Single Dose or Divided Dose of Polyethylene Glycol in Treatment of Pediatric Functional Constipation: A Randomized Clinical Trial

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Abstract

Background

This study aimed to compare different regimens of Polyethylene Glycol (PEG, single dose vs. divided dose) in the treatment of functional constipation among children aged 4-15 years.

Materials and Methods

This double-blind randomized clinical trial was conducted on the children (4-15 years old) with functional constipation who were visited in an outpatient pediatric clinic affiliated to Shiraz University of Medical Sciences between February and July 2021. Among the120 eligible patients, 80 ones who met the inclusion criteria were recruited. The patients were divided into two parallel groups; the children who received single-dose PEG (group A) and those who received PEG in divided doses (group B). The study was performed during 12 weeks and follow-up visits were scheduled at 1, 3, 6, and 12 weeks after enrollment. The outcomes were measured using the Bristol Stool Form Scale (BSFS).

Results

The study was performed on 78 cases including 45 boys (57.7%) and 33 girls (42.3%) with the mean age of 5.52±1.79 years. After 12 weeks, a significant difference was observed between groups A and B regarding the mean of BSFS (4.94±0.52 vs. 4.50±0.88, p=0.008). However, no significant difference was observed between the two groups regarding the number of defecation times during the study. The detected complications included mild abdominal pain in eight children in group A (5.3%), fecal incontinency in six children in group B (3.8%), and painful defecation in six children in group B (3.8%).

Conclusion

This study confirmed that the administration of the single dose (0.4 g/kg) of PEG early in the morning was more effective, well tolerated, and accompanied by fewer complications compared to the divided dose.

Introduction

Constipation is a common pediatric disorder (1) with an incidence of about 5% in children aged 4-17 years and accounts for nearly 30% of pediatric gastroenterologists' patients (2). Constipation does not have any structural, endocrinal, or metabolic causes in up to 90% of children, which is called idiopathic or Functional Constipation (FC) (3). Chronic idiopathic constipation is a type of constipation, in which the patient experiences constipation without any recognizable causes for more than three months (4). FC is a common problem amongst children worldwide, with a reported prevalence of 0.5-30% (3, 7).

The treatment of constipation consists of behavioral interventions (e.g., education, toilet training, and bowel diary) and use of laxatives. In many countries, Polyethylene Glycol (PEG) is the laxative of choice

for both disimpaction and maintenance treatment among children. PEG is a biologically inert, water-soluble polymer that is minimally absorbed in the gastrointestinal tract. It has no electrical charge and, consequently, does not influence the movement of other solutes. Due to these properties, PEG acts as an osmotic laxative. Although PEG has only been used for the treatment of constipation for approximately three decades, it has rapidly become the most widely used laxative in both children and adults. The popularity of PEG is primarily based on its effectiveness, safety, and administration route (5, 6). On the other hand, minor side effects have been reported for PEG including flatulence, bloating, abdominal pain, nausea, vomiting, diarrhea, fecal incontinence, and headache. These adverse events may also occur with similar frequency in patients receiving placebos (5). However, PEG is contraindicated in allergic patients as well as in those with known or suspected bowel obstruction. In patients predisposed to water and electrolyte imbalance (e.g., patients with impaired hepatic or renal function and those taking diuretics), PEG should be prescribed prudently with the regular monitoring of serum electrolytes. PEG should also be used cautiously in children with swallowing problems including those with severe neurological impairment, because of the risk of aspiration. PEG is a non-absorbable material whose aspiration may cause pulmonary complications and even death (8, 9).

In Iran, the incidence of FC has been reported as nearly 20% amongst school-age children, while the incidence of fecal incontinence as a side effect of constipation has been found to be about 30% in children with constipation (10). Up to now, few studies have been conducted on the dosage and time of administration of different laxatives, especially PEG. There is only a starting dose for each child that must be adjusted to achieve the desired therapeutic result (11, 12, 13). Therefore, the present study aims to compare two different PEG regimens (single dose vs. divided dose) for the treatment of FC in pediatric patients.

Materials And Methods

Study design

This double-blind randomized clinical trial was conducted on the children aged 4-15 years with FC, as defined by the Rome IV Criteria (Table 1) (14,15), who were visited in an outpatient pediatric clinic affiliated to Shiraz University of Medical Sciences between February and July 2021. During this period, 120 patients were eligible for participation in the study. The enrolled patients (n=80) who met the inclusion criteria were randomly assigned to the study groups using block randomization with the block size of 8 (the list blocks were extracted from www.sealedenvelope.com). Group A included the children who received single-dose PEG and group B included the children who received PEG in divided doses. **It is worth mentioning that** the investigator and the patients were kept blind to the study groups.

Setting and participants

In case the study participants had severe stool impaction, they underwent rectal disimpaction by paraffin and N/S enema and then, PEG was started. The drug was administered orally at a dose of 1 cc/kg body weight from a solution containing 40% PEG without electrolytes (0.4 g/kg) on a daily basis. Increasing

the dose up to 2 cc/kg body weight (0.8 g/kg) daily was allowed by the caregiver for the children who did not improve after at least three days of treatment. It should be noted that the use of other laxatives was not allowed during the study period. In addition, if the patients did not defecate for more than three days, they were referred to a physician. A proper toilet training with regular stool sittings for 5-10 minutes was advised after each meal. Furthermore, the patients and their parents were asked to keep a stool diary during the 12 weeks of treatment, with weekly reports of the frequency of bowel movements, stool consistency measured through the Bristol Stool Form Scale (BSFS) (Picture 1) (16), episodes of fecal incontinence, and presence of the associated gastrointestinal symptoms such as nausea, vomiting, flatulence, abdominal pain, painful defecation, and rectal bleeding.

Patients' follow-up and outcomes

Follow-up visits were scheduled at 1, 3, 6, and 12 weeks after enrollment. At each visit, the interim history was assessed, stool diaries were reviewed and discussed, and a physical examination was done. Clinical progress, compliance with the treatment program, stool frequency, stool consistency, episodes of fecal incontinence, and occurrence of abdominal pain and other possible gastrointestinal symptoms were assessed, as well. The primary outcome measure was the improvement of constipation defined as ≥2 bowel movements per week, ≥2 stool consistency grade on BSFS, and absence of fecal incontinence, abdominal pain, pain on defecation, and rectal bleeding. The secondary outcome measure was the improvement of other associated gastrointestinal symptoms such as nausea, vomiting, and flatulence.

Data collection

At first, the necessary arrangements were made with the Pediatrics Department of Shiraz University of Medical Sciences to access the cases. All the children aged 4-15 years who were referred to the pediatric clinics of Shiraz University of Medical Sciences due to suffering from FC were eligible for the study. The diagnosis of FC was made by the Rome IV Criteria (Table 1). The inclusion criteria of the study were aging 4-15 years, suffering from FC based on the Rome IV criteria, and having complete information and follow-up. The exclusion criteria were non-compliance with the treatment, having organic causes of constipation including Hirschsprung disease, spinal bifida (occulta), and hypothyroidism, suffering from other metabolic renal abnormalities, mental retardation, and other organic problems, being suspicious for bowl obstruction, and having used lactulose or other laxatives, prebiotics, or probiotics within four weeks prior to the first visit.

Sample size

Based on a pilot study reporting the mean of BSFS among 30 patients and considering the effect size of 0.60, power of 80%, type 1 error of 5%, and drop-out rate of 10%, a 40-subject sample size was estimated for each study group. Totally, 80 patients were randomly assigned to the study groups.

Statistical analysis

In this study, continuous variables were reported as mean and standard deviation, and the comparisons between and within the study groups were made using independent sample t-test and paired sample t-test, respectively. Categorical variables were presented as number and percentage, and the comparisons between the groups were made through chi-square and Fisher's exact test. Moreover, repeated measures ANOVA was used to compare the two groups over time. All data analyses were done using the Statistical Package for Social Sciences (SPSS Inc., Chicago, version 23) and $p<0.05$ was considered statistically significant.

Ethics

Human dignity, preservation of individuals' medical secrets, and commitment to Helsinki Ethics were respected throughout the study. Written informed consent forms for using the patients' information were completed by either the patients or their parents. The executive protocol of the study was confirmed by the Ethics Committee of Shiraz University of Medical Sciences and investigation of the cases was conducted in the pediatric clinics affiliated to Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1397.498). This study has also been accepted by Iranian Registry of Clinical Trials by the code IRCT20090908002434N9.

Results

The study participants included 45 boys (57.7%) and 33 girls (42.3%) with the mean age of 5.52±1.79 years. The patients were randomly divided in two groups. Group A (the single-dose group) included 38 children who received single-dose PEG and group B (the divided dose group) included 40 children who received divided doses for 12 weeks (Figure 1). The two groups were homogenous in terms of age, sex, and dosage (Table 2).

According to Figure 2, time was effective in BSFS after the first week ($p<0.001$). The results also revealed a significant difference between the two groups regarding the mean of BSFS ($p=0.018$). In addition, a significant difference was observed in BSFS within the study groups between weeks ($p<0.001$), but no significant difference was detected in this regard between the sixth and twelfth weeks.

Based on the results, both treatments exerted a similar effect on the number defecations per week (Figure 3). The detected complications included mild abdominal pain in eight children in group A (5.3%), fecal incontinency in six children in group B (3.8%), and painful defecation in six children in group B (3.8%) (Table 3).

Discussion

Constipation is a common chronic disorder in the pediatric age group, affecting 1-30% of children globally. It has a considerable effect on the quality of life (18). FC is a common problem in childhood, with an estimated incidence of about 5% worldwide (19). FC is diagnosed by the Rome IV criteria and can be easily distinguished from organic causes by detailed history and precise clinical examination (17, 20).

The symptoms of FC in both children and adults include hard, infrequent bowel movements often accompanied by bloating and abdominal pain. In addition, children often present with the symptoms of fecal incontinence including the involuntary loss of stool in the underwear after being toilet trained, resulting in the overflow of soft stool (21). In a recent study, Elena Scarpato et al. evaluated 13,750 children (4-18 years old) in the Mediterranean-European area and reported that the most frequent disorders were FC (11.7%), Irritable Bowel Syndrome (IBS, 4%), aerophagia (3.5%), and abdominal migraine (3.1%) (22). However, few documents are available regarding constipation in developing countries. Questionnaire-based studies performed on adolescents and adults in Iran and China indicated the mean stool frequencies of 13.5±7.5 and 7 per week, respectively, with about 85% of the participants having daily passage (23, 24). Another study demonstrated that almost one-third of the patients referred due to abdominal pain had FC followed by Familial Adenomatous Polyposis (FAP), IBS, functional dyspepsia, functional nausea, and abdominal migraine (25).

FC in infants is usually treated medically via dietary modification, behavior change, and using enemas and laxatives (26). Previous studies revealed the superiority of PEG over other laxatives due to its therapeutic effects, tolerability, and lack of serious complications. In a randomized, single-blind, parallel group study comparing a PEG-only laxative to a PEG-electrolyte laxative for the treatment of fecal impaction and chronic constipation in Italy, the PEG-only laxative was better tolerated and accepted compared to the PEG-electrolyte laxative among children with chronic constipation (27). PEG 3350 without electrolytes has been used as a laxative in constipated children in both short and long runs. PEG is a chemically inert, tasteless, odorless medication with no grits when stirred in juice, Kool-Aid, or water for several minutes. PEG is not degraded by bacteria and is not readily absorbed, thereby acting as an excellent osmotic agent (28). Saneian et al. conducted a randomized clinical trial in Iran and disclosed that considering the therapeutic results and absence of serious complications, PEG could be used as the first pharmacological alternative to treat FC in children compared to magnesium hydroxide and lactulosein (29). In addition, PEG has been found to be effective and safe for the treatment of constipation in infants and toddlers. Therefore, it can be added to the list of useful laxative agents for the treatment of constipation in these populations (30). Loening Baucke V et al. reported that the mean dose of PEG for the initial treatment of FC in infants and toddlers was 1.1 g/kg body weight daily, which was higher than that used for school-age children (0.6 g/kg body weight daily). Besides, the mean effective dose was 0.8 g/kg body weight/d in the long-term follow-up, which was still higher than the 0.4 g/kg body weight dose required in older children during the 12-month follow-up. These results were in agreement with those of the current investigation (31).

The most important finding of the present study was that the usage of the single-dose PEG significantly improved the number of defecations per day among the children aged 4-15 years and was accompanied by fewer complications compared to the patients receiving PEG in divided doses. Specifically, at least one defecation per day was reported in the single-dose group during the follow-up period.

Conclusion

One of the most important principles in the success of pediatric treatment is the cooperation of children and their families. Better tolerability of drugs and fewer side effects also play an important role in this regard. The present study findings confirmed that the single dose of PEG was more effective and well tolerated compared to the divided dose. PEG, as an osmotic agent, increased the water content of the stool and resulted in easier bowel evacuation during the day. Considering the patients' better compliance and fewer side effects, physicians are recommended to prescribe the single dose of PEG (0.4 g/kg) to be administered early in the morning.

Abbreviations

BSFS: Bristol stool form and stool frequency

FC : Chronic functional constipation

PEG: Polyethylene glycol

IBS: Irritable Bowel Syndrome

FAP: Familial Adenomatous Polyposis

Declarations

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The authors declare that they have no conflicts of interests.

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All information and materials was available for declaration.

Code availability:

Not applicable

Author contributions:

Data curation, Writing - Original Draft, Visualization, Writing - Review & Editing, Methodology, Validation: [Heidar Safarpour], Conceptualization, Methodology,Resources, Funding acquisition, Writing - Review & Editing, investigation:[Mohammad Hadi Imanieh], Methodology, Writing - Review & Editing, investigation: [Naser Honar] Resources: [Sajad Hekmati], Formal Analysis: [Naeimehossadat Asmarian]. All authors read and approved the final manuscript.

Mohammad Hadi Imanieh & Naser Honar are equally participated in Writing - Review & Editing, investigation and responsibility for communication with the journal during the manuscript submission and considered as co-corresponding author.

Ethics approval:

The Ethics Committee of Shiraz University of Medical Sciences approved this study (IR.SUMS.MED.REC.1397.498). This study has also been accepted by Iranian Registry of Clinical Trials by the code IRCT20090908002434N9.

Consent to participate:

The patients provided written informed consent.

Consent for publication:

Not applicable

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Tables

Table 1. The ROME IV criteria for functional constipation

The child must have two or more of the following criteria for at least one month in the absence of organic pathologies to explain the symptoms.	
Developmental age 4 years	Developmental age ≥ 4 years
≤ 2 bowel movements per week	
At least one episode of incontinence per week if toilet trained	At least one episode of incontinence per week
History of stool retention	History of volitional stool retention
History of painful bowel movements	
Large fecal mass present in the rectum	
History of clogging the toilet or large-diameter stools	
Symptoms such as early satiety, fussiness, and poor appetite that disappear immediately after having a bowel movement	Does not meet the criteria for irritable bowel syndrome

Table 2. Demographic and clinical variables

	Single-dose group N=38	Divided-dose group N=40	P-value
Age	5.47±1.72	5.59±1.87	0.723
Sex, male, n (%)	21 (55.3)	24 (60)	0.672
Dosage	19.22±6.47	18.92±6.59	0.841

Table 3. Frequency distribution of the complications in the study groups during the follow-up period

Complication	Single dose N=38	Divided dose N=40	P-value
Fecal incontinency	0 (0)	6 (3.8%)	0.026
Painful defecation	0 (0)	6 (3.8%)	0.026
Rectal bleeding	1 (0.7%)	0 (0)	0.478
Mild abdominal pain	8 (5.3%)	2 (1.3)	0.045
Nausea and vomiting	0 (0)	0 (0)	-
Flatulence	0 (0)	2 (1.3)	0.494
Other symptoms	0 (0)	0 (0)	-
Total	9 (6%)	16 (10.2)	0.125

Figures

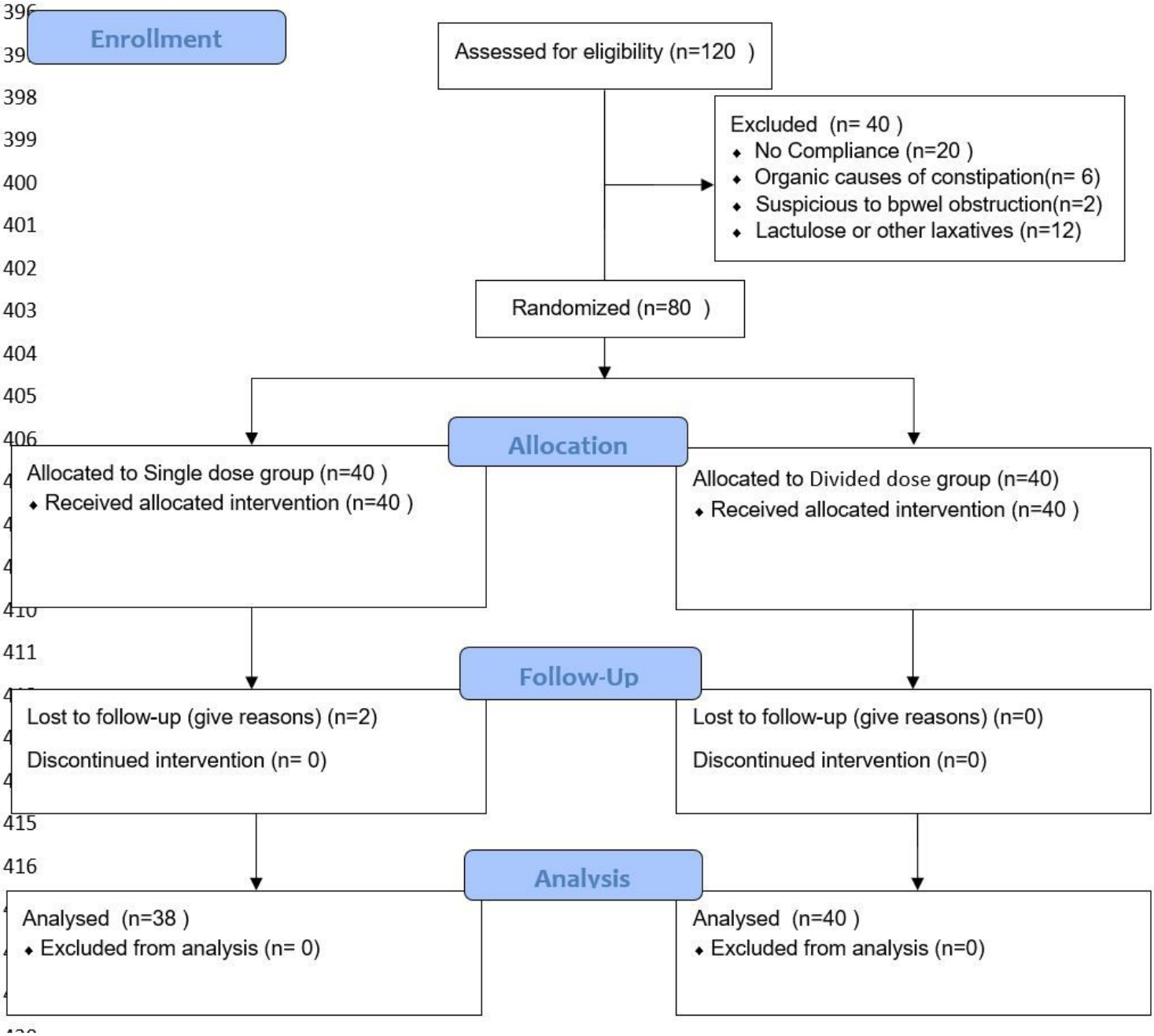

Figure 1

Consort chart

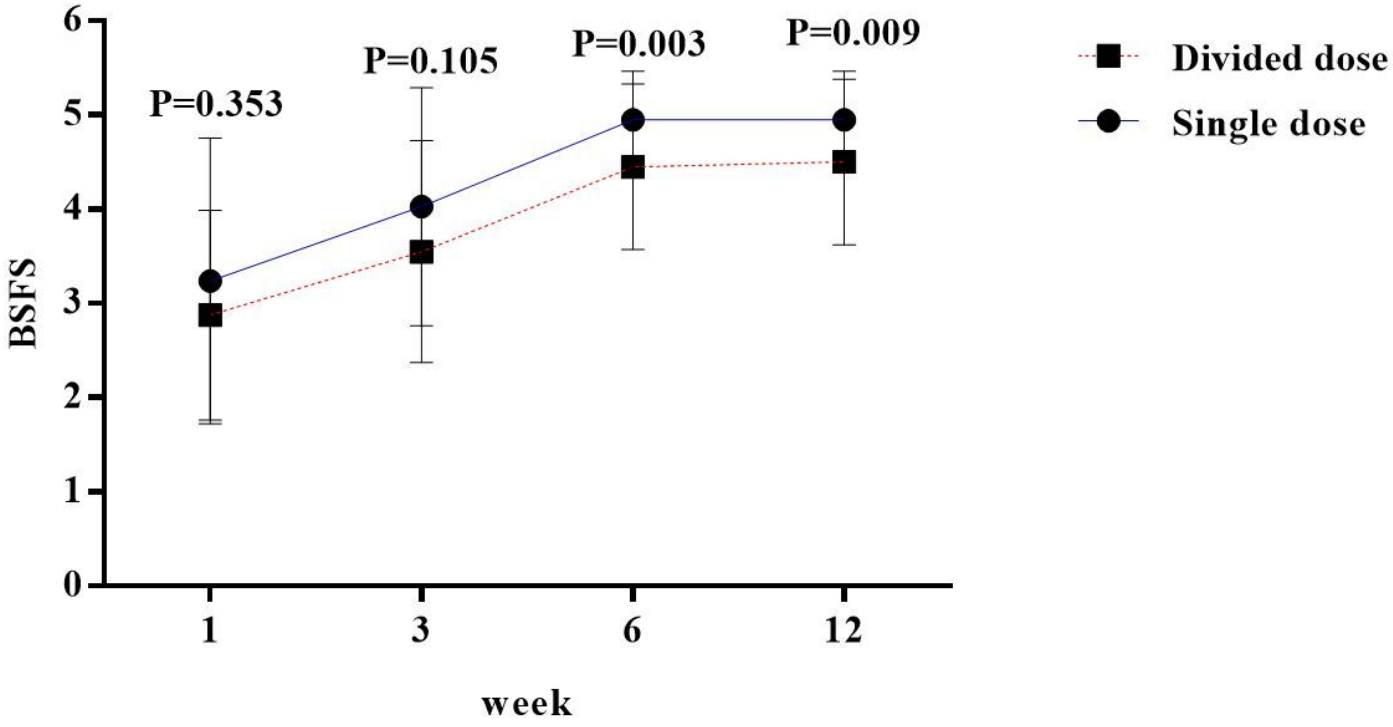

Figure 2

The mean of BSFS in the two groups during the 1st, 3rd, 6th, and 12th weeks

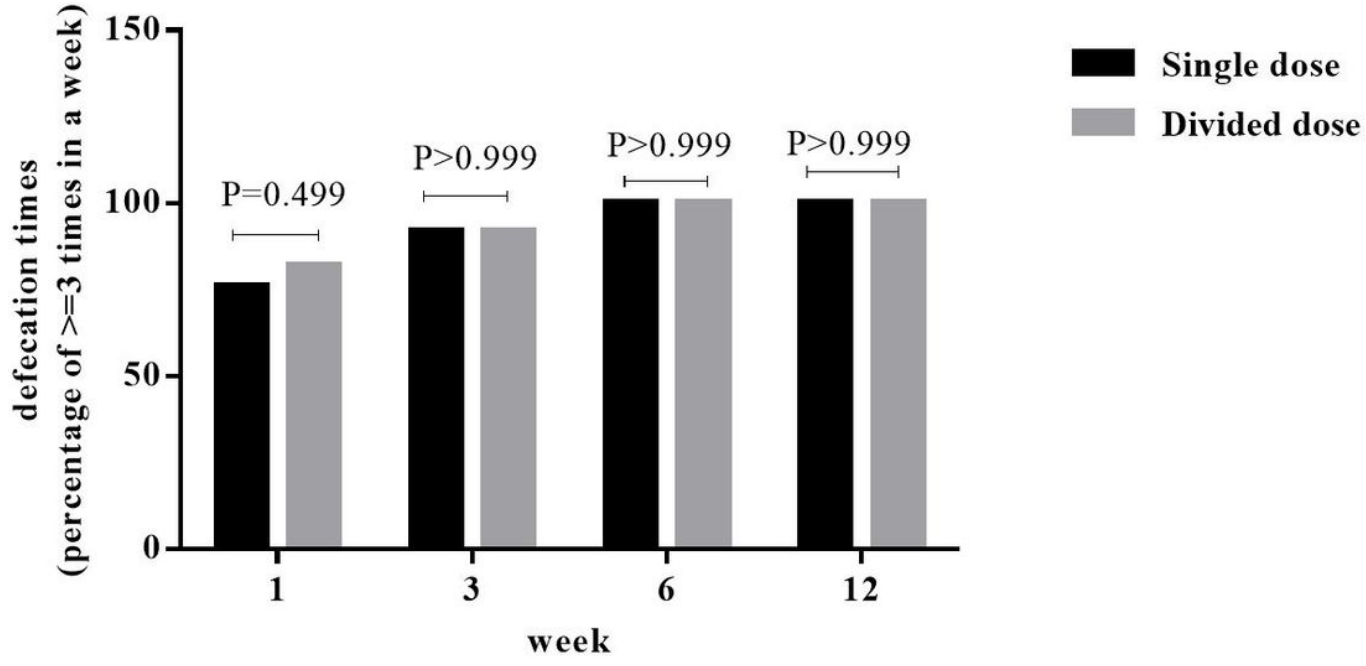

Figure 3

The percentage of defecation times (>3 times in each week) in the two groups during weeks 1, 3, 6, and 12

Supplementary Files

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- picture1.jpg