

Comparing the Effect of a Herbal-based Laxative (Goleghand®) and Polyethylene Glycol on Functional Constipation among Children: A Randomized Controlled Trial

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Received: 03-09-2020.
Accepted: 23-01-2021.
Published: 13-05-2021.

INTRODUCTION

Constipation is one of the most common complaints in children, ranged from 0.7% to 29.6% (median: 8.9%).^[1] It includes 3% of general pediatric consultations and 25%–30% of pediatric gastroenterology visits.^[2] Despite treatment and follow-up, only 50%–70% of children demonstrate long-term improvement.^[3,4] In up to 95% of children with the complaint of constipation, there is no underlying medical disease such as structural, endocrinal, or metabolic causes; thus, it is called idiopathic or functional

ABSTRACT

Objective: This study aimed to evaluate the effectiveness, safety, and document the reported adverse effect of a herbal-based laxative (Goleghand®) for the maintenance treatment of functional constipation in young children. **Methods:** We conducted a randomized clinical trial from April 2019 to September 2020. Children aged 2–15 years with functional constipation defined according to the Rome IV criteria were eligible for study inclusion. Eligible children were randomly allocated to receive polyethylene glycol (PEG) or Goleghand®. The number and consistency of stools per day, painful defecation, abdominal pain, and fecal incontinence were reported weekly by parents. The statistical analyses were performed by determining means and standard deviations, *t*-test, Chi-square test, ANOVA repeated measures, and Fisher's exact test, with significance, accepted at the 5% level. **Findings:** Sixty patients have been enrolled in the study. Parental satisfaction scores did not change significantly in either group or over the follow-up period. Our results showed that the effect of time ($P < 0.001$) and also the effect of group type ($P = 0.01$) on the number of fecal defecations was significant. The mean number of defecations increased first and then decreased significantly over time, but this decrease was more significant in the PEG group than in the Goleghand® group ($P = 0.001$). Furthermore, the effect of time on the fecal consistency score was significant ($P = 0.047$). The mean score of fecal consistency in both groups decreased over time. **Conclusion:** Goleghand® was similar in efficacy to PEG for 8 weeks of pediatric functional constipation treatment in this randomized clinical trial. Goleghand® can be considered as a new herbal laxative drug for pediatric functional constipation.

KEYWORDS: Child, Constipation, Herbal-based Laxative, Polyethylene glycol

constipation.^[5] Pediatric functional constipation (FC) is a common gastrointestinal disorder that can affect the child's and parents' quality of life.^[4] Although there is no unique definition, Rome IV has been used

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How to cite this article: Saneian H, Ghaedi S, Famouri F, Khademian M, Ahmadi N, Memarzadeh M, et al. Comparing the effect of a herbal-based laxative (Goleghand®) and polyethylene glycol on functional constipation among children: A randomized controlled trial. J Res Pharm Pract 2021;10:43-9.

Access this article online	
Quick Response Code: 	Website: www.jrpp.net
	DOI: 10.4103/jrpp.JRPP_20_133

as a diagnostic criterion of FC in children.^[6] Treatment for this disorder aims to establish a good defecation pattern (normal frequency and consistency of stools) without fecal incontinence and rectal bleeding. The key management steps include education, disimpaction, maintenance therapy, and behavioral modification. Oral laxatives and regular toilet training are the principles of successful treatment. It has been proposed that changing lifestyles, including a high-fiber diet, can improve constipation.^[7] The commonly used laxatives include polyethylene glycol (PEG), lactulose, magnesium hydroxide, and mineral oil.^[6,8]

PEG is a high molecular chemical compound that binds water molecules through hydrogen bonds; this leads to increased water in the colonic content, which facilitates bowel movements and painless defecation.^[9,10] Children easily tolerate it because of its tastelessness.^[11-13] A Cochrane review of randomized clinical trials demonstrated that PEG is superior to placebo, lactulose, milk of magnesia, and mineral oil to treat childhood constipation.^[14] Thus, PEG has been proposed to be effective and well tolerated as a first-line treatment for maintenance therapy.^[8,11-13]

Despite the widespread use of laxatives to manage childhood constipation, it has tended to rely on empirical treatment choices due to the lack of high-quality studies in this field.^[13,15,16] Although drug discovery has many various methods, it has a very complicated and expensive process.^[17] The use of traditional medicines can facilitate this process.^[18,19] Persian medicine is one of the traditional medicine disciplines that support various treatment modalities.^[20,21]

Goleghand®, a herbal-based laxative, is composed of honey and petals of *Rosa damascene* (also known as the Damask rose), used as a traditional medicine product for treating constipation. In Iranian traditional medicine, the decoction of Damask rose is used to treat chest and abdominal pains, menstrual bleeding, and as a laxative and antispasmodic agent. It does not have the side effects of other chemical and herbal laxatives such as Bisacodyl and Sana.^[22,23]

This study aimed to evaluate the effectiveness and safety of PEG and Goleghand® for the maintenance treatment of functional constipation in children and to document their probable adverse effects.

METHODS

We conducted a randomized clinical trial from April 2019 to September 2020 at the Department of Pediatrics of Isfahan University of Medical science, Imam Hosein University hospital, Isfahan, Iran.

This study was conducted independently of any commercial entities and was registered at the Iranian registry of clinical trials (www.irct.ir) with registration number ID: IRCT44560. Isfahan University of medical science's ethics committee approved the study protocol (IR.MUI.MED.REC.1399.082). Informed consent was obtained from at least one parent or guardian of each child included in our study.

Children 2–15 years of age with functional constipation defined according to the Rome IV criteria were eligible for the study inclusion.^[24] We made sure that patients were not under treatment for at least 2 weeks before the study recruitment. We ruled out children with a diagnosis of irritable bowel syndrome, mental retardation, endocrine disease (e.g., hypothyroidism), a structural cause of defecation disorders (e.g., Hirschsprung disease, spinal anomalies, anorectal pathology, a history of gastrointestinal surgery), functional nonretentive fecal incontinence, or intake of medications influencing gastrointestinal motility. Furthermore, we excluded children who showed intolerance and severe side effects of drugs during the study.

Once the diagnosis of functional constipation was made, the child was assessed for eligibility, and written informed consent to participate in the study was obtained from his/her parents. Eligible children were randomly allocated to receive PEG 4000 in powder form, at a dose of either 0.7 g/kg, or Goleghand® Barij Majun (Barij Essence Pharmaceutical Co., Kashan, Iran) at a dose of 0.5 g/kg, in three divided doses daily for 8 weeks. If there was any complication such as diarrhea, parents were allowed to reduce the amount of PEG and Goleghand® to 2/3 of the initial dose. If any fecal impaction symptoms were during the study period observed, an additional laxative such as Parafine 1–3 cc/kg was administered as a rescue treatment.

The following outcome measures were assessed each week: the number and consistency of stools per day, painful defecation, abdominal pain, and fecal incontinence. All patients were followed for 8 weeks, and the data were recorded in eight sheets of questionnaires (one for each week, each one contained seven boxes for each item, and 7 days of the week) by the parents. Stool consistency was reported based on the Bristol Stool Scale.^[25-28] Moreover, all of the suspected adverse events were recorded, and their possible relation to the study product consumption was clinically evaluated. Parental satisfaction with the treatment was assessed using a visual analog scale, and it could be chosen by parents, from 1 (less satisfied) to 3 (the most comfortable) each week. We had regular phone calls with the parents during the

study to check the probable complications, treatment (taking the prescribed drugs), and the data filling process. If there were any serious questions or problems, we visited the child. At the end of 8 weeks of treatment, the children were visited, and the filled out forms were taken and evaluated.

The sample size was based on the following formula:^[29]

$$N = \frac{(Z_{\alpha} + Z_{\beta})^2 * (S1^2 + S2^2)}{(\mu_1 - \mu_2)^2}$$

$$Z_{\alpha} = 1.96 S1 = 5.71 \mu_1 = 10.98$$

$$Z_{\beta} = 0.84 S2 = 3.5 \mu_2 = 7.25$$

Finally, with random assignment to the groups in a ratio of 1:1 and assuming 5% withdrawals or losses, it was calculated that sixty children had to be included in the study.

Block randomization was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial. Clinicians who enrolled the patients or assessing the outcomes, and the parents were blinded to randomization codings during the study.

The statistical analyses were performed by determining means and standard deviations (SDs), t-test, Chi-square

Table 1: Children characteristics with functional constipation in the two treatment groups (polyethylene glycol 4000 and Golghand®)

Variables	PEG (%)	Golghand® (%)	P
Age (mean±SD)	5.8±3.2	5.7±2.3	0.86*
Gender			0.89 [†]
Girl	15 (50)	14 (51.9)	
Boy	15 (50)	13 (48.1)	
Education			0.72 [†]
Preschool	17 (56.7)	14 (51.9)	
School-aged	13 (43.3)	13 (48.1)	
Past medical history			0.13 [†]
No disease	26 (86.7)	23 (85.2)	
Gastroesophageal reflux	0	2 (7.4)	
CHD	1 (3.3)	0	
Epilepsy	1 (3.3)	0	
ADHD	1 (3.3)	0	
Vesicoureteral reflux	1 (3.3)	0	
Anal fissure	0	1 (3.7)	
Anemia	0	1 (3.7)	

*Calculated by t-test, [†]Calculated by Chi-square test. CHD=Congenital heart disease, ADHD=Attention deficit hyperactivity disorder, PEG=Polyethylene glycol 4000, SD=Standard deviation

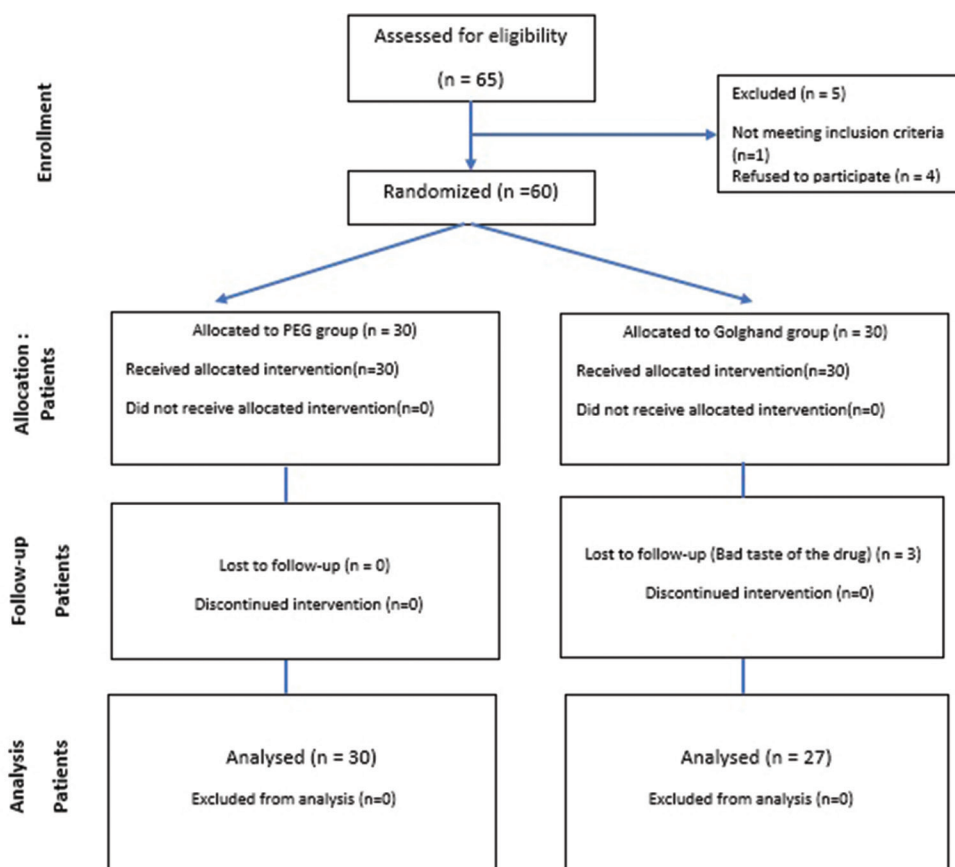


Figure 1: CONSORT flow diagram

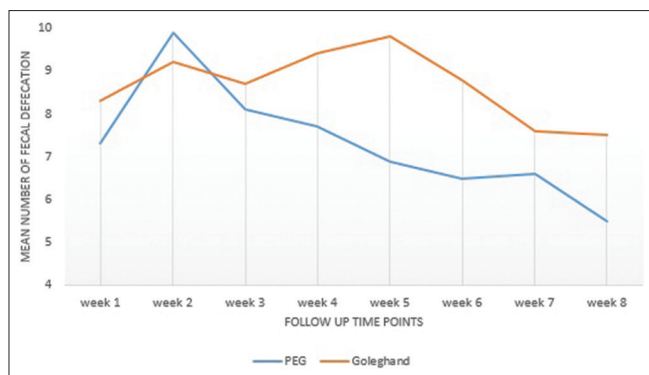


Figure 2: Mean number of fecal defecations in two groups over time of follow-up

Table 2: Parental satisfaction score of treatment in two groups (polyethylene glycol 4000 and Goleghand®) over time*

	Mean±SD		P [†]	P [‡]
	PEG	Golghand®		
Week 1	2±0.8	1.7±0.9	0.07	0.83
Week 2	2.2±0.7	1.9±0.8		
Week 3	2.2±0.6	2.1±0.7		
Week 4	2.1±0.7	2.1±0.8		
Week 5	2.2±0.6	2.1±0.8		
Week 6	2.3±0.5	2.3±0.8		
Week 7	2.4±0.6	2.6±0.8		
Week 8	2.3±0.7	2.5±0.8		

*Calculated by ANOVA, [†]Time effect, [‡]Group effect. SD=Standard deviation, PEG=Polyethylene glycol 4000

test, ANOVA repeated measures, and Fisher's exact test, with a significance level of 0.05 ($P < 0.05$ was considered as statistically significant). The results were described as mean \pm SD or percentage. SPSS IBM version 24 (64 bit edition) was used for analysis.

RESULTS

From April 2019 to September 2020, sixty patients completed our inclusion criteria and enrolled in the study. They were under observation for functional constipation by a pediatric gastroenterologist for 8 weeks after randomization. They randomly received one type of treatment. Finally, after losing follow-ups of three patients in the Goleghand® group, thirty patients in the PEG group, and 27 patients in the Goleghand® group were analyzed [Figure 1]. There were no significant differences between age, gender, education, and past medical history of children in the two groups [Table 1]. Furthermore, all of our participants lived in urban areas.

Parental satisfaction scores did not change significantly in either group or over the follow-up period based on the Chi-square test [Table 2].

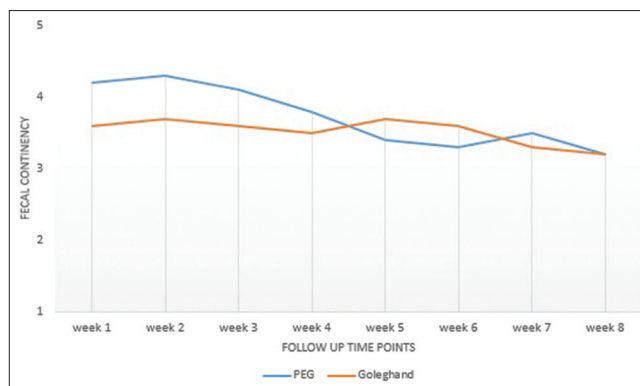


Figure 3: Fecal consistency in two groups over time of follow-up

According to the ANOVA test, our results showed that the effect of time ($P < 0.001$) and also the effect of group ($P = 0.01$) on the number of fecal defecations were significant. The mean number of defecations increased first and then decreased significantly over time, but this decrease was more notable in the PEG group than in the Goleghand® group [Table 3 and Figure 2].

Furthermore, the effect of time on the fecal consistency score was significant ($P = 0.047$). However, the effect of group type was not significant ($P = 0.53$). The mean score of fecal consistency in both groups decreased over time [Table 3 and Figure 3].

Our results based on the Chi-square test demonstrated that pain during defecation was significantly more reported among children in the Goleghand® group in week 5 ($P = 0.04$). Furthermore, diarrhea was significantly observed more in children under the treatment of Goleghand® in week 5 ($P = 0.001$). Other outcomes over other weeks of follow-up revealed no significant differences between the two groups [Table 4].

DISCUSSION

This randomized controlled trial showed that both medications were equally effective in treating children with functional constipation. After an 8-week intervention, the study groups did not differ concerning the number of defecation and stool consistency. Furthermore, parental satisfaction was not significantly different in the two groups.

Literature reviews showed that PEG was compared with placebo^[30,31] or other laxatives, including lactulose,^[32-35] milk of magnesia,^[36,37] and liquid paraffin.^[38,39] As the PEG is proposed as a first-line drug in FC, it was chosen for our study's control group. Our study's follow-up duration was 8 weeks, an acceptable period based on similar studies conducted from 2 weeks up to 12 months.^[30,31,35,40] A double-blind, multicenter, placebo-controlled trial assessed the efficacy

Table 3: Fecal defecation and consistency of stools in two studied groups (polyethylene glycol 4000 and Golghand®) of the pediatric functional constipation*†

	Fecal defecation (mean±SD)		P‡	P§	Consistency of stools (mean±SD)		P‡	P§
	PEG	Goleghand®			PEG	Goleghand®		
	Week 1	7.3±4.3			8.3±4.2	<0.001		
Week 2	9.9±4.3	9.2±5.8			4.3±1.3	3.7±1.4		
Week 3	8.1±2.9	8.7±4.7			4.1±1.3	3.6±1.3		
Week 4	7.7±2.9	9.4±5.1			3.8±1.3	3.5±1.4		
Week 5	6.9±3.4	9.8±5.8			3.4±1.5	3.7±1.3		
Week 6	6.5±3.8	8.8±4.9			3.3±1.8	3.6±1.4		
Week 7	6.6±4.2	7.6±3.9			3.5±1.6	3.3±1.5		
Week 8	5.5±4.1	7.5±5.3			3.2±1.8	3.2±1.7		

*Fecal defecation is expressed as no/week and consistency of stool is based on Bristol Stool Scale, †Calculated by ANOVA, ‡Time effect, §Group effect. $P < 0.05$ was considered significant. SD=Standard deviation, PEG=Polyethylene Glycol 4000

Table 4: Treatment outcome in two studied groups of the pediatric functional constipation, with polyethylene glycol 4000 and Golghand®*†

Time	Groups, frequency (%)											
	Pain during defecation			Side effect (diarrhea)			Fecal incontinence			Abdominal pain		
	PEG	Goleghand®	P	PEG	Goleghand®	P	PEG	Goleghand®	P	PEG	Goleghand®	P
Week 1	12 (40)	13 (48.1)	0.54	11 (36.7)	10 (37)	0.98	6 (20)	9 (33.3)	0.25	15 (50)	11 (40.7)	0.48
Week 2	9 (30)	10 (37)	0.57	8 (26.7)	7 (25.9)	0.95	9 (30)	4 (14.8)	0.17	12 (40)	8 (29.6)	0.41
Week 3	8 (26.7)	9 (33.3)	0.58	4 (13.3)	7 (25.9)	0.23	7 (23.3)	4 (14.8)	0.42	9 (30)	11 (40.7)	0.40
Week 4	10 (33.3)	10 (37)	0.77	4 (13.3)	6 (22.2)	0.38	7 (23.3)	5 (18.5)	0.66	6 (20)	9 (33.3)	0.25
Week 5	5 (16.7)	11 (40.7)	0.04	1 (3.3)	10 (37)	0.001	5 (16.7)	4 (14.8)	0.85	8 (26.7)	8 (29.6)	0.80
Week 6	11 (36.7)	6 (22.2)	0.23	6 (20)	2 (7.4)	0.16	10 (33.3)	4 (14.8)	0.11	10 (33.3)	5 (18.5)	0.21
Week 7	8 (26.7)	8 (29.6)	0.80	4 (13.3)	5 (18.5)	0.43	10 (33.3)	4 (14.8)	0.11	10 (33.3)	5 (18.5)	0.21
Week 8	6 (20)	9 (33.3)	0.25	7 (23.3)	7 (25.9)	0.82	8 (26.7)	5 (18.5)	0.46	8 (26.7)	7 (25.9)	0.95

*Values are expressed as no/week, †Calculated by Chi-square test, $P < 0.05$ was considered significant. PEG=Polyethylene glycol 4000

of three different doses of PEG 3350 in 103 children with idiopathic functional constipation showed that all doses resulted in significantly higher rates of treatment success.^[31] Another study also revealed that the efficient daily dose of PEG 4000 was approximately 0.5 g/kg/day in >90% of children with constipation.^[41] We used PEG at a dose of 0.7 g/kg and an 8-week follow-up based on Koppin *et al.*'s recommendation.^[42]

Although Goleghand® has been produced and is prescribed for constipation as a laxative agent in traditional medicine,^[23] there was no clinical trial in the pediatric population for evaluating its effectiveness. Arezoomandan *et al.* showed significant laxative effects for the boiled extract of *R. Damascena* in rats. The effect's mechanism seems to be due to osmotic infiltration of fluids into the intestinal lumen.^[43] According to our study results, Goleghand® was as effective as PEG in the treatment of children with FC. However, in a randomized clinical trial study in the elderly population, in a comparison between psyllium and Goleghand®, psyllium was better, while, Goleghand® could also increase the number of defecation.^[22] Eliasvandi *et al.* also showed that herbal capsules' consumption consisted

of Goleghand® and some other herbal products improved chronic constipation in postmenopausal women.^[44] As it is evident, these findings showed conflicting results even in the adult population. To the best of our knowledge, this study is the first clinical trial evaluating the effect of Goleghand® in the pediatric population.

An appropriate method of randomization, adequate generation of the allocation sequence, and a low percentage of patients lost to follow-up minimized the risk of selection and attrition biases in our study. Moreover, this trial enrolled a homogeneous population of children diagnosed with functional constipation based on Rome IV criteria. Furthermore, the follow-up duration was relatively appropriate. This study's primary limitation was the lack of blinding, which increases the risk of performance and detection bias. As the two drugs differed in colors, tastes, and smell and were administered to children in different ways, it was impossible to perform a blind study. However, it is similar to other studies in this aspect.^[34,36-38,40]

In this randomized clinical trial, Goleghand® was similar in efficacy to PEG for 8 weeks of pediatric

functional constipation treatment. Moreover, pain during defecation and diarrhea were significantly more reported in some weeks in the Goleghand® group. Regarding the effectiveness of Goleghand® as a new herbal drug, it might be recommended to the parents who have particular concerns in chemical drug application for their children. For more conclusive results about the side effect and outcomes of treatments of Goleghand®, further clinical trial studies are needed to clarify the long-term effectiveness of this medication for the treatment of childhood constipation.

Acknowledgments

The authors wish to thank the support from the Isfahan University of Medical Science. The funding agency had no role in study design, data collection, analysis, decision to publish, or manuscript preparation. We also thank for the cooperation of parents and all their children in our study.

AUTHORS' CONTRIBUTION

Hosein Saneian, Saeedeh Ghaedi and Peiman Nasri have contributed to the concept and design. Fatemeh Famouri, Majid Khademian, Najmeh ahmadi and Somayeh Sadeghi have contributed to the definition of intellectual content and literature search. Saeedeh Ghaedi and Peiman Nasri contributed to the data analysis. Hosein Saneian, Saeedeh Ghaedi and Peiman Nasri contributed to the manuscript preparation and all authors edited the final version of the manuscript.

Financial support and sponsorship

This study was funded by the Isfahan University of Medical Science.

Conflicts of interest

Dr Memarzadeh is the R and D manager of Barij Essence Pharmacocical Co.

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