Clinical Characteristics, Etiology of Pediatric Constipation and Effectiveness of Polyethylene Glycol in the Management

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Abstract

Introduction: Constipation is a common pediatric problem worldwide. This study aims to describe the clinical characteristics, etiology of pediatric constipation in Misurata Teaching Hospital, Libya, according to gender and age group and to assess the efficacy of polyethylene glycol (PEG) plus as oral monotherapy for fecal impaction and as a maintenance.

Methods: All patients with constipation managed at our pediatric gastroenterology clinic between April 2015 and September 2016 were included. Demographic data, clinical characteristics, final diagnosis, and effect of treatment were recorded. Data were analyzed according to gender and age groups (infants, preschool, school age, and adolescents.

Results: During the study period, 74 patients were enrolled, the number (%) according to age was the following infants: 28 (37.8%), preschool: 28 (37.8%), school age: 14 (18.9%), and adolescents: 4 (5.5%). Majority of patients 56 (75%) are below 6 years of age (P = 0.0.003). Males made up 52% and there were no statistical gender differences in any age group. The most common symptom was dry and hard stool (93.2%). Infrequent defecation (50%) the patients. Fecal incontinence was more common in school-aged children (69%) compared to pre-school-aged and adolescent. Abdominal pain was seen in almost 34% of patient and with per-rectal bleeding was more prevalent in school age children. Functional constipation was the most common etiology. Disimpaction on PEG was achieved in 50 (96%) of 52 children who presented with fecal impaction (71.3% of all children) without additional interventions, median time to disimpaction was 3.4 days (range: 3-7 days). Only 4 (5.4%) reimpacted, others are improved with no adverse events were reported on 3 months follow-up.

Conclusion: Functional constipation is the most common cause of childhood constipation. Clinical characteristics in children vary according to age group and gender. Older children had higher prevalence of long-standing fecal incontinence and abdominal pain. PEG is safe and highly effective as a single orally administered laxative to be used for disimpaction without recourse to invasive interventions and it is significantly effective as maintenance therapy and prevent reimpaction.

Key words: Children, Constipation, Fecal impaction, Infants, Polyethylene glycol

INTRODUCTION

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Constipation is a common problem in children. The worldwide prevalence varies between 0.7% and 29.6%.¹ Constipation is the reason for 3-5% of physician visits by children² and accounts for almost one-fourth of pediatric gastroenterology consults.³ Constipation has a significant

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impact on the use and cost of medical services.⁴ Childhood constipation is a family issue that negatively affects children's physical, social, emotional, and school functioning.⁵ As normal bowel habits differ with age,⁶ features of constipation are expected to differ between age groups. Prevalence and symptoms of constipation are often different in very young children than in older children. For example; constipation prevalence is not the same through childhood. It peaks at the age of toilet training.⁷ A longer duration of constipation before the diagnosis has been associated with complications (e.g., fecal incontinence) and poorer long-term outcome (persistent of symptoms and continuous need for laxatives).⁷ The clinical profile of childhood constipation has been well described in many studies;⁷⁻¹⁰ In our country, the prevalence of pediatric constipation is unknown. Although

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no epidemiological studies have been performed to accurately identify the true size of the problem, we believe that constipation is not uncommon in our society. Since, the establishment of a pediatric gastroenterology clinic in our hospital, constipation was noted as the most common cause for consultation. Because no studies have been published on constipation in children from our hospital, we performed a prospective analysis to evaluate the etiology and clinical characteristics of patients with constipation according to age group and gender.

The recommended approach is to empty the constipated bowel and keep it empty.^{11,12} Unfortunately, the current means of achieving disimpaction add to the distress caused by the complaint. The administration of repeated enemas, suppositories, and manual evacuation under general anesthesia are distressing for the child.

Once an impaction exists, efforts to remove it by catharsis from above are not only ineffectual but may worsen the abdominal pain and may compound the retention problems in children. Polyethylene glycol 3350 (PEG) is a particularly suitable molecule up on which to base an oral laxative because a solution of PEG exhibits a linear dose-response relationship when ingested,¹³ retaining water in the bowel to potentially produce an almost unlimited laxative action, as demonstrated by the high volume PEG bowel lavage solutions. This is in contrast with laxatives like lactulose or senna, which, as prodrugs need metabolism in the large bowel to an active moiety. The ingestion of increasing amounts of these laxatives will saturate the metabolic capability of the colon; hence, the dose-response curve shows a plateau after which increasing the dose does not produce any greater effect. Once disimpaction is achieved are liable maintenance treatment is required to prevent the need for repeated attempts at disimpaction.

MATERIALS AND METHODS

Consecutive children with constipation (organic and functional) who presented to the Pediatric Gastroenterology Clinic at Misurata Teaching Hospital, Misurata, Libya between April 2015 and September 2016 (18 months period) were included in the study and followed until 30th November 2016.

Data collected include age, sex, duration of constipation, symptoms and signs such as bowel motion frequency, consistency, presence of blood, pain with defecation, stool withholding behavior, fecal incontinence (soiling), and the presence of fecal impaction or an abdominal mass. The likely cause that reported by the parents considered as risk factors include, time of weaning, changing formulae, toilet training, school entry, a dietary history that focused on the acceptance of fibers (fruits and vegetables) and fluids, and family history of constipation. Clinical evaluation (history and physical examination) of all patients was done by the same physician (the author). The digital anorectal examination is indicated in children when the diagnosis of functional constipation remains uncertain or in children with intractable constipation, to exclude underlying medical conditions. Laboratory and radiological investigations were performed according to the patient's presentation. Investigation for celiac disease and hypothyroidism is suggested in intractable constipation and in cases where there is evidence off altering growth. Hirschsprung's disease was confirmed only after rectal biopsy. Routine elimination of cow's milk formula to establish the diagnosis of cow's milk protein allergy was not recommended in our practice. Neurological disorders were diagnosed with appropriate investigations with pediatric neurology input.

The large variation in prevalence is mainly due to different methods of data collection and criteria of constipation were used in different studies. To solve the problem of nonuniformity in diagnostic criteria, we follow the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines which recommend the Rome III criteria for the definition of functional constipation be used for all ages.⁸

Rome III Diagnostic Criteria for Functional Constipation in Children

Symptoms must occur at least once per week for at least 2 months and include two or more of the following in children:

- Two or fewer defections in the toilet per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet.

During disimpaction phase, PEG was administered orally (dose, 4 g powder dissolved in at least 150 mL water or Juice) according to an escalating daily dose regimen until disimpaction was achieved (Table 1). This was a dose regimen that had been shown to be effective in many studies.^{14,15} This regimen used an escalating dose of PEG to maximize compliance, with a higher dose given to children in the 5-14 years age group than to 1-4 years olds. Followed by maintenance treatment of constipation over a 3-month period.

Statistical Analysis

For data analysis and comparison, we categorized the patients according to gender and age: Infants (0-24 months), preschool (25-72 months), school age (73-120 months), and adolescents (121-216 months).

The SPSS Statistics (version 18) was used. Results were expressed as the means with ranges. Categorical data were tested using Fisher's exact test, and continuous data were tested using the *t*-test. P < 0.05 were considered significant.

RESULTS

During the study period, our clinic saw 244 patients of whom 80 had constipation, comprising 31.9% of our gastroenterology clinic consults. 74 were included in the analysis after exclusion of 6 patients with organic causes.

Patient's Distribution by Age, Sex, Duration of Constipation and Treatment Exposure

Of the 74 patients, 39 patients (52.6%) were male (Figure 1). No statistically significant gender differences were seen in any age groups (P = 0.816). Infants and preschool children (n = 28, 37.8% each of them) were the most commonly affected age groups, followed by school-age children (n = 14, 18.9%), and adolescents (n = 4, 5.4%). The average duration of constipation before consultation significantly increased with age (5.5, 10.8, 17.8, and 26 months for infants, preschool, school age, and adolescents, respectively) (Table 2). Half of them (37 patients, 50%) reported taken at least 1 laxative medication, most commonly was lactulose.

Clinical Characteristics of Bowel Motions and Associated Symptoms

Regarding bowel motion characteristics, hard, and dry stool were the most common symptom seen in all age groups, affecting 93.2% of constipated children. On the other hand,

Table 1: PEG (Macrogol 4000) dosing regimen						
Number of PEG sachets daily divided to 2 doses						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
2	4	4	6	6	8	8
4	6	6	8	8	10	10
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PEG: Polyethylene glycol

infrequent bowel motion (<3 bowel motions per week) was seen in almost half of our patients. The prevalence of infrequent defecation showed a nonsignificant increase as children got older. Fecal incontinence (soiling) was most commonly seen in school-age children (69.3%) and was significantly different compared to preschool children (P < 0.001). Except for infants who did not report urinary problems, urinary complaints were more prevalent in older children (6.9%, 7.7%, and 25% of preschool, school age, and adolescents, respectively). Abdominal pain was seen in almost 34% of patients (10.7%, 34.5%, 76.9%, and 50% in infants, preschool, school age, and adolescents, respectively) (Table 3 and Figure 2). Abdominal pain and per-rectal bleeding were more prevalent in school-age children.

Functional (non-organic) constipation was the most common diagnosis in all age groups. 9 of our patient had family history of constipation (1.1%). Surgical motility-

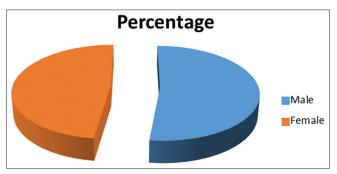


Figure 1: Sex distribution of childhood constipation

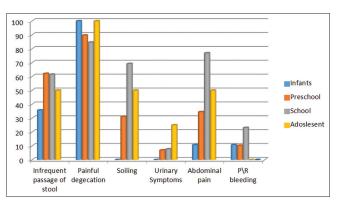


Figure 2: Clinical characteristic of bowel motion and associated symptoms of pediatric constipation

Demographic variable	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	Р
Patient	28 (37.8)	28 (37.8)	14 (18.9)	4 (5.5)	74 (100)	-
Male	18 (64.3)	11 (37.9)	8 (53.8)	2 (50)	39	NS
Female	10 (35.7)	17 (62.1)	6 (46.2)	2 (50)	35	NS
Average duration of constipation (months)	5.5 (2-12)	10.8 (2-42)	17.6 (4-52)	26 (6-36)	-	Significant between all age groups <0.05

Clinical characteristics	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	Р
Infrequent passage of stool	10 (35.7)	18 (62.1)	8 (61.5)	2 (50)	38 (51.4)	NS
Painful defecation	28 (100)	26 (89.7)	11 (84.6)	4 (100)	69 (93.2)	NS
Soiling	0 (0)	9 (31)	9 (69.2)	2 (50)	21 (28.4)	Significant betweer all age groups <0.0
Urinary symptoms	0 (0)	2 (6.9)	1 (7.7)	1 (25)	4 (5.4)	
Abdominal pain	3 (10.7)	10 (34.5)	10 (76.9)	2 (50)	25 (33.8)	
PR bleeding	3 (10.7)	3 (10.3)	3 (23.1)	0 (0)	9 (12.2)	

related organic causes (Hirschsprung's disease) were the leading causes for organic constipation, followed by neurological disorders. Celiac disease was considered in five patients (constipation with faltering growth or family history of constipation), but celiac serology was normal, hypothyroidism, and allergy to cow's milk protein was not reported in our patients (Table 4).

Disimpaction on PEG was achieved in 50 (96%) of 52 (71.3% of all children) without additional interventions. A maximum dose of 6 sachets (for 1-5 years old) or 8 sachets (for 5-14 years old) was required; median time to disimpaction was 3.4 days (range: 3-7 days). 4 of children (5.4%) reimpacted whilst taking PEG, others are improved with good adherence. No adverse events were reported on 3 months follow-up.

DISCUSSION

We have conducted the first prospective study to evaluate the prevalence of constipation among children treated in a pediatric gastroenterology clinic in Misurata Teaching Hospital, Libya. Patients were categorized into four pediatric age groups: Infants, preschool, school-age children, and adolescents. Our study showed that older children had less frequent bowel motions, a longer duration of symptoms, and a higher prevalence of long-standing constipation compilations (fecal incontinence and abdominal pain). Infants and Preschool children were the most commonly affected age groups. We believe that the low number of adolescents does not reflect a low prevalence rate in this age group, but a referral bias, as our clinic treats children 14 years old and younger.

Fewer than three bowel motions per week is a commonly used definition of constipation, using only this definition will lead to underdiagnosis of constipation.⁹ In a study of 178 children with constipation in Iowa, 58% had <3 bowel movements per week,¹⁶ and in another study 41.3% of children with symptoms of constipation were found to have infrequent stools.⁷ Children <2 years of age had constipation with symptoms of passage of hard or pebble

Table 4: Etiology of constipation in study subjects

Etiology	n (%)
Functional	74 (92.5)
Motility-related organic causes Hirschsprung's disease	2 (2.5)
Congenital anomalies (Spina bifida)	1 (1.3)
Neurologic disorders (CP, unexplained D. D.)	2 (2.5)
Autism	1 (1.3)
Celiac disease	0 (0)
Hypothyroidism	0 (0)
Cow's milk protein allergy	0 (0)

like stools with straining, withholding or painful defecation. The diagnosis would be missed in 50% if infrequent stools were the only criteria used for diagnosis. In our study, infrequent defecation was reported by only half of our patients.

Room III criteria which include hard, dry stool, and painful defecation appear to be more sensitive indicators. More than 90% of constipated children in all age groups described their bowel motions as dry, hard, and painful this is consistent with the work of Loening-Baucke,¹⁰ who concluded that using stool consistency and painful bowel motion to define constipation is more sensitive than using symptom duration or frequency of bowel motions.

Retentive fecal incontinence (associated with constipation) has been reported in up to 85% of constipated children.¹³ In our study, school-age children exhibited the highest rate (69.2%) of fecal incontinence, which was significantly different compared to preschool children (P < 0.05).

The urinary system is anatomically adjacent to the gut and shares neurological control, rectal pathology leads to urinary symptoms through mechanical compression of the stool mass over the bladder in addition to a voiding dysfunction caused by pelvic floor muscle spasms. Constipation may cause urinary tract infections and enuresis due to uninhibited bladder contraction.^{7,9} Urinary symptoms have been reported in 9-13% of children with a diagnosis of constipation, and urinary incontinence 10.5%, and it has been implicated in the pathoetiology of enuresis.¹⁷ Asymptomatic constipation may exacerbate urinary symptoms in children with enuresis.¹⁸ Urinary symptoms were seen in 5.4% of patients in our study, a rate that is less compared with the previous studies.^{19,20} Urinary morbidities were seen more often in adolescent compared to other age groups (P < 0.05).

Non-specific abdominal pain has been reported in 33% of children with constipation in one study.²¹ In our study, almost 33.8% of our patients had abdominal pain, which is the same, and the prevalence rate was higher in schoolaged group (P < 0.05) compared to other age groups. The small number of adolescents in this cohort limits the generalization of our results to this pediatric population.

The suspected underlying cause of functional constipation according to parent's report was considered in our study (Table 5), this study supports findings from the previous studies that a positive history of toilet training and low consumption of dietary fibers and fluids are significantly associated with constipation in children.²²⁻²⁴ Interestingly, it was noted in this study that toilet training was found to be significantly associated with a higher constipation rate, Perhaps coercive toilet training in toddlers can lead to reluctance to defecate. A positive family history has been found in 28-50% of constipated children and a higher incidence reported in monozygotic than dizygotic twins,²⁵ in our study only 9 of patients had a family history of constipation (1.1%).

Although radiological confirmation of the diagnosis of fecal impaction was not part of the protocol for this study, the children recruited had symptoms of fecal impaction, such as infrequent, painful defecation, vomiting, abdominal pain, and many also had palpable abdominal fecal masses. There is considerable controversy about the need to conduct rectal examinations in children to confirm the diagnosis of and success of treatment for fecal impaction. At our hospital, rectal examinations are not routinely conducted on constipated children; thus, there was probably less certainty about diagnosis and successful outcome of treatment than if a rectal examination had been carried out.

Functional constipation was the most common cause of chronic constipation, 94.8% in our study. The rates of

functional constipation in our cohort are similar compared to reported rates.²⁶ The clinician has an important role in identifying the small fraction of children with organic causes of constipation. Organic causes of constipation are more likely among young infants, and among infants, and children presenting with atypical features or "alarm signs" (Table 6).

Treatment for chronic constipation is based on the concept that chronic constipation causes the colon to be unresponsive to stool burden, due to distension, it follows that effective treatment requires consistent and complete emptying of the colon, so that it becomes conditioned to work on its own a concept known as "bowel retraining". There are four general steps in bowel retraining, we were followed:

- Disimpaction.
- Prolonged laxative treatment and behavior therapy to achieve regular evacuation and avoid recurrent constipation.
- Dietary changes (primarily increasing fiber content) to maintain soft stools.
- Gradual tapering and withdrawal of laxatives as tolerated.

The goal of therapy is the passage of soft stools, ideally once per day, and no less than every other days. This goal of frequent defecation is important to overcome constipation, although less frequent defecation patterns are common and acceptable in children without a history of constipation. Weeks to months of laxative and behavior therapy may be necessary before this goal is achieved. The child's parents must be effectively educated about bowel retraining and behavior modification so that they can carry out the sustained treatment.

Guidelines for management of infants and children with constipation were developed by the NASPGHAN, and ESPGHAN.⁸ These guidelines were followed in our practice, include a management with:

PEG

Macrogol 4000, is an osmotic laxative, it is more palatable and has fewer adverse effects than other

Risk factor	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	Р
Low fibers and fluid	3 (10.7)	9 (31)	11 (84.6)	4 (100)	27 (36.5)	-
Weaning	9 (32.1)	0 (0)	0 (0)	0 (0)	10 (13.5)	
Change formula	3 (10.7)	0 (0)	0 (0)	0 (0)	3 (4.1)	
School entry	0 (0)	0 (0)	3 (21.4)	0 (0)	3 (5.4)	Significant between all age groups <0.05
Finicky eating	5 (17.9)	6 (20.7)	0 (0)	0 (0)	11 (14.9)	
Toilet training	0 (0)	4 (13.8)	0(0)	0 (0)	4 (5.4)	

Table 6: Alarm signs and symptoms inconstipation

Constipation starting extremely early in life (<1 mol) Passage of meconium >48 h Family history of HD Blood in the stools in the absence of anal fissures Failure to thrive Bilious vomiting Severe abdominal distension Decreased lower extremity strength/tone/reflex Tuft of hair on spine Sacral dimple Gluteal cleft deviation

agents, it is preferred by most experts for disimpaction and treatment of chronic constipation, although it is not yet labeled for this use it is approved for shortterm management of constipation.⁸ Adverse effects include diarrhea (10%), bloating or flatulence (6%), and abdominal pain (2%).²⁷ These symptoms tend to be mild, transient, and responsive to dose reduction.²⁸ In the interim, NASPGHAN has published a statement with frequently asked questions about the use of PEG in children.²⁹

The typical dose is 0.4-0.8 g/kg/day (up to 17 g). The effective dose in an individual patient is not predictable, and many patients require relatively high doses for initial treatment of constipation, with somewhat lower maintenance dose.

A total of 52 children (71.2% of all our patient) disimpacted successfully with PEG, this was achieved in 96% of children, the median time to disimpaction for the children, overall was 3.4 days, with a range of 3-7 days.

Disimpaction was judged if feces became watery (type 7 on the Bristol stool form scale.³⁰ Within 7 days of commencing treatment. The dose required to achieve watery stools was continued to ensure complete disimpaction of the bowel, only one 10-year-old boy and one 8-year-old girl failed to disimpact within the time allowed. The adverse effects reported to be seen when taking the relatively high doses needed for disimpaction taken in consideration and, we advice to reduce the dose than that which was consumed. In our study, none of the adverse events was reported. After 12 weeks on treatment with PEG as maintenance, only one child taking PEG, senna was needed as additive rescue medication.

On entry to the study, about half of the children (50%) reported taking at least 1 laxative medication, the most common of which was lactulose and use enemas at time of fecal impaction, also one patient report disimpaction with

manual removal under general anesthesia, and reimpacted again within short period, all were responding very well to PEG with only low risk of recurrence (5.4%) and reimpaction as we mentioned before.

Children who have problems with constipation should be treated with care and consideration, it cannot be right to administer an invasive treatment to a child, as the insertion of a nasogastric tube, administration of enemas or suppositories, or manual removal of feces, if an equally or more effective noninvasive alternative exists. Although the invasive rectal approach leads to faster disimpaction within hours, it is invasive, unpleasant and carry not only physical risks to the child but also the risk of significant psychological trauma.

This study shows that PEG is safe and highly effective as a single, orally administered laxative in the treatment of fecal impaction in children and was easily be administered at home, no additional treatment was required to clear fecal impaction in children in this study, which means that the use of invasive treatments can be eliminated or at least substantially reduced in the treatment of impacted feces in children, also this will result in much lower cost to the health-care system and also eliminate the stress of hospital admission to the child and to the family. The studies cover the different scenarios of treatment: Oral resolution of impaction and maintenance therapy for relief of constipation, and in comparison with other laxatives were summarized in (Table 7).

CONCLUSION

To the best of our knowledge, this is the first study describing the clinical profile of childhood constipation in our hospital according to age group and gender, the clinical characteristics differed according to age group and gender, and according to the results of this successful treatment protocol using PEG in disimpaction and maintenance therapy, we have to outline the current trends in the assessment and treatment of constipation and introduce the current evidence base for the therapies currently in wide use, within the context of recent NICE and ESPGHAN/NASPGHAN guidance to our primary care to decrease the burden on referrals to gastroenterology clinic, and the indication of seeking advice of pediatric gastroenterologist should be restricted only if:

- Organic cause of constipation is suspected.
- Disimpaction orally was unsuccessful.
- Soiling/abdominal pain continues despite treatment.
- Children <1 year with fecal impaction.
- Children not responding to maintenance therapy.

Table 7: Efficacy of PEG

PEG 4000				
Authors	Study group	Methods+key outcomes		
Thomson <i>et al</i> . (2007) ³¹	51 children	Methods: Double-blind crossover RCT PEG+E or placebo for 2 weeks Results: Mean number of defecations higher for PEG+E group versus placebo (<i>P</i> <0.001). Also PEG+E reduced pain on defecation (<i>P</i> =0.041), straining on defecation (<i>P</i> <0.001), stool consistency (<i>P</i> <0.001), and percentage of hard stools (<i>P</i> =0.001). Adverse events were all mild or moderate and were similar for those children on PEG+E and placebo		
Candy <i>et al.</i> (2006) ³²	63 children	Methods: Initial open cohort study of PEG+E (disimpaction) then double-blind RCT of PEG+E (Movicol) vs. Lactulose (maintenance) Results: Disimpaction successful in 92% children. Maximum dose=4 sachets-4-year old) or 6 sachets (5-11-year olds); median time to disimpaction was 6 days Maintenance: Greater mean stool frequency in PEG+E group (<i>P</i> =0.007)		
Dupont <i>et al</i> . (2005) ³³	96 children	Method: Random allocation, open-label cohort study Results: More than 90% of children recovered normal bowel habits. Fecal mass in the rectum and abdominal pain was markedly reduced and appetite improved		
Youssef <i>et al</i> . (2002) ³⁴	40 children	Methods: Prospective, double-blind, parallel RCT 4 doses of PEG 3350 Results: Disimpaction in 75% of children overall but significant difference between two higher doses vs. lower doses (95% vs. 55%, <i>P</i> <0.005). All groups had an increased number of bowel movements during the 5-day study versus baseline		
Loening-Baucke <i>et al.</i> (2006) ³⁵	79 children	Methods: Double-blind RCT PEG 3350 versus magnesium hydroxide Results: Significant improvement in both groups, (frequency of bowel movements, reduced frequency of incontinence, and resolution of abdominal pain). Compliance=95% (PEG) versus 65%= milk of magnesia. At 12 months, 62% of PEG-treated children and 43% of MoM-treated children improving.		
Pashankar <i>et al</i> . (2003) ³⁶	83 children	Methods: Cohort study for at least 3 m PEG given at 0.8 g/kg/day then adjusted to give 2 soft painless stools/day Results: Mean duration=8.7 months. Mean PEG dose was 0.75 g/kg daily. No major adverse effects. All children preferred PEG to other laxatives, Good daily compliance in 90% of children		
Wang <i>et al.</i> (2012) ²⁷	105 children	Methods: RCT, PEG vs lactulose 1 week of treatment Results: 72.4% clinical remission rate, lactulose 41.4%		

PEG: Polyethylene glycol

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