Efficacy of polyethylene glycol 4000 on constipation of posttraumatic bedridden patients

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Abstract

Objective: To investigate the efficacy and safety of polyethylene glycol 4000 (Forlax®) on adult patients with functional constipation due to posttraumatic confinement to bed.

Methods: A total of 201 posttraumatic bedridden patients were studied in this prospective, open-labeled, single-group study. Polyethylene glycol 4000 was administered orally for 14 days and the dosage was adjusted according to the Bristol stool types. Demographic characteristics, disease status, treatment period and factors affecting clinical outcome, especially the concomitant medications, were recorded.

Results: After administration of polyethylene glycol 4000, 194 cases (96.52%) showed remission of constipation, including 153 (76.12%) persistent remission. The average defecation frequency increased significantly after treatment and the percentage of patients with stools of normal types (Bristol types 3-5) increased as well. Genders, ages and concomitant medications showed no significant influence on the persistent remission rate. After consecutive treatment for two weeks, patients with slight movement showed a significantly higher remission rate than those without movement (95% vs 80%). At the end of treatment, most accompanying symptoms were relieved obviously. Patients with a medical history of constipation or ever taking laxatives showed a lower remission rate. Sixty cases (29.85%) developed diarrhea during the observational period, among whom 6 (10%) withdrew from the clinical observation voluntarily at the first onset of diarrhea. Two cases suffered from abdominal pain.

Conclusions: Polyethylene glycol 4000 (Forlax®) has efficacy on functional constipation in posttraumatic bedridden patients. Furthermore, patients with milder symptoms, more movement in bed, and longer duration of treatment but without accompanying symptoms can achieve a higher remission rate.

Key words: Polyethylene glycols; Wounds and injuries; Bed rest; Constipation; Therapeutics

Constipation is one of the most common chronic gastrointestinal problems. The estimated incidence of constipation in the United States is 3% to 19% in general population. Patients with head injuries, spinal cord injuries, pelvic fractures, lower extremity fractures or multiple traumas require a long-term bed rest, during which the incidence of constipation reached as high as 50%. Constipation always brings inconvenience and tremendous suffering to patients and strongly influences the recovery from primary disease.

Irritants or lubricants can relieve the symptoms, but long-term application of them may lead to side effects like melanosi coli and cathartic colon. The absorption of fat soluble vitamins is also affected. Polyethylene glycol 4000 (trade name: Forlax®), a long chain polymer with a high molecular weight, can conjugate with water molecule through hydrogen bond to increase the water content and volume of stools, thereby, facilitate bowel movement and defecation. It is neither absorbed nor metabolized in the digestive tract, hence it is highly safe and well tolerable. Thus, long-term medication of polyethylene glycol 4000 is conducive to the reconstruction of normal defecation pattern. Therefore, polyethylene glycol 4000 is now being widely used as the mainstay adult chronic functional constipation management. The aim of this study was to verify the efficacy and safety of polyethylene glycol 4000 on adult functional constipation of posttraumatic bedridden patients.
METHODS

Patients
A total of 201 posttraumatic patients in bed rest admitted to the Department of Traumatic Surgery, Research Institute of Surgery, Daping Hospital, Third Military Medical University between May 2007 and September 2008, who received the treatment of polyethylene glycol 4000, were included in this prospective, open-labeled, single-group, single-center study. There were 143 males (71.14%) and 58 females (28.86%), aged 18-75 years including 141 younger than 50 years, mean 43.29 years. Among them, 24 (11.94%) had a history of constipation and 9 (4.48%) had ever received laxatives for treating constipation. Of the 201 posttraumatic bedridden patients, 104 had lower extremity fractures, 55 spinal fractures (including 4 with paraplegia), 13 pelvic fractures and 29 chest or head injuries. Among the 104 patients with lower extremity fractures, 100 had received internal or external fixation surgeries and 4 had taken plaster external fixation. Totally, there were 140 cases (69.65%) unable to move voluntarily, 61 (30.35%) able to move slightly on their beds, and 123 (61.19%) having taken drugs likely to cause constipation during the bedridden period. During one week before treatment, 98 patients (48.76%) had one defecation, 63 (31.34%) twice, 22 (10.95%) three times and 18 (8.96%) more than three times. Stools of all patients were classified into Bristol types 1-4 and the patients’ number of each type was 91 (45.27%), 53 (26.37%), 40 (19.90%) and 17 (8.46%).

Inclusion and exclusion criteria
Written informed consents of patients were obtained and documented before their participation in the trial. Patients were included in this trial according to the following criteria: (1) age between 18 and 75 years irrespective of genders; (2) being bedridden and unable to defecate on bedside or toilet for more than 1 week; (3) having returned to a normal diet for at least 5 days; (4) with an expected bedridden duration more than 2 weeks; and (5) having presented with at least one of the symptoms for more than 3 days (hard and lumpy stools in Bristol types 1-2, hand-assisted defecation, no defecation in consecutive 3 days or less than 3 times of defecation in the past week).

Patients were excluded from this trial if they met any of the following criteria: (1) nothing by mouth (NPO) patients; (2) with dysphagia, severe hepatic or renal dysfunctions; (3) having abdominal surgeries in recent 6 months; (4) allergic to polyethylene glycol 4000; (5) with organic intestinal diseases such as colorectal tumor, inflammatory bowel disease, polyposis, diverticulum, hypogenesis or malformation identified by history of present illness, physical examination or other examinations; and (6) taking other laxatives.

Drug and dosage
Polyethylene glycol 4000 (Forlax®; 10 g/sachet) manufactured by Beaufour Ipsen Industrie (Dreux, France) was given orally for 14 consecutive days and the dosage was adjusted according to the Bristol stool classification as follows: (1) Bristol types 1-2, 20 g for 4 times a day; (2) Bristol types 3-5, 10 g for 4 times a day; (3) Bristol types 6-7, discontinuation of treatment for 24 hours; and (4) those with no defecations in the past 24 hours, continuation of treatment with the same dosage as the previous day.

Endpoints of the treatment were: (1) completion of the 14-day treatment, or (2) more than 3 times of defecation per day for consecutive 2 days or stools of Bristol types 6-7.

Outcome assessment
Recruitment and completion status, demographic data, disease conditions, treatment duration, achievement of the endpoint or not, and slight movement in bed or not were all documented. Concomitant medications were also recorded accurately, especially those likely to cause constipation, such as opioid analgesics, antipsychotic drugs, anticonvulsants, calcium channel blockers, anticholinergics, dopamine analogues and bile salts binders.

There are three main indexes in this study to evaluate the therapeutic effects of polyethylene glycol 4000. (1) Constipation remission, which was described by the remission and persistent remission rate, remission duration, time of the first remission, and restoration of normal defecation pattern. The proportion of patients achieved constipation remission for more than 3 days with 1-2 times of defecation/day and stools of Bristol types 3-5 was recorded. The persistent remission rates of patients with stools of Bristol types 1-2, less than 3 times of defecation/week before treatment and hand-assisted defecation at the first day of treatment were calculated. We compared the persistent remission rates
among patients with different ages, genders, concomitant medications and accompanying symptoms at different time points. (2) Accompanying symptoms, which were described by incidence of accompanying symptoms at the beginning of treatment and the end of the first or second weeks. And (3) adverse effects such as diarrhea and abdominal pain. The conditions of diarrhea were also described, including the onset of diarrhea, withdrawal from the observation due to diarrhea, and diarrhea when withdrawing from the study. Persistent Remission was defined as 1-2 times of defecation per day with Bristol type $\geq 3$ in 3 consecutive days during the 14-day treatment period.

**Statistical analysis**

All subjects were included in a full analysis set (FAS). Descriptions of the numerical variables included sample size, mean, standard deviation, median, maximum and minimum values. And descriptions of categorical variables included the number and percentage of cases falling into various categories. The statistical analysis was bilateral and data were recognized statistically significant when $P<0.05$. By means of cochrane-Mantel-Haenszel (CMH) test, comparison was performed on the persistent remission rates of different genders. The same method was also used to compare the persistent remission rates of patients with different ages, Bristol types before medication, history of constipation and laxative medications, concomitant medications and accompanying symptoms respectively, also the efficacy of polyethylene glycol 4000 and medication for subsequent treatment.

**RESULTS**

**Efficacy**

Totally, 171 cases (85.07%) finally reached the treatment endpoint, among whom 127 (63.18%) received the polyethylene glycol 4000 treatment for 14 days and the rest (44 cases) had more than 3 times of defecation in 2 consecutive days or with stools of Bristol types 6-7. The other 30 cases (14.93%) failed to reach the treatment endpoint due to various reasons. The mean duration of polyethylene glycol 4000 therapy was (11.81 ±3.26) days. In this clinical observation, 35 patients withdrew in the first week and 39 in the second week.

After the administration of polyethylene glycol 4000, 194 patients (96.52%) showed a constipation remission. The first remission occurred (3.65±2.22) days after treatment and 153 cases (76.12%) achieved a persistent remission. Patients with less than 3 times of defecation in one week before treatment had a remission rate of 74.86%. Patients with Bristol stool types 1-2 and hand-assisted defecation showed a remission rate of 72.92% and 100%, respectively. Seventy-five cases (37.31%) restored a normal defecation pattern after discontinuation of the drug. Only 7 cases (3.48%) showed no improvement at all. The bowel movements increased significantly after treatment (Figure 1). The percentage for patients with stools of Bristol types 1-2 decreased significantly, while that for patients with stools of Bristol types 3-5 increased (Figure 2). The persistent remission rate was 45.71% for patients taking medications for less than one week, and 85.04% for those taking medications for 2 weeks. Genders ($\chi^2=0.46$, $P=0.4992$), ages ($\chi^2=0.93$, $P=0.3341$) and concomitant medications ($\chi^2=0.22$, $P=0.6411$) showed no considerable impact on the persistent remission rate. After two weeks of consecutive treatment, the remission rate was 95.00% for patients who could move slightly on the bed, and 80.46% for those unable to move (Table 1). The remission rate was 78.95% for patients who had reached the treatment endpoint, while 60.00% for those failed ($\chi^2=5.04$, $P=0.0248$, Table 2).

**Concomitant symptoms of constipation**

In this study, 36 cases (17.91%) had accompanying symptoms before treatment, including 22 (10.95%) with abdominal pain, 13 (6.47%) with difficult defecation, 6 (2.99%) with anorexia and 1 (0.50%) with hand-assisted defecation. At the end of treatment, most symptoms were relieved significantly, with a 100% remission rate in patients with difficult defecation or anorexia. But the hand-assisted defecation and abdominal pain in 3 cases (1.49%) remained.

**Adverse effects**

Totally, 60 patients (29.85%) developed diarrhea, among whom 6 (10%) withdrew from the clinical observation at the first onset of diarrhea, and 43 (71.67%) stayed until the end. Only 2 cases complained of abdominal pain during the treatment, one relieved spontaneously and the other relieved after drug discontinuation.
DISCUSSION

Pathogenesis of constipation of posttraumatic bedridden patients

Of the 201 patients in our study, the number of male patients was more than that of female patients and the mean age was less than 50 years, for trauma frequently happens to young adults, which is significantly different from the demographic characteristics of population with chronic constipation. Besides, patients with a history of constipation only accounted for 11.94%, and most of them developed constipation after confinement to bed. Mostafa has reported an incidence of constipation as high as 83% in 48 cases of critically ill patients with a normal diet, which also demonstrates that confinement to bed is an important factor for the development of constipation. Causes of confinement to bed after trauma in this study included lower extremity fractures (51.74%), spinal cord fractures (27.63%), pelvic fractures (6.47%) and so on. Other possible mechanisms of constipation in such cases were listed as follows: (1) inappropriate dietary habits, malabsorption resulting from blood loss and pain during posttraumatic period, or dehydration caused by decreased fiber intake and inadequate water intake; (2) psychological problems or psychiatric disorders such as anxiety and depression as a result of incapacitated self-care and defecation in need of others’ help especially; (3) changes of the living environment or being unaccustomed to defecating in bed in a lying position; (4) application of medications that may cause constipation; and (5) decreased activity due to absolute bedridden status. As a result of trauma and surgery, 69.65% cases in the study were unable to move voluntarily and 30.35% could only move slightly on the bed. In this study, 61.19% of the cases took drugs possibly causing constipation, such as proton pump inhibitor (PPI), calcium channel blocker, antibiotics, especially analgesics which can suppress bowel movements and was significantly associated with constipation.

Treatment of constipation of posttraumatic bedridden patients

The treatment of constipation should aim at curing the primary disease and adjusting patients’ dietary structure and life habits. Appropriate medications should be considered to relieve constipation symptoms guided by the principle that only drugs with minimum toxicity, side effects and drug dependence, such as leavening agents...
and osmotic laxatives could be chosen. For patients with fecal impaction, symptoms should be first relieved by cleaning enema, or short-term administration of irritants before the application of leaving agents or osmotic laxatives. For those with constipations caused by long-term bedridden status, stimulants or lubricants could be used to relieve the short-term symptoms. However, constipation may relapse due to persistent existence of inducing factors. Repeated use may weaken the effectiveness of the above laxatives and result in anorectal burning. The use of irritants may cause abdominal cramp; a long-term use may lead to melanosis coli and cathartic colon and affect the absorption of fat soluble vitamins. In some severe cases, water and electrolyte disorders may be arisen, thereby affecting the recovery of patients. Therefore, the first-line treatments for constipation of bedridden patients should be osmotic and bulk forming laxatives, with the treatment goal set as one or two times of defecation per day.

Polyethylene glycol 4000 (Forlax®), a long chain polymer with a high molecular weight, can conjugate with water molecule through hydrogen bond to increase the water content and volume of stools, thereby, facilitate bowel movement and defecation. It is neither absorbed nor metabolized in the digestive tract, hence it is highly safe and well tolerable. Thus, the long-term medication is conducive to reconstruct the normal defecation pattern of patients, and has now been widely used for adult chronic functional constipation. It has been reported to be more effective than lactulose and safer than Tegaserod.

Of the 201 patients treated with polyethylene glycol 4000, 194 (94.52%) showed remission of constipation, in whom 153 (76.12%) showed persistent remission and 75 (37.31%) restored their normal defecation pattern with standard treatment, indicating the efficacy of polyethylene glycol 4000 (Forlax®) on such constipation patients. Meanwhile, 91 cases who had accompanying symptoms such as abdominal pain, difficult defecation, feeling of incomplete evacuation and anorexia showed a significant relief at the end of treatment. The genders, ages, concomitant medications and types of trauma showed no significant influence on the persistent remission rate. Factors that influenced the therapeutic effects included severity of constipation, duration of treatment, situation of accompanying symptoms, history of constipation and ability of slight movement in bed.

Patients with milder constipation showed a higher remission rate. Remission rates for those with less than three times of defecation per week or stools of Bristol types 1-2 before treatment were 74.86% and 72.92% respectively, which were significantly lower than the total remission rate of this group (76.12%). The persistent remission rate of patients with Bristol types 1-2 after the 2-week treatment was 81.18%, lower than that of those with Bristol types 3-5 (92.86%). The persistent remission rate increased with the prolongation of treatment. The remission rate was 85% for patients completing the 2-week treatment, while 78.95% for those reached the treatment endpoint, as polyethylene glycol 4000 is an osmotic laxative and needs a long-term administration to keep the normal bowel movement. Patients without accompanying symptoms had a higher remission rate. Patients with a history of constipation and laxative medication had a poorer remission rate. Patients who could move slightly in bed showed a remission rate as high as 95% at the end of the second week, indicating that an appropriate movement in bed should be advocated.

Adverse drug reactions of polyethylene glycol 4000 include abdominal distension, abdominal pain, diarrhea and nausea. During the treatment with polyethylene glycol 4000, 60 cases (29.85%) developed diarrhea associated with drug administration at different dosages. This indicates that it is necessary to adjust the dosage promptly and individually according to different responses to drugs in order to ensure the overall efficacy of the drug. Only 2 patients complained of an abdominal pain, which was resolved spontaneously or after discontinuation of treatment. No allergic reaction was reported in this trial, consistent with other studies. Our study shows the excellent safety of polyethylene glycol 4000 among posttraumatic bedridden patients.

REFERENCES


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