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Comparison of *Ziziphus jujube* Mill. Syrup versus polyethylene glycol in children with functional constipation: a randomized clinical trial

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Functional constipation is a common disorder of the gastrointestinal tract in children without specific treatment. Ziziphus jujuba has been used in traditional medicine for various diseases such as constipation. A safe and inexpensive treatment with few side effects can be used as an effective alternative to current medications. In this study, we sought to compare Ziziphus jujuba syrup (ZS) with polyethylene glycol (PEG) for the treatment of pediatric functional constipation. A double-blind, randomized clinical trial was performed on children aged 2–10 years with functional constipation who were referred to the gastroenterology clinic of the 17-Shahrivar Hospital in Rasht, Iran. Eligible patients were randomized into two groups: PEG group; 1–5 cc/kg/day (40% w/v solution without electrolytes; average dose: 0.2–1 g/kg), and ZS group; 1–5 cc/kg/day (average dose: 5–25 mg/kg). All patients were followed up for three months, every 2 weeks in the first month, and then monthly for 2 months. At the beginning and end of the study, liver and kidney function tests and blood sugar levels were checked. Data were analyzed using SPSS software version 19 at a significance level of 0.05. Out of 90 eligible children, 32 patients in the PEG group and 30 patients in the ZS group completed the follow-up visits. The mean age of the subjects was 4.31 ± 1.97 years. There was no significant difference between the two groups in terms of age ($P = 0.181$), gender ($P = 0.218$), age at onset of constipation ($P = 0.083$), and weight ($P = 0.199$). The average therapeutic response score in the ZS group improved prominently compared to the PEG group ($P < 0.05$). The average number of encopresis and visual analog scale pain scores significantly decreased in the ZS group compared to the PEG group ($P < 0.05$). Other indices, including frequency of defecation, and medication adherence in the ZS group were significantly improved compared to the PEG group ($P < 0.05$). Only in the PEG group, a few cases reported self-limiting side effects. ZS can be a treatment choice for functional constipation without any adverse events or liver or kidney injury in children. However, further studies are necessary to find potential side effects.

Keywords Functional constipation, *Ziziphus jujube* Mill., Polyethylene glycol, Clinical trial

Functional constipation is one of the most frequent complaints in childhood, which is often difficult to manage[1]. It accounts for more than 3% of visits to general pediatricians and 10–25% of pediatric gastroenterology consultations[2,3]. Constipation is defined as infrequent and painful defecation, hard or large stools, and fecal incontinence, usually associated with abdominal pain[4,5]. In about 95% of children suffering from constipation, no underlying pathological condition is responsible for the development of symptoms[6]. The global prevalence of pediatric functional constipation varies from 0.7 to 29.6% (median 12%)[7–9]. The peak incidence of constipation

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occurs during toilet training, between the ages of 2 and 4 years[10]. Genetic susceptibility, insufficient fluid and fiber intake, immobility, postponing defecation in public places, especially in schools, early or poor toilet training, and introduction of solids during the process of weaning are some of the predisposing factors for functional constipation[11]. The pathophysiology of this disorder is biopsychosocial, lacking an identifiable structural or biochemical etiology[12]. Withholding behavior is the most common etiology of functional constipation, usually occurring after an episode of painful defecation, which leads to a vicious cycle of stool withholding, pain, and infrequent bowel movements[13].

Functional constipation is diagnosed clinically, based on history, physical examination, and the ROME IV criteria[14,15]. The delay in diagnosis and intervention leads to more severe functional constipation and a worse prognosis[16,17]. Childhood constipation negatively impacts children's physical, social, emotional, and school functioning[18]. Treatment of functional constipation includes a combination of non-pharmacological and pharmacological options[19]. Pharmacological treatment of functional constipation with laxatives comprises three stages: disimpaction, maintenance therapy and finally weaning[4].

Laxative drugs mainly include bulking, osmotic, lubricating, and stimulant agents[20]. Polyethylene glycol (PEG) 3350 is widely prescribed as the first-choice drug in pediatrics. Common side effects of PEG include diarrhea, bloating, flatulence, nausea, and abdominal pain[3,21].

Lactulose, mineral oil, and magnesium hydroxide are prescribed as the second therapeutic options. However, they are limited to certain age groups and can cause serious adverse effects[22]. They have minimal therapeutic effects but considerable side effects, while the symptoms tend to recur[23]. The evidence of non-pharmacological modalities is weak[24]. Therefore, finding an effective and safe therapeutic option for the treatment of functional constipation in children is essential.

The trend of using natural-based drugs and complementary and alternative medicine is increasing[25]. Ziziphus jujuba is one of the medicinal plants used as an analgesic, anticonvulsant, and anti-constipation in the folk medicine of different countries[26–29]. Clinical trials on Ziziphus fruit showed anti-inflammatory, antihyperglycemic, and anti-hyperlipidemic effects on type 2 diabetes mellitus patients[30].

Medicinally active peptides such as cyclopeptide alkaloids, flavonoids, sterols, jujuboside A, jujuboside B, lauric acid, and triterpenoid saponins have been sequestered and chemically identified from various Ziziphus species[26]. It has been considered safe in a wide range of doses[31]. Despite its laxative effects in traditional medicines, there are limited investigations in the context of pediatric constipation. A previous study in the adult population showed appropriate laxative effects[32].

Material and methods

Study design and population

A prospective, double-blind, randomized controlled-trial (12-week follow-up) was conducted in the 17-Shahrivar tertiary referral hospital in Rasht, Iran, from April 2020 to January 2021. Children aged between 2 and 10 years who referred to the pediatric gastroenterology clinic with functional constipation were included in our study.

The sample size was calculated using the mean scores and standard deviation of the severity of pain based on the visual analog scale (20 ± 19.9) in the study of Mozaffarpur et al.[33] by OpenEpi version 3 software. After calculating the dropout rate up to 10%, with power $(1-\beta) = 0.90$, and type I error probability and $\alpha = 0.01$, a sample size of 30 was obtained for each group.

Eligibility

Diagnosis of functional constipation was based on the ROME IV criteria after ruling out organic causes by history taking, physical examination, and laboratory tests. The physical examination consisted of a thorough abdominal examination, evaluation of growth parameters, inspection of the perianal region (for fissures, skin tags, polyps, or any obvious anomalies), and lumbosacral region (for pits, dimples, and creases), and a digital rectal examination. Each patient was assessed in terms of red flags, abdominal distension, and fecal impaction in the lower abdominal quadrant and hypogastric region.

Patients with organic causes of constipation (including hypothyroidism, Hirschsprung's disease, celiac, diabetes insipidus, cystic fibrosis, renal, cardiac, and neurological disorders), FTT or weight loss greater than 5%, those with a history of colorectal surgery and medication use in the last 3 months (such as antidepressants, anticonvulsants, and sedatives), and children with fecal impaction were not eligible for study participation. Patients with incomplete follow-up visits and those who declined to participate were excluded.

Randomization and blinding

Eligible patients were randomly allocated to PEG or ZS groups, by block randomization with a block size of four (ratio 1:1). The order of the blocks was randomly determined in the PEG or ZS group, and the subjects were assigned with the order of admission. A random allocation method was employed to determine sequences using non-transparent envelopes sealed with random sequences (sequentially numbered, sealed, and opaque envelopes).

The pediatric gastroenterologist (principal investigator) and patients/parents were both blinded to the treatment allocation. Another medical practitioner not involved in the data analysis was unblinded to the treatment groups and was responsible for allocating the drug to each patient and determining the dose. The statistician was also blinded and used coded trial data in SPSS.

Intervention

In the PEG group, patients received oral PEG solution (Sepidaj Company, Iran) at a dose of 1–5 cc/kg/day (0.2–1 g/kg) given as two divided doses. In the ZS group, oral consumption of Ziziphus jujuba syrup at a dose of 1–5 cc/kg/day (5–25 mg/kg) was administered similarly in two divided doses. In both groups, treatment was continued

for a total of 12 weeks. All parents were educated about proper diet, including increased fluid intake and dietary fiber, and behavioral modifications such as a regular toileting schedule, sitting on the toilet for 5–10 min after each meal, and considering rewards for appropriate toileting behavior.

PEG and ZS preparation and standards

The plant was identified and authenticated as a *Ziziphus jujube* Mill. by an academic pharmacognosist. The fruits of *Ziziphus jujuba* Mill. were collected from Birjand, Iran, in September 2019. Five kilograms of fruits were shade dried and coarsely powdered. About 3.3 kg of powder was extracted with water and ethanol by percolation method in the Faculty of Pharmacy, Mashhad, Iran by a pharmacist. After the extraction was completed, the solvent was recovered by distillation and concentrated in vacuo. The formulation of syrup was prepared with sucrose, distilled water, and sodium benzoate, and the syrup with 10% (v/v) of the extract was provided (the concentration was 5 mg/ml). All microbiologic, stability, and physicochemical tests of syrup were performed, and total phenolic content and fructose content were determined by the HPLC method in the final sample (Supplementary Table S1–3).

PEG was initially prepared as a solution, in which 1 cc contains 0.2 g of PEG. The PEG solution and ZS were packaged in the same dark 250 mL glass bottles. To ensure successful blinding, only the treatment code and lot number were placed on the outside of each bottle.

Assessment and follow-ups

For each patient, a checklist containing demographic data (age, sex, developmental status, age at onset of constipation, surgical history) was completed. Frequency of defecation, stool consistency measured through the Bristol Stool Form Scale, visual analog scale (VAS) pain score, presence of fecal incontinence, and other related gastrointestinal symptoms (such as nausea, vomiting, flatulence, and abdominal pain), and positive findings in the physical examination were documented at the first visit. In addition, we used the scoring system of functional constipation criteria according to the Karami et al. study[34]. To determine therapeutic response as a variable, we calculated scores for the following variables at each visit: painful defecation, blood in stool, stool frequency per week, number of encopresis per month, and stool consistency. The minimum score was six, and the maximum was 21. Therapeutic response was classified as follows: poor (6–10), moderate (11–15), and good (16–21).

All patients were visited every 2 weeks in the first month, then monthly for 2 months (a total of 3 months). Parents were requested to fulfill a weekly checklist to record the number of defecations, encopresis, bloody stool, VAS pain score, and fecal consistency according to the Bristol stool chart. In each visit, symptoms, adherence to medication, and side effects were controlled. Medication adherence was evaluated based on the 4-item Morisky scale[35]. Blood sugar levels and kidney and liver function tests were checked at the beginning and the end of the trial for each participant. The primary endpoint was the VAS pain score, and the secondary one was adverse drug events. Parents had access to an on-call physician in case of any complications or side effects.

Ethics declaration

This research was conducted in conformance with the principles stated in the Helsinki Declaration and was approved by the ethical committee of Guilan University of Medical Sciences (Ethics code: IR.GUMS.REC.1397.157). The study was also registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20131006014915N3) on 26/09/2018. Written informed consent was obtained from parents or legal guardians of all patients after explaining the purpose of the study.

Data analysis

All data were entered into SPSS software version 19 (SPSS Inc. Chicago, Il, The USA). Descriptive statistics were expressed as mean, standard deviation, frequency, and percent. The normal distribution of quantitative data was evaluated by the Shapiro–Wilk test. The independent t-test was applied for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. For analysis of repetitive quantitative data during the study follow-ups, the repeated measures ANOVA test was employed. The significance level was set at $P < 0.05$ in all tests.

Results

Forty-eight patients were assigned to the PEG group and 42 to the ZS group. However, during the study, 16 subjects in the PEG group and 12 subjects in the ZS group were excluded. The study flowchart is depicted in Fig. 1.

The mean age of the subjects was 4.31 ± 1.97 years and 53.2% of them were females. There was no statistically significant difference between the two groups regarding the baseline demographic data ($P > 0.05$). Demographic characteristics are presented in Table 1.

As shown in Table 2, baseline clinical manifestations of patients in both groups were not significantly different (P-value > 0.05).

Laboratory findings

There were significant differences in hemoglobin ($P = 0.026$) and TSH ($P = 0.023$) between ZS and PEG groups. Other baseline laboratory data are listed in Table 3.

Laboratory data at the last follow-up showed significant differences in AST (ZS group: 23.60 ± 6.81 vs. PEG group: 33.35 ± 10.17; $P = 0.003$) and blood sugar levels (ZS group: 95.90 ± 9.56 vs. PEG group: 84.36 ± 9.40; $P = 0.005$) between the two groups. Despite the statistically significant difference, it was not clinically relevant and both of them were in the normal range.

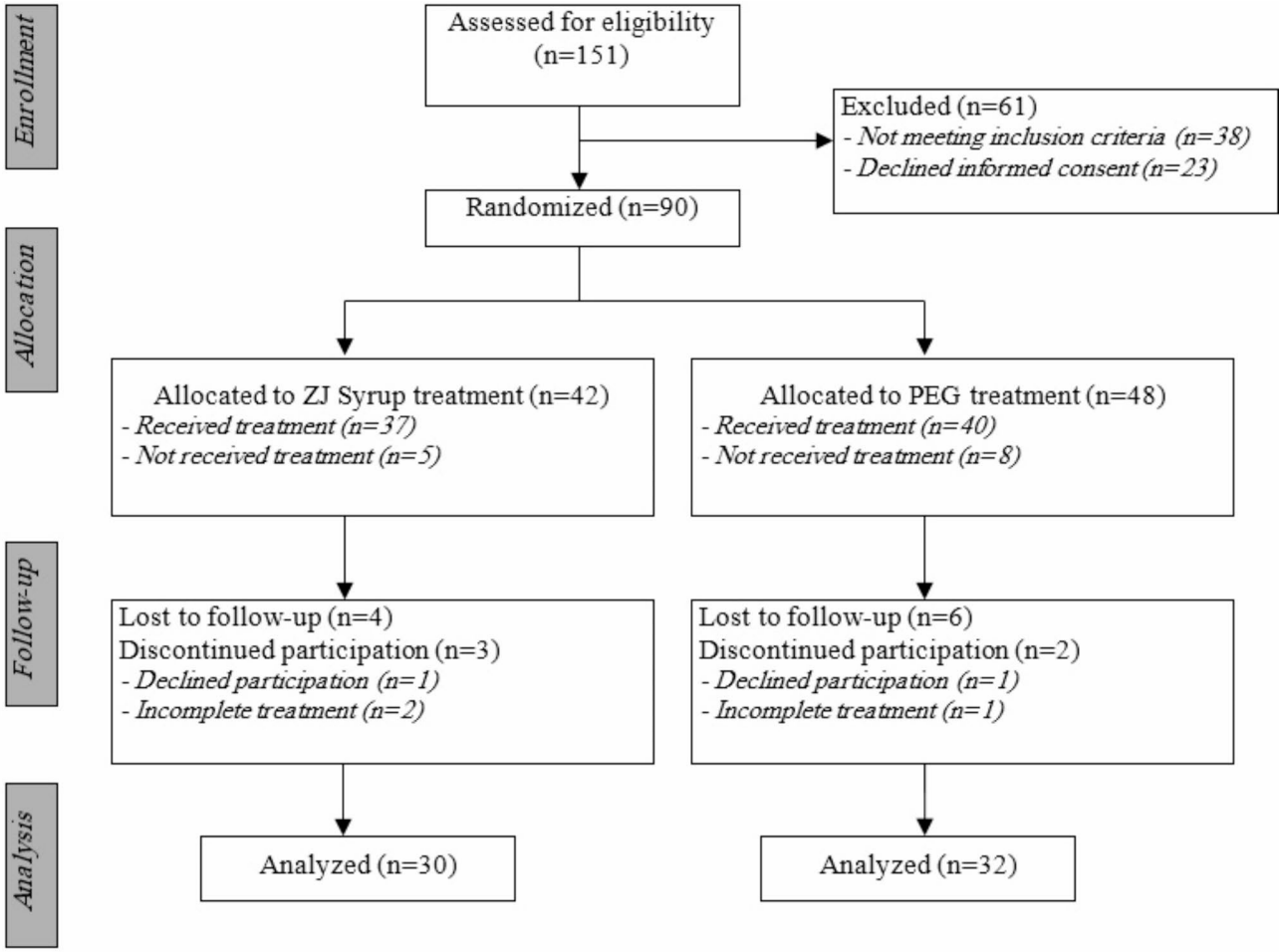

Fig. 1. The study flowchart.

Characteristics	ZS group ($n=30$)	PEG group ($n=32$)	*P*-value
Gender, n (%)	Male 12 (40)	Male 17 (53.1)	0.218
	Female 18 (54.5)	Female 15 (46.9)	
Age (mean ± S.D) years	4.66 ± 2.36	3.97 ± 1.48	0.181
Age at onset of constipation (mean ± S.D) months	37.40 ± 26.97	27.50 ± 16.19	0.083
Weight (mean ± S.D) kg	19.42 ± 7.83	17.17 ± 5.71	0.199
Familial history, n (%)	5 (16.7)	1 (3.1)	0.084

Table 1. Comparison of demographic data in the ZS and PEG groups. *ZS* Ziziphus jujuba syrup, *PEG* polyethylene glycol, *S.D* standard deviation.

Characteristics	ZS group ($n=30$)	PEG group ($n=32$)	*P*-value
Abdominal distention, n (%)	2 (6.7)	1 (3.1)	0.475
Stool retention on the DRE, n (%)	6 (20)	13 (40.6)	0.068
Abnormal sphincter tone, n (%)	0	1 (3.1)	–
Anal fissure, n (%)	7 (23.3)	4 (12.5)	0.217

Table 2. Baseline clinical manifestations of patients in the ZS and PEG groups. *ZS* Ziziphus jujuba syrup, *PEG* polyethylene glycol, *DRE* digital rectal examination.

Characteristics	ZS group ($n=30$)	PEG group ($n=32$)	*P*-value
WBC (mean ± S.D)	7088.18 ± 0.43	1.48 ± 0.26	0.181
Hemoglobin (mean ± S.D) g/dL	11.82 ± 1.07	12.49 ± 1.05	0.026
Platelet (mean ± S.D)	303.05 ± 70.93	297.40 ± 78.90	0.791
Blood sugar (mean ± S.D) mg/dL	94.81 ± 14.54	87.58 ± 12.78	0.081
Sodium (mean ± S.D)	137.42 ± 1.89	138.77 ± 2.68	0.066
Potassium (mean ± S.D)	4.18 ± 0.23	4.33 ± 0.44	0.146
Calcium (mean ± S.D)	9.86 ± 0.62	9.61 ± 0.50	0.147
Phosphorus (mean ± S.D)	4.74 ± 0.82	4.88 ± 0.83	0.581
AST (mean ± S.D) U/L	31.21 ± 7.08	35.72 ± 19.24	0.258
ALT (mean ± S.D) U/L	15.16 ± 5.23	20.14 ± 16.62	0.211
Bun (mean ± S.D) mg/dL	14.85 ± 4.97	15.51 ± 7.30	0.722
Creatinine (mean ± S.D) mg/dL	0.65 ± 0.14	0.59 ± 0.12	0.159
TSH (mean ± S.D)	2.05 ± 0.67	2.96 ± 1.65	0.023
FT4 (mean ± S.D)	9.80 ± 6.50	8.74 ± 5.91	0.562

Table 3. Comparison of baseline laboratory data in the ZS and PEG groups. *ZS* Ziziphus jujuba syrup, *PEG* polyethylene glyco, *S.D* standard deviation, *WBC* white blood cell, *AST* aspartate aminotransferase, *ALT* Alanine transaminase, *TSH* thyroid stimulating hormone, *FT4* free thyroxine.

		Week 2	Week 4	Week 8	Week 12
Therapeutic response	PEG group	10.59 ± 1.77	11.09 ± 2.23	11.62 ± 2.73	11.62 ± 2.73
	ZS group	13.03 ± 3.54	14.83 ± 3.64	15.10 ± 3.59	16.86 ± 4.56
	P-value	0.001	0.001	0.001	0.001

Table 4. Comparison of therapeutic response in the ZS and PEG groups in follow-up visits. *ZS* Ziziphus jujuba syrup, *PEG* polyethylene glycol.

Clinical findings

As shown in Table 4, the therapeutic response in the ZS group was prominently better than the PEG group at all follow-up visits ($P=0.001$). In addition, the frequency of defecation in the ZS group was significantly higher than the PEG group at all follow-up intervals ($P<0.05$; Fig. 2a). The number of encopresis in the ZS group significantly decreased compared to the PEG group ($P<0.05$; Fig. 2b). VAS scores in the ZS group were significantly lower than the PEG group at weeks 4, 8, and 12 after the intervention ($P<0.05$; Fig. 2c). In terms of fecal consistency, there was no significant difference in the ZS group and PEG group at follow-up intervals ($P>0.05$; Fig. 2d).

Adverse events

Vomiting and abdominal pain were reported in the first, second, and third weeks of the intervention in two cases and in the fourth week in three cases of the PEG group. There were no drug-related complications in the ZS group. Improper consumption of the medication was reported in three cases of the PEG group in the second week, in two cases of the PEG group in the third week, in five cases of the PEG group and two cases of the ZS group in the 12th week.

Medication adherence

Medication adherence of the patients at 2, 4, 8, and 12 weeks of follow-up was significantly better in the ZS group compared to the PEG group ($P<0.001$) (Fig. 3).

Discussion

Although pediatric constipation is a common chronic problem, few studies have compared different laxatives. Among children who were referred to pediatric gastroenterologists, 50% would improve and be taken off laxatives after 6–12 months. About 10% of patients do well when using laxatives, and 40% will continue to have symptoms despite using laxatives[19]. In this trial, we sought to compare the efficacy and safety of ZS and PEG in children with functional constipation. To the best of our knowledge, this was the first study to assess the efficacy of ZS in pediatric functional constipation. Our findings revealed that the mean therapeutic response score, frequency of defecation, encopresis, and medication adherence were significantly better in the ZS group compared to the PEG group. The average number of encopresis and VAS pain score was significantly decreased in the ZS group than in the PEG group.

PEG is one of the choice therapeutic options, but children are not interested in its flavor. Despite different options in the treatment of functional constipation, there is limited evidence of their efficacy. *Ziziphus jujube* fruit contains betulinic acid, oleanolic acid, maslinic acid, glucose, sitosterol, stigmasterol, desmosterol, resin,

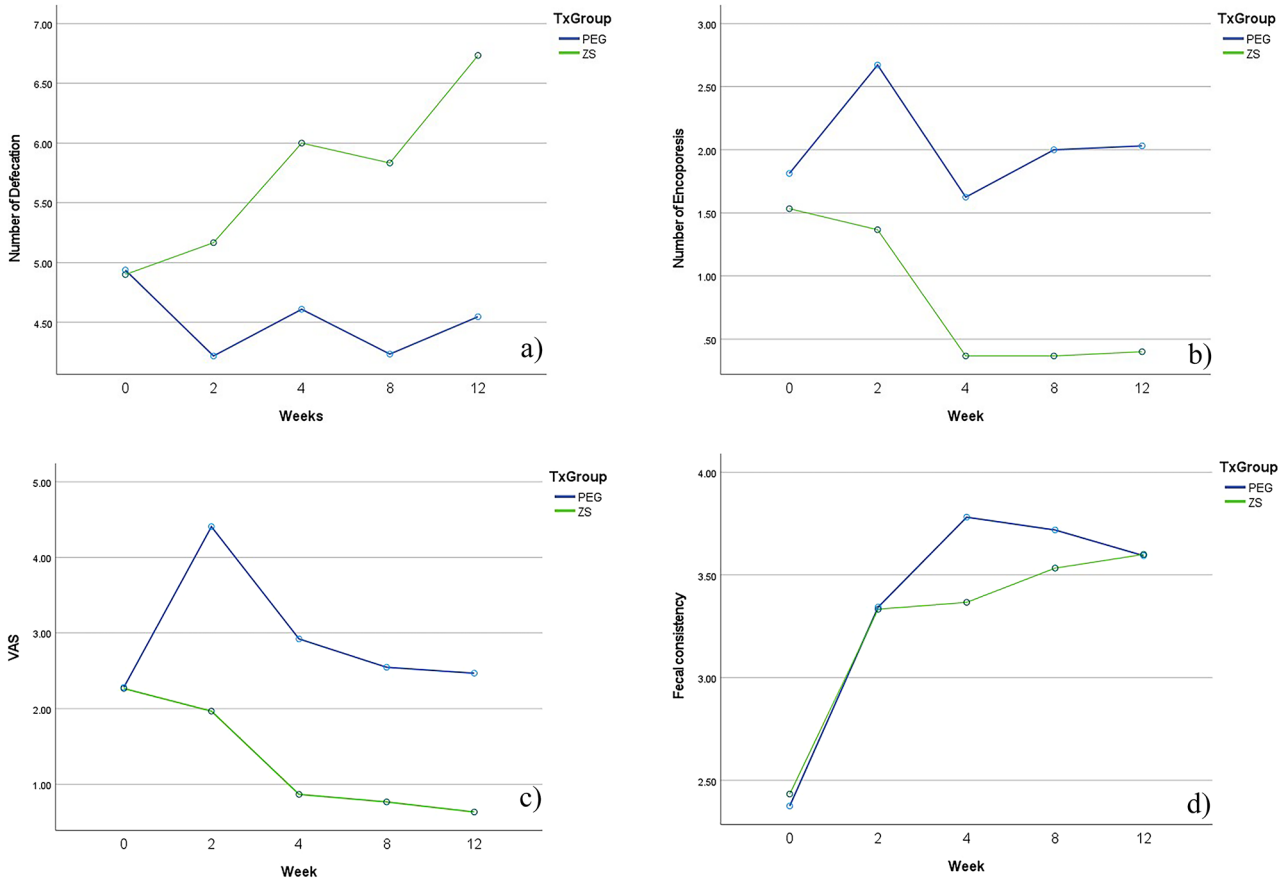

Fig. 2. Comparison of clinical findings at baseline, 2, 4, 8, and 12 weeks of follow-up in the PEG and ZS groups using the general linear model. (**a**) Number of defecation; The upper curve, representing the ZS group, shows an increase in the frequency of defecation with a much faster course. (**b**) Fecal encopresis; The lower curve representing the ZS group shows a decrease in the frequency of fecal encopresis over time, but the upper curve shows an increasing trend despite a good decrease in the first 4 weeks. (**c**) VAS pain score; The lower curve that represents the ZS group indicates a significant decrease over time. (**d**) Fecal consistency; The difference between the two groups is not statistically significant.

catechol, tannin, essential oil, 13 types of amino acids, selenium, calcium, phosphorus, iron, cAMP, and cGMP[31]. Its toxicity has been investigated in mice and doses up to 150 g/kg did not show any signs of toxicity. LD50 for intraperitoneal injection was 14 g/kg The LD50 for intraperitoneal injection was 14 g/kg[36].

In a double-blind clinical trial, the efficacy of Ziziphus jujuba extract for chronic idiopathic constipation in adults was examined, using both subjective self-reports and objective measurement of transit time. Their findings demonstrated that Ziziphus jujuba is effective for the treatment of chronic constipation. The transit time was markedly improved in the treatment group. Furthermore, most patients expressed their satisfaction with the treatment based on the severity of symptoms and quality of life questionnaire[32].

In this study, we found that the most abundant carbohydrate in standardized ZS is fructose, with 40 g/100 g of dried extract. In an in vivo experimental study on hamsters, the dried extract of Ziziphus jujuba (~82.4 g/kg of dried jujube) was shown to have high water-soluble carbohydrates (~77% by weight on a moisture-free basis). Their results suggested that feeding diets with medium and high doses of water-soluble carbohydrate concentrate extract (5–15 g/kg of diet) significantly shortened transit time and improved intestinal motility in comparison with the control group. The fecal moisture content in the group with medium- and high-dose diets was considerably higher than the control group. It was concluded that a significant reduction in transit time decreases water reabsorption in the intestinal lumen, which leads to an increase in moisture retention in feces. These changes may have a substantial impact on the intestinal mucosa by reducing exposure to toxic ammonia and other harmful contents[37].

In a clinical trial study on 121 neonates, the effect of Ziziphus Jujuba extract and phototherapy on the reduction of bilirubin level and also the hospitalization period for neonatal jaundice were examined. Patients were compared into two groups. In the intervention group, 1 cc/kg of Ziziphus Jujuba extract was given orally three times a day in addition to phototherapy and was compared with another group that received only phototherapy. This study revealed that administration of Ziziphus Jujuba extract can lead to bilirubin excretion in neonates owing to laxative effects and increased urine output. ZS is prepared from the extract of a naturally growing fruit and contains several compounds. Now, we cannot attribute the laxative effect to a particular ingredient. In

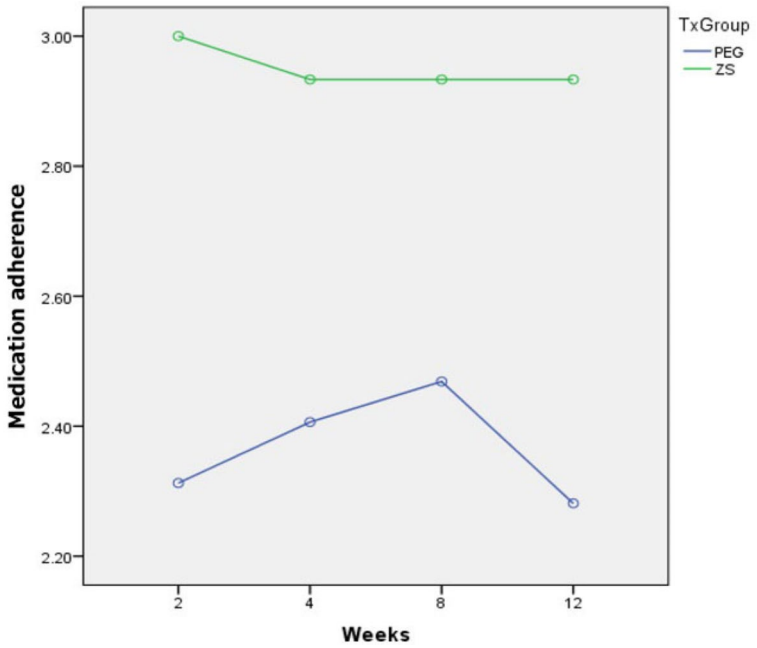

Fig. 3. Comparison of the medication adherence based on the 4-item Morisky scale at 2, 4, 8, and 12 weeks of follow-up in the PEG and ZS groups.

a previous study, it was contributed to a form of anthraquinone, as contained in senna and other plant-based laxatives[32]. However, according to the analysis of ingredients in our study, it could also be attributed to its high fructose content and high total phenolic content.

This was the first clinical trial in evaluating the efficacy of standardized ZS in functional constipation. We also assessed patients' medication adherence in each follow-up.

Limitation

The primary limitation of this investigation was the lack of an objective index for assessing the improvement of constipation, which can be considered in future research by measuring colonic transit time. Long-term drug safety should also be assessed. We educated all parents about proper diet, behavioral modifications, and proper physical activity. As the study did not include any measurement tools to evaluate these aspects among patients, this should be considered as another potential limitation.

Conclusion

ZS is a potentially safe and effective therapeutic choice for functional constipation without adverse effects and can be prescribed for at least 3 months. Further investigations are recommended to assess the long-term efficacy and safety of the syrup using both subjective and objective methods.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Received: 3 August 2024; Accepted: 6 January 2025
Published online: 11 January 2025

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Author contributions

S.M., F.K., A.S., and S.S. designed the study. F.K. and A.S. participated in syrup preparation. S.M. visited the patients and F.K. allocated the drugs and collected the data. S.S. performed the statistical analysis. A.P. contributed to data interpretation. F.K., S.M., and A.S. wrote the first draft of the manuscript. All authors contributed to revising the manuscript and approved the final version of the submitted manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-85801-w.

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