

A Randomized Clinical Trial on Treatment of Chronic Constipation by Traditional Persian Medicine Recommendations Compared to Allopathic Medicine: A Pilot Study

Abstract

Background: The aim of this study was to compare the efficacy and side effects of lactulose plus traditional Persian medicine with only lactulose on the functional chronic constipation. **Methods:** Participants included 20 patients (10 in each group) aged 18–80 years, with major inclusion criteria of ROME III. They were assigned into two parallel therapeutic groups, including the intervention group (lactulose plus traditional Persian medicine [TPM] advices) and control group (only lactulose) through a block randomization. Weekly follow-up was done for 1 month for both groups. **Results:** After the intervention, the frequency of bowel habit increased significantly in patients of both groups ($P = 0.001$), and the frequency of hard stool defecation, sensation of painful defecation, sensation of incomplete evacuation, sensation of anorectal obstruction, and manual maneuver for evacuation were decreased significantly in patients of both groups ($P < 0.001$ for all comparisons and 0.025 for manual maneuver). However, the only significant difference between the two groups was more reduction in the sensation of painful defecation in the lactulose group versus lactulose plus TPM advices ($P = 0.014$). **Conclusions:** Based on the pilot study, no significant difference was shown between TPM with lactulose and lactulose only in the management of chronic functional constipation. However, the easy recommendations of TPM can be useful in improving chronic constipation.

Keywords: Chronic functional constipation, lactulose, traditional Persian medicine

Introduction

Chronic constipation is a common complaint in practical evaluations.^[1] Prevalence of constipation is up to 12% of people worldwide.^[2] People in the United States and Asia-Pacific suffer twice as much as their European counterparts.^[2] An epidemiological survey, which explored duration and frequency of constipation in Iran, showed the high frequency of constipation in our country.^[3] In a systematic review by Peppas *et al.*, a high prevalence of constipation was reported as a cause for high economic and low-life quality in Pacific and European counterparts.^[4] Constipation is a common complaint in clinical practice and usually refers to persistent, difficult, infrequent, or seemingly incomplete defecation; however, low-stool frequency alone is not the sole criterion for diagnosis of constipation.^[1] According to the traditional Persian medicine (TPM) resources, *E'ateghql-e-batn* is a condition in which

the afflicted patients develop a decrease in the frequency of bowel movements and dry and hard stool.^[5] Based on important TPM articles, constipation may be due to food dryness, low food ingestion, warmth and dryness of the colon, neurologic colon problem (intestinal sensory loss), high urination, high air temperature, hardworking, or high exercise.^[5,6] Management of chronic constipation should be highly individualized and dependent on cause, coexisting morbidities, and cognitive status.^[7,8]

Based on TPM, prophylaxis and healthcare are preferred compared to treatment.^[9,10] Attention should be paid to healthy lifestyle with six important principles (1 - healthy air; 2 - healthy water and food; 3 - physical activity and repose; 4 - control of stress; 5 - control of “retention and release”; and 6 - management of awakening and sleep).^[11,12] Usage of the six causes must be on the basis of everybody's need.^[13] In TPM, diagnosis

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and treatment are based on the patient's temperament and affected organs.^[14] Other TPM-commented curative drugs are “*Golghand*” (a pharmaceutical composition of roses and honey) and “*Cassia fistula* fruit”, *Descurainia Sophia*, and locally abdominal massage with castor oil or olive oil.^[11,14,15]

Important drugs in allopathic medicine, for example, lactulose are not the final and exclusive treatment, and they have transient or intermittent effect only with long- or short-term side effects; thus, there is no effective treatment without side effects for chronic constipation.^[16] This study aims to compare the impacts of some of TPM recommendations with lactulose on functional chronic constipation.

Methods

Study design

This pilot randomized controlled clinical trial was conducted from September 2014 to October 2014 at Shahid Motahari Polyclinic in Shiraz, Iran. This project was approved by the Ethics Committee of Shiraz University of Medical Sciences and registered in IRCT (ID: IRCT2014070915587N6). The sample size was determined based on similar studies.^[17,18] From all the patients, 20 patients, who met the ROME III criteria, were enrolled in this study (10 in each group).

Inclusion and exclusion criteria

Patients of both sexes were considered for inclusion in the study if they were 18–80 years old and suffered from chronic functional constipation. The diagnosis of chronic functional constipation was based on the following criteria which were fulfilled for the past 3 months with symptoms onset at least 6 months before diagnosis:

1. Must include two or more of the following:
 - a. Straining during at least 25% of defecations
 - b. Lumpy or hard stool in at least 25% of defecations
 - c. Sensation of incomplete evacuation for at least 25% of defecations
 - d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
 - e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
 - f. Fewer than three defecations per week
2. Loose stool being rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome.

The exclusion criteria were based on the suspicion to metabolic etiologies and organic disorders such as obstructive disorders and neurologic problems. Moreover, patients taking concomitant medications which may modify bowel habits were excluded from the study as were those suffering from severe liver, renal or cardiac diseases, and pregnant or breastfeeding women. For patients older than

45 years of age, exclusion of constipation secondary to colonic disease was verified by colonoscopy or a barium enema performed within the past 5 years. An organic cause of constipation was excluded by the practitioner. Patients previously exposed to lactulose were not excluded from the study.

Randomization and blinding

Random allocation software Ink (Version 1.0, May 2004) was used for randomization by a block size of five. According to a randomized, double-blind design (at the level of researcher and the person who did the statistical analysis), the patients received active lactulose or traditional medicine lifestyle^[17,18] including prophylactic and curative health orders for 4 weeks.

Interventions

One group received lactulose syrup and the second group took lactulose plus traditional medicine lifestyle (prophylactic and curative health) recommendations. The reference drug was lactulose syrup containing 10 g lactulose diluted in 15 ml water (lactulose, Sobhan Pharmaceuticals, Tehran, Iran).

The maximum daily dose for lactulose was 60 ml, and it was divided into 3 doses/day. Lactulose dosage alterations before and after each period were recorded. The patients were asked to increase the dose up to 50% every 3 days, if they had no bowel movements for 3 days or suffered painful defecation and hard stool, up to at most twice as much as the initial doses.

If the stool was loosened, they could reduce the dosage to half or one-third of the routine doses. After each week, the patients were also given an option to change the dosage, depending on the efficacy and their tolerance of the drug. No other treatments for constipation were allowed during the study.

Throughout the study, the patients in the lactulose group were instructed to follow their usual diet, but those of the lactulose group plus TPM schemes were instructed to follow their diet based on TPM schemes or instruction. The recommendation of TPM administered to the patients of the other group is shown in Box 1.

Data collection and evaluation of the patients

At enrollment, a complete history was taken and physical examination done by a physician who was not involved in the study. Some variables including the number of stool frequency, hard stool, painful defecation, sensation of incomplete evacuation, sensation of anorectal obstruction, and manual maneuvers were recorded. The patients were requested to refer to the on-call physician if they developed more than 7 days lack of bowel movement or were confronted with any complication. TPM schemes were evaluated with a questionnaire filled out daily by patients

Box 1: Recommendations from traditional Persian medicine giving to the patients

Chew the food until it is almost a liquid
 Have three regular meals per day
 Relax during meals and allow time for digestion
 Do not drink water or any other drinks near, within and just after meals
 Do not drink cold water or any other drinks when fasting in the morning
 Have one kind of food for each meal
 Fruits, yogurt, and salads should be only eaten during the day and not within a meal
 The best kinds of meats could be selected as chickens or lamb kebab
 Have 1-2 tablespoonful olive oil with salads
 Avoid some foods such as eggplant, lentil, tomato, cabbage, mushroom, and beef
 Preferably, drink warm milk with a spoon of honey
 Take light starters such as soups before the main course in a meal
 Avoid fries, chili, or salty foods
 Avoid heavy meals

of the lactulose group plus TPM and followed weekly by the staff.

Efficacy and tolerance assessment

Clinical efficacy and tolerance were assessed using a weekly card in which the patients reported the number of defecations and the following symptoms: hard stool, painful defecation, sensation of incomplete evacuation, sensation of anorectal obstruction, and manual maneuvers. These symptoms were evaluated on a five-point Likert scale ranging from 0 (never or rarely), 1 (sometimes), 2 (often), 3 (most of the times), and 4 (always) separately. At the 4th and 8th weeks of the follow-up of the patients, the patients' overall improvement and tolerance to treatment were assessed, regardless of discontinuation of the medication. After the first 2 weeks, the medication continued for further 2 weeks after obtaining the patients' agreement.

Outcome measures

Response to treatment was defined as a reduction or elimination of ROME III criteria after the 4th week. Patients were considered as failure and withdrawn from the study if they had no bowel movement for 7 days or developed fecal impaction at any stage. The incidence and severity of gastrointestinal (GI) adverse events including flatulence, abdominal pain, and treatment compliance were monitored at the end of the 2nd and 4th weeks.

Long-term follow-up of the patients

After completion of the protocol, the patients were followed to take lactulose or lactulose plus TPM schemes for 2 additional months to evaluate the long-term efficacy and safety of the treatment. Body weight and height were measured for all the patients at the time of selection for body mass index measurement.

Ethics

This project was approved by the Ethics Committee of the Shiraz Medical University. All the patients were informed verbally by a physician and gave their written informed consent for the study before enrollment. The patients were referred by the gastroenterologist after careful examination and with the diagnosis of chronic functional (idiopathic) constipation.

Statistical methods

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean \pm standard deviation (SD) for quantitative data and frequency plus percentage of quantitative data. Student's *t*-test, repeated measure ANOVA, and Chi-square were used to determine the differences. The statistical significance level of α was considered 0.05.

Results

Demographic characteristics

Among 28 patients who were referred to polyclinic, 22 cases who met the ROME III criteria for constipation were enrolled in the study. Four out of 22 patients (two per groups) withdrew from the study due to personal causes. At the end of the study, 18 patients (lactulose: 9 and lactulose plus TPM advices: 9) were analyzed [Figure 1].

The participants' age mean \pm SD in the lactulose and lactulose plus TPM advices were 46.66 ± 15.73 and 42.44 ± 11.30 , respectively ($P > 0.05\%$). Demographic characteristics of participants are presented in Table 1.

In all patients, the duration of constipation was more than 6 months. Five out of nine patients in the lactulose and three out of nine in the lactulose plus TPM groups had a history of receiving multiple medications over 6 months without suitable therapeutic effects.

Response to treatments

The effects of 4-week treatment with lactulose only and lactulose plus TPM advices for patients with chronic constipation are shown in Table 2. Increasing significantly in bowel habit times in patients of both groups, following the intervention ($P = 0.001$). The frequency of hard stool defecation, sensation of painful defecation, sensation of incomplete evacuation, sensation of anorectal obstruction, and doing manual maneuver for evacuation were decreased significantly in patients of both groups, following the intervention ($P < 0.001$ for all except 0.025 for manual maneuver) as shown in Table 2 and Figure 2.

The same pattern was observed in both groups in all outcomes due to interventions, except in sensation of painful defecation which was significantly decreased in patients who received lactulose only in comparison to the another group ($P = 0.014$).

Table 1: Baseline characteristics in the lactulose and lactulose plus traditional Persian medicine advice groups

Variable	Group A: Lactulose (n=9)	Group B: Lactulose plus TPM schemes (n=9)	P
Age (mean±SD)	46.66±15.73	42.44±11.30	0.429
BMI (mean±SD)	23.46±2.97	23.58±4.51	0.186
Sex, n (%)			
Male	5 (56)	2 (22)	0.167
Female	4 (44)	7 (88)	
Residency, n (%)			
Rural	6 (67)	2 (22)	0.077
Urban	3 (33)	7 (88)	
Baseline frequency of ROME III criteria at week zero (mean±SD)			
Bowel habit occurrence	1.00±1.00	1.11±1.16	0.831
Hard stool	3.56±0.52	3.44±0.52	0.661
Sensation painful defecation	2.89±1.05	3.22±0.97	0.496
Sensation of incomplete evacuation	3.00±0.86	2.89±0.92	0.626
Sensation of anorectal obstruction	2.22±1.48	1.89±1.36	0.796
Manual maneuvers for evacuation	0.44±0.72	0.78±1.30	0.512

TPM=Traditional Persian medicine, SD=Standard deviation, BMI=Body mass index

Table 2: Comparison of stool frequency, hard stool, painful defecation, sensation of incomplete evacuation, sensation of anorectal obstruction, manual maneuvers in the lactulose and lactulose+ schemes groups in the weeks of follow-up

Outcomes (mean±SD of times)	Intervention	Week 0 (before Intervention)	Week 1	Week 2	Week 3	Week 4	P
Bowel habit occurrence	Group A ^a	1.00±1.00	2.67±1.32	2.78±1.20	3.00±1.00	3.00±1.00	Time ^c : 0.001
	Group B ^b	1.11±1.16	1.89±1.05	2.87±0.86	2.78±0.83	3.11±0.78	Group ^d : 0.550
Hard stool	Group A	3.56±0.52	0.56±0.72	0.78±1.09	0.44±0.72	0.78±0.97	Time: <0.001
	Group B	3.44±0.52	1.00±1.41	1.11±0.92	1.22±1.09	1.44±1.01	Group: 0.215
Sensation painful defecation	Group A	2.89±1.05	0.56±0.52	0.22±0.66	0.44±0.72	0.44±0.72	Time: <0.001
	Group B	3.22±0.97	1.11±1.05	1.33±1.11	1.44±1.01	1.22±0.97	Group: 0.014
Sensation of incomplete evacuation	Group A	3.00±0.86	1.00±1.32	0.44±0.88	0.67±0.86	0.78±1.09	Time: <0.001
	Group B	2.89±0.92	1.22±0.83	1.22±0.97	0.78±1.09	0.67±1.11	Group: 0.607
Sensation of anorectal obstruction	Group A	2.22±1.48	0.78±1.30	0.22±0.66	0.22±0.66	0.22±0.66	Time: <0.001
	Group B	1.89±1.36	0.67±0.86	1.22±1.39	0.78±1.09	0.89±1.16	Group: 0.309
Manual maneuvers	Group A	0.44±0.72	0.22±0.44	0.00±0.000	0.00±0.000	0.22±0.66	Time: 0.025
	Group B	0.78±1.30	0.22±0.66	0.22±0.66	0.11±0.33	0.00±0.00	Group: 0.889

^aGroup A: Lactulose; ^bGroup B: Lactulose plus TPM advices, ^cP-value within groups, ^dP-value between groups. Repeated measures ANOVA was used for analyzing the data. Significant level of α was considered as ≤ 0.05 . SD=Standard deviation

Changing occurrence in the dosage of lactulose consumption

In six out of nine patients who received lactulose plus TPM recommendation, the dose of lactulose consumption decreased, and two of them discontinued consumption of lactulose during the study due to sensation of well-being and cure of constipation. Table 3 shows a statistically significant difference in decreasing the dosage of lactulose consumption between the two groups ($P = 0.001$).

The outflow of the patients from ROME III criteria of constipation

At the end of the study, eight out of nine in the lactulose group and seven out of nine in the lactulose plus TPM advices did not have ROME III criteria at the end of 4 weeks of the follow-up. We did not find any

significant difference between the two groups in this subject [Table 4].

Adverse events

Significant adverse events were not reported for the patients in both groups.

Discussion

TPM sages suggest several viewpoints for the treatment of chronic constipation. TPM is a holistic medicine, and its therapeutic advice is based on individual differences among patients.^[19] The first-line intervention for treatment of the chronic disease as well as constipation (*E'ateghql-e-batn*) is correcting the lifestyle of the patients based on TPM suggestion.^[19,20] Modern medicine has defined changing lifestyle as an important way for treatment of functional

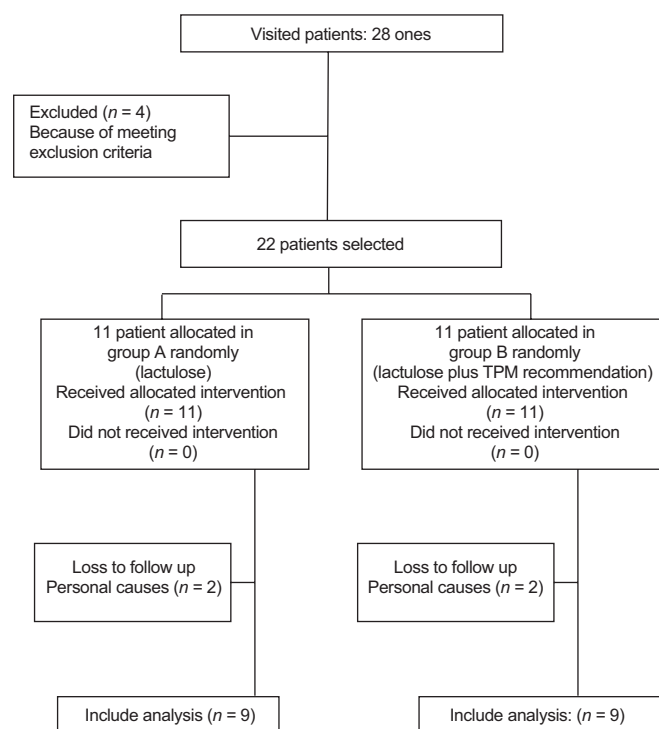
Table 3: Lactulose consumption during the 4 weeks individually and treatment success

Outcome	Group A (lactulose), n (%)	Group B (lactulose plus TPM), n (%)	P
Not decreased lactulose use during 4 weeks	9 (100)	1 (11)	0.001
Decreased lactulose use during and till the end of 4 week	0	6 (67)	
Discontinue of lactulose usage till the end of 4th week	0	2 (22)	
Total	9 (100)	9 (100)	

TPM=Traditional Persian medicine

Table 4: The outflow of the patients from ROME III criteria of constipation during four weeks of the follow-up

Week (follow-up)	Week 0 (%)	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)
Group A (lactulose)	0	5 (60)	7 (80)	8 (90)	8 (90)
Group B (lactulose plus TPM)	0	6 (63)	5 (54)	6 (63)	7 (72)
<i>P</i> ^a		0.629	0.317	0.257	0.527

^aChi-square test; No statistics are computed because the numbers of 0-week is constant. TPM=Traditional Persian medicine**Figure 1: Consolidated standards of reporting trials chart of the clinical trial of assessment of the impacts of traditional Persian medicine devices on the functional chronic constipation compared to those of allopathic medicine**

constipation.^[21] Recent studies revealed the effect of facilitation of natural anthraquinone drugs such as *Senna*, *cascara*, *Frangula*, and *Olea* for stool defecation.^[22] Besides, most patients with chronic constipation prefer to use available, simple, and safe ways and take natural laxative rather than chemical medicine to cure their problems.^[23]

The primary aim of this study was to compare the efficacy, acceptability, and cost-effectiveness of the combination of lactulose plus TPM suggestions and lactulose without TPM suggestions.

As lactulose is metabolized by the colonic bacterial flora to produce short-chain fatty acids, one would expect that its laxative effect would be associated with a notable production

of gases including carbon monoxide, methane, and hydrogen. Most of the common side effects attributed to lactulose such as abdominal pain, bloating, and flatus are thought to result from this colonic fermentation. In oral drugs, laxatives have been used very frequently in constipated patients.^[24]

Some studies have focused on the comparison of different medicaments with lactulose. Polyethylene glycol is a well-tolerated medicine which has been repeatedly compared to lactulose in constipated patients.^[25] On the other hand, some herbal medicaments such as a *Senna*-fiber combination (10 ml/daily) have also been compared to lactulose (15 ml/twice daily) and a matched placebo in geriatric constipation. During a period of 14 days in that study, the mean daily bowel frequency as well as ease of evacuation and stool consistency scores was found greater in *Senna*-fiber as compared to lactulose.^[16,26]

In this study, both treatment methods had similar efficacy in relieving the symptoms, and most patients in both groups were did not have ROME III criteria of constipation. Pain sensation during defecation decreased more in patients who received lactulose only compared to the patients of the other group; the recent result needs to be investigated further, but also this may be referred to palliative effect of lactulose.^[27] These results reveal that the lactulose plus TPM advice group was better than the lactulose group in practice and patients verbally.

No significant adverse events were reported by the patients. The lesser chance of recovery in this study may be due to chronicity of the disease in most of the patients and history of receiving multiple drugs and tolerance to medication. Finally, it should be noted that the study was designed as a pilot, the number of the cases was low, and the intervention period lasted only for 1 month.

Preventive measures (six basic principles) and therapeutic schemes according to TPM sources maintain the health of other body organs, especially alleviating GI problems and constipation.^[19,28] According to this study, preventive measures recommended by TPM sages show their positive

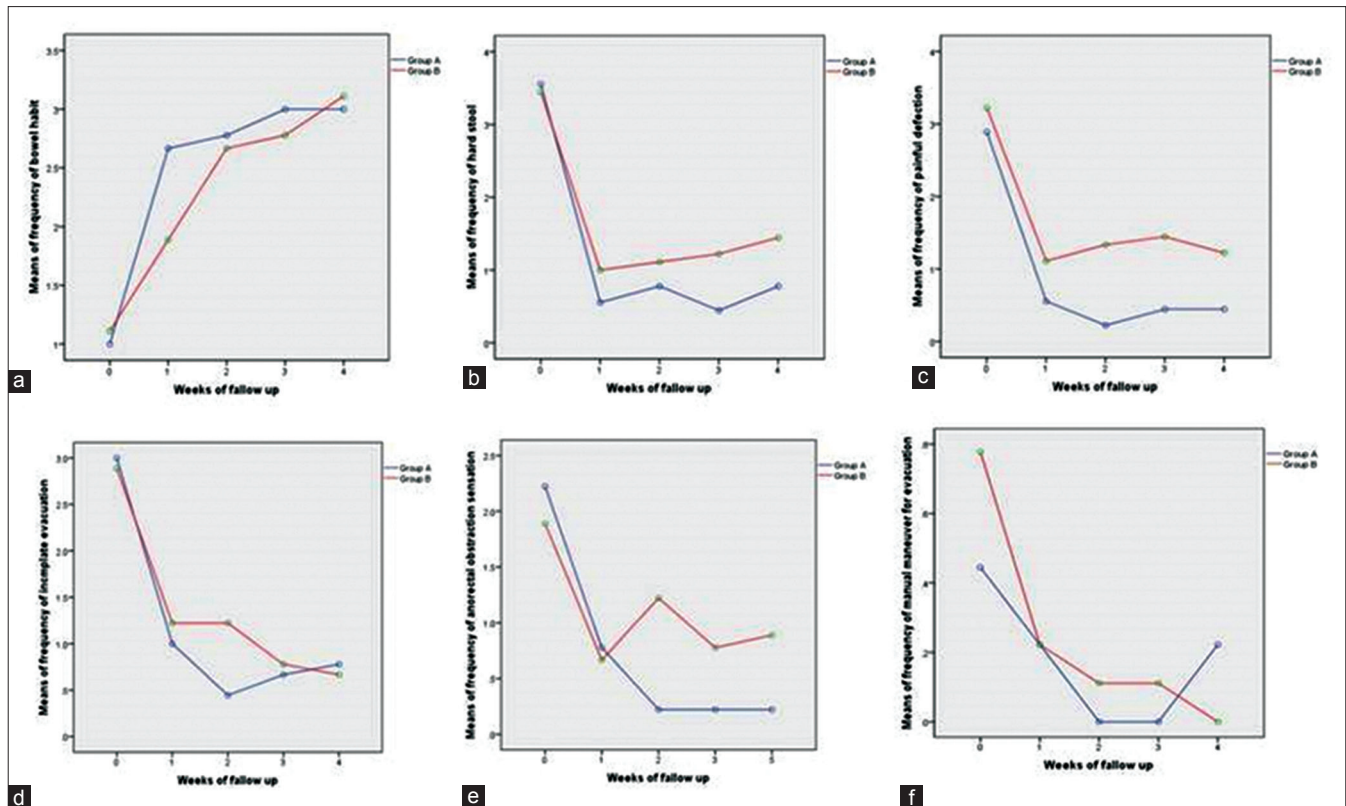


Figure 2: Difference between both groups in responses to therapeutic interventions in repeated measures ANOVA. (a) Frequency bowel habit, (b) Frequency of hard stool. (c) Frequency of painful sensation during defecation. (d) Frequency of sensation of incomplete evacuation. (e) Frequency of anorectal obstruction sensation. (f) Frequency of manual maneuver for evacuation. Group A: Treatment with lactulose; Group B: Treatment with lactulose plus traditional Persian medicine advices

effects gradually and more prominent by reducing the consumption dosage of lactulose by patients located in B group. These measures are safe and inexpensive; however, having a healthy lifestyle based on TPM recommendations seems difficult at the starting point. Many patients are interested in using TPM recommendations and prioritize it to conventional medicines.

Strengths and limitations

The blinded trial and close follow-up were done in the study. Clinical efficacy and tolerance were assessed weekly by the staff. Necessary visits by gastroenterologist and laboratory tests were repeated for all patients if needed. The small sample size of the study was the main limitation of this study.

Conclusions

Traditional medicine lifestyle method is a cheap and available method with good efficacy and can be used in treatment of chronic constipation.

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Conflicts of interest

There are no conflicts of interest.

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