±fecal impaction	For fecal disimpaction: PEG 3350+E arm (n=7) PEG 4000 arm (n=7) Dose: 1.5 g/kg/day in two divided doses until resolution or for maximum 6 days	Fecal disimpaction rate: PEG 3350+E arm: 85.7% PEG 4000: 100%	Not reported separately for fecal disimpaction
Boles et al. [13] USA, 2015	Retrospective comparative PEG 3350 vs. PEG 3350+Electrolytes	Recruited retrospectively based on ICD codes	Both arms: >0.8 gm/kg/day PEG 3350 arm: (n=28) PEG 3350+E arm: (n=23)	No statistically significant difference in fecal disimpaction rate between 2 arms PEG 3350: 86% vs. PEG 3350+E: 87%	PEG 3350: 4% 1-Dyselectrolaemia PEG 3350+E: 48% 3-Dyselectrolaemia 4-Abdominal pain 3-Nausea/vomiting
Shatnawi et al. [14] Jordan, 2019	Open-label randomized controlled trial PEG 4000 vs. Lactulose	1–14 years with functional constipation with fecal impaction	Lactulose arm (n=33): 4–6 mL/kg/day until resolution or for 6 days PEG 4000 arm (n=32): 1.5 g/kg/day until resolution or for 6 days	100% successful disimpaction in each arm PEG 4000 arm showed a faster response by day 2 of treatment	Lactulose: 1-Diarrhea and vomiting 1-Abdominal pain PEG 3350+E: 3-Abdominal pain
Acharyya et al. [15] India, 2021	Single blind randomized controlled trial PEG 3350+E vs. PEG 3350+E+SP	2–14 years with functional constipation with fecal impaction	Dose as per weight band PEG 3350+E arm: (n=50) PEG 3350+E+SP arm: (n=51)	PEG 3350+E+SP arm had significantly better stool numbers compared to PEG 3350+E on day 1&day 2	PEG 3350+E: 15-Abdominal pain, 2-vomiting PEG 3350+E+SP: 3-Abdominal pain, 3-nausea/vomiting

PEG: polyethylene glycol, E: electrolytes, ICD: international classification of diseases, SP: sodium picosulphate.

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compared PEG 3350+E and PEG 4000 as maintenance therapies. In a previous double-blind RCT of 96 patients from Italy, the PEG 3350+E group had significantly more complaints of nausea than the PEG 4000 group (p=0.003) [10]. However, the later study, which was also an RCT, did not find any significant difference in the side effects between the two and reported no major drug-related side effects with either formulation [9].

We did not observe any serious side effects, such as dehydration or severe electrolyte imbalance, in the current study. The most common side effects were abdominal discomfort and vomiting, which were documented in both treatment arms without any statistically significant difference in their frequency. This is in contrast to the findings from the study by Boles et al. [13], who observed greater adverse events in the PEG 3350+E arm (48%), including severe symptomatic hypokalemia and metabolic alkalosis (requiring ICU care) as compared to the PEG 3350 arm (4%). However, these findings must be interpreted cautiously, as this was a retrospective study with poorly defined inclusion and exclusion criteria and intervention protocols. Our findings are consistent with those of Candy et al. [18], who used PEG 3350+E to treat fecal disimpaction. Other prospective RCTs comparing PEG with lactulose did not report any major side effects (apart from abdominal discomfort and nausea/vomiting) with either of the PEG formulations, which is consistent with our findings [17-21]. However, although no life-threatening side effects occurred in our cohort, two patients in the PEG 3350+E arm and one patient in the PEG 4000 arm discontinued treatment because of persistent vomiting and abdominal discomfort, respectively, which affected the overall efficacy of the formulations for fecal disimpaction in the intention-to-treat analysis.

Owing to the added salts, PEG 3350+E is suggested to have a saltier taste than PEG 4000, which might be unpleasant for some patients, resulting in poor acceptability. Two studies conducted in adults have shown that PEG has better acceptability than PEG+E [6,22]. According to the palatability data collected from subjects of >5 years of age in our study, 55.9% (19/34) in the PEG 3350+E arm reported the taste as “bad,” which was significantly (approximately two times) higher than that observed in the PEG 4000 arm [30.3% (10/33)]. This corroborates with the only other available pediatric study that has compared the palatability of these two formulations and documented a significantly greater number of subjects describing the taste of PEG 3350+E as “bad/very bad” (26%) in contrast to PEG 4000 (2%). In their study, 43% of PEG 4000 and 2% in the PEG 3350+E arm reported the taste as “good” [10]; however, none of our patients described any of the formulations as having “good” taste. They reported that it was either “not good, not bad” or “bad.” Despite the significant difference in the reported taste of the formulations, there was no statistically significant difference in the compliance rate (i.e., intake of >80% of prescribed medicine), although it was slightly higher (92%) in the PEG 4000 arm than the PEG 3350+E arm (88%).

The strengths of our study are its strict inclusion and exclusion criteria, double-blind, randomized methodology, well-defined endpoint for assessing efficacy, and patient-reported objective scale for comparing palatability, along with information regarding tolerability and compliance to the two formulations during the disimpaction process, which were lacking in previous studies.

However, this study has certain limitations. This study was conducted in a hospital-based setting with close monitoring, and the outcomes may differ from those of home-based disimpaction. The resolution of fecal impaction was evaluated clinically; we did not perform abdominal radiography after completion of the intervention because of obvious ethical

concerns about radiation exposure. As the molecular weights of PEG 3350 and PEG 4000 differ, this could be a potential confounder; hence, a three-armed RCT between PEG 3350, PEG 3350+E, and PEG 4000 could have been an ideal comparison. Similarly, the sample size was calculated to detect a 25% difference between the formulations; however, a larger sample size would have been better to detect smaller differences. Finally, we did not perform follow-up of the patients after discharge regarding re-impaction/recurrence of symptoms. Despite these limitations, our study is the first prospective study that compared two commonly available PEG formulations, PEG 3350+E and PEG 4000, in an RCT exclusively focusing on the treatment of fecal impaction in pediatric patients.

Conclusion

PEG 3350+E and PEG 4000 have similar efficacy (84–86%) for fecal disimpaction in pediatric functional constipation. In addition to abdominal discomfort and vomiting, no major side effects occurred with either formulation; hence, both formulations can be safely used for disimpaction. PEG 4000 showed a better palatability profile than PEG 3350+E However, compliance with both drugs was good and comparable. In the future, a three-armed RCT comparing PEG 3350 vs. PEG 3350+E vs. PEG 4000 with a larger sample size could provide additional information.

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