

Original Research Article

Tolerance and Efficacy of Polyethylene Glycol 4000 in Elderly Patients with Chronic Constipation: A Retrospective, Single-center, Observational Study

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Abstract

Objectives: This retrospective, observational study aimed to evaluate the tolerance and efficacy of polyethylene glycol 4000 plus electrolytes (PEG 4000) in elderly patients with chronic constipation.

Methods: PEG 4000 powder was orally administered once daily at a dose of one or two 6.9 g sachets as the initial dose. The outcome measures were changes in the Cleveland Clinic Constipation Score (CCCS) and the Bristol Stool Form Scale (BSFS) value before and 2 weeks after drug administration.

Results: This study included 324 patients aged ≥ 65 years (mean age: 78.6 ± 7.6 years, range: 65-100 years) with chronic constipation. The total CCCS was noted to significantly improve from 11.5 ± 4.6 at baseline to 7.4 ± 5.2 after drug administration. All CCCS sub-scores also improved significantly. The average BSFS value at baseline (2.5 ± 1.6) significantly improved to 4.3 ± 1.1 after treatment. Side effects (16 events) were observed in 13 patients (4.0%), with the most common being diarrhea (6 patients, 1.9%). All events were mild in severity, with none of the symptoms being serious. The cumulative treatment continuation rate at 1 year was 83.1%.

Conclusions: PEG 4000 treatment was safe, effective, and well tolerated in elderly patients with chronic constipation. Thus, it appears to be a promising drug that can be continued for a long time.

Keywords

chronic constipation, polyethylene glycol, laxatives, elderly, evacuation difficulty

J Anus Rectum Colon 2021; 5(3): 291-296

Introduction

Chronic constipation (CC) is a common disorder characterized by unsatisfactory defecation due to infrequent bowel movements and/or difficulty in defecation[1]. Non-pharmacological measures (i.e., dietary fiber intake, correction of underlying causes, and lifestyle changes) have been proposed as the primary treatment for CC, and the next step in expanding the treatment options is the addition of osmotic laxatives such as lactulose, magnesium salts, and polyethylene glycols (PEGs)[2]. Among these, magnesium

oxide (MgO) has been frequently used in Japan since the 1980s[3]. MgO has been identified to have adsorptive and antacid effects and may affect the activity, absorption, and excretion of other drugs. Thus, it should be administered with caution in patients with polypharmacy[4]. Although MgO is minimally absorbed in the intestinal tract, it can lead to hypermagnesemia in the elderly and patients with impaired renal function. Therefore, the serum magnesium level needs to be measured regularly in such populations[1,4]. Given that the treatment of CC will be potentially necessary over a long period among the elderly, laxatives

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Received: January 5, 2021, Accepted: April 6, 2021

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must be safe and well tolerated.

PEGs are high-molecular-weight, water-soluble polymers that can form hydrogen bonds, and the resulting colon hydration favors colon transit in a dose-dependent manner[5]. Since PEGs are non-adsorptive and not absorbed from the gastrointestinal tract, they can be taken at any time without precautions for concomitant use of other medications[6]. In Europe and the United States, the use of PEGs as first-line pharmacological treatment for CC is recommended in both children and adults[2,7]. Furthermore, a cost-effectiveness analysis showed that PEGs, as first-line therapy, may reduce the overall costs in the management of patients with CC[8].

PEG 4000 was the first PEG preparation indicated for the treatment of CC in Japan; this was first introduced in 2018. In a placebo-controlled double-blind clinical trial among adults in Japan, the PEG-treated group demonstrated a significant increase in spontaneous bowel movement frequency compared to that in the placebo group[9]. In the subsequent 52-week consecutive administration period, spontaneous bowel movement frequency was maintained in most cases[9]. However, the mean age of the study population was 44 years, indicating insufficient clinical outcomes in elderly patients. Therefore, we examined the efficacy and safety of PEG 4000 in patients aged ≥ 65 years with CC.

Methods

1. Study design

This retrospective, observational cohort study was based on the medical records of patients who were referred to our hospital for refractory constipation. All procedures in this study were approved by the institutional review board of our hospital (approval code, K18-003), and written informed consent to use the medical records was obtained from all patients.

2. Study participants

This study included patients aged ≥ 65 years with CC who started treatment with PEG 4000 between November 2018 and April 2020. Patients were excluded if intestinal obstruction was suspected or confirmed or anal stricture was detected by proctologic examination. Before the treatment, a questionnaire regarding various CC symptoms and Cleveland Clinic Constipation Score (CCCS)[10] was administered to all patients. In addition, the patients were instructed to select the predominant stool form from the Bristol Stool Form Scale (BSFS) diagram[11]. However, some of the questionnaires were not administered to those with dementia or stoma.

3. Method of drug administration

PEG 4000 powder (macrogol 4000 plus electrolytes, EA

Pharma Co., Ltd., Tokyo, Japan) was orally administered once daily at a dose of one or two 6.9 g sachets as the initial dose. One sachet was dissolved in 60 mL of water immediately before administration. The treatment dose was increased or decreased depending on symptoms. The maximum daily dose was six sachets (up to four sachets at once). Any drugs that the participants were already taking for the treatment of constipation were allowed during the study period.

4. Main outcome measures

The CCCS and BSFS values at baseline and 2 weeks after drug administration were compared. The safety endpoints were side effects, including their incidence and rate of discontinuation.

5. Statistical analysis

The Wilcoxon signed-rank test was used to comparatively analyze the CCCS and BSFS values. The results are presented as the mean \pm SD values. The two-sided significance level was set at 5%. The cumulative treatment continuation rate was then assessed using the Kaplan-Meier method. All statistical analyses were performed using EZR software version 1.11 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

1. Patient demographics

During the study period, PEG 4000 was administered to 540 patients, of whom 364 (67.4%) were aged ≥ 65 years. Of these, 324 who visited the outpatient clinic at least once after drug administration were included in this study. The characteristics of the study population are shown in Table 1. The mean patient age was 78.6 ± 7.6 years (range: 65-100 years). The pretreatment for constipation included MgO (124 cases), stimulant laxatives (99), enemas or suppositories (64), elobixibat (39), lubiprostone (28), linaclotide (19), and others (overlapping).

2. Changes from the baseline in the CCCS and BSFS value

The CCCS was analyzed in 271 patients who completed the questionnaires. The total CCCS of 11.5 ± 4.6 at baseline significantly improved to 7.4 ± 5.2 , which is 2 weeks after drug administration. All CCCS sub-scores were also observed to improve significantly (Table 2). As for the duration of constipation, no test was conducted since the treatment period was 2 weeks.

Figure 1 shows the histogram of BSFS values before and 2 weeks after drug administration. Values of 1 and 2 indicate that hard stool markedly decreased, and values of 4 and

Table 1. Patients' Baseline Characteristics (n = 324).

Parameter	Classification	Number of patients (%)
Sex	Men	144 (39.6)
	Women	180 (60.4)
Age	65–74 yrs.	109 (33.6)
	≥75 yrs.	215 (66.4)
Stool frequency	≥3 times/week	136 (42.0)
	≥1 to <3/week	128 (39.5)
	<1 time/week	22 (6.8)
	Unknown	38 (11.7)
Bristol Stool Form Scale	1, 2	177 (54.6)
	3–5	102 (31.5)
	6, 7	16 (4.9)
	Unknown	29 (9.0)
Symptom classification	Infrequent bowel motions	4 (1.2)
	Evacuation difficulty	135 (41.7)
	Mixed type	147 (45.4)
	Unknown	38 (11.7)
Pretreatment for constipation	None	64 (19.8)
	Yes	260 (80.2)
Initial dosage of PEG 4000	One 6.9 g sachet/day	25 (7.7)
	Two 6.9 g sachets/day	299 (92.3)

PEG: polyethylene glycol

Table 2. Changes in the CCCS before and after Drug Administration (n = 271).

	Baseline	After 2 weeks	<i>p</i> -value
Total CCCS	11.5 (4.6)	7.4 (5.2)	<0.001
Frequency of bowel movements	0.9 (1.0)	0.4 (0.7)	<0.001
Difficulty in evacuation	2.7 (1.3)	1.4 (1.6)	<0.001
Feeling incomplete evacuation	2.2 (1.6)	1.5 (1.7)	<0.001
Abdominal pain	0.7 (1.3)	0.5 (1.1)	0.035
Minutes in lavatory per attempt	1.2 (1.0)	1.0 (1.0)	<0.001
Assistance (e.g., laxatives and enemas)	1.5 (0.7)	1.1 (0.7)	<0.001
Unsuccessful attempts for evacuation	0.9 (0.9)	0.5 (0.7)	0.001
Duration of constipation	1.6 (1.4)	1.5 (1.4)	-

CCCS: Cleveland Clinic Constipation Score

Data are shown mean (SD)

5 indicate that normal stool increased. The average BSFS value of 2.5 ± 1.6 at baseline significantly improved to 4.3 ± 1.1 after a 2-week treatment ($p < 0.001$).

3. Side effects

Treatment side effects (16 events) were noted in 13 patients (4.0%, 1 [0.3%] in men and 12 [3.7%] in women; Table 3). The most common event was diarrhea (n = 6, 1.9%). Of the 13 patients who showed side effects, 9 (2.8%) discontinued the treatment, while three reduced the dosage. All events were mild in severity, with no serious symptoms.

4. Treatment continuation

The mean follow-up duration was 4.1 (range, 1-13)

months. Dose escalation of PEG 4000 was observed in 19 patients (5.9%), while 28 (8.6%) patients reduced the dosage due to side effects or improved symptoms. Six patients (1.9%) discontinued treatment because of the salty taste of PEG 4000. Figure 2 indicates the probability of continuing treatment with PEG 4000. The cumulative continuation rate at 12 months was 83.1% (95% CI: 77.0 to 87.7).

Discussion

Our study has added further insight into osmotic laxative treatment in elderly Japanese patients with CC. Evaluation using the CCCS showed that PEG 4000 improved not only stool frequency but also the overall symptoms of constipa-

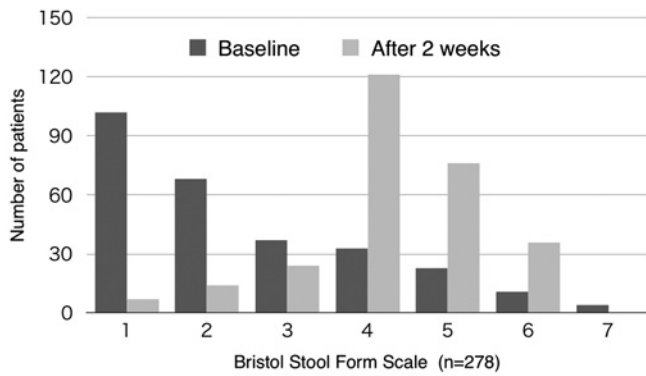


Figure 1. Histogram of Bristol Stool Form Scale values at baseline and 2 weeks after polyethylene glycol 4000 administration. Values of 1 and 2 indicate that hard stool markedly decreased, whereas values of 4 and 5 mean that normal stool increased.

tion without safety concerns.

Regarding the baseline CCCS of our study population, sub-scores for “difficulty in evacuation” and “feeling incomplete evacuation” were particularly high and that of “frequency of bowel movements” was rather low. Furthermore, 20% of the patients used enemas or suppositories before treatment. In patients with these evacuation difficulties or outlet obstruction, oral laxatives are less effective, resulting in the frequent use of suppositories or enemas[1,10]. In addition, the prevalence of evacuation difficulty increases in elderly patients due to a diminished recto-anal sensation and/or reduced abdominal muscle strength[1].

PEGs have been shown to be effective for the prevention and resolution of pediatric fecal impaction[5]. Bekkali et al. reported that PEG and enemas were equally effective in treating fecal impaction in children[12]. PEGs have also been used with promising results in adults with fecal impaction or obstructed defecation[13]. Our results further indicate that PEG 4000 is useful in terms of managing evacuation difficulties in the elderly. PEGs tightly bind water to polymer chains, increase the ratio of free water in bowel contents, and inhibit the dehydration of stool through the whole gastrointestinal tract[6]. As a result, soft stool can reach the rectum, and even patients with evacuation difficulty may be able to defecate easily.

Few studies have investigated the use of PEGs in only elderly patients[14]. Chassagne et al. reported no changes in biochemical and nutrition parameters and no unanticipated side effects due to PEG treatment in patients aged >70 years[15]. Seinela et al. also demonstrated good clinical tolerance of PEG in patients aged ≥65 years[14]. In a study conducted in Japanese patients with a mean age of 44 years, the most frequent side effects due to PEG treatment were diarrhea (3.6%) and abdominal pain (3.6%)[9]. In our study, diarrhea and abdominal pain were observed in 1.9% and

Table 3. Breakdown of Side Effects (n = 324).

Number of patients with side effects	13
Number of side effects	16
Type of side effect	Event (%)
Diarrhea	6 (1.9)
Fecal incontinence	3 (0.9)
Abdominal pain	2 (0.6)
Bloating	2 (0.6)
Nausea	2 (0.6)
Nettle rash	1 (0.3)

0.6% of the patients, respectively. Thus, PEG treatment seems to be safe and well tolerated even in the elderly. However, in our study, three women (0.9%) were reported to develop fecal incontinence after PEG administration. Hence, the risk of fecal incontinence should be explained to the elderly female patients in advance.

The PEG 4000 used in this study contained electrolytes (i.e., sodium chloride and sodium bicarbonate) to maintain the electrolyte balance in the intestinal tract. Such electrolytes lend an unpleasant salty taste to the PEG solution. In our study, 2% of patients discontinued treatment due to salty taste; however, the treatment continuation rate at 1 year was good (83%), suggesting that the taste seems to be acceptable to most elderly patients.

The limitations of this study include its non-randomized, retrospective, open observational design and the lack of analysis of comorbidities and concomitant drugs. Thus, the results should be reconfirmed by conducting further randomized controlled trials. Comparative studies with other osmotic laxatives are also needed.

PEG 4000 is chemically inert, non-absorbable, and cannot be metabolized by colonic bacteria; therefore, elderly patients on polypharmacy can take it without concern about drug interactions[6]. PEG 4000 does not deprive the body of hydration, and the water used for dissolution at the time of administration is completely discharged together with the stool. Therefore, PEG 4000 can be used for patients with limited fluid intake[13].

In conclusion, PEG 4000 treatment was deemed safe, effective, and well tolerated in elderly patients with CC. Thus, it appears to be a promising drug that can be continued for a long time and could be increasingly used as a first-line treatment in elderly patients.

Conflicts of Interest

Tatsuya Abe received lecture fees from Mochida Pharmaceutical Co., Ltd.

Author Contributions

Tatsuya Abe contributed to the concept and design, data

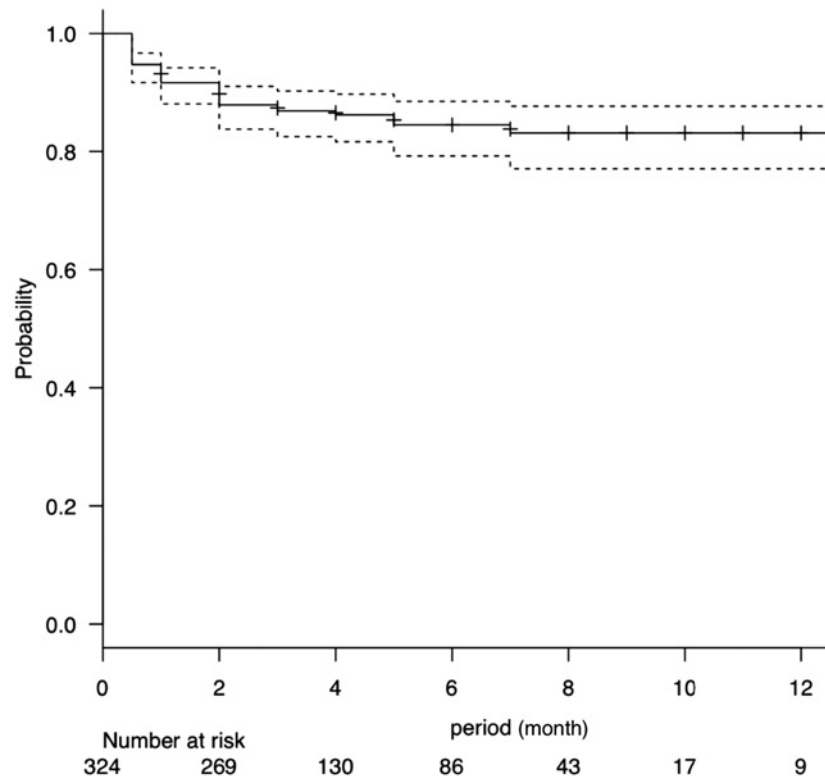


Figure 2. Kaplan-Meier plots indicating the probability of continuing treatment with polyethylene glycol 4000. The cumulative continuation rate at 12 months was 83.1% (95% CI: 77.0 to 87.7).

acquisition, and analysis and also drafted and revised the manuscript. Masao Kunimoto, Yoshikazu Hachiro, Kei Ohara, Mitsuhiro Inagaki, Houhei Hishiyama, and Masanori Murakami contributed to data acquisition and revision of the manuscript, and they also approved the final version.

Approval by Institutional Review Board (IRB)

This research was approved by the institutional review board of Kunimoto Hospital (approval code, K18-003).

References

1. Research Society for the diagnosis and treatment of chronic constipation, the Japanese Society of Gastroenterology. [Evidence-based clinical practice guidelines for chronic constipation 2017 ed.]. Nankodo Co, Ltd. 2017. Japanese.
2. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013 Jan; 144(1): 211-7.
3. Mori S, Tomita T, Fujimura K, et al. A Randomized double-blind placebo-controlled trial on the effect of magnesium oxide in patients with chronic constipation. *J Neurogastroenterol Motil*. 2019 Oct; 25(4): 563-75.
4. Abe T, Hachiro Y, Ohara K, et al. [Current developments in pharmacological therapeutics for chronic constipation]. *J Japan Soc Coloproctol*. 2019 Nov; 72(10): 600-8. Japanese.
5. Minguez M, Lopez Higuera A, Judez J. Use of polyethylene glycol in functional constipation and fecal impaction. *Rev Esp Enferm Dig*. 2016 Dec; 108(12): 790-806.
6. Lyseng-Williamson KA. Macrogol (polyethylene glycol) 4000 without electrolytes in the symptomatic treatment of chronic constipation--a profile of its use. *Drugs Ther Perspect*. 2018 Jul; 34(7): 300-10.
7. National Institute for Health and Care Excellence (NICE). Clinical management of idiopathic constipation in children and young people. Manchester: NICE; 2015.
8. Christie AH, Culbert P, Guest JF. Economic impact of low dose polyethylene glycol 3350 plus electrolytes compared with lactulose in the management of idiopathic constipation in the UK. *Pharmacoeconomics*. 2002 Jan; 20(1): 49-60.
9. Nakajima A, Shinbo K, Oota A, et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation: a 2-week, randomized, double-blind, placebo-controlled study with a 52-week open-label extension. *J Gastroenterol*. 2019 Sep; 54(9): 792-803.
10. Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. *Dis Colon Rectum*. 1996 Jun; 39(6): 681-5.
11. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997 Jan; 32(9): 920-4.
12. Bekkali NLH, van den Berg MM, Dijkgraaf MGW, et al. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics*. 2009 Dec; 124(6): 1108-15.
13. Sgouros SN, Mantides A. Polyethylene glycol in chronic constipation. *Ann Gastroenterol*. 2004 Jun; 17(2): 142-4.
14. Seinela L, Sairanen U, Laine T, et al. Comparison of polyethylene

glycol with and without electrolytes in the treatment of constipation in elderly institutionalized patients. *Drugs Aging*. 2009 Aug; 26(8): 703-13.

15. Chassagne P, Ducrotte P, Garnier P, et al. Tolerance and long-term efficacy of polyethylene glycol 4000 (Forlax[®]) compared to lactulose in elderly patients with chronic constipation. *J Nutr Health Aging*. 2017 Apr; 21(4): 429-39.

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