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Original Article

Polyethylene glycol versus lactulose in the treatment of chronic functional constipation in children: A randomized clinical trial

Hassan Talakesh[1], Alizamen Salehifard Jouneghani[1], Karamali Kasiri[1*], Farnoush Kochekian[2], Afsaneh Malekpour Tehrani[3]

[1]Department of Pediatrics, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Department of Community Medicine, School of Medicine, Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

*Corresponding Author: Karamali Kasiri, Email: kasiri207@yahoo.com

Abstract

Background and aims: Constipation in children is a serious problem that affects both children and their families. We aimed to compare the clinical efficacy of lactulose and polyethylene glycol in the treatment of constipation in children.

Methods: This randomized clinical trial was performed on 92 patients referred to a private gastroenterology clinic in Shahrekord, Iran. The patients were randomly assigned into two groups receiving polyethylene glycol or lactulose. Defecation patterns and complications were assessed 0, 3, 7, and 21 days after the intervention. Data were analyzed using the chi-square test, repeated measures test, Mann–Whitney U test in SPSS version 16.0. $P<0.05$ was considered statistically significant.

Results: No difference was found between the two interventional groups in terms of the frequency of painful defecation ($P=0.31$), fecal incontinence ($P=0.50$), hard stools ($P=0.69$), fear of defecation ($P=0.09$), poor appetite ($P=0.29$), straining at stool ($P=0.50$), and abdominal pain ($P=0.07$) within a follow-up period of 21 days. There were significant differences in the frequency of defecation on days 7 and 21 ($P=0.02$). The mean frequencies of abdominal cramps were significantly higher in those who received lactulose ($P=0.001$). The rate of nausea and vomiting was 10.6% in the lactulose group and 4.3% in the polyethylene glycol group, indicating no difference between the two groups ($P=0.221$).

Conclusion: The administration of polyethylene glycol and lactulose had no significant difference in reducing the symptoms of chronic functional constipation in children. However, it seems that polyphenol glycol played a role in increasing the frequency of defecation.

Keywords: Constipation, Polyethylene glycol, Lactulose, Children

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Introduction

Functional constipation in childhood is a common problem that negatively affects children's quality of life in terms of their health and imposes a significant financial burden on the healthcare systems and societies (1). Due to symptoms such as delay in defecation, hard stools, and fecal incontinence due to the formation and retention of large masses of feces in the rectum, constipation causes discomfort to the child and parents and leads to an increase in medical expenses (2). Various studies at the community level show that the prevalence of constipation in adults from Western to Asian countries varies from 10% to 20% and in children from 0.7% to 29.6%, and this problem accounts for 3% of all visits to primary care physicians and up to 30% of referrals to pediatric gastroenterologist (3-5). Various factors such as genetic predisposition, social and economic status, low fiber consumption, insufficient fluid intake, and inactivity are among the factors that can cause constipation (6,7). Timely and appropriate treatment plays an essential role in reducing pain and other problems of gastrointestinal patients, such as disruption in daily life activities (8). The basic principle of constipation treatment is to relieve the patient's symptoms and pain intensity and make the medicine safe and secure. Improvement of symptoms and treatment of chronic constipation require long-term treatment. Medicinal treatments and laxatives are recommended in the next step (9).

Currently, different treatments have been tried for this problem in children, none of which have been totally successful. Lactulose is a type of non-digestible carbohydrate that causes water to be absorbed into the colon and loosens the stool (10). Lactulose in the intestine is converted into lactic acid, formic acid, and acetic acid by natural intestinal bacteria, creating hyperosmotic pressure (11). This action causes the absorption of water and increases the volume of the intestinal contents, thus

increasing the peristaltic movements of the intestine. The use of lactulose can cause side effects such as cramps, diarrhea, gas, belching, hiccups, upset stomach, bloating, and increased thirst (12).

Polyethylene glycol is a high molecular weight water-soluble polymer that can form hydrogen bonds with 100 water molecules per polyethylene glycol molecule. The oral administration of polyethylene glycol causes the hydration of colon contents and facilitates intestinal passage and painless excretion in a linear dose-dependent manner (13). Therefore, polyethylene glycol-based laxatives can be more beneficial than rectal treatment for complete stool elimination (14,15).

When simple methods, such as nutritional and biofeedback training, fail to treat constipation, the next step is to use one or more laxatives. Studies show that the most prescribed drugs for children's constipation are osmotic laxatives (47%), stimulants (38%), and stool-bulking agents (15%) (16). Osmotic laxatives are the most popular drugs used to treat constipation in children, and there is little evidence that stimulant laxatives or bulking agents are helpful in children. The results show that polyethylene glycol is more effective than other laxatives, but the information is still insufficient. Considering these points, we decided to compare the effects of two of the most commonly used laxatives prescribed for children's constipation, including lactulose and polyethylene glycol.

Materials and Methods

This randomized clinical trial was performed on patients referred to a private gastroenterology clinic in Shahrekord, Iran, in 2022. The sample size was determined to be 47 people in each group based on the following formula and similar studies (17).

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{d}\right)^2$$

$$d \quad \frac{\mu_1 \quad \mu_2}{\sigma\sqrt{2}}$$

$Z_{1-\alpha/2} = 1.96$

$Z_{1-\beta} = 0.84$

$d = 0.5$

Convenience sampling was used to select the participants for this study. All eligible patients aged 2 to 15 years and suffered from chronic functional constipation without any evidence of intestinal disorders, allergic reaction to lactulose or polyethylene glycol, intestinal obstruction, or kidney and heart failure. Having diarrhea following drug use, unwanted allergic reactions after drug use, and suffering from underlying diseases such as hypothyroidism and Hirschsprung's disease were considered as the exclusion criteria. Before the implementation of the intervention, baseline characteristics, including demographics and defecation behaviors (number of defecation, number of unwanted bowel movements, number of painful bowel movements, number of abdominal pain, and stool consistency) were considered by interviewing the parents and children. The patients were then randomly (based on a single sequence of random assignments or simple randomization method) assigned into two groups receiving polyethylene glycol (3 mg for children aged younger than 6 years and 6 mg for those older than 6 years) or lactulose (6 mL for children aged younger than 6 years and 12 mL for those older than 6 years). The medical secretary also kept the patient's information form, which was not disclosed to the physician or researchers. Moreover, the children's parents did not know the type of medicine that was administered. Moreover, parents were given the necessary training in using the toilet to encourage the child to go to the bathroom 5 minutes after each meal. The Global Physical Activity Questionnaire (GPAQ) was completed at the end of the intervention to check physical activities (18). In addition, children's height and weight were also recorded. The dietary education program was implemented equally in the studied groups. The required information was collected on days 0, 3, 7, and 21. The study duration for each patient was three weeks, and two visits were made before the start and after the end of the treatment. In the second follow-up, the effectiveness, tolerance, and possible side effects of the drugs were evaluated. Accordingly, if the initial dose was high, the drug was reduced by 50%, and if constipation continued, the drug dose was increased by 50%. The treatment success was defined as three or more painless, soft, and normal -consistent bowel movements per week.

The SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. Results were expressed as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables. Data were analyzed using the chi-square test, repeated measures test, and Mann–Whitney U test. In all tests, $P < 0.05$ was considered statistically significant.

Results

Initially, 94 children suffering from chronic functional constipation were included in the study and randomly assigned into two groups: lactulose (n = 47) and polyethylene glycol (n = 47). Two of those who planned to receive lactulose could not tolerate the medication and were thus excluded from the study. Finally, 45 participants in the lactulose group and 47 participants in the polyethylene glycol group underwent interventions (Figure 1).

The two groups had similar baseline characteristics, including age and anthropometric parameters (Table 1). No difference was observed between the two interventional groups in terms of the frequency of painful defecation,

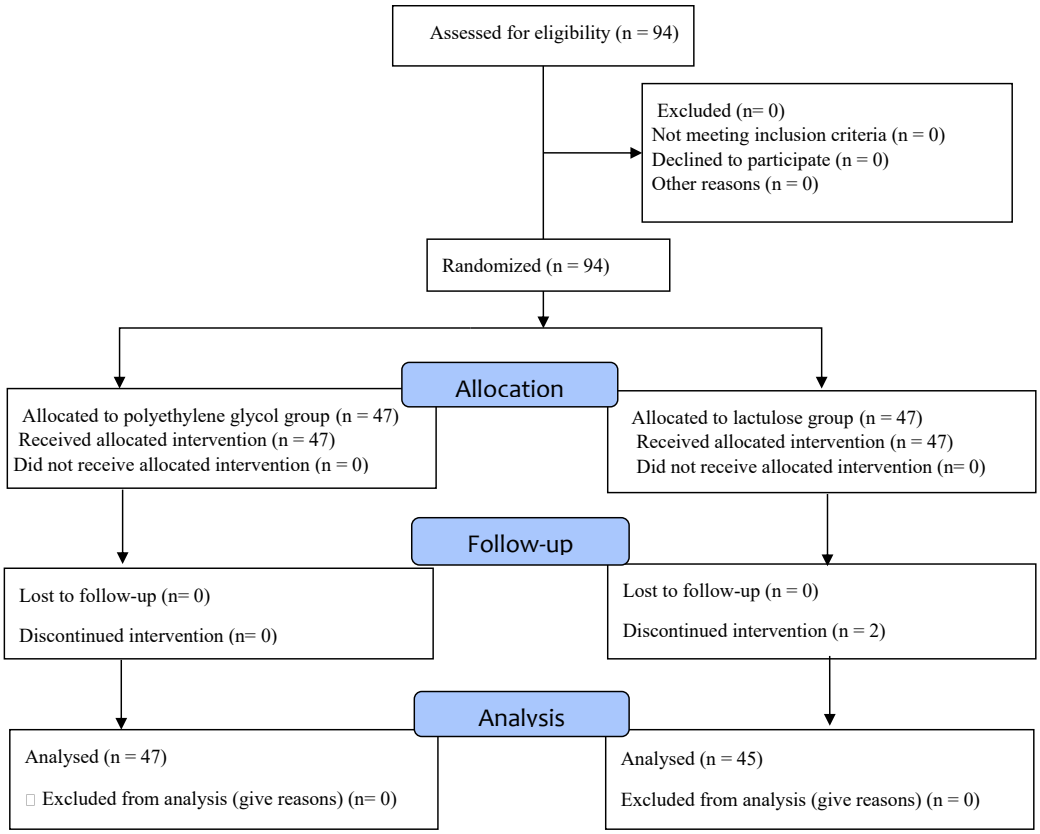

Figure 1. CONSORT flow diagram of the study population

Table 1. Baseline Characteristics of the Study Population

Characteristics		Lactulose group (n = 47)	Polyethylene glycol group (n = 45)	*P* value
Mean age (y)		4.85 ± 2.29	5.91 ± 2.81	0.085[a]
Mean weight (kg)		17.86 ± 6.24	20.72 ± 8.43	0.121[a]
Mean height (cm)		111.73 ± 17.40	116.90 ± 18.65	0.223[a]
Place of residence %	Urban area	13 (27.7)	19 (72.3)	0.143[b]
	Rural area	34 (57.8)	26 (57.8)	

[a] Mann–Whitney U test.
[b] Chi-squared test.

fecal incontinence, hard stools, fear of defecation, poor appetite, straining at stool, and abdominal pain within a follow-up period of 21 days (Table 2). However, these manifestations significantly improved in both groups within the follow-up time. The mean frequencies of diarrhea in the groups receiving lactulose and polyethylene glycol were 0.13 ± 0.33 and 0.09 ± 0.35, respectively, indicating no significant difference ($P = 0.317$), while the mean frequencies of abdominal cramps were 0.79 ± 0.72 and 0.11 ± 0.37, respectively, indicating a significantly higher rate of this complaint in patients receiving lactulose ($P = 0.001$). In the lactulose and polyethylene glycol groups, there was a significant change in the frequency of defecation at different times. In the lactulose group, there was a significant change in abdominal pain at other times (except on the third day compared to the seventh day). In the polyethylene glycol group, abdominal pain improved significantly at different times. Regarding treatment-related complications, the rate of nausea and vomiting was 10.6% in the lactulose and 4.3% in the polyethylene glycol group, indicating no difference between the two groups ($P = 0.221$).

Discussion

The results of the present clinical trial study showed that the frequency of painful defecation, fecal incontinence, hard stool, fear of defecation, poor appetite, hematochezia, and straining before the intervention and on days 3, 7, and 21were not significantly different between the two groups under study. The average abdominal pain score before the intervention and on the third day in the polyethylene glycol group was significantly higher compared to the lactulose group, but there was no significant difference between the two groups on days 7 and 21. The average frequency of defecation before the intervention and on the third day was not significantly different between the two groups, but on days 7 and 21, it was significantly higher in the polyethylene glycol group than in the lactulose group. In general, the defecation frequency increased by 6.92% in the lactulose group and 8.45% in the polyethylene glycol group after three weeks. The frequency of abdominal pain was also reduced in the lactulose group by 1.64% and in the polyethylene glycol group by 3.63% after three weeks, which indicates the better efficiency of lactulose in reducing abdominal pain and increasing stool frequency.

Several studies conducted in this field show the higher effectiveness of polyethylene glycol compared to lactulose. In the study of Treepongkaruna et al, which examined and compared the effect of polyethylene glycol and

Table 2. Symptoms of Constipation within a 21-day Follow-up Period

Characteristics		Lactulose group (n=47)	95% CI	Polyethylene glycol group (n=45)	95% CI	*P* value*
Painful defecation	Before intervention	37 (78.7)	0.79(0.67-0.91)	43 (91.5)	0.91(-0.83-1.0)	0.082
	3rd day	25 (53.2)	0.53(0.38-0.68)	33 (70.2)	0.70(0.57-0.84)	0.090
	7th day	11 (23.4)	0.23(0.11-0.36)	12 (25.5)	0.26(0.13-0.38)	0.810
	21th day	0 (0.0)	0	1 (2.1)	0.02(-0.02-0.06)	0.31
P value*		<0.0001		<0.0001		
Fecal incontinence	Before intervention	21 (44.7)	0.45(0.30-0.59)	18 (38.3)	0.38(0.24-0.53)	0.53
	3rd day	18 (38.3)	0.38(0.24-0.53)	16 (34.0)	0.34(0.20-0.48)	0.66
	7th day	14 (29.8)	0.30(0.16-0.43)	10 921.3)	0.21(0.09-0.33)	0.34
	21th day	6 (12.8)	0.13(0.03-0.23)	4 (8.5)	0.09(0.0-0.17)	0.50
P value*		0.038		0.025		
Hard stools	Before intervention	46 (97.9)	0.98(0.94-1.02)	43 (91.5)	0.91(0.83-1.0)	0.16
	3rd day	25 (53.2)	0.53(0.38-0.68)	31 (66.0)	0.66(0.52-0.80)	0.20
	7th day	16 (34.0)	0.34(0.20-0.48)	12 (25.5)	0.26(0.13-0.38)	0.36
	21th day	4 (8.5)	0.09(0.00-0.17)	3 (6.4)	0.06(-0.01-0.14)	0.69
P value*		<0.0001		<0.0001		
Fear of defecation	Before intervention	29 (61.7)	0.62(0.47-0.76)	37 (78.7)	0.79(0.67-0.91)	0.71
	3rd day	15 (31.9)	0.32(0.18-0.46)	22 (46.8)	0.47(0.32-0.62)	0.39
	7th day	11 (23.4)	0.23(0.11-0.36)	10 (21.3)	0.21(0.09-0.33)	0.80
	21th day	5 (10.6)	0.11(0.01-0.20)	1 (2.2)	0.02(-0.02-0.06)	0.09
P value*		0.003		<0.0001		
Appetite	Before intervention	16 (34.0)	0.34(0.20-0.48)	18 (38.3)	0.38(0.24-0.53)	0.66
	3rd day	19 (40.4)	0.40(0.26-0.55)	22 (46.8)	0.47(0.32-0.62)	0.53
	7th day	25 (53.2)	0.53(0.38-0.68)	25 (53.2)	0.53(0.38-0.68)	0.62
	21th day	25 (53.2)	0.53(0.38-0.68)	30 (63.8)	0.64(-0.50-0.78)	0.29
P value*		0.115		0.321		
Hematochezia	Before intervention	8 (17.0)	0.17(0.06-0.28)	13 (27.7)	0.28(0.14-0.41)	0.21
	3rd day	6 (12.8)	0.13(0.03-0.23)	6 (12.8)	0.13(0.03-0.23)	0.50
	7th day	3 (6.4)	0.06(-0.01-0.14)	4 (8.5)	0.09(0.0-0.17)	0.69
	21th day	0 (0.0)	0	1 (2.1)	0.02(-0.02-0.06)	0.31
P value*		0.095		0.104		
Straining at stool	Before intervention	44 (93.6)	0.94(0.86-1.01)	44 (93.6)	0.94(0.86-1.01)	0.66
	3rd day	27 (57.4)	0.57(0.43-0.72)	33 (70.2)	0.70(0.57-0.84)	0.19
	7th day	13 (27.7)	0.28(0.14-0.41)	15 (31.9)	0.32(0.18-0.46)	0.65
	21th day	3(6.4)	0.06(-0.01-0.14)	2 (4.3)	0.04(-0.02-0.10)	0.50
P value*		<0.0001		<0.0001		
Frequency of defecation	Before intervention	2.15±1.50	2.13(1.68-2.59)	1.91±1.19	1.91(1.56-2.27)	0.44
	3rd day	4.36±3.10	4.36(3.42-5.29)	4.13±3.56	4.13(3.08-5.17)	0.74
	7th day	6.61±3.11	6.71(5.79-7.63)	8.17±3.27	8.17(7.21-9.13)	0.03
	21th day	9.07±2.38	9.09(8.36-9.81)	10.36±2.72	10.36(9.56-11.16)	0.02
P value**		<0.0001		<0.0001		
Abdominal pain	Before intervention	2.87±2.74	3.00(2.18-3.82)	4.02±2.69	4.02(3.23-4.81)	0.04
	3rd day	2.21±2.68	2.31(1.50-3.12)	3.38±2.68	3.38(2.60-4.17)	0.03
	7th day	1.87±2.40	1.96(1.23-2.69)	1.81±2.36	1.81(1.12-2.50)	0.89
	21th day	1.23±2.08	1.29(0.65-1.92)	0.57±1.29	0.57(0.19-0.96)	0.07
P value**		0.001		<0.0001		

*Chi-squared test.
**Repeated measures test.

lactulose in the treatment of constipation in children, it was observed that in the lactulose group, the frequency of stools increased from 0.7 to 0.8 and in the polyethylene glycol group from 0.5 to 1.10, indicating the higher effectiveness of polyethylene glycol. The consistency of feces and satisfaction with defecation in the polyethylene glycol group compared to the lactulose group significantly improved (17). In the study of Rendeli et al, which evaluated the effectiveness of polyethylene glycol versus lactulose in the treatment of neurogenic constipation in children with myelomeningocele, it was observed that the treatment success rate was higher in the polyethylene glycol group compared to lactulose (19). In a large study with a sample size of 216 people conducted by Wang et al on Chinese children aged 8-18 years, polyethylene glycol was also shown to be more effective than lactulose (20). In a study conducted in France by Gordon et al on 96 children aged 3 months to 6 years, it was observed that lactulose and polyethylene glycol significantly improved constipation, but the effectiveness of polyethylene glycol was significantly higher in the field of stool consistency, appetite, new-onset fecal impaction, and recourse (21). In the study of Gremse et al, it was observed that the colon transit time was significantly lower in the polyethylene glycol group compared to the lactulose group, but there was no significant difference in stool frequency, stool shape, and ease of defecation between the two groups (22). In another study by Attar et al, which evaluated the effectiveness of polyethylene glycol and lactulose in the treatment of chronic constipation, it was observed that after four weeks, patients in the polyethylene glycol group had more frequent bowel movements and the median daily score for straining at stool in them was also lower compared to the lactulose group. However, overall improvement was similar in the two groups (23). In another study, it was found that in treating infants and children's constipation, polyethylene glycol 3350 was more efficient than lactulose and it had fewer adverse effects (24). Another study indicated that lactulose and polyethylene glycol treatments were well tolerated, and no serious side effects were noted. Both treatments were safe, efficient, and well tolerated. Lactulose may be a good substitute for polyethylene glycol in treating fecal impaction in children with constipation (25). These results were consistent with the results of the present study.

Overall, it seems that polyethylene glycol is preferred over lactulose based on the more significant improvement in clinical manifestations related to defecation habits as well as greater tolerability of the drug in children. This issue is especially considered with the confirmation of fewer treatment complications in the first group. In the current study, the frequency of side effects was 21.6% in the lactulose group and 8.6% in the polyethylene glycol group, which were not significantly different; however, the prevalence of side effects was lower in the polyethylene glycol group. Taken together, more clinical studies are needed to draw more reliable conclusions.

Conclusion

In general, the results of the present study showed the administration of polyethylene glycol and lactulose had no significant difference in reducing the symptoms of chronic functional constipation in children. However, it seems that polyphenol glycol played a role in increasing the frequency of defecation. Based on the results, there were fewer side effects in the polyethylene glycol group compared with the lactulose group, but this difference was not statistically significant.

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Authors' Contribution

Conceptualization: Hassan Talakesh, Karamali Kasiri.
Data curation: Afsaneh Malekpour Tehrani.
Formal analysis: Afsaneh Malekpour Tehrani.
Funding acquisition: Karamali Kasiri.
Investigation: Alizamen Salehifard Jouneghani.
Methodology: Afsaneh Malekpour Tehrani, Hassan Talakesh.
Project administration: Farnoush Kochekian.
Resources: Alizamen Salehifard Jouneghani.
Writing-original draft: Hassan Talakesh, Karamali Kasiri.
Writing-review & editing: Hassan Talakesh, Karamali Kasiri.

Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

The study protocol was approved by the Vice-Chancellor for Research and Technology of the University and registered at the Iranian Registry of Clinical Trials (IRCT20190717044239N1). This study was conducted in accordance with the principles of the Declaration of Helsinki and its protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1398.074).

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