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Chinese herbal formula Tongxie Yaofang granules for diarrhoea-predominant irritable bowel syndrome: a randomised, double-blind, placebo-controlled, phase II trial

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ABSTRACT

Objectives To assess the therapeutic effects and safety of Tongxie Yaofang (TXYF) granules vs placebo as an alternative treatment for diarrhoea-predominant irritable bowel syndrome (IBS-D). We hypothesised that TXYF would improve clinical responses among patients with IBS-D.

Design A randomised, double-blind, placebo-controlled, phase II, superiority trial.

Setting Outpatients attending the Fangshan Hospital, Beijing University of Chinese Medicine, Beijing, China.

Participants 96 eligible participants included men and women ranging from late adolescence to middle adulthood (18–65 years), diagnosed with IBS-D according to the Rome IV criteria. In addition, they were required to have an irritable bowel syndrome symptom severity score (IBS-SSS) of at least 75.

Interventions TXYF granules (3.7 g) twice daily (taken orally before meals) or placebo for 8 weeks.

Primary and secondary outcomes The primary outcome was the response rate measured by the change in IBS-SSS compared with baseline at week 8. Secondary outcomes included stool frequency; stool consistency at weeks 4, 8 and 20; and quality of life, anxiety and depression at week 8; and safety was monitored throughout the trial.

Results The TXYF and placebo groups each comprised 48 participants. The response rate was not significantly different at week 8 between the two groups (the unadjusted treatment effect estimate (intention-to-treat analysis) was 1.12 (95% CI (0.89, 1.41)), p=0.348). Both groups had a high and similar rate of symptom reduction (79.2% (38/48) *vs* 70.8% (34/48)). There were no statistically significant differences between the two groups on secondary outcomes, although both groups showed substantial improvements. Adverse events in the TXYF and placebo groups were one (sinus arrhythmia) and two (elevated transaminases, weakly positive faecal occult blood), respectively. No serious adverse events occurred.

Conclusions Despite showing clinically meaningful improvements in IBS-D symptoms and a reasonable safety profile after 8 weeks, no significant differences were observed between the TXYF and placebo groups. This suggests that the severity of IBS-D symptoms in both treatment arms might have decreased over time, regardless of the treatment, and highlights the need to investigate the relationship between IBS-D and patient psychology. Future large-scale, rigorously designed trials with longer treatment and follow-up periods are essential to evaluate the therapeutic effects and safety of TXYF, and to explore the psychological factors.

Trial registration number ISRCTN12453166.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A rigorous randomised, double-blind, placebo-controlled trial design was used, confirmed by a blinding test, to minimise biases and enhance the reliability of the study results.
⇒ This study used a longer 8 week treatment period and 12 week post-treatment follow-up compared with most previous studies of traditional Chinese medicine for IBS-D.
⇒ The results were analysed with the adjustment for baseline variables to exclude possible effects of confounding factors on the veracity of the findings.
⇒ This was a small sample, single-centre clinical trial, and the results may not be demographically and characteristically representative of the broader IBS-D population.
⇒ Outcome data were collected at only three time points, without additional measurement intervals, which limits our ability to precisely identify changes in efficacy or potential turning points over time.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder,

with a global population prevalence of approximately 10%.[1] Patients experience abdominal pain and discomfort and altered bowel habits that occur in the absence of other organic gastrointestinal diseases, with either predominantly diarrhoea (IBS-D), constipation (IBS-C), mixed (IBS-M) or with unspecified (IBS-U).[2–4] IBS significantly impacts the quality of life, work productivity and social activities of patients and further affects their psychological health status (eg, many patients have comorbid anxiety and depression).[5–8] Research on IBS global prevalence has documented a pooled prevalence of 23.4–40% for the subtype of IBS-D.[2 8 9] Many patients with IBS-D will seek healthcare, making it one of the most common gastrointestinal disorders in primary care settings.

The underlying pathogenesis of IBS-D is complex and not yet fully understood; the precise molecular pathophysiology remains unclear, and no specific therapeutic agents for IBS-D have been identified.[7 10] Despite an array of currently available treatments, such as loperamide, otilonium bromide, pinaverium bromide, trimebutine and alverine citrate, these treatments often fail to relieve the major symptoms of diarrhoea, such as stool frequency and abdominal pain. There remains an unmet clinical need for effective treatments that can alleviate multiple symptoms simultaneously.[8 11 12]

Given the limitations of existing treatments, an alternative treatment option is warranted.[13] A variety of alternative treatments are available for managing IBS-D.[13 14] Among these, Chinese herbal medicine has shown promise, supported by high-quality randomised controlled trials (RCTs) and other clinical studies.[15–18] Tongxie Yaofang (TXYF) is one of the most commonly used Chinese herbal medicine formulas and is widely used in clinical practice for IBS-D. It is composed of *Atractylodes macrocephala* Koidz. *(Asteraceae; Rhizoma Atractylodis Macrocephalae.)*, *Paeonia lactiflora* Pall. *(Ranunculaceae; Paeoniae Radix Alba)*, *Citrus×aurantium*L. *(Rutaceae; Citri Reticulatae Pericarpium)* and *Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk. (*Umbelliferae; Saposhnikoviae Radix)* and was first recorded in the Yuan Dynasty (1271–1368 AD).[19] Modern pharmacological research has found that Atractyl*odes macrocephala* Koidz. has two-way regulation of the gastrointestinal tract (ie, it can promote intestinal peristalsis and inhibit intestinal peristalsis), regulation of intestinal microbiota and anti-inflammatory effects[20 21]; *Paeonia lactiflora* Pall. has analgesic, anti-inflammatory and immune-regulating effects[22 23]; *Citrus×aurantium*L. has two-way regulation of the gastrointestinal tract[24 25]; *Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk. has analgesic, anti-inflammatory and immune-enhancing effects.[26 27] TXYF has known mechanisms, including modulating the brain-gut axis, protecting the permeability of the intestinal mucosa, improving visceral hypersensitivity and enhancing the body's immune function, which may be effective in the treatment of IBS-D.[28–31] These mechanisms suggest that TXYF may be effective in treating IBS-D.

A recent systematic review and meta-analysis has indicated that TXYF has potential benefits for IBS-D and appears to be safe.[32] However, the overall inadequate design of the included trials, such as the lack of blinding and placebo control, limits the ability to draw definitive conclusions. Previous research has highlighted critical issues in establishing the efficacy of IBS treatments, including efficacy measurement, placebo response, trial length and maintaining blinding.[17] It was concluded that the only reliable way to evaluate IBS therapies is through randomised, double-blind, placebo-controlled trials with at least 8–12 weeks of treatment, given the chronic nature of IBS. Although one completed trial comparing TXYF to its placebo for IBS-D has been published to date, it used only 4 weeks of treatment.[33]

To further evaluate the therapeutic effects and safety of TXYF in IBS-D, we designed and conducted a randomised, double-blind, placebo-controlled, superiority trial with an 8 week treatment period and a 3 month (12 weeks) post-treatment follow-up period. The trial hypothesised that TXYF would improve clinical responses among patients with IBS-D.

METHODS

Study design and participants

This was a randomised, double-blind, placebo-controlled, phase II, superiority trial of TXYF granules vs placebo granules for adults with IBS-D. The trial was conducted in the outpatient department of Fangshan Hospital of Beijing University of Chinese Medicine (FSH-BUCM), China. The trial was carried out in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice Guideline. It was approved by the Medical Ethics Committee of FSH-BUCM on 4 February 2021 (ref: FZY LK-2021–002). The trial protocol was registered in the ISRCTN registry (Reference number: ISRCTN12453166) on 23 March 2021 and published in *Trials*.[19] This study followed the Consolidated Standards of Reporting Trial reporting guideline.[34]

Participants were recruited through electronic posters on social media (eg, WeChat Moments) or posters in the hospital. Eligible participants included men and women ranging from late adolescence through middle adulthood (18–65 years), diagnosed with IBS-D according to the Rome IV criteria. Additionally, eligible patients were required to have a diagnosis of liver depression and spleen deficiency syndrome according to the diagnostic criteria for the traditional Chinese medicine (TCM) syndromes (2017)[35]; an irritable bowel syndrome symptom severity score (IBS-SSS) of no less than 75; and had not taken any medication related to IBS-D treatment for at least 1 week prior to trial participation. Other trial inclusion criteria were not participating in other ongoing trials; had a colonoscopy in the last 12 months and having had an examination report that showed no underlying organic pathology causing their symptoms. Patients were asked to volunteer, and to participate in the trial, they had to

sign an informed consent form and must have lived in the local area for at least 6 months.

Patients excluded were those with alternating diarrhoea and constipation (relying on patient recall); with severe tumours or organic lesions of the heart, liver, or kidneys; with severe mental illness or speech disorders affecting communication; with severe tumours or organic lesions of the gastrointestinal tract (ie, pancreatitis, history of colon or rectal cancer, intestinal tuberculosis, ulcerative colitis or Crohn's disease); with metabolic diseases affecting gastrointestinal motility, such as hyperthyroidism; with an allergic constitution or allergic to the composition of the studied medication; and/or with a history of gastrointestinal surgery. Pregnant women, lactating women, and women planning to have a baby or fertility treatment were also excluded. All participants gave written informed consent before study entry.

Randomisation, allocation concealment and blinding

A sequence of random numbers (block randomisation with a block size of 6) was generated by the R software (Version 4.0.3). Specifically, we used the 'blockrand' package. Allocation concealment was achieved using the method of coding the drug packaging to minimise selection bias. Patients who consented to the study and agreed to randomisation were randomly assigned in a 1:1 ratio to receive either TXYF or a placebo. Treatment assignment was blinded to participants, treatment providers, outcome assessors and statistical analysts until after the analysis was complete. Only the designated persons (SBL and JPL from the Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine (CEBCM-BUCM)) retained the key to unblind the randomisation sequence and allocation during the trial. The medicinal product packs produced for the trial were indistinguishable in appearance and packaging, and each was labelled with a unique identification number (method of coding the drug packaging) to maintain allocation concealment.

To assess the success of blinding, participants were contacted by telephone at the end of the study and asked which treatment they believed they had received, TXYF or placebo. Participants' answers were categorised into three—unknown, correct and incorrect—and analysed to see if there was a statistical difference in the guesses between the two groups.

Procedures

Participants were randomly assigned to receive TXYF granules (3.7 g per bag) twice daily (orally before meals) or matched placebo granules over an 8 week period. The placebo granules were made of lactose, flour, sucrose, edible caramel pigment, bitters and aspartame, among other ingredients. Their appearance, taste and specifications were consistent with those of TXYF granules. Both the TXYF and the placebo were manufactured by Anhui Jiren Pharmaceutical Co, Ltd (Anhui, China). Participants were allowed to take other medications recommended by the guidelines when they were unable to tolerate the IBS-D symptoms or were dissatisfied with the therapeutic effects during the treatment. The medications used by participants, including the medication name, dosage and duration of administration, were recorded in detail in their individual case report forms (CRFs).

Study visits and data collection were conducted at weeks 0 (baseline), 4, 8 and at the end of post-treatment follow-up (8 weeks of treatment plus 12 weeks of follow-up, ie, week 20). The regulations for trial quality control were as follows, the designated personnel from FSH-BUCM (HJCh, QYZ) were responsible for the monitoring of the entire trial, and the designated personnel (JPL, SBL, ZYY, LYK) from CEBCM-BUCM assisted in monitoring the entire trial. The content of quality control included (i) ensuring that the trial process complied with the protocol; (ii) ensuring the truth, accuracy and completeness of the data; (iii) monitoring the progress of the trial, ensuring the timely recording and reporting of adverse events; and (iv) ensuring the informed consent and protection of the participants.

The procedures, including the schedule for enrolment, treatment and assessments, are presented in figure 1.

Outcomes

The primary outcome was the response rate, measured by the change in IBS-SSS compared with baseline at week 8.[36] According to our protocol, disease severity was divided into four levels: normal (score <75), mild (75–174.9), moderate (175–299.9) and severe (≥300). If the disease severity remained at the baseline level or worsened (eg, from mild to moderate) post-treatment, it was judged as no response; otherwise, it was considered as a response. To explore whether different methods of IBS-SSS analysis might affect the primary outcome, we conducted a post-hoc analysis, ie, we calculated the proportion of patients who achieved a clinically significant improvement post-treatment that compared with baseline in IBS-SSS scores by defining a threshold for minimal clinically important difference (MCID=50)[36] and compared the proportion of patients meeting this threshold between the treatment groups. Additionally, we compared the response rate and the proportion of patients meeting the MCID threshold at weeks 4 and 20, as well as the IBS-SSS scores between groups at weeks 4, 8 and 20 as part of the additional analyses of IBS symptom severity.

Secondary outcomes were stool frequency (the average number of daily defecations recorded a week before each timepoint), and stool consistency using the Bristol Stool Scale[37] (the average score recorded a week before each time-point) at weeks 4, 8 and 20; quality of life measured using the scale of IBS-quality of life (IBS-QOL),[38] anxiety measured using the self-rating anxiety scale (SAS),[39] depression measured using the self-rating depression scale (SDS)[40] at week 8. Safety assessments during the treatment period included (1) routine examinations such as blood tests, urine tests and stool tests (including occult blood); (2) biochemical indices were assessed, focusing on liver function (aspartate aminotransferase (AST) and

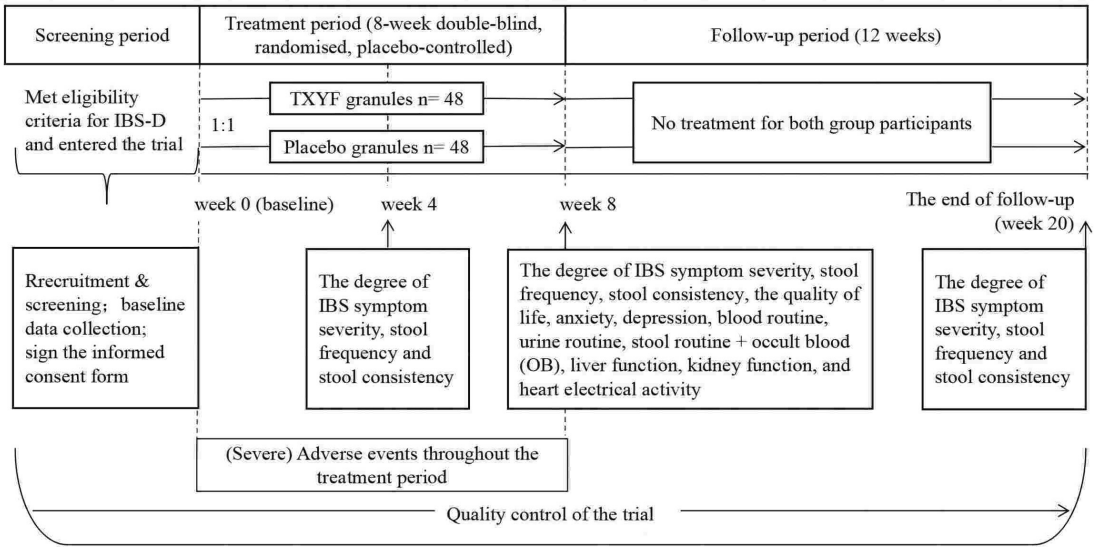

Figure 1 The procedures of this trial. *No washout period was set for all participants as they met the inclusion criteria of 'had not taken any medication related to the treatment of diarrhoea-predominant irritable bowel syndrome for at least one week prior to trial participation'. IBS-D, diarrhoea-predominant irritable bowel syndrome; TXYF, Tongxie Yaofang.

alanine aminotransferase (ALT)) and kidney function (blood urea nitrogen (BUN) and creatinine); (3) heart electrical activity was measured using ECG; (4) other adverse events such as rash, constipation or other special symptoms were recorded throughout the treatment, with the incidence calculated as (number of adverse events / total cases) × 100%; (5) severe adverse events, including loss of function, disability, life-threatening conditions or death, were also recorded, with the incidence calculated as (number of severe adverse events / total cases) × 100%.

To ensure the success of blinding, we compared the packaging, appearance, smell and taste of TXYF and placebo before recruiting participants. After completing the trial, enrolled patients were asked to guess whether they received TXYF or a placebo to further test whether blinding had been achieved.

Data were recorded in the CRF and entered into the computer using EpiData v3.1 Software.

Statistical analysis

It was estimated based on a previous study[41] that TXYF can produce a response (according to IBS-SSS) in 73% of participants with an 8 week treatment. We expected TXYF to have a 30% higher response rate than the placebo in the primary outcome, based on previously published relevant studies,[33 42] with a superiority margin of 10% (δ=10%). The participants' ratio of TXYF to placebo was 1:1. Allowing for a 10% loss of participants, a sample size of 96 participants was planned to achieve at least 80% power for the response rate of TXYF vs placebo (assuming 73% and 43% response rates, respectively) using a two-sided χ^2 test at a 0.05 significance level.

Data analysis followed the statistical analysis plan and was performed by the designated personnel (MH, YFL, HJCa) from CEBCM-BUCM. All analyses were conducted according to the intention-to-treat (ITT) principle, which included all randomised patients. A per-protocol set (PPS) analysis, which included all participants who completed the treatment period (taking 80%–120% of the required number of granules and having no major protocol deviations), and a follow-up period, was conducted as a sensitivity analysis for the primary outcome. To further validate the robustness and reliability of the response rate at weeks 4, 8 (primary outcome) and 12, we conducted a post-hoc complete case analysis (CCA) as a sensitivity analysis. CCA aims to assess the stability and consistency of our findings in the presence of any missing data, thereby reinforcing the integrity of the study outcomes.[43] A safety set (SS), which included all randomised patients who received at least one dose of study treatment, was used for the safety evaluation of the study treatment. For missing outcome data per patient, multiple imputation with predictive mean matching was used to impute it with M=20 imputed datasets.

Continuous data of baseline conforming to a normal distribution were presented as mean±SD, and those nonconforming to normal distribution were presented as the median and IQR; categorical data were described as the number and percentage of occurrences.

For the analysis of primary and secondary continuous outcomes, simple or multiple linear regression was applied to estimate the difference between TXYF and placebo. One pre-adjusted analysis included only baseline variables (eg, age, gender, disease duration, smoking and drinking) was done. Although another pre-adjustment analysis was planned for the concomitant treatment, it was not performed because the concomitant treatment occurred in only one participant. These variables are common in clinical practice and are thought to be likely to affect the effectiveness of treatment. To ensure the rationality of the selection of these variables, we discussed

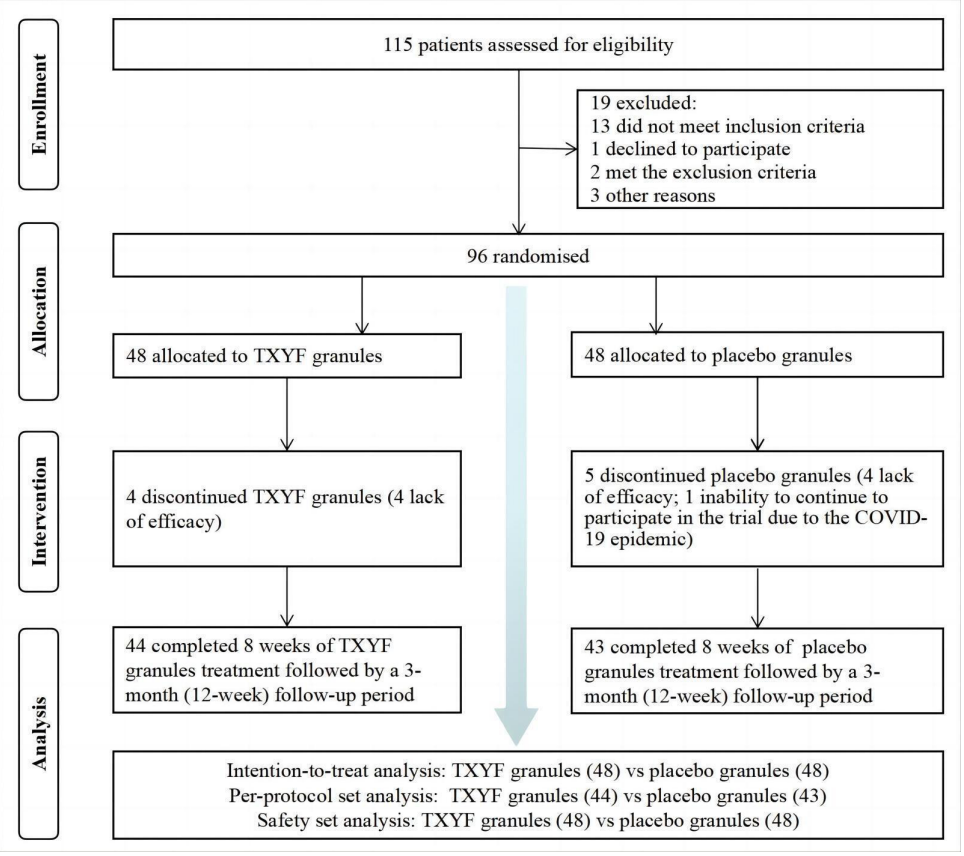

Figure 2 Trial profile. TXYF, Tongxie Yaofang.

them with clinical experts before making a decision. For primary and secondary categorical outcomes, estimates of the risk ratio were obtained using a generalised linear model with a log link and a Poisson distribution with robust standard errors. A pre-adjusted analysis was also conducted that adjusted for only baseline variables (eg, age, gender, disease duration, smoking and drinking).

Estimates of treatment effects were reported with 95% CIs). Two-tailed p values of ≤0.05 were considered statistically significant. All statistical analyses were performed using SPSS 22.0 for Windows (Chicago, Illinois).

Patient and public involvement

No patient or public member was involved in the design and conduct of the study.

RESULTS

Participants

Between April 2021 and November 2022, a total of 115 patients were assessed for eligibility to participate in the trial. Of those screened, 19 (17%) were found to be ineligible (see figure 2). Consequently, 96 patients were enrolled in the study, with 48 randomly assigned to either the TXYF group or the placebo group.

As of April 2023, 87 out of 96 participants (90%) who received the study medication completed the 8 week blinded treatment period and subsequent 12 week post-treatment follow-up: 44 participants in the TXYF group and 43 participants in the placebo group. Reasons for premature discontinuation included patient-reported lack of efficacy (four participants in the TXYF group and four participants in the placebo group) and inability to continue participation due to the COVID-19 epidemic (one participant in the placebo group). Details of participants who prematurely discontinued the study are provided in online supplemental table S1.

No participants were considered protocol violators, and none were unblinded before all outcomes were ascertained. Additionally, no participants took any other IBS-D treatment-related medications during the trial. Baseline characteristics of all randomised patients were fairly similar between the TXYF group and the placebo group (table 1).

Efficacy outcomes

Primary outcome

Both groups demonstrated a higher response rate according to the IBS-SSS at week 8. The response rate in the TXYF group was 79.2% (38/48), compared with 70.8% (34/48) in the placebo group; however, the difference between the groups was not statistically significant (unadjusted treatment effect estimate was 1.12 (95% CI 0.89 to 1.41); p=0.348; ITT; figure 3, table 2). When the treatment effect estimate was adjusted for baseline age, gender, disease duration, smoking, drinking, SAS score, SDS score and IBS-SSS score, the results were

Table 1 Baseline characteristics of all participants

Variable	TXYF group (n=48)	Placebo group (n=48)
Sex		
Female, n (%)	16 (33.3)	22 (45.8)
Male, n (%)	32 (66.7)	26 (54.2)
Age, median (IQR), years	41.5 (19.0)	40.0 (13.8)
Weight, mean (IQR), kg	70.0 (15.0)	67.5 (24.3)
Height, mean (SD), cm	168.5 (9.6)	167.5 (8.4)
Disease duration, median (IQR), years	2.3 (4.8)	2.0 (4.4)
Nationality		
Han nationality, n (%)	46 (95.8)	47 (97.9)
Other nationality, n (%)	2 (4.2)	1 (2.1)
Profession		
Non-manual worker, n (%)	15 (31.3)	20 (41.7)
Manual worker, n (%)	13 (27.1)	15 (31.3)
Other professions, n (%)	20 (41.7)	13 (27.1)
Married, n (%)	45 (93.8)	41 (85.4)
Current smokers, n (%)	18 (37.5)	13 (27.1)
Current drinkers, n (%)	6 (12.5)	8 (16.7)
IBS-SSS score at baseline, mean (IQR)	232.5 (120.0)	227.5 (102.5)
Stool frequency at baseline, median (IQR), times	2.2 (1.2)	2.1 (1.4)
Stool consistency at baseline, median (IQR)	5.6 (0.6)	5.6 (0.7)
IBS-QOL score at baseline, median (IQR)	62.4 (105.8)	53.9 (90.2)
Anxiety (SAS) score at baseline, median (IQR)	36.0 (17.3)	38.0 (13.8)
Depression (SDS) score at baseline, median (IQR)	33.0 (10.5)	33.0 (6.0)

Continuous variables are presented as mean (SD) or median (IQR).
IBS-SSS score, SAS score and SDS score: a higher score means worse.
IBS-QOL score: a lower score means better.
There were no missing baseline covariates in this study.
IBS-QOL, irritable bowel syndrome quality of life; IBS-SSS, irritable bowel syndrome symptom severity score; SAS, self-rating anxiety scale; SDS, self-rating depression scale; TXYF, Tongxie Yaofang.

almost unchanged (adjusted treatment effect estimate was 1.18 (95% CI 0.93 to 1.51); p=0.180; ITT; table 2). The PPS analysis also indicated no significant difference in response rates between the two groups at the end of 8 weeks of treatment (79.5% (35/44) vs 69.8% (30/43); unadjusted treatment effect estimate was 1.14 (95% CI 0.89 to 1.46), p=0.299; adjusted treatment effect estimate was 1.20 (95% CI 0.94 to 1.55), p=0.151; table 2). At week 20, both groups again showed higher response rates, but there were no statistically significant differences between the TXYF and placebo groups (table 2). Similar results were observed for the proportion of patients who met the threshold for MCID (table 2).

Comparisons of IBS-SSS scores at weeks 8 and 20 between the groups showed that IBS-SSS scores were numerically lower in the TXYF group than in the placebo group, but none of these differences reached statistical significance (table 2).

The CCA analysis (table 2) further confirmed the robustness and reliability of the response rates at weeks 4, 8 and 12.

Secondary outcomes

Similar to the primary outcome, all secondary outcomes improved in both groups. However, with the exception of IBS-QOL, there were no significant differences between the two groups, whether or not adjustments were made for baseline variables. For IBS-QOL, there was a statistically significant difference between the two groups after adjustment (table 2).

Adverse event reporting

Most participants tolerated the study medication well during the treatment period. One participant (1/48) in the TXYF group developed sinus arrhythmia, characterised by heart rate fluctuations during the breathing cycle with no significant symptoms. Two participants (2/48) in

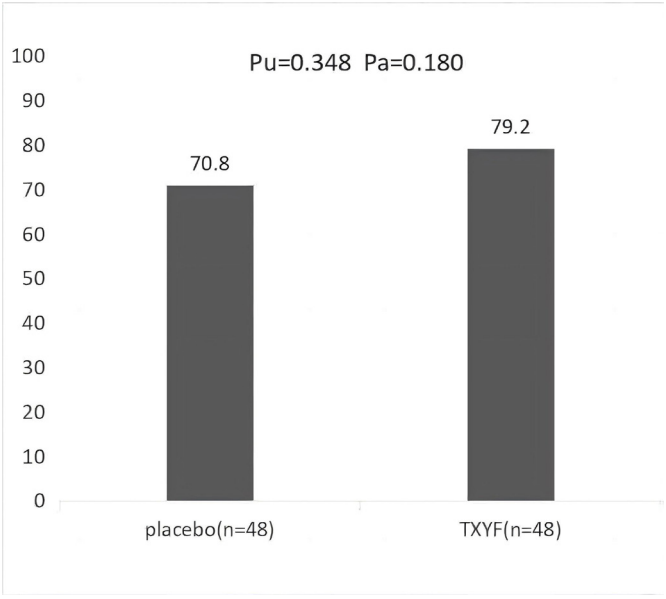

Figure 3 Response rate evaluated via irritable bowel syndrome symptom severity score at week 8. Pa, p value of adjusted treatment effect estimate; Pu, p value of unadjusted treatment effect estimate; TXYF, Tongxie Yaofang.

the placebo group experienced elevated transaminases and weakly positive faecal occult blood (faecal occult blood test result was weakly positive with no signs of significant gastrointestinal bleeding), respectively. These adverse events were mild and did not lead to patient withdrawal from the study. All events were promptly monitored and managed. We conducted a detailed analysis to determine the potential causal relationship between the adverse events and the study medication: (1) sinus arrhythmia was possibly related to the study medication, based on the timing of the event and the known effects of the herbs in TXYF on the cardiovascular system; (2) elevated transaminases were unlikely to be related to the placebo, as there were no known mechanisms by which the placebo could cause elevated transaminases; (3) weakly positive faecal occult blood was unlikely to be related to the placebo, as there were no signs of significant gastrointestinal bleeding and the placebo did not contain any components known to cause such an effect. Participants did not report any serious adverse events.

There were no significant abnormalities in blood routine, urine routine, stool routine+OB, liver function (AST, ALT), kidney function (BUN, creatinine) and heart electrical activity at the end of the 8 week treatment.

Blinding test

A total of 83 participants were successfully contacted for the blinding test. The results showed no difference between the groups, indicating that participants could not reliably distinguish between TXYF and the placebo (table 3). This suggests the success of the trial's placebo production and maintenance of blinding throughout the study.

DISCUSSION

Main findings and implications for clinical practice and future study

To the best of our knowledge, this is the first randomised, double-blind, placebo-controlled, superiority trial with an 8 week treatment period and a 12 week post-treatment follow-up to evaluate the therapeutic effects and safety of TXYF in IBS-D. The TXYF group and the placebo group each comprised 48 patients. Patients in both groups exhibited balanced baseline characteristics.

The results indicated improvements in IBS symptoms and quality of life in both the TXYF and placebo groups, with no significant difference between them. Notably, both treatments showed higher response rates in alleviating IBS symptom severity compared with previous studies.[33 44 45] The notable effect of the placebo could be attributed to several factors:

1. Psychological factors: research has confirmed that the symptomatic manifestations of IBS-D are closely linked to patient psychology, and psychological factors play a significant role in the condition's severity.[46] Patients enrolled in the study who received either treatment might have experienced improvements due to the increased attention and continuous care provided during the trial, which likely offered psychological support. Being part of a clinical trial, with regular check-ins and interactions with healthcare providers, can significantly enhance a patient's sense of being cared for and supported. This heightened level of attention and emotional comfort can reduce stress and anxiety, which are known to exacerbate IBS symptoms. Therefore, the psychological well-being of the participants was likely improved, leading to a reduction in symptom severity.
2. Cultural context: all participants were from a TCM hospital setting and might have had greater confidence in the medication's efficacy. In Chinese culture, TCM is deeply rooted and highly respected. Patients often have a strong belief in the effectiveness of TCM, which can enhance the placebo effect. The cultural trust in TCM practices and the holistic approach to health and wellness provided by TCM practitioners may have further reinforced the patients' positive expectations and beliefs about the treatment.

Another point is the length of IBS-D treatment with TXYF. Based on previously published trials, it has been suggested that a treatment period of 8–12 weeks seems to be the shortest treatment duration.[17] The reason for this argument is that IBS is usually a chronic, sometimes life-long condition with unpredictable periods of exacerbation and remission. Thus, clinical trials of only a few days to weeks are of very limited relevance for evaluating whether a treatment is effective.[17] So, in our study, the length of an 8 week treatment and the post-treatment follow-up of 12 weeks were agreed upon through expert discussions, and we also collected data on outcomes at 4 weeks of treatment. We found that the longer the duration of treatment, the greater the benefit to patients.

Table 2 The degree of irritable bowel syndrom symptom severity and other efficacy outcomes

	TXYF group (*n* (%), or mean (SD))	Placebo group (*n* (%), or mean (SD))	Unadjusted treatment effect estimate (95% CI), p value	Adjusted treatment effect estimate (95% CI), p value
Degree of IBS symptom severity				
Response rate				
Week 4*	19 (39.6)†	28 (58.3)†	0.68 (0.44, 1.04), 0.073‡	0.80 (0.52, 1.24), 0.320‡
Week 4§	18 (39.1)†	27 (58.7)†	0.67 (0.43 1.03), 0.067‡	0.78 (0.50, 1.21), 0.273‡
Week 8*	38 (79.2)†	34 (70.8)†	1.12 (0.89, 1.41), 0.348‡	1.18 (0.93, 1.51), 0.180‡
Week 8¶	35 (79.5)†	30 (69.8)†	1.14 (0.89, 1.46), 0.299‡	1.20 (0.94, 1.55), 0.151‡
Week 8§	35 (79.5)†	30 (69.8)†	1.14 (0.89, 1.46), 0.299‡	1.20 (0.94, 1.55), 0.151‡
Week 20*	41 (85.4)†	40 (83.3)†	1.03 (0.86, 1.22), 0.779‡	1.02 (0.86, 1.20), 0.851‡
Week 20§	38 (86.4)†	36(83.7)†	1.03 (0.87, 1.23), 0.730‡	1.02 (0.87, 1.20), 0.811‡
Proportion of patients who met the threshold for MCID				
Week 4*	26 (54.2)†	35 (72.9)†	0.74 (0.54, 1.02), 0.062‡	0.77 (0.57, 1.04), 0.090‡
Week 8*	41 (85.4)†	42 (87.5)†	0.98 (0.83, 1.14), 0.766‡	1.00 (0.87, 1.16), 0.959‡
Week 8¶	37 (84.1)†	38 (88.4)†	0.95 (0.80, 1.13), 0.563‡	0.98 (0.84, 1.13), 0.734‡
Week 20*	42 (87.5)†	41(85.4)†	1.02 (0.87, 1.20), 0.766‡	1.00 (0.87, 1.15), 0.995‡
IBS-SSS score				
Week 4*	174.1 (73.1)**	163.5 (72.0)**	10.57 (-18.82, 39.96), 0.477††	6.47 (-16.79, 29.72), 0.582††
Week 8*	120.2 (57.6)**	123.1 (61.2)**	−2.89 (-26.97, 21.19), 0.812††	−2.99 (-25.45, 19.47), 0.792††
Week 20*	100.1 (78.8)‡‡	100.9 (78.8)‡‡	−8.86 (-33.41, 15.69), 0.476††	−11.76 (-35.65, 12.13), 0.330††
Stool frequency				
Week 4*	2.0 (1.3)‡‡	2.0 (1.2)‡‡	0.03 (-0.37, 0.44), 0.873††	−0.08 (-0.37, 0.22), 0.612††
Week 8*	1.9 (1.2)‡‡	1.7 (1.1)‡‡	0.02 (-0.36, 0.39), 0.935††	−0.12 (-0.40, 0.16), 0.386††
Week 20*	1.7 (1.3)‡‡	1.7 (1.0)‡‡	0.06 (-0.30, 0.43), 0.738††	−0.01 (-0.33, 0.30), 0.931††
Stool consistency				
Week 4*	5.0 (1.1)‡‡	5.1 (1.0)‡‡	−0.08 (-0.39, 0.23), 0.609††	−0.05 (-0.36, 0.27), 0.773††
Week 8*	4.8 (0.8)**	4.9 (0.8)**	−0.13 (-0.44, 0.19), 0.432††	−0.11 (-0.43, 0.21), 0.513††
Week 20*	4.4 (1.0)‡‡	4.6 (1.0)‡‡	−0.29 (-0.58, 0.01), 0.054††	−0.21 (-0.51, 0.10), 0.179††
IBS-QOL				
Week 8*	29.6 (49.9)‡‡	38.2 (51.7)‡‡	−3.54 (-26.11, 19.04), 0.756††	−16.97 (-33.80,−0.15), 0.048††§§
Anxiety (SAS)				
Week 8*	32.5 (9.0)‡‡	33.0 (10.0)‡‡	0.49 (-2.77, 3.75), 0.764††	−1.31 (-3.74, 1.13), 0.289††
Depression (SDS)				
Week 8*	30.0 (12.0)‡‡	32.5 (7.8)‡‡	1.01 (-2.55, 4.57), 0.574††	−1.00 (-4.03, 2.03), 0.515††

The following covariates were included in the multivariate analysis for all outcomes: age, sex, disease duration, smoking, drinking, height, weight, marriage and baseline scores on SAS and SDS; for the response rate, the proportion of patients who meet the threshold for MCID, IBS-SSS score, stool frequency, stool consistency and quality of life, their respective corresponding baseline assessment values were also included (response rate, proportion of patients who meet the threshold for MCID and IBS-SSS both correspond to baseline scores of IBS-SSS).
IBS-SSS score, SAS score and SDS score: a higher score indicates worse symptoms.
IBS-QOL score: a lower score indicates better quality of life.
*intention-to-treat analysis (n_{TXYF}=48, $n_{placebo}$=48).
†*n* (%).
‡RR (95% CI), p value.
§complete case analysis (n_{TXYF}=46$_{week\ 4}$, 44$_{week\ 8}$, 44$_{week\ 20}$, $n_{placebo}$=46$_{week\ 4}$, 43$_{week\ 8}$, 43$_{week\ 20}$).
¶Per protocol set analysis (n_{TXYF}=44, $n_{placebo}$=43).
**mean (SD).
††*b* (95% CI), p value.
‡‡median (IQR).
§§p ≤0.05.
IBS-QOL, IBS-quality of life; IBS-SSS, IBS symptom severity score; MCID, minimal clinically important difference; RR, risk ratio; SAS, self-rating anxiety scale; SDS, self-rating depression scale; TXYF, Tongxie Yaofang.

Table 3 Result of the blinding test

Result of guessing	TXYF group (n=44)	Placebo group (n=39)	p value
Correct, n%	2 (4.55)	1 (2.56)	0.470
Unknown	41 (93.18)	35 (89.74)	
Incorrect	1 (2.27)	3 (7.69)	

TXYF, Tongxie Yaofang.

More interestingly, during the post-treatment follow-up period, the patients obtained a sustained efficacy benefit, as found in previous studies.[33 45] A trial conducted by Chen *et al* found that a 4 week treatment with TXYF resulted in relief of IBS-D symptoms for 6–8 weeks.[33] Another trial carried out by Lai *et al* revealed that the positive therapeutic effects of modified TXYF could last up to 25 weeks after the treatment was discontinued, and after the 25 weeks, the profile of IBS could be considered as the IBS natural history.[45] In our study, the therapeutic effects appeared to show a cumulative increase from the start of treatment to the end of follow-up, with no occurrence of a turning point of decline of therapeutic effects. Therefore, considering the findings of these studies together, we hypothesise that the longer the duration of TXYF use, the greater the benefit for IBS-D patients, and the therapeutic effects may last longer after discontinuation of treatment. The findings of these studies also suggest the possibility of intermittent treatment for IBS-D patients in clinical practice, which would ensure maximum treatment benefit while allowing patients to save on treatment costs.

In any case, however, these speculations need to be validated in future multi-centre, randomised, large-sample, blind, placebo-controlled trials with longer treatment duration and post-treatment follow-up. More and more intensive measurement time points should be set up to collect data for evaluation to identify more definitive efficacy turning points and provide a more accurate reference of evidence for clinical practice. Meanwhile, attention should be paid to the safety of long-term use of herbal medicines. These trials should also explore the potential role of psychological factors in managing IBS-D. In clinical practice, patients should consider integrating psychological support and lifestyle adjustments to manage IBS-D, rather than relying solely on medication. Doctors should adopt a comprehensive treatment strategy, incorporating psychological interventions and individualised treatment plans, to better manage and alleviate IBS-D symptoms.

Strengths and limitations

Our study has several strengths. *First*, we adopted the study design of a randomised, double-blind, placebo-controlled trial, for example, not only were the patients and treatment providers blinded, but also the outcome assessors and statistical analysts. The blinding test confirmed the successful implementation of blinding in our study. This allowed the study to avoid the occurrence of performance bias and detection bias, thus making the study results more realistic and reliable.[47] *Second*, we used a longer 8 week treatment and 12 week post-treatment follow-up to observe the therapeutic effects and safety of TXYF for IBS-D compared with most previous studies of TCM for IBS-D. This is even more informative in assessing whether TXYF is effective in treating a chronic condition like IBS-D. *Last but not the least*, the results were analysed with adjustment for baseline variables (eg, age, sex, duration of disease, smoking and alcohol consumption) to exclude possible effects of confounding factors on the veracity of the results (eg, the possibility of exaggerated efficacy).

Despite providing some insights, this study has some limitations. *First*, the small sample size may limit the generalisability and statistical power of the findings, and the single-centre trial may introduce site-specific biases, potentially affecting the external validity. Therefore, the results may not be broadly applicable to other settings or populations, and further multi-centre trials with larger, diverse patient populations are needed to validate these preliminary findings. *Second*, we only collected outcome data at 4 weeks of treatment, 8 weeks of treatment, and 12 weeks of post-treatment follow-up, without additional measurement time points, which left us with no way to observe the efficacy turning points more precisely. We expect that future studies will improve on these limitations.

CONCLUSIONS

In this superiority trial, both TXYF and the placebo demonstrated clinically meaningful improvements in IBS-D symptoms after an 8 week treatment period, with both showing a reasonable safety profile. However, no significant differences were observed between the groups. This result suggests that the relationship between IBS-D and patient psychology merits further investigation.

Future large-scale, rigorously designed trials with longer treatment durations and extended post-treatment follow-up are essential to comprehensively evaluate the therapeutic effects and safety of TXYF in IBS-D. Additionally, these trials should explore the potential role of psychological factors in managing the condition.

In clinical practice, patients should consider integrating psychological support and lifestyle adjustments to manage IBS-D, rather than relying solely on medication. Doctors should adopt a comprehensive treatment strategy, incorporating psychological interventions and individualised treatment plans, to better manage and alleviate IBS-D symptoms.

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