TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 6, Issue 4, Autumn 2021

Original Research

Comparing Golqand (Persian Medicine Product) with Magnesium Hydroxide in Adult Constipation: A Randomized Clinical Trial

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Received: 19 Apr 2021 **Revised:** 25 Jul 2021 **Accepted:** 26 Jul 2021

Abstract

Chronic constipation is a highly prevalent digestive problem in the community, which would decrease the quality of life of individuals. There is not any conclusive drug of choice for constipation. Golqand (combined *Rosa* × *damascena* Herrm. and honey) has been introduced as an effective safe laxative in Persian medicine (PM). This study aimed to investigate the effects of Golqand in comparison with Magnesium hydroxide suspension (MOM) in chronic constipation. In this clinical trial, fifty-six patients with chronic constipation were randomly assigned to the study groups of Golqand or MOM. Patients received Golqand (20 g daily) or MOM (40 mL daily) for 2 weeks. Patients took the drug twice a day, MOM group used it in the morning (20 mL) and at night before going to bed (20 mL). The Golqand group used it 10 g before lunch and 10 g before dinner, dissolved it in lukewarm water and swallowed. Then, they were followed for the second two weeks without any medication. The primary outcome was frequency of defecation. Patients were evaluated before the study and two weeks and four weeks after the beginning study. Estimated marginal mean frequency of defecation in the MOM group in the first two weeks was significantly higher than the Golqnd group ($P < 0.05$). There was no significant difference among the groups in the third week when treatment was discontinued ($P = 0.155$) but in the fourth week, the Golqand group had more count of defecation than the MOM group ($P = 0.001$). There was no significant difference between the two study groups in terms of treatment satisfaction and drug side effects ($P > 0.05$). Golqand medication can be used in the treatment of constipation with very few drug side effects and a more lasting effect than MOM drug

Keywords: *Rosa* × *damascena* Herrm.; Laxatives; Herbal; Constipation; Persian medicine

Citation: Ghorbanoghli S, Mozaffarpur SA, Vakili MA, Amiriani T, Qaraaty M. **Comparing Golqand (Persian Medicine Product) with Magnesium Hydroxide in Adult Constipation: A Randomized Clinical Trial.** Trad Integr Med 2021;6(4): 348-359.

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Introduction

Chronic constipation is a common disease, especially in industrialized countries [1] due to machine life, immobility, and poor nutrition status of people [2]. Rate of constipation in adults could vary in range of 4 to 28% in various communities, and it is more common in women [3-6]. Chronic constipation is defined as infrequent defecations or a painful and difficult passage of stools in defecation that continues for few weeks or longer [7]. Constipation has rarely been regarded as a significant problem because its hospitalization and mortality rates are not high; while it could be a symptom of a disease [1-7]. The constipation would decrease the quality of life among the patients because it could lead to long-term complications such as fissure, hemorrhoid and psychological problems [8-9]. The studies have shown that dietary habits, physical activities, socioeconomic status, psychological factors, drugs, age and gender could be effective in constipation [3]. There is no definitive and effective treatment for constipation. Although there is evidence in traditional medicines about the laxative effects of some drugs, not enough clinical studies have been provided in this field [7]. The main treatments for chronic constipation depending on the severity of constipation and the patient's condition include non-pharmacological interventions such as increasing fluid intake, increasing physical activity and increasing fiber intake [8] or medications known as laxatives including magnesium hydroxide syrup (MOM) [9], polyethylene glycol, and psyllium [10]. Patients who do not respond to lifestyle changes should take laxatives [11]. However, some patients may not be able to tolerate these medications due to side effects including bloating, nausea, and electrolyte disturbances and are reluctant to use these drugs [12]. The effect of constipation on the quality of life of individuals and dissatisfaction with conventional drugs explains the growing tendency of patients and researchers to use other methods of complementary and alternative medicine [13]. Persian medicine (PM) as one of the complementary and alternative therapies tries to provide simple and useful solutions to maintain health and treat diseases of different groups in the community. Compounds of medicinal plants including *Rosa × damascena* Herrm. and Golqand are the most common drugs used in PM in treatment of constipation [14].

R. damascena is a pink/red and fragrant flower that is cultivated and rain-fed in various parts of Iran [15]. Historical documents show that this plant was first cultivated in the ancient land of Persia and other regions of the Middle East. In the studies performed on *R. damascena*, various effects such as antibacterial, antioxidant, anti-inflammatory, antispasmodic, anxiolytic, sedative, laxative, and hypoglycemic properties have been mentioned [16,17]. There are also several animal studies on the laxative effects of this plant. These animal studies have shown that the mechanism of the aqueous components of *R. damascena* affecting the intestinal contraction can be due to their stimulatory effects on cholinergic receptors and colonic histamine [18]. A human study has been performed on Golqand and its laxative effects have been shown in the elderlies [21].

In routine dosage of *R. damascena* (3 to 6 g per day) prescription, there were no evidences of toxicity and its safety is well documented in various studies [17,19]. Golqand is a Persian medical product that is the combination of R. damasena and honey. Honey which is used in Golqand product is also appreciated for its laxative advantages [20]. There is a lot of evidence in PM about the laxative effects of Golqand that needs further investigation [12]; however, not enough studies have been done so far in this field. This study aimed to evaluate Golqand laxative effects in comparison with MOM in treatment of chronic constipation.

Materials and Methods

Trial design and randomization

This study was a randomized, parallel-group clinical trial that compare the effects of MOM and Golqand in chronic constipation in adult from September 2019 to March 2020. Fifty-six patients were selected according to the inclusion criteria by convenience sampling method. They were divided into two groups of Golqand and MOM by simple random sampling method. Random allocation of patients was performed using simple sampling method and data were analyzed using SPSS 18 software.

Participants

In this study, 158 patients with a diagnosis of constipation were referred from the Gastroenterology clinic to the Persian Medicine Clinic, Gorgan University of Medical Sciences, Iran.

Inclusion criteria

The patients with the age range of 20 to 70 years old, who were diagnosed with chronic constipation based on the ROME IV criteria, after obtaining written informed consent, entered to the study. They must meet at least 2 of the following criteria: (i) need for high force in at least 25% of cases of defecations (ii) Hard or bullet-like stools in at least 25% of defecations (iii) Feeling of incomplete emptying in at least 25% of defecations (iv) Feeling of rectal obstruction or cramping in at least 25% of defecations (v) need for maneuvering for the pelvic floor at least in 25% of defecations, (vi) have less than 3 defecations per week; Also in the last three months, without the use of laxatives rarely have soft stools, and when diagnostic criteria for irritable bowel syndrome are not enough [21].

Exclusion criteria

Pregnant and lactating women and patients taking drugs like opioids were not included in the study. Individuals with a history of mechanical and pseudo-gastrointestinal obstruction based on previous colonoscopy or radiography or medical record were not included in the study. Also, people with underlying metabolic and endocrine diseases, neurological and myopathic diseases, progressive systemic sclerosis, renal failure and special surgical and medical conditions such as inability to move, history of bowel surgery, etc., were not included in the study. Patients with endoscopic and radiological reports and medical reports in the last 5 years showing abnormality, malignancy, or inflammatory bowel diseases (IBD) were not included in the study.

Intervention

The selected patients entered the study after obtaining informed written consent. After fulfilling the inclusion and exclusion criteria a socio-demographic checklist was completed. The patients received a full explanation about the study and how to consume the drugs. Patients were randomly assigned to two groups of MOM or Golqand. The first group used MOM (Soha company, Iran) in two tablespoons or about 40 mL (considering that the standard dose in the book of Iranian generic drugs [19] is between 30 to 60 mL) in two divided doses. They used it in the morning (20 mL) and at night before going to bed (20 mL). The second group of patients used Golqand one tablespoon before lunch and one tablespoon before dinner. That is, 10 g before lunch and 10 g before dinner of Golqand (NIAK company, Iran) dissolved in lukewarm water and swallowed. Medication and questionnaires were given to patients for the next two weeks. In the first stage (first two weeks), the patients received the drug according to the prescribed dose. In the second stage (the second two weeks), the medications were stopped and the patients were monitored without the drug. Patients were asked not to change their diet and exercise during the intervention and not to use any other laxative.

At the beginning of the study, a questionnaire related to demographic characteristics including name, sex, level of education, as well as a checklist of gastrointestinal symptoms in terms of PM, which includes changes in defecation pattern, bloating, nausea, heartburn, and stomach pain were completed. After how to fill in the questionnaires using Bristol criteria (photos and descriptions) and ROME IV criteria were explained to patients in detail. The constipation questionnaire was according to ROME IV criteria, which include stool characteristics such as frequency of defecation, the need for manual maneuvering, high defecation force, hard or bullet-like stool, feeling of incomplete emptying or rectal obstruction. After that, the constipation questionnaire was given to the patients for two weeks. People had to fill out questionnaires daily. All patients were followed up by telephone each week and visited two weeks after taking the drug. Filled forms were received and blank forms were given back to patients so that over the next two weeks, patients filled out questionnaires without medication. At the end of the fourth week, the third visit was performed and the filled forms were received from the patients. At the end of the study, the form of side effects for patients was completed.

Herbal medicinal product

Golqand is a combination of honey and *R. damascena*, which is prepared in a process of 40 days. The drug was analyzed by NIAK Company. The concentration of the phenolics content in the hydroalcoholic extract of the *R. damascena* preparation was determined via the spectrophotometric method and the Folin-Ciocalteu reagent, NaHCO3 solution, and gallic acid as the standard. Analysis showed the presence of reducing sugars 39.5 g (39%) - sucrose 19.5 g (19%) - fructose 10.2 g (10%) - total volatile oil 17.5 g (17%) - geranium 7 mg (007%) - citronellol was 5 mg (005%) (Amount of material

per 100 g of Golqand).

Primary and secondary outcomes

The main outcome of this study was the frequency of defecation and other dependent variables, the amount of tension, the frequency of hard defecation, the use of manual maneuvers, incomplete defecation, and the time of daily defecation.

Sample size

Based on the study of Hatefi et al. in 2017 [21] and taking into account at least 6 units difference in average number of defecation in two methods, a difference of 3 units difference in average of defecation before and after the intervention, a depletion rate of 20% and a statistical power of 80%, 28 samples in each group was calculated. Sampling was done by available sampling and among the patients referred to PM clinic of Gorgan Educational and Medical Center.

Statistical analysis

The normality of numerical variables such as frequency of defecation and age in both groups was examined by Shapiro-Wilk test and the hypothesis of normality of the data was not confirmed. Baseline characteristics and outcome measures were compared between two groups using Mann-Whitney U test for numeric variables, and Pearson's chi-square for categorical variables. Proportions of rare events were assessed by Fisher's exact test. In addition, the mean rank of defecation in case of lack of normality assumptions in the previous time points, one, two, three, and four weeks after the start of the study in each of the two groups was analyzed by Friedman test. The statistical software used to analyze the data was statistical package for the social sciences (SPSS) 18. The significance level of all tests was considered 0.05.

Results

In the present study, 158 patients were studied and finally, 56 patients were selected for this study. During the study, 6 people (three in the Golqand group and three in the MOM group) were excluded from the trial. In the Golqand group, one patient withdrew from the study due to the impossibility of referring to follow up, one due to influenza, and one person for not completing the questionnaire (severe bloating) were excluded from the study. In the MOM group, one person due to travel, one person due to severe diarrhea and one patientsdue to incomplete questionnaires were excluded from the randomization. Finally, 50 patients (25 subjects in the Golqand group and 25 people in the control group) completed the study (Figure 1). According to table 1, the mean age of participants in Golqand and MOM groups were 46.48 ± 11.02 and 49.8 ± 11 years, respectively, with no significant difference between them ($P = 0.292$). There was no significant difference in terms of gender distribution, occupation, and level of education between participants in the two groups ($P > 0.05$). In the two groups, the severity of constipation with the variables of the feeling of incomplete emptying before the intervention, feeling of obstruction in the anus, feeling of need for manual maneuvers, number of defecations in the previous week of interven-

tion, and the amount of pressure were not significantly different (P > 0.05). In assessment of Rome IV criteria, most cases fit with the criteria and there was no significant difference among both groups in the inclusion criteria and ROME IV criteria (Table 1). Manual maneuvers to facilitate defecations were needed for 13 and 15 subjects in Golqand and
MOM groups, respectively; with no significant difference (P = 0.9).

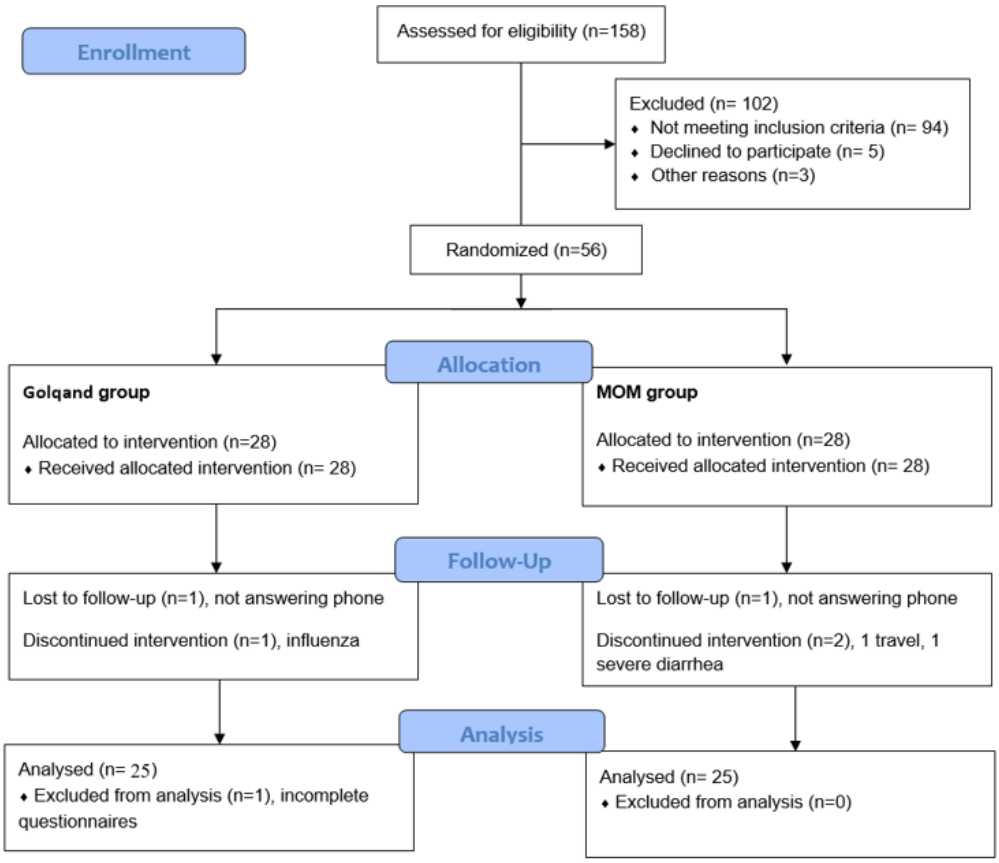

Figure1. flow chart of the sample selection

In the study of the number of defecations per week, the data collected during 4 weeks were analyzed by McNemar's test. The results showed a significant difference between the two groups (P = 0.001). The estimated marginal mean in the MOM group in the first two weeks of consumption was significantly higher than the Golqand group (P < 0.05). There was no significant difference with drug discontinuation in the third week (P = 0.155). But in the fourth week, the Golqand group had more defecation than the MOM group (P = 0.001) (Table 2). The results of Friedman test in MOM and Golqand groups showed that the trend of changes in the frequency of defecation was increasing in the first week, relatively stable in the second week and decreasing in the third and fourth weeks, and these changes were significant according to Friedman test (P = 0.000).

Table 1. Baseline characteristics of study subjects

		Golqand N=28	MOM N=28	P value**
Age (year), M±SD		47.82±11.31	48.86±10.77	0.61
Gender	Male, n (%)	5(17.9)	8(28.6)	0.34
	Female, n (%)	23(82.1)	20(71.4)	
Education level	Diploma and lower, n (%)	12(42.9)	10(35.7)	0.58
	Bachelor, n (%)	15(53.6)	17(60.7)	
	Higher education level, n (%)	1(3.6)	1(3.6)	
Occupation	Homeworker, n (%)	11(39.3)	10(35.7)	0.16
	Employee, n (%)	12(42.9)	7(25)	
	Freelancer, n (%)	5(17.9)	11(39.3)	
Number of defecations in the week before the intervention	Once every 10 days, n (%)	8(28.6)	8(28.6)	1
	Once a week, n (%)	10(35.7)	10(35.7)	
	Twice a week, n (%)	10(35.7)	10(35.7)	
ROME IV criteria*				
Pressure to evacuate		28(100)	28(100)	1
Hard stools		28(100)	28(100)	1
Sensation of incomplete evacuation		26 (92.9)	25(89.3)	0.64
Manual maneuvers to facilitate defecations		13(46.4)	15(53.6)	0.59
Less than three evacuations per week		28(100)	28(100)	1

* In more than 25% of defecations ** Chi-square and Mann-Whitney U test

Table 2. Frequency of defecation

	Drug	N	$\bar{X} \pm SD$	Mean Rank	P value*
Before intervention	Golqand	25	1.24 ± 0.55	25.84	0.861
	MOM	25	1.22 ± 0.56	25.16	
First week	Golqand	25	8.08 ± 2.02	20.04	0.007
	MOM	25	9.68 ± 1.97	30.96	
Second week	Golqand	25	8.04 ± 1.86	19.96	0.006
	MOM	25	9.64 ± 1.98	31.04	
Third week	Golqand	25	5.20 ± 0.82	28.22	0.155
	MOM	25	4.80 ± 1.12	22.78	
Forth week	Golqand	25	4.88 ± 0.78	32.32	0.0004
	MOM	25	3.88 ± 1.13	18.68	

* Mann-Whitney U test

Table 3 shows the number of patients who met the ROME criteria before and after the study. Before the study, there was no significant difference in the number of symptomatic individuals. In the first phase of the study, improvement in ROME IV criteria was observed in all patients, but no significant difference was observed between the two groups. In the second phase of the study, the number of symptomatic patients increased and a number of patients complained of recurrence of symptoms. But except for the feeling of incomplete emptying, which was a significant difference between the two groups, no significant difference was observed in the other criteria.

The estimated marginal mean (score of ROME IV criteria) in the MOM group in the first two weeks of consumption was significantly lower than the Golqand group ($P < 0.05$). In the fourth week, the Golqand group had lower mean score of ROME IV criteria than the MOM group ($P = 0.001$).

Table 3. Number of symptomatic individuals before and after the interventions

ROME IV criteria	Before			After 2 weeks			After 4 weeks		
	Golqand N (%)	MOM N (%)	P value	Golqand N (%)	MOM N (%)	P value	Golqand N (%)	MOM N (%)	P value
Pressure to evacuate, n (%)	25(100)	25(100)	-	8(32)	6(24)	0.53**	21(84)	25(10)	0.06**
Hard stools, n (%)	25(100)	25(100)	-	6(24)	3(12)	0.23*	14(56)	20(80)	0.69**
Sensation of incomplete evacuation, n (%)	24(96)	24(96)	0.76*	11(44)	9(36)	0.56**	19(76)	24(96)	0.049*
Need to Manual maneuvers, n (%)	13(52)	15(60)	0.57**	2(8)	3(12)	0.50*	5(20)	7(28)	0.51**
Less than three evacuations per week, n (%)	25(100)	25(100)	-	0	0	-	0	2(8)	0.25*

*Test: Fisher Exact test, **Test: Chi-square test

Patients were asked about the first day of defecation after taking the drug. In Golqand group, 17 patients (68%) and in MOM group, 18 patients (72%) had defecation on the first day of taking medication. On the second day of intervention, 8 patients (32%) in Golqand group and 6 patients (24%) in MOM group reported the first defecation after taking the drug. All patients in Golqand group reported the first bowel movement by the second day. On the third day, one patient (4%) in the MOM group reported the first defecation.

There was no significant difference between the two study groups in terms of treatment satisfaction and drug side effects ($P > 0.05$). No serious side effects were reported in patients. Fecal incontinence, headache, rectal bleeding, and aggravation of the need for maneuvering were not seen in any of the subjects. A member of the MOM group experienced episodes of moderate vomiting and loose stools; while in the Golqand group, no such side effects were observed.

Discussion

In recent decades, medicinal plants have been getting more attention in research and in clinical practice. Medicinal plants are usually easily accessible and people are more inclined to use medicinal plants [22]. Chronic constipation is one of the disorders in which patients are willing to use complementary medicine and herbal medicines. Golqand is one of the drugs used for chronic constipation in PM.

In the present study, MOM showed a better response than Golqand during treatment. However, after discontinuation of the drug, the number of defecations in the MOM group decreased sharply; however, subjects using Golqand had a significantly higher number of bowel movements per week in the fourth week than MOM group. Previous studies have investigated the effect of Golqand on animal models [23-24] and clinical studies [21].

In a study on dogs, the laxative effects of *R. damascena* extract were investigated. Five groups of dogs (number = 5) received this extract in doses of 0.5-8 g. This dosage is traditionally considered to be 180 mg/kg for daily human consumption. Placebo and lactulose were considered as negative and positive control groups, respectively. Ten days after the test, diarrhea occurred in a dose-dependent manner; however, no significant change was observed in fecal water. Thus, it was concluded that the extract of *R. damascena* had a laxative effect on dogs [23].

The effect of decoction of *R. damascena* extract in comparison with lactulose and salt solution has been evaluated in mice. In a study, the number of stools and the percentage of water in stools significantly increased in response to 1.5 g/kg of *R. damascena*, but the duration of intestinal transition did not change. Therefore, the osmotic penetration of fluids into the intestine can be considered as a mechanism for the laxative effect of *R. damascena* [24].

In another study, the effect of hydroalcoholic extract of *R. damascena* grown in Kashan (Iran) was investigated on the motility of rat colon. Colonic contractions were caused by electric field stimulation. *R. damascena* extract (10-100 µg/mL) caused a contraction in the protruding colon of mice; while, at a concentration of 1 mg/mL, it had a shutting effect on the rat colon. The concentration of hydroalcoholic extract of *R. damascena* (1-8 mg/mL) indirectly inhibits colonic contraction due to the presence of potassium chloride-acetylcholine and electric field stimulation. It was concluded that specific concentrations of *R. damascena* extract had a stimulating effect on colonic smooth muscle and this confirms the effectiveness of *R. damascena* in the treatment of constipation [25].

In another study, the effect of different concentrations of aqueous components of *R. damascena* (0.66, 0.83, and 1.3 mg / ml) was assessed on the contraction of the protruding colon of guinea pigs, in comparison with acetylcholine and in the presence or the absence of atropine. According to the results, the aqueous components of *R. damascena* , in a dose-independent manner, increased mild contractions of the lower colon of guinea pigs. As a result, the aqueous components of *R. damascena* have a stimulating effect on colonic contraction and may be considered

as a laxative. The action of the aqueous component of rosemary on intestinal contraction can be due to its stimulatory effect on cholinergic receptors and colonic histamine [26].

In a clinical study at Rafsanjan University in 2018, Hatefi et al. examined the effects of Golqand and psyllium on improving constipation in the elderlies aged 60 to 70 years. The results of this study showed that the frequency of defecation increased in both intervention groups. Between the two groups, the frequency of defecation in the psyllium group increased more than the Golqand group ($p < 0.001$) and it was suggested that Golqand as a non-pharmacological intervention can be effective in improving constipation in the elderly patients [21].

The main and effective ingredients of rose essential oil include 30-40% geraniol, 40-60% citronellol, 20-30% linalool, which all are being completely absorbed from the gastrointestinal tract and metabolized in the liver. *R. damascena* reduces the activity of the sympathetic system and strengthens the parasympathetic system, which has effects such as skin repair, moisturizing, anti-itch, and antiemetic. [27]. Citronellol and geraniol as the main compounds of *R. damascena* can inhibit the inflammatory process by decreasing nitric oxide (NO) [28]. NO has an inhibitory effect on bowel movement as a neurotransmitter [29]. This could be a possible explanation for physiological role of *R. damascena* in relieving constipation. Also, geraniol was reported to reduce intestinal dysbiosis and be efficient in relieving the symptoms of patients with irritable bowel syndrome [30]. It was suggested that the plant can change the human intestinal microbiota by increasing number of Collinsella and Faecalibacterium, which helps patients with IBD [31]. Gut microbiota imbalance has been seen to have a significant effect on the bowel movements [27]. But further studies are needed to exactly determine the physiologic pathways that are responsible for laxative effects of *R. damascena*.

The strength of our study was the method of matching patients in both groups and evaluates several aspects of constipation. This study was not blinded by patients and researchers, and this was a limitation of our study. So, we suggest further studies with blinded methodology.

Conclusion

The results of our study showed that the use of Golqand can be effective in the treatment of chronic constipation and its laxative benefits the last longer after medication discontinuation. However, due to the limited number of subjects in our study further studies seem necessary and useful.

Ethical Issues

This Study was a randomized clinical trial that approved by the Medical ethics committee of Golestan University of Medical Sciences with the code of IR.Goums.Rec.1397.276 and was registered in Iranian registry of clinical trials (IRCT20180114038354N1) to August 2019.

Abbreviations

MOM: Magnesium hydroxide

PM: Persian medicine

Conflict of Interest

The authors declare no conflict of interest related to this work.

Acknowledgements

We would like to appreciate Health management and social development research center and Niak Pharmacy Company for their collaboration in this research. This work was a PhD student dissertation.

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