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Research Article

THE EFFICACY AND SAFETY OF AN AYURVEDIC PETSAFFA FORMULATION IN SUBJECTS WITH CONSTIPATION: AN OPEN-LABEL, NON-RANDOMIZED CLINICAL STUDY

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ABSTRACT

Constipation is a common gastrointestinal complaint among 16% of the world's population. Several conventional treatments are recommended; however, these sometimes do not provide satisfactory results for many patients or cause unpleasant side effects. In this context, Ayurvedic medicine can be an alternative, cost-effective and satisfactory treatment for constipation. Hence, this clinical study aimed to evaluate the efficacy and safety of an Ayurvedic PetSaffa formulation in subjects with functional constipation. **Design, Setting, Participants and Intervention:** This open-label, non-randomized clinical study was conducted to evaluate the safety and efficacy of an Ayurvedic PetSaffa formulation in healthy volunteers with functional constipation. Subjects were selected based on inclusion and exclusion criteria. Participants received PetSaffa granules for 21 days. Outcome parameters of the study, including frequency of bowel movements, constipation score, constipation symptoms, gas, acidity, and serum level of SGPT, were evaluated at screening and after 21 days of treatment. **Results:** A total of 120 participants completed the 21-day treatment. At the end of the treatment period, all clinical outcomes, including frequency of bowel movement and constipation score, were significantly ($p<0.001$) improved. The analysis of constipation symptoms' frequencies and severity also significantly ($p<0.001$) improved without any significant adverse effects. Additionally, PetSaffa granules also reduced gas and acid symptoms. As part of the safety study, serum levels of SGPT were within the normal range before and after treatment. **Conclusion:** The study intervention, PetSaffa granules, significantly improved bowel movements, gas and acidity symptoms without causing any adverse effects. Therefore, the Ayurvedic PetSaffa granules are a clinically effective and safe alternative for the treatment of functional constipation.

INTRODUCTION

Chronic constipation is a common gastrointestinal problem in the general population, as well as in patients with various disorders such as hypothyroidism, diabetes, stroke, Parkinson's disease, and local neurogenic disorders.[1] Constipation is estimated to affect 16% of the world's population, and the frequency of constipation increases with age, reaching 33% in people over 60 years of age.[2]

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According to a recent Indian survey, nearly 16.8% of India's adult population suffers from constipation.[3] Constipation is associated with fecal incontinence and impaction, hemorrhoids, fissures, urinary incontinence, and cardiovascular complications,[4] all of which have a significant impact on patients' quality of life (QoL). The risk factors for constipation include age, gender, depression, physical inactivity, certain medications, and diseases.[5] Non-pharmacologic treatments, such as lifestyle interventions (e.g., exercise, a high-fiber diet, and high fluid intake), are generally not tolerated by older patients because of their limited motility, polypharmacy, and other underlying medical conditions.[4] Various drugs, including bulking agents, stimulants, stool softeners, and osmotic agents, are

used in clinical practice depending on the severity and chronicity of the condition.[6,7] Even though conventional treatment is well established and safe, it does not provide satisfactory improvement for many patients.[8] Most frequently, laxative drugs are prescribed for the management of constipation, but these drugs are sometimes associated with unpleasant side effects such as diarrhea, abdominal cramps, electrolyte imbalance, bloating, and abdominal distension.[9]

A large number of medicinal plants and herbal and mineral formulations have been mentioned in traditional Indian systems of medicine, including Ayurveda, for the treatment of constipation and its associated symptoms. The efficacy of these ingredients for constipation is based primarily on their traditional applications and the clinical experience of traditional practitioners. There have been few studies on the clinical efficacy and safety of these herbal products. The present study evaluated the efficacy and safety of the use of an Ayurvedic formulation, PetSaffa Granules, in the treatment of subjects with functional constipation.

METHODS

Participants and Study Criteria

This open-label, non-randomized, single-center study involved 120 subjects with functional constipation and was conducted at the Medlife Clinic in Bangalore, India. There has been no statistical consideration for the sample size estimation. Male and female patients with functional constipation, and/or gas, and acidity who were between the ages of 18 and 80 years and willing to sign an informed consent form were included in this study. Subjects who had undergone any surgery or participated in any other clinical trial in the previous three months, as well as pregnant and lactating women, were excluded.

Study Design

This was a single-center, non-randomized, open-label clinical study. The study was carried out at the Medlife Clinic in Bangalore, India, between June 2021 and September 2021, under strict adherence to the ICMR, ICH-GCP guidelines, and the Declaration of Helsinki. The total duration of the study was 21 days, including three scheduled clinic visits on day 0 (screening visit), day 1 ± 5 days (baseline visit), and day 21 (final visit). In addition, a telephone follow-up visit was conducted on day 14. Subjects were assessed for eligibility based on inclusion and exclusion criteria after giving informed consent. Physical examinations, vital signs, demographic information, and medical and surgical histories were taken into account for each enrolled participant at the screening. All subjects received the study intervention for 21 days.

Intervention

The study intervention, PetSaffa granules, was manufactured and provided by Divisa Herbal Care, Chandigarh, India. PetSaffa granules consist of *C.angustifolia*, Black Salt, *T.ammi*, *T.chebula*, *O.turpethum*, Sodium bicarbonate, Rock Salt, *F. vulgare*, *T. belerica*, *E. officinalis*, *R.communis*, *P.longum*, *P.nigrum*, *Z. officinale*, *C.fistula*, and *G. glabra*. Participants were instructed to take 1 teaspoon of Petsaffa granules with lukewarm water before going to bed.

Outcome Measures

Primary outcomes

The primary outcome of this study was an improvement in the bowel movement frequencies in the week before and after treatment. A modified version of the Wexner Constipation Scoring System (WCSS) was used to evaluate the constipation score before and after treatment [10]. The WCSS included an 8-item questionnaire about bowel movements frequency, anal/rectal pain during evacuation, abdominal pain, incomplete evacuation, time taken for evacuation per attempt, number of attempts for a successful bowel movement in the previous 24 hours, type of assistance for defecation, and duration of constipation. All items are scored from 0 to 4 except for the "type of assistance for defecation," which is scored from 0 to 2. The total score was calculated by summing all item scores [11].

Secondary outcomes

Secondary outcomes of this study included the reduction in the frequency and severity of the constipation symptoms from screening to the end of the study using a 6-item subject assessment questionnaire. Symptom scores were rated on a 4-point scale (0–3): 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe. The sum of each item was used to calculate the overall constipation symptoms. In addition to constipation symptoms, frequency of gas and acidity symptoms were also evaluated. As part of the safety study, serum levels of SGPT before and after treatment were measured to evaluate liver function. Additionally, the occurrence of adverse events during the treatment period was also evaluated.

Ethical Considerations

This study protocol was approved by the ACE Independent Ethics Committee with Protocol No. SBS/DIV/002/2021. The study was registered with the Clinical Trials Registry-India (CTRI Number: CTRI/ 2021/07/034540) on July 2, 2021.

Statistical Analysis

Demographic characteristics and results of the study were summarised with descriptive statistics, including average, standard deviation (SD), frequency, and percentages. Changes in the mean constipation

score and symptom severity score from screening to the end of the study were assessed by a paired t-test. Statistical analysis was carried out using SPSS statistical software version 23.0 (SPSS Inc., USA). The P value of 0.05 was considered statistically significant.

RESULTS

Demographic Data

A total of 126 subjects were screened, and six of them failed to meet the eligibility criteria. Hence, 120 subjects were enrolled in this treatment, of which 88 (73.33%) were males and 32 (26.67%) were females, with a mean age of 32.99±10.89 years. There were 83 (69.17%) subjects between the ages of 18-45 years, and 37 (30.83%) subjects between the ages of 46-80 years.

Primary Outcome Measures

Bowel movement

The frequency of bowel movements of the subjects was assessed at the start and end of the study. The frequency of bowel movements among the subjects was reported as once per day (36.6%), 2–3 times a week (38.2%), and once a week (25.1%) at the screening, and the frequency of bowel movements reportedly improved to 85.5%, 13.2%, and 1.3%, respectively, after 21 days of treatment.

Constipation Score

The constipation score was evaluated at screening and after 21 days of treatment. The results of the constipation score items are presented in Table 1. As shown in Table 1, after 21 days of treatment, each item score was significantly ($p<0.0001$) lower than at screening. The overall constipation score dropped from 14.72±1.94 (screening) to 7.36±1.34 (end of the study) with a mean difference 7.37, 95% confidence interval 6.979 - 7.758 ($p<0.0001$).

Table 1: Constipation score before and after treatment

Questionnaire	Severity score (mean ± SD)		Mean diff.	95% CI	P-value
	Day 0	Day 21			
Frequency of bowel movements	2.95 ± 0.75	1.63 ± 0.67	1.32	1.191 - 1.441	< 0.0001
Anal/rectal pain during evacuation	2.34 ± 0.60	1.08 ± 0.56	1.26	1.149 - 1.378	< 0.0001
Abdominal pain	2.36 ± 0.72	1.12 ± 0.71	1.24	1.108 - 1.366	< 0.0001
Incomplete evacuation	2.14 ± 0.67	0.88 ± 0.71	1.26	1.127 - 1.40	< 0.0001
Average time for evacuation per attempt	2.16 ± 0.69	1.37 ± 0.49	0.79	0.630 - 0.949	< 0.0001
Number of attempts for a successful bowel movement in last 24 hours	2.05 ± 0.65	0.87 ± 0.64	1.18	1.068 - 1.301	< 0.0001
Type of assistance for defecation	0.42 ± 0.50	0.13 ± 0.34	0.29	0.185 - 0.394	< 0.0001
Duration of constipation	0.30 ± 0.46	0.29 ± 0.46	0.01	-0.013 - 0.039	< 0.0001
Total score	14.72 ± 1.94	7.36 ± 1.34	7.37	6.979 - 7.758	< 0.0001

Secondary Outcome Measures

The frequency and severity of constipation symptoms were assessed at screening and at the end of the study by administering a questionnaire related to these symptoms. Table 2 displays the results of the frequency of constipation symptoms. At the screening, most subjects reported mild to moderate constipation symptoms. But, after 21 days of treatment, constipation-related symptoms were found to be resolved in most of the patients.

The severity of each symptom was also evaluated on a 4-point scale. After 21 days of treatment, there was a significant reduction in the severity of each symptom. The total score of symptom severity was also reduced from 8.49±2.10 at the start of the study to 1.84±1.13 at the end, with a mean difference of 6.65, 95% confidence interval 6.315-6.986, $p<0.0001$ (Table 3). Among the 120 subjects, 44 (36.67%) subjects had experienced additional gas and acidity symptoms before treatment. At the end of study, only 7 (5.83%) subjects reported gas and acidity symptoms out of 44 subjects.

As part of the safety study, no significant differences were observed in serum levels of SGPT at screening (27.225U/L) and after 21 days of treatment (27.25U/L). Adverse effects during the treatment period were observed in 2 subjects; however, these were not related to the study intervention. No other SAEs or deaths were observed during this study.

Table 2: Participant Reported Frequencies of Constipation Symptoms

Symptoms	Day 0 (N = 120) n (%)				Day 21 (N=120) n (%)			
	Absent	Mild	Moderate	Severe	Absent	Mild	Moderate	Severe
Abdominal discomfort	9 (7.5)	46 (38.3)	62 (51.7)	3 (2.5)	93 (77.5)	23 (19.2)	4 (3.3)	0 (0)
Stomach cramps	17 (14.2)	30 (25)	66 (55)	7 (5.8)	90 (75)	20 (16.7)	10 (8.3)	0 (0)
Rectal bleeding during defecation	53 (44.2)	32 (26.7)	35 (29.2)	0 (0)	103 (85.8)	16 (13.3)	1 (0.8)	0 (0)
Too hard defecation	10 (8.3)	43 (35.8)	59 (49.2)	8 (6.7)	89 (74.2)	23 (19.2)	8 (6.7)	0 (0)
Too small bowel movements	4 (3.3)	50 (41.7)	58 (48.3)	8 (6.7)	96 (80)	18 (15)	6 (5)	0 (0)
Straining or squeezing during defecation	9 (7.5)	42 (35)	67 (55.8)	2 (1.7)	87 (72.5)	29 (24.2)	4 (3.3)	0 (0)

Table 3: Symptom severity of constipation before and after treatment (n=120)

Symptoms	Severity score (mean ± SD)		Mean diff.	95% CI	P-value
	Day 0	Day 21			
Abdominal discomfort	1.48 ± 0.67	0.30 ± 0.53	1.18	1.075 - 1.283	< 0.0001
Stomach cramps	1.54 ± 0.79	0.36 ± 0.63	1.18	1.049 - 1.309	< 0.0001
Rectal bleeding during defecation	0.88 ± 0.82	0.18 ± 0.41	0.67	0.573 - 0.825	< 0.0001
Too hard defecation	1.55 ± 0.73	0.35 ± 0.59	1.20	1.060 - 1.346	< 0.0001
Too small bowel movements	1.56 ± 0.64	0.30 ± 0.56	1.26	1.145 - 1.375	< 0.0001
Straining or squeezing during defecation	1.48 ± 0.66	0.35 ± 0.54	1.13	0.998 - 1.262	< 0.0001
Total score	8.49 ± 2.10	1.84 ± 1.13	6.65	6.315 - 6.986	< 0.0001

DISCUSSION

Ayurveda is one of the oldest traditional medical systems in India and has been practiced since ancient times. The use of complementary and alternative therapies, including Ayurveda, is frequently used for the treatment of numerous gastrointestinal ailments, including constipation. A large number of medicinal plants have been mentioned in Ayurveda for the treatment of constipation, including *C. angustifolia*, *F. vulgare*, *Z. officinale*, *O. turpethum*, *R. communis*, *C. fistula*, *T. belerica*, *E. officinalis*, *T. chebula*, and *G. glabra*.[12–14] These plants have been said to correct the vata imbalance, allowing the digestive system to function normally, which ensures normal bowel movements.[12] However, the efficacy and safety of these plants or their formulations have not been validated through clinical studies in constipation patients.

This study evaluated the efficacy and safety of an Ayurvedic "PetSaffa Granules" formulation consisting of *C. angustifolia*, Black Salt, *T. ammi*, *T. chebula*, *O. turpethum*, Sodium bicarbonate, Rock Salt, *F. vulgare*, *T. belerica*, *E. officinalis*, *R. communis*, *P. longum*, *P. nigrum*, *Z. officinale*, *C. fistula*, and *G. glabra*. In Ayurveda, these ingredients are said to provide a wide range of gastrointestinal benefits. *F. vulgare* can help to improve digestion by promoting the production of gastric enzymes, whereas *Z. officinale* is known for its stomach-soothing properties.[12] *C. angustifolia* is a laxative stimulant with gastric motility-enhancing properties that helps increase bowel frequency.[15,16] Triphala (a combination of *T. chebula, T. belerica*, and *E. officinalis*) helps to cleanse the colon and reduces gastrointestinal symptoms like anorectal blockage, incomplete evacuation, flatulence, and bloating.[17] *O. turpethum* is useful in anorexia, constipation, haemorrhoids, fistulas, and jaundice.[18]

Results of the study showed that the administration of PetSaffa granules for 21 days significantly improved bowel movements as well as the constipation score. Besides, the formulation was also found to reduce the frequency and severity of constipation symptoms as well as gas and acidity without causing any adverse drug reactions. However, while the exact mechanism of the PetSaffa granules is not clear, the synergistic effect of the different types of laxative herbs and their active compounds may be responsible for this improvement in bowel movement and constipation symptoms. Thus, this study demonstrated the efficacy and safety of the PetSaffa granules in the treatment of functional constipation.

CONCLUSION

The results of the present study demonstrated that the PetSaffa granules are highly effective for the treatment of chronic functional constipation, as evidenced by the decrease in constipation score, frequency, and symptom severity. It is also effective in reducing gas and acidity symptoms. During the treatment period, no significant change in liver function parameters was observed. There were no treatment-related side effects reported by any of the study participants. In conclusion, the results of the study demonstrated that the PetSaffa granules are highly effective and safe for clinical use in humans for the treatment of functional constipation.

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