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Original Article

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Efficacy and Safety of Combined Oral and Enema Therapy Using Polyethylene Glycol 3350-Electrolyte for Disimpaction in Pediatric Constipation

Taeyeon Yoo and Sun Hwan Bae

Department of Pediatrics, Konkuk University school of Medicine, Seoul, Korea

Purpose: We evaluated the efficacy and safety of combined oral and enema therapy using polyethylene glycol (PEG) 3350 with electrolyte solution for disimpaction in hospitalized children.
Methods: We retrospectively studied 28 children having functional constipation who received inpatient treatment between 2008 and 2016. The amount of oral PEG 3350 electrolyte solution administered was 50-70 mL/kg/d (PEG 3350, 3-4.1 g/kg/d), and an enema solution was administered 1-2 times a day as a single dose of 15-25 mL/kg (PEG 3350, 0.975-1.625 g/kg/d). A colon transit time (CTT) test based on the Metcalf protocol was performed in some patients.
Results: Administration of oral and enema doses of PEG 3350 electrolyte solution showed 2.1±0.3 times and 2.9±0.4 times, respectively. After disimpaction, the frequency of defecation increased from 2.2±0.3 per week to once a day (1.1±0.1 per day). The number of patients who complained of abdominal pain was reduced from 15 (53.6%) to 4 (14.3%). Before hospitalization, nine patients underwent a CTT test, and 5 of 9 patients (55.6%) were classified as belonging to a group showing abnormalities. And in some patients, mild adverse effects were noted. We examined electrolytes and osmolality before and after disimpaction in 16 of 28 patients, and no abnormalities were noted.
Conclusion: In terms of therapeutic efficacy and safety, combined oral and enema therapy using high-dose PEG 3350 with electrolytes is considered superior to conventional oral monotherapy or combined oral and enema therapy on an outpatient basis.

Key Words: Constipation, Child, Therapeutics, Polyethylene glycols

INTRODUCTION

Constipation, a common childhood condition is the commonest cause of acute abdominal pain in children [1]. The prevalence of childhood constipation is 0.7-29.6% (mean, 14%), noted in 3-5% of children who present to the Pediatrics Department, and 18% of children who visit Pediatric Gastroenter-

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Corresponding author: Sun Hwan Bae, Department of Pediatrics, Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea. Tel: +82-2-2030-7554, Fax: +82-2-2030-7748, E-mail: baedori@hanafos.com

ology Clinics [2-4]. Pediatric constipation may have organic causes, although in most cases it is a chronic functional condition without an organic cause. Despite a high prevalence, constipation is generally recognized as a mild disease not requiring treatment. Children are brought to the hospital only after constipation gets worse and is accompanied by symptoms such as vomiting, abdominal pain, and encopresis. It has been observed that 30-75% of pediatric functional constipation patients experience fecal impaction [5]. If constipation progresses without treatment after fecal impaction, defecation becomes increasingly difficult in children, which often leads them to withhold stools, with repetition of this vicious cycle.

Treatment of constipation consists of three phases: disimpaction-maintenance-withdrawal. Disimpaction is essential prior to initiation of maintenance therapy [6]. Disimpaction can generally be carried out on an outpatient basis; however, if patients failed disimpaction with outpatient treatment or in patients showing severe dehydration accompanied by acute symptoms such as repeated vomiting, inpatient treatment becomes necessary.

Various oral and enema solutions have been used for disimpaction in cases of pediatric constipation [7]. Polyethylene glycol (PEG), a biologically inactive and neutral polymer, used as an endoscopic pre-treatment solution has been widely used in the treatment of pediatric constipation since 2000 [3]. PEG, which is effective not only for disimpaction but also for maintenance therapy, is mainly used as an oral solution [6]. In this study, we attempted to confirm the efficacy and safety of combined oral and enema therapy using PEG 3350 electrolyte solution (PEG 3350 E) for disimpaction in patients who had failed general outpatient disimpaction or had severe acute symptoms. This is the first study evaluating the efficacy and safety of combined oral and enema therapy using PEG 3350 E for disimpaction in functional constipation in pediatric patients.

MATERIALS AND METHODS

This study was performed between 2008 and 2016 at Konkuk University Medical Center and included 28 children having functional constipation who received inpatient treatment with combined oral and enema therapy using PEG 3350 E for disimpaction. We performed retrospective chart reviews including the patients' demographic information such as age, sex, and weight and clinical information such as accompanied symptoms, duration of constipation, and previous treatment. Management and results during admission were also reviewed. Verbal informed consent were obtained from patients when starting treatment. And this study got exemption from Institutional Review Board of Konkuk University Medical Center (IRB no. KUH1090056). Diagnostic criteria for constipation were based on Rome III criteria [8,9]. Organic causes of constipation such as Hirschsprung's disease, thyroid disease, and electrolyte abnormalities were ruled out after interviewing patients, performing a physical examination including a digital rectal examination, laboratory tests on blood and urine, a plain abdominal X-ray, and a colon transit time (CTT) test.

A digital rectal examination was performed at the first visit to check for fecal impaction, and a plain abdominal X-ray examination revealed presence of stool completely filling the rectum and colon. Among the 28 patients we studied, 20 patients failed disimpaction attempts in the outpatient clinic. In the outpatient setting, we used lactulose (n=1, Duphalac Syrup®; JW Pharmaceuticals, Seoul, Korea), lactulose+bisacodyl (n=4, Dulcolax®; Boehringer Ingelheim, Ingelheim am Rhein, Germany), PEG 4000 without electrolytes (n=1, Forlax®; Beaufour Ipsen, Paris, France), PEG 4000 without electrolytes+ bisacodyl (n=14, 9 of 14 patients did not show relief of symptoms with lactulose). We did not attempt disimpaction in eight patients on an outpatient basis because they complained of severe abdominal pain and/or were at risk of dehydration because of sustained vomiting, and rapid relief of symptoms was a priority in them. One patient had been hospitalized

earlier for constipation and another could defecate only after use of glycerin or finger enema. In 19 patients, hard stool could be palpated by performing a digital rectal examination, although in nine patients, digital rectal examination did not reveal this finding. We noted 6 of 9 patients in whom stool was not palpable in the rectum had defecated the day prior (Table 1).

Disimpaction was performed with combined oral and enema therapy using PEG 3350 E (Colyte®; Taejoon Pharm Co., Ltd., Seoul, Korea). The amount of oral PEG 3350 E administered was 50-70 mL/kg/d (PEG, 3-4.1 g/kg/d) divided into intervals of 1-2 times a day with each dose taken within 3 hours each time. An enema was administered 1-2 times a day with a single dose of 15-25 mL/kg (PEG, 0.975-1.625 g/kg/d).

Disimpaction was considered successful if after treatment the patient passed a diarrheal stool more than three times a day, and if improvement in clinical symptoms was accompanied by improvement noted on abdominal examination, as well as on a plain abdominal radiograph [10]. Depending on the patient's condition, combined oral and enema therapy was administered once or twice a day over 1-3 days. Patients were monitored for the development of adverse effects, and safety of the regimen was checked by observing clinical symptoms and assessment of laboratory blood tests including electrolytes and osmotic pressure, among others.

Some patients underwent a CTT test based on the Metcalf protocol [11], and based on the results obtained, they were divided into two groups; normal transit type if the total number of remaining markers was not more than 35 (42 hours as a CTT), and an abnormal transit type if the remaining markers were $\geq$36 (43 hours) [12]. Abnormal transit type was classified into: 1) outlet obstruction type. 2) slow transit type [13].

For statistical analysis IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) was used. Paired t-test was performed for change of stool frequency during disimpaction process. p-value less than 0.05 was considered as statistically significant.

RESULTS

Of the 28 subjects studied, 20 were male patients and 8 were female patients aged 2-17 (8.9±0.8) years and weighed 13.9-93.2 (33.7±3.6) kg. Mean duration of constipation was 41.6±5.0 months, and five patients showed constipation with encopresis.

Table 1. Demographic and Clinical Characteristics of Patients

Demographic and clinical characteristic	Total (n=28)	Groupfailed disimpaction in outpatient clinic (n=20)	Group with acute severe symptoms (n=8)
Age (y)	8.9±0.8	8.0±0.9	11.3±1.4
Sex (male)	20	14	6
Weight (kg)	33.7±3.6	30.4±4.3	42.0±6.4
Duration of constipation (mo)	41.6±5.0	44.4±6.5	34.5±6.2
Encopresis	5 (17.9)	3 (15.0)	2 (25.0)
Previous treatment			
Lactulose		1 (5.0)	
Lactulose+bisacodyl		4 (20.0)	
PEG		1 (5.0)	
PEG+bisacodyl		4 (70.0)	
Frequency of stools (per week)	2.2±0.3	2.1±0.4	3.2±0.9
Abdominal pain	15 (53.6)	0 (50.0)	5 (62.5)
Stool in rectum on digital rectal examination*	20 (71.4)	17 (85.0)	3 (37.5)

Values are presented as mean±standard error, number only, or number (%).
PEG: polyethylene glycol.
*Six patients who were negatives on the digital rectal examination defecated the day prior.

Frequency of defecation had been 2.2±0.3 per week before initiation of inpatient treatment, and 15 patients complained of abdominal pain.

During the hospital stay, the mean of the number of oral and enema doses of PEG 3350 E was 2.1±0.3 times and 2.9±0.4 times, respectively. The frequency of defecation increased from 2.2±0.3 per week to at least once a day (1.1±0.1 per day) after disimpaction. There was an increase in the frequency of defecation in 26 patients (92.9%), although two patients did not show this effect. The remaining two patients even before the study used to defecate once a day, but now showed remarkable improvement in clinical symptoms and consistency of stool.

The number of patients who complained of abdominal pain was reduced from 15 (53.6%) to 4 (14.3%) after disimpaction, in addition to a reduction in the intensity of pain. Prior to disimpaction plain abdominal radiography revealed that notwithstanding the difference in the degree of severity, all cases demonstrated a dilated rectum filled with a large amount of stool. After disimpaction, the amount of stool was significantly reduced in all cases and dilatation of the rectum was not seen (Table 2).

Patients were divided into two groups, based on those who failed disimpaction on an outpatient basis (n=20) and those who did not receive treatment earlier but complained of acute symptoms (n=8). The number of times oral PEG 3350 E was administered was 2.5±0.4 and 1.4±0.2 and the number of times PEG 3350 E enema was administered was 3.1±0.5 and 2.3±0.4, respectively. The frequency of defecation increased from 2.1±0.4 per week, 2.4±0.7 per week to at least once a day (1.1±0.2 per day [p=0.000], 1.5±0.3 per day [p=0.007]) in both groups. Increase in frequency of stool was 18/20 (90.0%) and 7/8 (87.5%). Patients who complained of abdominal pain decreased from 10/20 (50.0%), 5/8 (62.5%) to 4/20 (20.0%), 0 (0%). It means that not only for patient who need rapid symptom relief but also for severely constipated patient who failed disimpaction attempt in outpatient clinic, oral and enema combined therapy using PEG 3350 E is effective.

Some patients who were administered PEG 3350 E for disimpaction showed mild adverse effects. Electrolytes and osmolality were evaluated in 16/28 patients prior to and after disimpaction, and no abnormalities were detected. Watery diarrhea occurred in two patients a few times a day, but reducing or stopping administration of the PEG 3350 E reversed these symptoms. In three patients, the PEG 3350 E could not be administered orally because they developed vomiting owing to disagreeable taste of PEG 3350 E, and had to be administered via a nasogastric

Table 2. Results of Oral and Enema Combination Therapy Using PEG 3350 with Electrolyte

	Total (n=28)	Group failed disimpaction in outpatient clinic (n=20)	Group with acute Severe symptom (n=8)
Frequency of PEG administration (oral)	2.1±0.3	2.5±0.4	1.4±0.2
Frequency of PEG administration (enema)	2.9±0.4	3.1±0.5	2.3±0.4
Stool frequency			
Before PEG administration (/wk)	2.2±0.3	2.1±0.4*	2.4±0.7†
After PEG administration (/d)	1.1±0.1	1.1±0.2*	1.5±0.3†
Subjects whose stool frequency was increased	26 (92.9)	18 (90.0)	7 (87.5)
Abdominal pain			
Before PEG administration	15 (53.6)	10 (50.0)	5 (62.5)
After PEG administration	4 (14.3)	4 (20.0)	0
Fecal impaction on plain abdominal radiography			
Before PEG administration	28 (100.0)	20 (100.0)	8 (100.0)
After PEG administration	0	0	0

Values are presented as mean±standard error or number (%).
PEG: polyethylene glycol.
*,† Increase in stool frequency after disimpaction was statistically significant in both groups (p-value=0.000 and 0.007 by paired t-test).

tube. Additionally, one patient complained of mild dizziness, but without any abnormalities noted on physical examination and laboratory tests.

Prior to hospitalization, we performed a CTT test in 9 of 28 patients and found that 5 of 9 patients (55.6%) showed 36 (43 hours) or more markers remaining in the gut and were therefore classified as the group showing an abnormal transit time. Among patients belonging to the abnormal transit time group, two patients showed outlet obstruction and three showed a slow transit type of pattern. One patient revealed a total of 35 markers left in the gut, a value indicating the upper limit of normal. We found 4 patients belonged to the normal transit type group who demonstrated a total marker count of 35 (42 hours) or lesser.

DISCUSSION

This is the first study investigating the role of combined oral and enema therapy using PEG 3350 E for disimpaction in functional constipation in pediatric patients. We evaluated the efficacy and safety of combined oral and enema therapy using PEG 3350 E in patients who failed to disimpact in an outpatient clinic, or other patients who needed urgent disimpaction having presented with severe acute gastrointestinal symptoms. We found this therapy is effective and safe.

Treatment of constipation comprises three steps: fecal disimpaction, maintenance, and a period of tapering of the drug dose [14]. Fecal impaction occurs in 30-75% of patients with functional constipation and disimpaction is the essential first step in its management [5,6]. Agents commonly used for fecal disimpaction in an outpatient setting are oral solutions such as mineral oil, lactulose/sorbitol/lactitol, magnesium hydroxide, and PEG 4000/3350 without electrolytes, and enema solutions such as bisacodyl, normal saline, and glycerin.

Fecal disimpaction can be achieved via the oral route or as an enema. Enemas can be a frightening and painful experience for children compared to oral therapy, and may reduce treatment compliance. However, an advantage with the use of enemas is that the medication acts directly on the rectum and distal colon, and because of immediate action can rapidly alleviate symptoms such as severe vomiting, abdominal pain, and the like. Although oral therapy achieves better compliance compared to enemas, it requires 1-2 days to work and is not suitable for rapid symptom control. Additionally, during the period of fecal disimpaction, the possibility of stool leakage in the presence of hard stools is higher than it is with the administration of an enema [5,15]. Although similar effects were noted with administration of oral therapy using PEG without electrolyte solution and enema using drugs other than PEG [5], combination therapy can be considered a better approach with individual therapies complementing each other regardless of their advantages and disadvantages. We analyzed combined oral and enema therapy using PEG 3350 E and found the success rate of fecal disimpaction, based on the frequency of defecation was 92.8% (p=0.000). Although PEG 3350 E is not widely used for enema therapy currently, our experience and the results obtained in this study show that PEG 3350 E is effective in enema therapy. We reckon a comparative study using other enema solutions is necessary.

PEG, which has been used for bowel cleansing prior to endoscopy and treatment of adult constipation, has been tried for treatment of pediatric constipation since 2000. Currently, it is widely used as one of the most effective agents for fecal disimpaction in pediatric constipation [16]. PEG, a neutral and biologically inactive water-soluble polymer, acts as an osmotic laxative that interacts with molecules of intestinal contents, increases the fecal water content and stimulates a bowel movement. PEG does not draw water from the body, but from orally ingested contents. Because it is biologically inactive and not acted upon by bacteria, adverse effects such as flatulence, abdominal discomfort and the like associated with its use, are significantly lower than observed with other laxatives [6]. Additionally, as a neutral substance it does not cause any electrolyte migration [17].

Generally, the amount of PEG used for fecal dis-

impaction in outpatient clinics is 1-1.5 g/kg/d for up to 6 days as oral preparations [6,18]. Based on our experience with treating pediatric constipation for 20 years, the dose and duration of medications administered for treatment of constipation do not depend upon the weight of the child but on the associated clinical conditions (underlying disease, number of bowel movements for a month, concomitant encopresis, type of CTT test, and the like). For disimpaction, we used a combination of oral solution (lactulose or PEG 4000 without electrolytes) for 5-7 days and enema solution (glycerin or bisacodyl) for 3-5 days in an outpatient setting. Inpatient treatment was advised for cases in which disimpaction failed on an outpatient basis [10]. In this study, disimpaction attempts failed in 20 of 28 patients on an outpatient basis (15 of 20 patients were administered PEG 4000 without electrolytes), and the remaining 8 patients needed rapid symptom relief. The dose of PEG 3350 E used during hospitalization was 3-4.1 g/kg/d as an oral solution, and 0.975-1.625 g/kg/d as an enema solution, with a total dose of 3.975-5.725 g/kg/d. This dose is higher than is generally used for disimpaction in outpatient settings. Following administration of this dose, we succeeded in achieving disimpaction as noted by better stool frequency and symptom reversal in all children who had failed disimpaction with a general dose of PEG 4000 without electrolytes in outpatient clinics. Injecting a large amount of PEG 3350 E through anus made sufficient hydration effect, as a result, made stools more soft. Because PEG 3350 E acted on the upper and lower parts of large intestine simultaneously, the fecaloma was removed more effectively.

PEG is used in two forms—a solution with and without electrolytes. The widespread use of the former was owing to its beneficial effect of preventing electrolyte imbalance, therefore more effective than PEG without electrolytes. In a study comparing the efficacy of PEG with and without electrolytes [19,20], it was found that there was no significant difference between the two solutions with respect to treatment of pediatric constipation. Additionally, a solution with electrolytes is not very palatable, particularly in the pediatric population, thereby reducing patient compliance. Thus, recently, PEG without electrolytes is being preferred. However, stability of the solution has not been established with use of high doses of PEG than generally used in outpatient clinics. Therefore, considering the likelihood of electrolyte abnormalities among other issues, we used PEG 3350 E and evaluated its safety and adverse effect profile.

Based on our previous study with respect to the adverse effects and safety of PEG 4000 without electrolytes, we found that although there were some mild adverse effects noted, no major adverse effects were reported [21]. Pashankar et al. [22], evaluated the stability of PEG without electrolytes in 83 constipated children, and observed watery diarrhea (10%), abdominal pain (6%), abdominal discomfort (2%), and nausea (1%) in the study subjects. However, reducing the amount of medicine administered did improve symptoms. Laboratory tests showed temporary elevation in alanine aminotransferase in some patients, although hemoglobin, hematocrit, electrolytes, osmolality, albumin, blood urea nitrogen, and creatinine were normal. In this study, there was no clinically significant adverse effect observed using large amounts of PEG 3350 E. In 16 patients, electrolytes and osmolality were measured before and after treatment, and a significant change in electrolytes was not found. One patient developed transient dizziness but without any abnormalities detected on physical examination and laboratory tests, and two patients complained of watery diarrhea, which improved with dose reduction. The medication could not be administered in three patients who developed vomiting owing to its disagreeable taste. In these patients, it was administered via a nasogastric tube. Other adverse effects, viz., convulsions, respiratory insufficiency, blurring/alterations in consciousness were not found. We can deduce from this study that although a small number of subjects was studied, short-term treatment with high doses of PEG 3350 E does not seem to be associated with any significant adverse effects, although more studies need to be performed

on a larger study group to obtain conclusive evidence.

Based on results of CTT tests, patients can be classified into three groups, and an individualized treatment plan can be established for each type [13]. In our previous study, we performed a CTT test on 154 children who were diagnosed as having constipation without encopresis based on Rome III criteria. Subjects were classified as: 1) Normal transit group (55%). 2) Outlet obstruction group (11.7%). 3) Slow transit group (33.8%) [12]. In this study, 9 of 20 children treated on an outpatient basis in whom disimpaction failed, underwent a CTT test, and six of them (66.7%) were classified as showing results in a range at the upper limit of normal (n=1) or abnormal group (n=5). Although the number of subjects studied was small, the proportion of patients belonging to the abnormal group was higher than that in previous studies. We reckon this was due to patients who failed disimpaction with the usual method employed on an outpatient basis, as they were more severely constipated. These results are in agreement with those obtained from our previous study demonstrating that the severity of constipation is related to CTT test results.

Prior to disimpaction, digital rectal examination, abdominal physical examination, plain abdominal radiography and CTT test were performed to diagnose constipation and check for fecal impaction. Although clinical usefulness of digital rectal examination is not clear until now [23], it is effective method to diagnose the fecal impaction, check the stool consistency and rule out the organic causes of constipation [5] and Rome III criteria for functional constipation also include a large fecal mass in the rectum [8,9]. So if it is accepted in cultural awareness, digital rectal examination for evaluating constipation can be considered. We perform digital rectal examination once at first visit.

The limitations of this study are that the number of subjects studied was small (28 patients) and only 16 underwent biochemical evaluation; thus, the study could not determine stability of the administered medication. Additionally, performing CTT test in only nine patients is not sufficient to provide definitive evidence of the link between constipation and CTT test.

In terms of therapeutic effect and safety, combined oral and enema therapy using high doses of PEG 3350 E is considered superior to conventional oral monotherapy or combined oral and enema therapy in an outpatient setting. We propose that research involving a larger sample size is necessary in the future.

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