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【 CASE REPORT 】

Using Polyethylene Glycol 3350 Plus Electrolytes in Constipated Hemodialysis Patients: A Case Series

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Abstract:
Appropriate management of constipation in hemodialysis patients has not been established, although constipation is the most frequent gastrointestinal complication in dialysis patients. We herein report the efficacy and safety of polyethylene glycol in constipated hemodialysis patients assessed prospectively. Seven patients using stimulant laxatives participated in this study. Polyethylene glycol was administered to reduce stimulant laxatives during the six-week intervention period. The amount of stimulant laxatives decreased and spontaneous bowel movements with ideal stool consistency increased significantly after the intervention. No serious adverse effects were observed throughout this study. In conclusion, polyethylene glycol can be a useful tool for managing constipated hemodialysis patients.

Key words: constipation, hemodialysis, polyethylene glycol, stimulant laxative, medication

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Introduction

Gastrointestinal complications, such as constipation, indigestion, abdominal pain and reflux, are prevalent symptoms in patients undergoing hemodialysis (1). Among them, constipation is the most frequent symptom in dialysis patients. It was reported to be more common in hemodialysis patients than in peritoneal dialysis patients (1-3).

The World Gastroenterology Organisation and the American Gastroenterological Association advocate guidelines for medical management of constipation in the general population (4, 5). In these guidelines, the first recommendation is a change of lifestyle (i.e. fluid intake, physical activity and fiber supplementation). The next step for treatment of chronic constipation is adding osmotic laxatives [i.e., polyethylene glycol (PEG), lactulose, magnesium]. Stimulant laxatives are recommended to be taken as rescue agents. Although there is little evidence regarding the efficacy and safety of long-term use of stimulant laxatives (6-8), Japanese constipation guidelines denote that long-term continuous use of stimulant laxatives may cause physical tolerance and psychological dependence. Therefore, clinical practice guidelines for chronic constipation in Japan recommend only short-term or rescue use of stimulant laxatives.

Most hemodialysis patients with severe constipation need medical treatment, as modification of their lifestyle, such as intake of fluid and dietary fiber, is difficult in terms of the risk of excessive fluid accumulation and hyperpotassemia. However, there are no reports on medications for constipated hemodialysis patients in PubMed references although Mimidis et al. reported the usefulness of PEG for constipated peritoneal dialysis patients (9). We speculate that many constipated hemodialysis patients in our country are dependent on long-term continuous use of stimulant laxatives.

The present study assessed the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG3350+E, MOVICOL®, EA Pharma, Tokyo, Japan) in constipated hemodialysis patients. We also focused on breaking away from the dependence on long-term continuous use of stimulant laxatives, which result in an increase of spontaneous

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Table 1. **Characteristics of Study Participants.**

	Sex	Age	Duration of dialysis (years)	Stimulant laxatives			Pseudo melanosis coli	Combined medicine
				Sort	Duration of use (years)	dose		
Case 1	M	59	26	herbal medicines	10~15	low	+	-
Case 2	M	66	10	herbal medicines	<5	low	+	probiotics
Case 3	M	56	10	sennoside	5~10	high	+	lubiprostone
Case 4	M	76	18	nonprescription drugs	>15	high	+	prokinetic agent
Case 5	F	62	27	herbal medicines	5~10	low	+	-
Case 6	F	71	36	sennoside	5~10	low	+	prokinetic agent
Case 7	F	70	31	nonprescription drugs	5~10	low	-	-

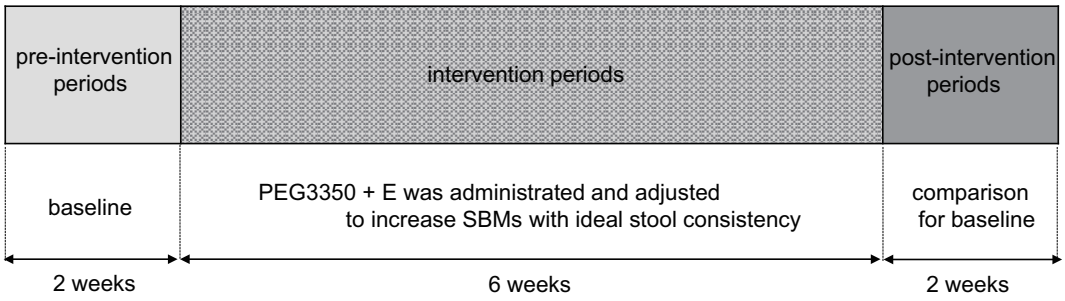

Figure 1. **Schematic time course of study protocol. The 10-week observation period was divided into three parts: pre-intervention period, intervention period and post-intervention period.**

bowel movements (SBMs).

Case Report

Participants

Among 66 patients on in-center hemodialysis in our hospital, 12 were dependent on stimulant laxatives for controlling functional constipation, which was diagnosed according to the Rome III criteria (10). Nine of the 12 patients agreed to participate, and 7 completed this study; their characteristics are summarized in Table 1. All patients had been receiving dialysis for more than 10 years. Stimulant laxatives included sennoside, nonprescription drugs containing sennna and herbal medicines containing rhubarb. The dose of stimulant laxatives just before the intervention was expressed as a low or high dose compared with the upper limit of the recommended dose. All patients had been examined by colonoscopy within the preceding three years to confirm that their constipation was not caused by organic diseases. Pseudomelanosis coli was observed in six patients, which may reflect long-term continuous use of stimulant laxatives.

Study design

There were 3 phases in total during the 10-week study period (Fig. 1). The first two weeks were pre-intervention periods to serve as a baseline. During the pre-intervention periods, patients took laxatives, including stimulant laxatives that had been used before this study. After the pre-intervention period, participants were treated with PEG3350 +E for six weeks (intervention period). PEG3350+E is a minimally absorbable iso-osmotic agent with a high molecular weight (11). It is a powder formulation delivered in sachets, each containing 6.5625 g of PEG, 0.1754 g of sodium chloride, 0.0893 g of sodium bicarbonate and 0.0251 g of potassium chloride. One sachet was dissolved in 62.5 mL of water. Since there was no evidence concerning the safety of PEG3350+E in hemodialysis patients, PEG3350+E was administered starting at the minimum dose. Initially, one sachet of PEG3350+E per day was administered in the first week of the intervention period, and then patients were allowed to take an additional sachet each week. Patients were allowed to take a maximum of six sachets of PEG3350+E per day in the final week of the intervention period. During the intervention period, patients were carefully observed in case they developed any adverse events. The amount of PEG 3350+E was adjusted in order to reduce stimulant laxatives and increase SBMs with the ideal stool consistency during the intervention period. The last two weeks were a post-intervention period for comparison with the baseline. The amounts of PEG3350+E and stimulant laxatives were fixed during the post-intervention period. Any changes in medications for hyperphosphatemia that might affect the control of constipation were allowed throughout the study.

Statistical analyses

Under the assumption of a Gaussian distribution, the measured variables are expressed as the mean±standard deviation. To evaluate the efficacy, a nonparametric Wilcoxon's signed rank test was used in order to avoid the influence of

Table 2. The Amount of Stimulant Laxatives and PEG3350+E, Changes of Medications for Hyperphosphatemia.

	PEG3350 + E in post-intervention periods (sachets/day)	Stimulant laxatives* in post-intervention periods (%)	Changes of medications for hyperphosphatemia
Case 1	2	0 (OFF)	-
Case 2	2	0 (OFF)	-
Case 3	2	30.8	-
Case 4	4	67	-
Case 5	2	0 (OFF)	-
Case 6	2	0 (OFF)	-
Case 7	4	83.3	increase of lanthanum carbonate

*The relative amount of stimulant laxatives is expressed as percentage of the baseline.
PEG3350+E: polyethylene glycol 3350 plus electrolytes

outliers. In the safety analyses, variables were measured in nested format (three measurements per week in a patient, repeated for several weeks) so that we applied the random-effect multilevel linear regression model. Two-sided $p<0.05$ was regarded as statistically significant. Statistical analyses were performed using the software program Stata ver. 13.1 (StataCorp LLC, College Station, USA) and Excel 2013 (Social Survey Research Information, Tokyo, Japan).

Ethical statement

This observational study was conducted between May and August in 2019, and it was performed in accordance with the ethical principles established in the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and informed consent form were approved by the ethics committee in our hospital. Although this was not an interventional study, patients were informed about the study via a document and agreed to participate by signing the informed consent form. Patients were allowed to drop out for any reason, and the safety of the patients received close attention throughout this study.

Measurements

During this study, patients recorded all of their bowel movements (BMs) and uses of stimulant laxatives with a paper diary. To assess BMs, the sensation of incomplete evacuation and severity of straining were scored as follows: absent=0, present=1. Stool consistency was scored using the Bristol Stool Form Scale (BSFS) (12). The patients' quality of life (QOL) with constipation was assessed in the final pre-intervention and post-intervention periods, based on the Japanese version of the Patient Assessment of Constipation Quality of Life Questionnaire (JPAC-QOL) (13). SBMs were defined as bowel movements without the use of a stimulant laxative, suppository or enema in the preceding 24 hours. Complete SBMs (CSBMs) were defined as SBMs associated with a sense of complete evacuation. We evaluated a BSFS of 4 or 5 as the ideal stool consistency according to the recent reports in Eastern cohorts (14, 15). The ratios of SBMs, CSBMs, BMs with ideal stool consistency and no straining to total BMs were calculated in the pre- and post-intervention periods.

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the beginning of every dialysis session (three times a week). Weight gain between every dialysis session was calculated based on the data of body weight at the beginning and end of every dialysis session (three times a week). The serum levels of sodium, potassium and albumin were monitored every week (once a week). The amount of sodium chloride intake was estimated using the serum sodium levels before and after the dialysis session according to the previous report (once a week) (16). These parameters were monitored throughout this study. The mean of SBP, DBP, weight gain, data of serum sample and sodium chloride intake were calculated every two weeks. The reduction or discontinuation of PEG3350+E was considered in any of the following cases: development of hypertension that required additional medications, body weight gain more than 1 kg compared to that average of the previous week, elevation of serum sodium concentration over 5 mEq/L and elevation of serum potassium concentration over 2 mEq/L compared to the previous week.

Results of efficacy

The amount of stimulant laxatives and PEG3350+E in the post-treatment periods and medications for hyperphosphatemia are summarized in Table 2. No stimulant laxatives were necessary in four of the seven patients (responders: Case 1, 2, 5 and 6). The remaining three patients (partial responders: Case 3, 4 and 7) achieved a reduction in the dose of stimulant laxatives. The medications for hyperphosphatemia did not change, except for in one case (Case 7) where the dose of lanthanum carbonate for hyperphosphatemia was increased during the intervention period.

The parameters concerning the efficacy are summarized in Table 3 and Fig. 2. By taking PEG3350+E, the average amount of stimulant laxatives decreased dramatically to 25.8% of the baseline (Fig. 2A, 2B). The ratio of SBMs and CSBMs to total BMs increased significantly in the post-treatment period compared to the baseline. As shown in

Table 3. Parameters for Assessing Efficacy of PEG3350+E Treatment.

	Pre-intervention periods	Post-intervention periods	p value
Total BMs (/2 weeks)	21.86±12.98	26.43±20.89	0.447
SBMs (/2 weeks)	1.0±1.15	13.43±11.43	0.028
CSBMs (/2 weeks)	0.71±1.11	7.29±11.38	0.043
The ratio of SBMs to total BMs (%)	5.99±6.69	64.0±45.73	0.028
The ratio of CSBMs to total BMs (%)	5.27±7.07	43.86±39.08	0.028
The ratio of BMs with ideal consistency to total BMs (%)	45.84±34.74	60.27±32.59	0.028
The ratio of BMs with no straining to total BMs (%)	47.37±35.26	28.0±36.14	0.345
JPAQ-QOL	38.0±13.96	30.28±15.99	0.046
			(n=7)

PEG3350+E: polyethylene glycol 3350 plus electrolytes, BM: bowel movement, SBM: spontaneous bowel movement, CSBM: complete spontaneous bowel movement, JPAC-QOL: Japanese version of the Patient Assessment of Constipation Quality of Life Questionnaire

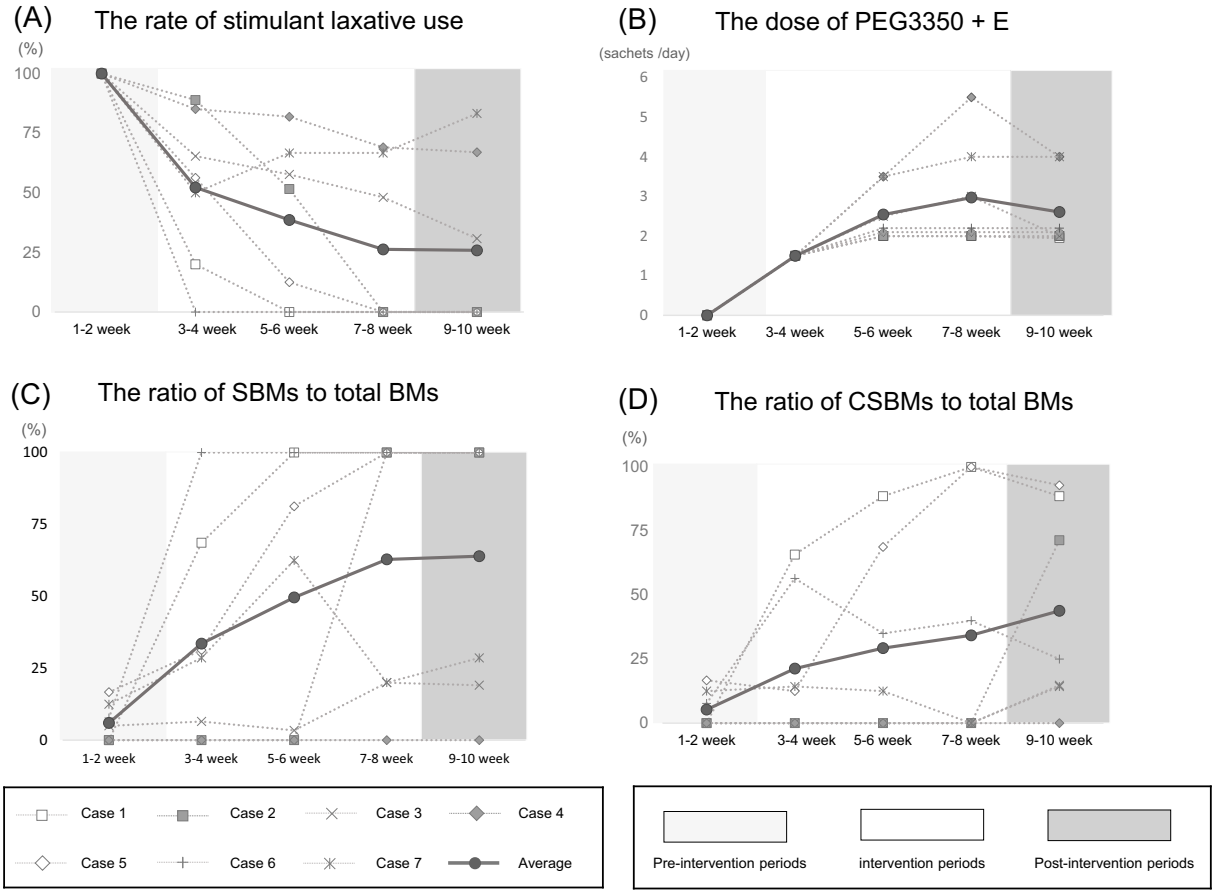

Figure 2. Changes in the dose of stimulant laxatives (A), the dose of PEG3350+E (B) and in bowel movement (C), (D) during the study period. The total amount of stimulant laxatives used was calculated every two weeks, and the relative amount of stimulant laxatives is expressed as the percentage of the baseline (1-2 weeks). The total numbers of BMs, SBMs and CSBMs were counted, and the ratios of SBMs or CSBMs to total BMS were calculated every two weeks.

Fig. 2C and D, BMs gradually improved during the six-week intervention period. The ratio of BMs with ideal stool consistency to total BMs was significantly higher at post-treatment period than at the baseline, although there was no significant change in the ratio of BMs with no straining. The JPAC-QOL was significantly lower at post-treatment period than at the baseline, indicating an improvement in the QOL concerning constipation.

Results of safety

The parameters for assessing PEG3350+E safety are summarized in Table 4. Patients took 2 or 4 sachets of PEG+E per day, which contained 13.125-26.25 g of PEG, 0.35-0.7 g of sodium chloride and 0.05-0.10 g of potassium chloride. The amount of water needed for the dissolution of PEG3350 +E was 125-250 mL per day. Despite electrolyte and water

Table 4. Parameters for Assessing Safety of PEG3350+E Treatment.

	Pre-intervention periods	Post-intervention periods	p value
SBP (mmHg)	136.85±18.53	142.35±18.90	0.354
DBP (mmHg)	70.78±12.42	76.63±12.67	0.014
sodium chloride intake (g/day)	9.45±4.10	9.23±2.24	0.956
body weight gain (kg)	2.25±0.94	2.35±0.98	0.94
Na (mEq/L)	140.50±2.77	140.83±2.08	0.665
K (mEq/L)	5.11±0.61	5.37±0.78	0.508
Alb (g/dL)	3.48±0.22	3.41±0.28	0.163
			(n=7)

PEG3350+E: polyethylene glycol 3350 plus electrolytes, SBP: systolic blood pressure, DBP: diastolic blood pressure

loading, there were no significant changes in the sodium chloride intake or body weight gain throughout the study. The serum levels of sodium, potassium and albumin showed no significant changes between pre- and post-intervention. The SBP did not show a significant difference before and after the intervention, although the DBP significantly increased after the intervention.

Discussion

Despite the high prevalence of chronic constipation in hemodialysis patients, there have been few clinical reports on the use of laxatives. Although PEG is not contraindicated to hemodialysis patients and has been widely used as the preparation for colonoscopy at a higher single dose, the efficacy and safety of PEG in continuous use as a laxative among hemodialysis patients has not been elucidated. This is the first report to assess the efficacy and safety of PEG 3350+E for continuous use in hemodialysis patients.

The administration of PEG3350+E resulted in a significant increase in the rate of SBMs and CSBMs in constipated hemodialysis patients. The ratio of BMs with ideal stool consistency also increased significantly. The improvement of the JPAC-QOL score may reflect these efficacies. By adding PEG3350+E, the amount of stimulant laxatives dramatically decreased, and four (Case 1, 2, 5, 6) out of seven patients overcame their dependence on the long-term continuous use of stimulant laxatives. Even the three partial responders (Case 3, 4, 7) were able to reduce their stimulant laxative amount to some degree after adding PEG3350+E. This was a meaningful outcome in the patients who were completely or partly relieved from the risk of intractable constipation caused by physical tolerance and psychological dependence on stimulant laxatives. These results indicate the positive impact of PEG3350+E on the treatment of constipated hemodialysis patients. However, there were no significant changes in the ratio of BMs with no straining. Although the reduction in stimulant laxatives increased SBMs and CSBMs, it also led to the attenuation of evacuation strength derived from stimulant laxatives. This may be the reason why no improvement on straining was observed in this study.

Next, we assessed the safety of PEG3350+E in continuous use among hemodialysis patients, since a certain amount of water is required to take the medicine, and the drug contains sodium, both of which can cause adverse effects on hemodialysis patients. As a result, the continuous administration of PEG3350+E did not change the SBP, body weight gain, serum levels of sodium, potassium or albumin or the sodium chloride intake in constipated hemodialysis patients. This indicates that the water needed for reconstitution of PEG3350+E and ingredients of PEG3350+E might not be absorbed into the patients. However, the significant elevation of DBP observed suggests two possibilities. First, the small amount of water needed for the reconstitution of PEG3350+E might be partly absorbed via the intestine. Alternatively, the reduction in stimulant laxatives may increase the absorption of water in the intestine via the attenuation of the evacuation strength, which might lead to the retention of water. However, neither possibility is clear, as the SBP and body weight did not change statistically. The discrepancy between the SBP and DBP was unclear; however, one possibility is that medications for blood pressure may have masked the change in the SBP. Even though the accurate assessment of the water absorption and blood pressure in hemodialysis patients was difficult, water and sodium loading with PEG3350+E did not induce serious adverse effects on the body fluid retention or blood pressure in this study. Therefore, we believe that PEG3350+E can be safely used in hemodialysis patients.

According to the data on the dose of PEG3350+E in Fig. 2B, partial responders (Case 4, 7) took a relatively high dose of PEG3350+E, indicating that the effect of PEG3350+E for these patients was limited. The difference in the response to PEG3350+E between responders and partial responders was unclear. However, we speculated that an increase in lanthanum carbonate for hyperphosphatemia may have affected the resistant response for PEG3350+E, as lanthanum carbonate can cause gastrointestinal side effects, including constipation (17, 18). Although there is no evidence of a resistant response for PEG derived from lanthanum carbonate, the increase in lanthanum carbonate for hyperphosphatemia during the intervention period in Case 7 may have affected the resistant response for PEG3350+E.

Through this study, we learned that constipated hemodialysis patients tend to defecate before a hemodialysis session because they want to avoid evacuation during hemodialysis and the assessment of an excessive body weight gain. Thus, they tend to expect a predictable and immediate effect of medications on constipation, which may be one reason for their stimulant laxative dependency. As a result, in two patients (Case 3, 4), the dose of stimulant laxatives was beyond the recommended dose in this study. In these two cases, PEG3350+E was not able to replace stimulant laxatives completely, although the amounts of stimulant laxatives were reduced slightly. These two patients did not express any wish for an additional increase in PEG3350+E because it carried a risk of inducing excessive body weight gain if their BMs did not improve. In such cases, we should not continue to administer PEG3350+E, and instead, other laxatives, such as lubiprostone, linaclotide or elobixibat, should be considered for the further reduction of stimulant laxatives. Worries about fluid accumulation and excessive body weight gain are characteristic in hemodialysis patients. Indeed, two patients discontinued PEG3350+E for that reason, although their safety parameters did not meet any reduction or discontinuation criteria. Therefore, the fluid accumulation and excessive body weight gain should be considered when administering PEG3350+E to hemodialysis patients.

Several limitations associated with the present study warrant mention. This was a single-center, open-label, nonrandomized controlled study. The number of patients who participated was small, and the observation period was short. The use of stimulant laxatives may have influenced the absorption of water, so it proved to be difficult to accurately assess the safety of PEG3350+E with regard to water absorption. However, this study suggests that the administration of PEG3350+E may decrease the use of stimulant laxatives and increase SBMs and CSBMs without causing serious adverse effects among constipated hemodialysis patients.

In conclusion, PEG3350+E can be useful and effective for the treatment of constipation in hemodialysis patients under careful observation. Further studies are needed to assess the efficacy and safety of PEG3350+E in constipated hemodialysis patients.

Author's disclosure of potential Conflicts of Interest (COI).
Atsushi Masamune: Lecture fee, EA Pharma.

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