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RESEARCH ARTICLE

Efficacy of acupuncture in refractory irritable bowel syndrome patients: a randomized controlled trial

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Abstract **Previous studies have confirmed that acupuncture for irritable bowel syndrome (IBS) provided an additional benefit over usual care alone. Therefore, we performed a multicenter, randomized, sham-controlled trial to assess the efficacy and safety of acupuncture versus sham acupuncture for refractory IBS in patients in the context of conventional treatments. Patients in the acupuncture and sham acupuncture groups received real or sham acupuncture treatment in 3 sessions per week for a total of 12 sessions. The primary outcome was a change in the IBS–Symptom Severity Scale (IBS-SSS) score from baseline to week 4. A total of 521 participants were screened, and 170 patients (85 patients per group) were enrolled and included in the intention-to-treat analysis. Baseline characteristics were comparable across the two groups. From baseline to 4 weeks, the IBS-SSS total score decreased by 140.0 (95% CI: 126.0 to 153.9) in the acupuncture group and 64.4 (95% CI: 50.4 to 78.3) in the sham acupuncture group. The between-group difference was 75.6 (95% CI: 55.8 to 95.4). Acupuncture efficacy was maintained during the 4-week follow-up period. There were no serious adverse events. In conclusion, acupuncture provided benefits when combined with treatment as usual, providing more options for the treatment of refractory IBS.**

Keywords acupuncture; functional gastrointestinal disorders; irritable bowel syndrome; clinical trial

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with a prevalence ranging from 10% to 20% worldwide and from 2% to 12% in China [1,2]. IBS mainly occurs in people younger than 50 years and is characterized by abdominal pain or discomfort that is associated with stool irregularities (e.g., diarrhea, constipation) but without obvious organic lesions [3,4]. Although IBS is not life-threatening, it has a substantial negative impact on quality of life (QOL) and a heavy disease burden and increases the risk of mental disorders such as depression because of its high prevalence and refractory characteristics in a relatively young population [5].

IBS is a multifactorial disorder of the gut-brain axis. Pathogenesis includes both personal factors and environmental agents, leading to the development of diverse treatment strategies [6]. Currently, pharmacological treatments are the primary choice for IBS and focus on management of the most common symptoms,

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i.e., abdominal pain and altered bowel habits. However, there is substantial heterogeneity in symptom profiles among IBS patients, with patients divided into IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), and IBS with mixed bowel habits (IBS-M); moreover, symptoms can differ over time, and patient symptomatology can change from one profile to another [7]. Limited symptom responses lead to considerable patient dissatisfaction (60%) with currently available IBS treatments [8]. Some IBS patients have symptoms that last more than 12 months and do not respond to psychological treatment, such as hypnotherapy or cognitive–behavioral therapy (CBT). Patients with IBS can be considered therapy resistant (i.e., refractory IBS) [9,10]. Therefore, it is not surprising for nonresponding patients to seek additional therapeutic options.

Traditional Chinese medicine (TCM), especially the application of acupuncture, has long been recognized to treat functional gastrointestinal disorders. For patients with inadequate responses to usual care, acupuncture provides additional benefits and might be considered as adjunctive therapy for IBS [11,12]. However, there are few trials to assist healthcare decision-making because most published studies have poor correspondence to clinical practice and a high risk of bias [13]. Sham control trials have yet to provide robust and stable evidence of the benefits of acupuncture [14]. Additionally, it is not certain whether acupuncture can promote symptom relief in patients with refractory IBS. Therefore, the main objective of this randomized controlled trial (RCT) was to evaluate the efficacy of true acupuncture (TA) vs. sham acupuncture (SA) in refractory IBS.

Materials and methods

Study design

This multicenter, sham-controlled trial was performed between October 12, 2020, and May 20, 2022, at 6 sites in China. Recruitment included contacting outpatient acupuncture and gastroenterology departments, posting on hospital social media sites (WeChat subscription), posting fliers and visiting surrounding community service centers. This trial was approved by the Ethics Committees and Institutional Review Boards of participating hospitals and registered at ClinicalTrials.gov. A Data and Safety Monitoring Board was established, which met every 3 months to review the data for ensuring the safety of the trial. The trial was performed in compliance with the *Helsinki Declaration*. The protocol, standard operation process and statistical analysis plan have been previously published [15]. All patients provided signed informed consent. This study followed the CONSORT reporting guidelines.

Participants

Clinicians mainly selected patients for detailed evaluation who fulfilled the Rome IV diagnostic criteria for functional gastrointestinal disorders and were suspected of having refractory IBS (including IBS-D, IBS-C, and IBS-M) (Tables S1 and S2). Patients were considered eligible if they were 18 to 70 years old, had IBS for 12 or more months, had normal results of tests for occult blood in stool within the past month, demonstrated absence of response to a minimum of 6 weeks of dietary intervention or advice, demonstrated absence of response to an adequate dose of at least one conventional pharmacological agent tried for a minimum of 6 weeks, and had normal results on colonoscopy within 1 year before study entry (if age above 50 years).

Patients were excluded for having at least one of the following conditions: (1) previous colonoscopy, meal barium fluoroscopy, abdominal ultrasound and other clinical examination revealing severe intestinal organic lesions; (2) the presence of one or more of the following warning symptoms: unexplained rectal bleeding, anemia, abdominal mass, ascites, fever and emaciate; (3) the presence of severe diseases of the heart, brain, rheumatic immune or endocrine system, an unstable psychological state or accompanying psychological disorder, pregnancy or lactation. Patients receiving acupuncture within 3 months before enrollment were also excluded.

Randomization and blinding

Eligible patients were randomly assigned in a 1:1 ratio to the TA or SA groups by a central web-based randomization system. Dynamic block randomization was used, and the block size was set at 4 or 6. A randomization sequence was generated by an independent biostatistician using R software (version 4.0.1). Allocation was concealed, with group assignments stored by a research assistant who did not take part in enrollment, treatment, or assessment. The clinical research coordinators obtained the random allocation number through a dedicated network port randomization process when eligible patients enrolled in the trial. However, the acupuncturists could not be blinded to group allocation. Patients, outcome evaluators and statisticians were blinded to group allocation. Data entry and management were conducted using a database software clinical trial data management system provided by data administrators of the China Academy of Chinese Medical Science.

Interventions

After the diagnosis of refractory IBS and random allocation to groups, patients continued to receive

treatment as usual (TAU) during the study period. TAU was defined as the continuation of the current therapeutic agents prescribed by a general practitioner or gastroenterologist [16]. Any changes in the medications of individual participants were recorded on defecation diary cards. If the patient added other new pharmacological drugs to treat IBS for more than one week so that the efficacy of acupuncture could not be evaluated, a violation of the study protocol was considered to have occurred. All acupuncturists had undergone standardized training before the start of the trial. Sterile disposable acupuncture needles (size 0.30 × 40 mm; Hwatuo) were used in both groups, and both groups received treatment performed by licensed acupuncturists with at least three years of experience.

Based on TCM theory, our early research and consensus meetings with clinical experts [17], the prespecified acupoints for the TA group included the bilateral *Tianshu* (ST25), *Shangjuxu* (ST37), *Zusanli* (ST36) and *Neiguan* (PC6) acupoints (Table S3 and Fig. S1). Twirling, lifting and uniform reinforcing-reducing manipulations were applied for 30 s at each acupoint to achieve the "deqi" sensation (including heaviness, numbness, pressure, soreness and aching), which is believed to be an essential component for acupuncture efficacy. Participants received 12 30-min sessions of treatment (3 times weekly for 4 weeks).

The participants in the SA group also received the same duration and frequency of sessions as the TA group. Similarly, SA was performed at predefined bilateral sites (nonacupoints 1–4) that did not correspond to the acupoints used in the TA group, traditional points or meridians (Table S4 and Fig. S1) [15]; needles were inserted to a slightly shallower depth than in TA and were not manipulated to induce the "deqi" sensation [18].

Outcomes

All patients received baseline assessments, which included the severity of symptoms, as determined by the Irritable Bowel Syndrome–Symptom Severity Scale (IBS-SSS), and disease-specific QOL, as determined by the IBS-QOL questionnaire and the Work and Social Adjustment Scale (WSAS). Daily defecations were characterized (scores and times) with the Bristol Stool Form Scale (BSFS) and diary card. Anxiety and depression symptoms were assessed via the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS). During the 4-week intervention period, adequate relief of IBS (IBS-AR) [19], including whether abdominal pain and discomfort were adequately relieved, was assessed weekly. The IBS-SSS, IBS-QOL, WSAS, BSFS, SAS and SDS scores were evaluated every 2 weeks. At weeks 6 and 8 (i.e., in the follow-up period), patients completed global assessments of the treatment effects via the IBS-SSS, WSAS, BSFS and diary card. Adverse events (AEs) were monitored throughout the trial.

The primary outcome was the change in IBS-SSS total scores from baseline to week 4. The IBS-SSS is a validated scoring system that reflects the severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, satisfaction with bowel habits and interference with QOL. A positive IBS-SSS response was defined as a 50-point reduction in IBS-SSS total scores [20].

The secondary outcomes were as follows: changes in IBS-SSS scores in each domain at week 4; changes in IBS-SSS total scores from baseline to weeks 2, 6 and 8; IBS-AR response rate (responders were defined as participants who reported adequate relief of their IBS symptoms for at least 50% of the 4-week period) [19]; changes in IBS-QOL total, SAS, and SDS scores from baseline to weeks 2 and 4; changes in IBS-QOL scores in each domain at week 4; changes in WSAS total scores from baseline to weeks 2, 4, 6 and 8; changes in average weekly stool from baseline to weeks 2, 4, 6 and 8 (normal defecation defined as a daily stool frequency ⩽ 3 with stool consistency of type 4) [17]; adherence; blinding success; and AEs.

Statistical analyses

The sample size calculation was based on clinical experience and a previous trial [21], that showed that acupuncture plus usual care (UC) decreased IBS-SSS scores by 27; the difference between acupuncture + UC group and the UC group was 18 points. Hence, we anticipated the scores of the two groups on the continuation of TAU as follows: the changes between the TA and SA in improvement of the IBS-SSS of refractory IBS were expected to be 30 and 20 from baseline to week 4. The standard deviation (SD) was amended to 25 and 18, respectively. The ratio between the TA and SA was 1:1. The sample size was calculated with a 20% type II error rate (80% power) and 5% type I error. Allowing for 10% loss to follow-up, the sample size was increased to 85 patients in each group. Therefore, a total of 170 participants were needed for this trial.

Intention-to-treat (ITT) populations were used in all efficacy analyses. Missing data on primary outcomes were handled using a multiple imputation procedure in R (version 4.1.2). For the analysis of dichotomous variables of IBS-AR, the missing data would be to consider the worst possible outcome in the acupuncture group and the best possible outcome in the sham group. For other categorical variables, missing data were not imputed, and the observed data were used in the analysis. Continuous variables such as IBS-SSS, IBS-QOL, WSAS, SAS and SDS scores are reported as the mean (SD) or median

(IQR); an independent *t* test was used for normally distributed values, and the Mann–Whitney *U* test was used for skewed data. Estimated between-group differences were calculated with the use of the Mann–Whitney *U* test and the Hodges–Lehmann estimate of 95% CIs for pseudomedians as appropriate. Categorical variables were summarized with frequencies and percentages. The differences in expectancy, adherence, and IBS-AR response rate between the groups were compared using χ^2 or Fisher's exact test.

The primary outcome was assessed using analysis of covariance and adjusted for baseline total IBS-SSS. The same approach was used for changes in total IBS-SSS at weeks 2, 6, and 8. Two sensitivity analyses were conducted to assess the robustness of the results. First, changes in total IBS-SSS from baseline to weeks 4 and 8 were analyzed by mixed-effect model. Second, other covariates, such as center, age, gender, disease duration and so on, were considered to explore whether these differences can have an influence on the reporting of patient-reported outcomes. A positive IBS-SSS response was considered a 50-point reduction in total IBS-SSS scores. IBS-SSS response rate was estimated using χ^2 tests. For other normally or approximately normally distributed continuous variables, in the general linear model, repeat measurement was used to evaluate differences between and within groups (Mauchly's sphericity test was performed to determine whether the violation of sphericity occurs, and the multivariate analysis of variance was used when the violation of sphericity occurs). The model included the time elapsed since enrolment, treatment assignment, and interaction between time and treatment. Prespecified subgroup analyses included subtypes of IBS.

Analyses were performed with SPSS statistical software version 22.0 (IBM). A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Among the 521 patients screened, 170 participants were included and randomly assigned to groups. A total of 160 patients completed all outcome measurements at week 8, and 10 patients (6%) dropped out of the study due to time commitment issues, personal issues, or lack of satisfactory effects (5 in the TA group and 5 in the SA group). Thus, 85 patients per group were included in the ITT analyses (Fig. 1). Table 1 shows the patient characteristics at baseline according to group. There was no difference between groups regarding the usual risk factors for IBS, such as the sex ratio (female sex is a risk factor for IBS) and age, which confirmed that the groups were well matched. Adherence results are shown in Table S5. There was no difference in the number of patients using new pharmacological drugs (including rescue medication) between the two groups (Table S6). Details of other medications taken for IBS are shown in Table S7.

Primary outcome

Regarding the primary outcome, the mean (95% CI) decrease in the IBS-SSS total score was 140.0 (126.0 to 153.9) in the TA group and 64.4 (50.4 to 78.3) in the SA group (between-group difference, 75.6; 95% CI: 55.8 to 95.4) (Table 2). The response rate was significantly higher in the TA group (90.6%, 77/85) than in the SA group (44.7%, 38/85), with a between-group difference of 45.9% (95% CI: 31.7% to 57.7%) at week 4 (Table 2). Similarly, patients with > 50% improvement in IBS-SSS was significantly higher in the TA group than in the SA group, with a between-group difference of 47.1% (95% CI: 32.1% to 59.2%) at week 4 (Table 2). The differences in relative changes between the two groups of primary outcomes are shown in Table S8. The primary outcome (decrease in IBS-SSS total scores) of the ITT analysis is shown as a scatter plot in Fig. 2. Similar results were observed in sensitivity analyses (Tables S9 and S10), and prespecified covariates had no significant effect on the results (Table S10). Similar results were observed in the IBS-D and IBS-M subgroups (Table S11, $P < 0.001$ and $P = 0.02$, respectively).

Secondary outcomes

The decrease in IBS-SSS total scores at week 2 was greater in the TA group (90.3) than in the SA group (48.6), with a between-group difference of 41.7 (95% CI: 20.2 to 63.1). At week 6, the mean difference in the change in IBS-SSS total scores was 44.0 (95% CI: 17.3 to 70.6). A similar result was observed at week 8, with a between-group difference of 62.3 (95% CI: 40.4 to 84.1) (Table 2). The decreases from baseline to week 4 in all domain scores of the IBS-SSS were greater in the TA group than in the SA group ($P < 0.05$ for all, Table 2 and Fig. 3). The repeated-measures ANOVA revealed the following results: (1) a significant main effect of time on the IBS-SSS total scores across weeks (Table S12), and (2) a trend indicating that the acupuncture effects were sustained for at least 8 weeks (Fig. 3 and Table S13).

The decrease in the IBS-QOL total score at week 4 was greater in the TA group (13.0) than in the SA group (4.5), with a between-group difference of 8.4 (95% CI: 4.6 to 12.2, Table 3). The four-week changes in all subscale scores ($P < 0.05$ for all) were greater in the TA group than in the SA group except for the sexual item score, which did not change ($P = 0.84$, Table 3). No difference was found between the groups in the SAS and SDS scores

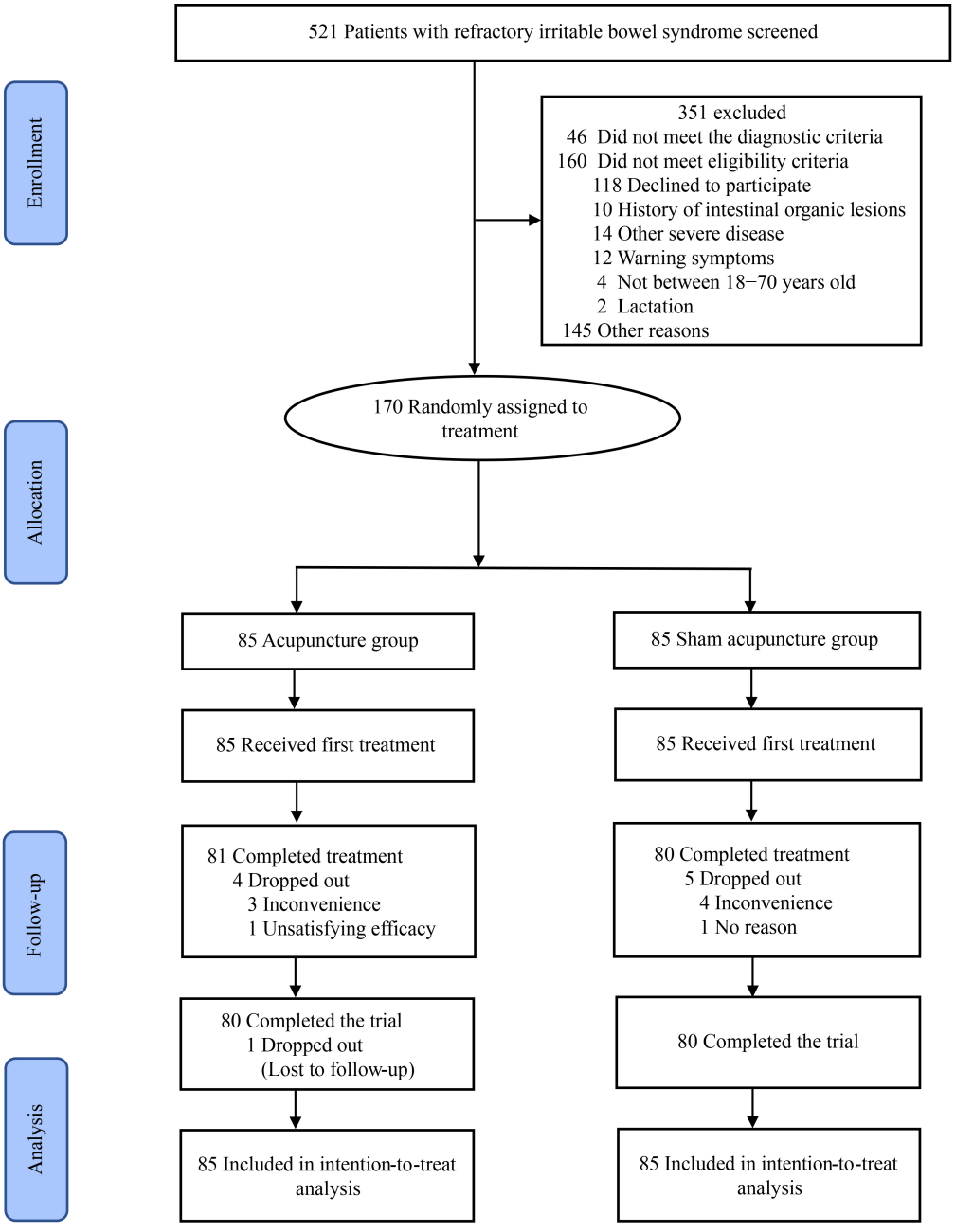

Fig. 1 The CONSORT flowchart of the patient flow throughout the study.

at week 4 ($P = 0.10$ and $P = 0.28$, respectively, Table 3). The IBS-QOL, SAS and SDS scores at different time points are shown in Table 3 and Fig. S2. At week 4 and each assessment time point during the trial period, the TA group had significantly better results than the SA group in terms of the decrease in WSAS total scores and the improvement in regular weekly stool ($P < 0.05$ for all, Table 3). The WSAS scores and regular weekly stool at different time points are shown in Fig. S3 and Fig. S4. The TA group exhibited a higher response rate in terms of IBS-AR at 4 weeks than the SA group, with a between-group difference of 60.0% (95% CI: 46.0% to 70.5%). The results of the assessment examining blinding success are shown in Table S14.

Adverse events

Acupuncture-related AEs were reported in 9 of 85 patients in the TA group and 4 of 85 patients in the SA group. Complications included subcutaneous hematoma and residual needle sensation after needle removal. All acupuncture-related AEs were mild and transient and required no specific treatment. There were no serious AEs (Table S15).

Table 1 Demographic and baseline characteristics of the patient population

Characteristic	Acupuncture group (n = 85)	Sham acupuncture group (n = 85)
Age, mean (SD), years	35.4 (12.1)	38.4 (12.1)
Gender (female), *n* (%)	52 (61)	42 (49)
Marital status, *n* (%)		
Married	55 (65)	59 (69)
Single	30 (35)	26 (31)
BMI, mean (SD), kg/m^2	22.2 (3.6)	23.0 (4.1)
Education, *n* (%)		
Graduate	14 (17)	15 (18)
Undergraduate	59 (69)	51 (60)
High school and below	12 (14)	19 (22)
Disease duration, median (IQR), months	60.0 (29.0 to 108.0)	60.0 (34.0 to 96.0)
Hypertension, *n* (%)	0	4 (5)
Diabetes, *n* (%)	1 (1)	1 (1)
Previous treatments, *n* (%)[a]		
Probiotics	58 (68)	65 (77)
Antispasmodics	20 (24)	17 (20)
Osmotic laxatives	4 (5)	5 (6)
Anti-diarrheal agents	12 (14)	10 (12)
Herbal medicine	28 (33)	26 (31)
Others[b]	10 (12)	10 (12)
Subtypes of IBS, *n* (%)		
IBS diarrhea	80 (94)	75 (88)
IBS constipation	1 (1)	4 (5)
Mixed IBS	4 (5)	6 (7)
IBS-SSS score, mean (SD)[c]	257.6 (70.2)	244.7 (71.8)
Regular stool per week, median (IQR)[d], days	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)
WSAS score, median (IQR)[e]	8.0 (4.0 to 12.0)	10.0 (4.0 to 12.0)
IBS-QOL score, mean (SD)[f]	27.3 (17.1)	23.4 (13.8)
SAS score, mean (SD)[g]	45.7 (10.4)	44.4 (9.4)
SDS score, mean (SD)[g]	46.3 (11.7)	45.4 (9.3)
Patient expectation of acupuncture success, *n* (%)		
Significant	40 (47)	42 (50)
Some	31 (37)	35 (41)
Slight	11 (13)	7 (8)
None	3 (3)	1 (1)

NOTE: BMI, body mass index; IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Score; IQR, interquartile range; WSAS, Work and Social Adjustment Scale; IBS-QOL, IBS-Quality of Life; SAS, Self-Rating Anxiety Scale; SD, standard deviation; SDS, Self-Rating Depression Scale.

[a] Medications for IBS include all current and past prescriptions for IBS, and some people have multiple medications.

[b] Others include medicines such as antibiotic, neurotransmitter pharmaceutical, health care medicine, and medication outside the guidelines.

[c] Score range 0–500 (best score 0).

[d] Normal defecation defined as a daily stool frequency ⩽ 3 times with stool consistency of type 4.

[e] Score range 0–40 (best score 0).

[f] Score range 0–100 (best score 0).

[g] Score range 25–100 (best score 25).

Table 2 Time to event outcomes

Variable	Acupuncture group (n = 85)	Sham Acupuncture Group (n = 85)	Difference (95% CI)	P
Primary outcome				
Change from baseline in total IBS-SSS at week 4, adjusted mean (95% CI)[a]	140.0 (126.0 to 153.9)	64.4 (50.4 to 78.3)	75.6 (55.8 to 95.4)	< 0.001
Secondary outcomes				
Change from baseline in each subscale score of IBS-SSS at week 4, mean (95% CI)				
Severity of abdominal pain	26.8 (22.2 to 31.4)	14.9 (9.9 to 19.9)	–	0.001
Frequency of abdominal pain	15.0 (8.5 to 21.6)	2.5 (−3.7 to 8.6)	–	0.006
Severity of abdominal distension	28.7 (22.8 to 34.5)	12.3 (8.9 to 15.8)	–	< 0.001
Satisfaction with bowel habits	34.1 (27.8 to 40.3)	13.9 (7.5 to 20.2)	–	< 0.001
Interference of IBS with life in general	32.7 (26.5 to 39.0)	16.1 (10.9 to 21.4)	–	< 0.001
Change from baseline in total IBS-SSS, adjusted mean (95% CI) [a]				
Week 2	90.3 (75.1 to 105.4)	48.6 (33.5 to 63.8)	41.7 (20.2 to 63.1)	< 0.001
Week 6	137.2 (118.3 to 156.0)	93.2 (74.4 to 112.0)	44.0 (17.3 to 70.6)	0.001
Week 8	147.4 (132.0 to 162.8)	85.2 (69.7 to 100.6)	62.3 (40.4 to 84.1)	< 0.001
IBS-SSS response rate, n (%)[b]				
Week 2	63 (74.1)	31 (36.5)	37.7 (22.1 to 50.8)	<0.001
Week 4	77 (90.6)	38 (44.7)	45.9 (31.7 to 57.7)	<0.001
Week 6	68 (80.0)	49 (57.6)	22.4 (7.6 to 35.9)	0.002
Week 8	73 (85.9)	54 (63.5)	22.4 (8.5 to 35.2)	0.001
Patients with > 50% improvement in IBS-SSS, n (%)				
Week 2	30 (35.3)	8 (9.4)	25.9 (12.7 to 38.1)	< 0.001
Week 4	54 (63.5)	14 (16.5)	47.1 (32.1 to 59.2)	< 0.001
Week 6	54 (63.5)	22 (25.9)	37.7 (22.1 to 50.8)	< 0.001
Week 8	56 (65.9)	19 (22.4)	43.5 (28.1 to 56.1)	< 0.001

NOTE: IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Score.

[a] The primary outcome was analyzed with analysis of covariates and adjusted for baseline total IBS-SSS.

[b] Patients with a reduction of 50 points or more on IBS-SSS total score were defined as responders.

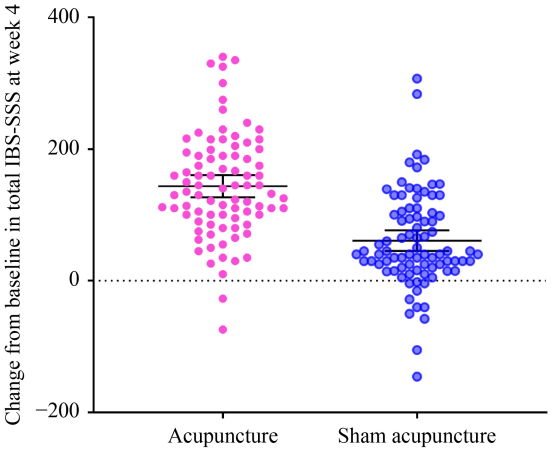

Fig. 2 Changes in the total IBS-SSS from baseline to week 4 in the acupuncture group (85 patients) and sham acupuncture group (85 patients) during the 4-week randomized intervention period. The middle solid horizontal lines show the mean values, the upper solid horizontal lines show the upper limits, and the lower solid horizontal lines show the lower limits. Each circle represents an individual patient. IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score.

Discussion

To our knowledge, this is the first multicenter, parallel group, randomized and sham-controlled clinical trial of acupuncture efficacy in the treatment of refractory IBS. The TA group had significantly lower IBS-SSS total scores by the end of the intervention period, and this improvement in refractory IBS symptoms persisted during the 4-week observational follow-up period. At the end of the intervention, we also found that patients who received true acupuncture had a better improvement in regular stool than patients who received sham acupuncture treatment. Moreover, patients in the acupuncture group also had improvements in QOL and anxiety symptoms. The low dropout rate (6%) and lack of serious AEs indicate that acupuncture was well tolerated and is safe for the relief of IBS symptoms.

Currently, clinicians have few options to offer people with refractory IBS, particularly in primary care settings. A trial applying group CBT with interoceptive exposure (GCBT-IE) to treat drug-refractory IBS reported

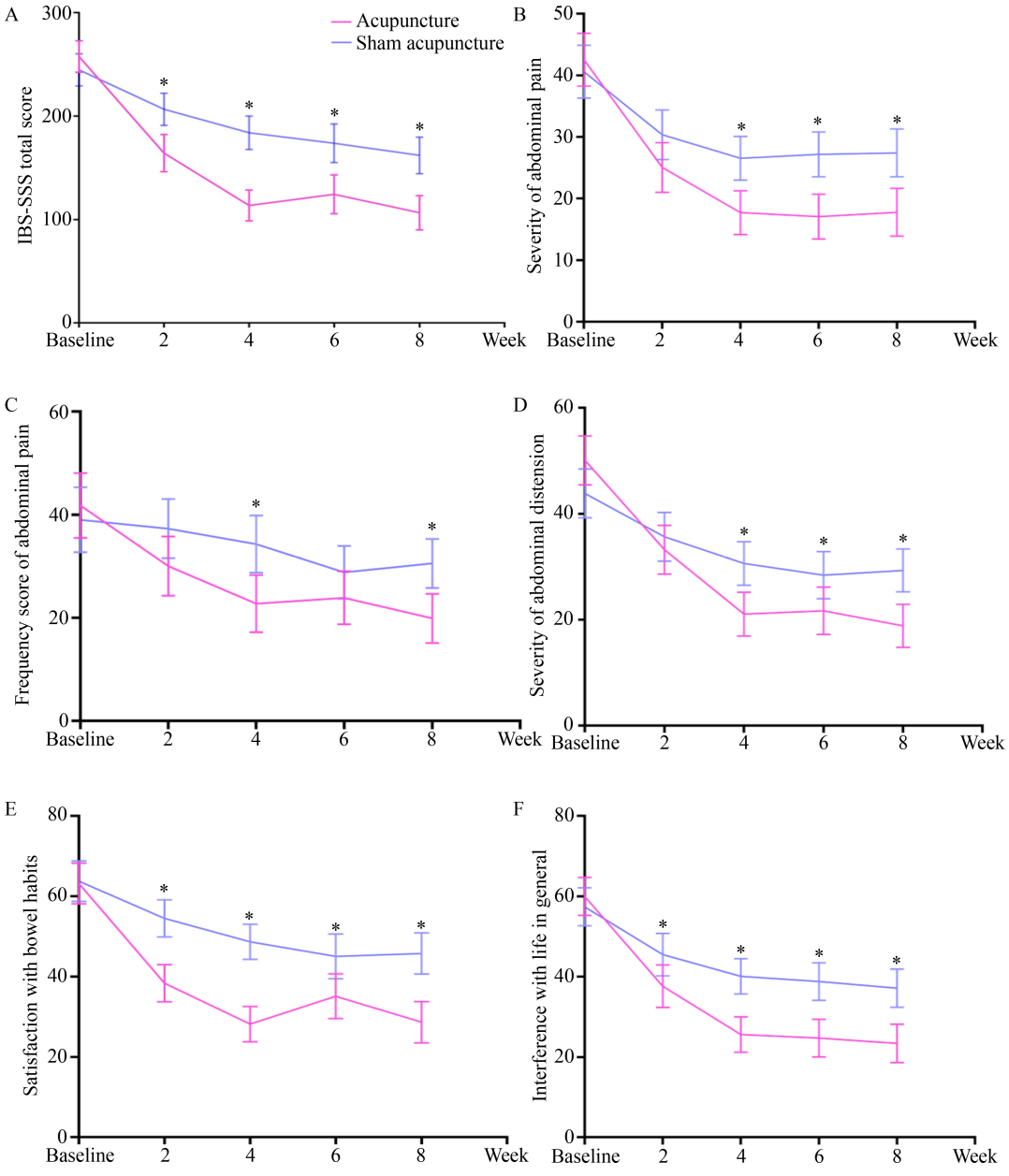

Fig. 3 The total IBS-SSS and scores for its individual domains over time during the study. Data are mean (95% CI). IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score. The decreases in total IBS-SSS at weeks 2, 4, 6 and 8 were greater in the acupuncture group than in the sham acupuncture group. (B–F) trends similar to those in (A) can be seen. (B) At weeks 4, 6 and 8, abdominal pain is significantly milder in the acupuncture group than in the sham acupuncture group. (C) The frequency of abdominal pain is significantly lower in the acupuncture group than in the sham acupuncture group at weeks 4 and 8. (D) At weeks 4, 6 and 8, abdominal distension is significantly milder in the acupuncture group than in the sham acupuncture group. (E) Participants in the acupuncture group are significantly more satisfied with their bowel habits at weeks 2, 4, 6 and 8 than participants in the sham acupuncture group. (F) At weeks 2, 4, 6 and 8, interference of IBS with daily life is lesser in the acupuncture group than in the sham acupuncture group. Asterisk (*) indicates significant difference between acupuncture and sham acupuncture.

promising results at the 13-week follow-up after random assignment to groups [16]. However, access to GCBT-IE for refractory IBS is still insufficient in the China Health Service System and worldwide. Therefore, an intervention that is easy to administer and has long-term effects is highly important. In previous trials with IBS patients, acupuncture resulted in a decrease in IBS-SSS total scores ranging from 6.2 to 215.0 points relative to baseline [12,22], whereas a reduction of 50 points is sufficient to reliably indicate clinical improvement [20]. Based on this evaluation standard, a study achieved a 49% response rate in the acupuncture + UC group and a 31% response rate in the UC group [12]. Another study achieved a 79.1% response rate in the acupuncture group

Table 3 Others secondary outcomes

Variable	Acupuncture group (n = 85)	Sham acupuncture group (n = 85)	Difference (95% CI)	P
Change from baseline in total IBS-QOL score, mean (95% CI)				
Week 2	7.4 (4.7 to 10.1)	1.7 (−0.1 to 3.5)	5.7 (2.5 to 8.9)	0.001
Week 4	13.0 (9.8 to 16.1)	4.5 (2.3 to 6.8)	8.4 (4.6 to 12.2)	< 0.001
Change from baseline in each subscale score of IBS-QOL at week 4, mean (95% CI)				
Dysphoria	18.3 (14.3 to 22.4)	6.4 (3.3 to 9.5)	−	< 0.001
Interference with activity	14.8 (11.0 to 18.6)	5.8 (2.4 to 9.1)	−	< 0.001
Body image	9.0 (6.0 to 12.0)	2.4 (0.0 to 4.7)	−	0.001
Health worry	21.4 (16.2 to 26.5)	8.4 (4.6 to 12.3)	−	< 0.001
Food avoidance	14.2 (9.5 to 18.9)	6.6 (1.5 to 11.6)	−	0.03
Social reaction	12.9 (9.2 to 16.7)	2.5 (−0.4 to 5.4)	−	< 0.001
Sexual	5.6 (2.5 to 8.7)	6.0 (3.0 to 9.1)	−	0.84
Relationships	7.6 (4.2 to 11.1)	−1.1 (−3.9 to 1.7)	−	< 0.001
Regular stool per week, median (IQR)[a], days				
Week 2	1.0 (0.0 to 3.0)	0.0 (0.0 to 2.0)	−	0.01
Week 4	1.0 (0.0 to 4.0)	0.0 (0.0 to 1.0)	−	< 0.001
Week 6	2.0 (0.0 to 5.0)	0.0 (0.0 to 2.0)	−	< 0.001
Week 8	2.0 (0.0 to 4.0)	1.0 (0.0 to 2.0)	−	0.007
Change from baseline in total WSAS score, median (IQR)[b]				
Week 2	2.0 (0.0 to 4.0)	0.0 (−2.0 to 2.0)	2.0 (2.0 to 4.0)	< 0.001
Week 4	4.0 (2.0 to 9.0)	2.0 (0.0 to 6.0)	2.0 (2.0 to 4.0)	0.002
Week 6	4.0 (0.0 to 8.0)	2.0 (0.0 to 4.0)	4.0 (2.0 to 4.0)	0.002
Week 8	4.0 (0.0 to 8.0)	0.0 (−2.0 to 4.0)	4.0 (2.0 to 6.0)	< 0.001
Change from baseline in total SAS score, mean (95% CI)				
Week 2	2.7 (1.2 to 4.2)	1.0 (−0.2 to 2.3)	1.7 (−0.2 to 3.6)	0.08
Week 4	5.2 (3.5 to 6.8)	3.3 (1.7 to 4.8)	1.9 (−0.3 to 4.2)	0.10
Change from baseline in total SDS score, mean (95% CI)				
Week 2	2.7 (1.1 to 4.2)	2.0 (0.4 to 3.6)	0.7 (−1.5 to 2.9)	0.55
Week 4	5.1 (3.1 to 7.2)	3.6 (1.8 to 5.5)	1.5 (−1.2 to 4.2)	0.28
Responder rate with adequate relief of IBS symptoms, n (%)[c]				
Week 4	78 (91.8)	27 (31.8)	60.0 (46.0 to 70.5)	< 0.001

NOTE: IQR, interquartile range; WSAS, Work and Social Adjustment Scale; IBS-QOL, IBS-Quality of Life; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

[a] Regular stool per week was assessed using Mann–Whitney U test.

[b] Change from baseline on WSAS scores at weeks 2, 4, 6 and 8 were analyzed with analysis of the Mann–Whitney U test. Between-group differences were analyzed with analysis of the Mann–Whitney U test and the Hodges-Lehmann.

[c] Responders were defined as participants who reported adequate relief of their IBS symptoms for at least 50% of the 4-week period.

and a 56.6% response rate in the polyethylene glycol 4000/pinaverium bromide group [23]. In our study, the changes in IBS-SSS total scores from baseline to 4 weeks differed between the TA and SA groups (mean decrease of 75.6; 95% CI: 55.8 to 95.4). In the TA group, 90.6% of participants demonstrated a decrease of 50 or more points in IBS-SSS total scores. The trend in IBS-AR rates was consistent with the IBS-SSS response rates. Our response rate is higher than that in previous studies, likely due to the enhanced benefits of acupuncture combined with TAU. This synergistic effect likely yielded substantial improvement in terms of the impact of IBS on work or life, symptom severity, stool characteristics and stool frequency.

Abdominal pain is an important factor that troubles IBS patients and negatively influences daily QOL and emotional psychology [24]. Frequency of abdominal pain showed the greatest decrease from baseline at the end of

treatment (4 weeks). Based on IBS-QOL, patients who received acupuncture had significant improvement in QOL, and the mean decrease in the total score was 13.0, which was similar to the result of a previous study at week 6 (13.4) [23]. Given that, we studied a nonclinical sample. The WSAS was introduced to evaluate functional impairment in refractory IBS and has good effectiveness and reliability in some patient populations (such as patients with depression and anxiety disorder) [25]. The baseline WSAS, SAS and SDS scores showed that some refractory IBS patients were in a subclinical state but did not have serious psychological disorders. Acupuncture cannot only improve work and social adaptability but also alleviate the anxiety symptoms of refractory IBS. Since there are several subtypes of IBS, changes in stool shape and frequency should be cautiously evaluated. Bristol classification and diary cards were used, and the quantitative index termed regular stool rate was created [26]. This evaluation standard was not only strict but could also avoid the stool shape alternation difference of different subtypes. Our study showed that acupuncture had a better effect on the frequency and shape of defecation in IBS patients. This was consistent with the latest research results in China [27]. Although we primarily assessed the overall efficacy of acupuncture for refractory IBS, exploratory subgroup analysis of IBS found that the sample sizes for IBS-C and IBS-M were insufficient. Hence, we could only determine that refractory IBS-D can benefit more from acupuncture treatment.

Until now, there have been ⩾ 5 double-blind, sham-controlled trials that have assessed the efficacy of acupuncture in IBS patients [28–32]. However, most tend to close the door on acupuncture. Conversely, more than 3 systematic reviews have supported that acupuncture is beneficial for symptom severity, abdominal pain and quality of life in IBS [11,14,33]. What can explain these divergent results? The most compelling explanation is that acupuncture has positive effects but that its benefit was masked by the lack of an appropriate sham condition in previous studies. The outcome measures utilized in these prior studies varied considerably, although most employed measures/instruments with which the IBS investigators in the current study had some familiarity. Moreover, the specifics of the acupuncture protocol varied greatly among studies. For example, the number of sessions and study duration varied considerably. Compared with SA, TA administered for 4 weeks (2 times per week) did not appear to improve IBS symptom scores [32]. Similarly, 6 sessions of acupuncture over 3 weeks might have been insufficient to achieve the maximum benefits of acupuncture, as there was no significant difference between the TA and SA groups on the IBS Global Improvement Scale [31]. Compared with the acupuncture frequency and duration (2 sessions per week) in previous studies, the acupuncture regimen in our trial was labor intensive and has been well implemented in clinical practice. Another study observed a greater reduction in IBS-SSS total scores in the acupuncture group (3 sessions per week for 6 weeks) than in the control group, with effects lasting up to 12 weeks [23]. Overall, administering acupuncture 3 times (rather than 2 times) per week could lead to relief of IBS symptoms.

Several noteworthy findings might support the use of shallow needle depths at nonacupoints as the sham control in this trial. First, in previous three RCTs, although a blunt acupuncture needle or blunted telescopic device (the Streitberger needle) can simulate acupuncture without penetrating the skin [30–32], this does not exclude the possibility of benefit from acupressure. This is an interesting point when one considers that all studies demonstrated improvement in IBS symptoms after acupuncture and sham acupuncture when compared with baseline. Second, for Chinese, blinding of patients is difficult with a noninvasive sham acupuncture group if they do not perceive any needling. In this trial, the results of the blinding assessment in the SA group indicated that the vast majority of patients that they received true acupuncture (rather than the control or sham treatment). In this specific setting (an acupuncture trial), a qualitative health study also confirmed that IBS participants could not reliably distinguish between sham and true treatment and acknowledged that participants' experiences of blinding related to their goals in participating the study and social aspects (e.g., trusting and valued relationships with acupuncturists) [34]. There are several possible explanations for this: (1) patients considered "acupuncture" as long as a needle was inserted into the skin, and they provided a true therapeutic response; (2) even if they received sham acupuncture, but after 12 treatment sessions did improve symptoms, they also believed that "true acupuncture" treatment effect; (3) the acupuncturists themselves were not responsible for group allocation, and patients' unconditional trust in acupuncturists resulted in IBS participants could not reliably distinguish between sham and true treatment. However, we might underestimate the patients' ability to know what they were receiving or to extract that information from the acupuncturists (e.g., it is very difficult for honest people to convincingly lie when directly asked). Therefore, the benefits of SA were at least partly attributable to psychological factors or placebo. In general, acupuncture seemed to relieve refractory IBS symptoms in a way that cannot be solely explained by nonspecific factors, such as placebo effects. Unlike SA, the cumulative effect of TA was obvious during the intervention period, and the therapeutic gain of acupuncture persisted with a negligible decrease after

treatment cessation.

This study also has some limitations. First, this study was a single-blind trial. Due to the nature of acupuncture, it is very difficult to achieve the blinding of acupuncturists. Second, due to the difference of patients' ability to know what they were receiving or to extract that information from the acupuncturists, the reported difference might be magnified. Third, we measured the types and dosage of new pharmacological drugs (including rescue medication) or TCM used by patients during treatment. Due to the small number of patients and the exclusion of two patients who slightly violated the protocol, no further analysis was performed. Finally, the trial was performed in China, and the prevalence of functional gastrointestinal disorders is generally higher in Western Europe than in Asia; hence, the findings should be generalized with caution.

Conclusions

During TAU, 4 weeks of TA (compared with SA) resulted in increased rates of patient-reported adequate relief of IBS symptoms, relieved abdominal pain and distension, and improved patient satisfaction with defecation and quality of life. The effects of TA persisted through the 4-week follow-up period without symptom relapse or rebound. Thus, acupuncture should be considered as an option for safe adjunctive treatment in alleviating refractory IBS symptoms.

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Compliance with ethics guidelines

Conflicts of interest Jun Zhao, Hui Zheng, Xin Wang, Xuefei Wang, Yunzhou Shi, Chaorong Xie, Qingfeng Tao, Da Li, Jingwen Sun, Junjian Tian, Junxia Gao, Huimin Liu, Suhua Shi, Jinxia Ni, Rongdan Xue, Hui Hu, Min Chen, Shuguang Yu, and Zhigang Li declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Min Chen, ShuGuang Yu, and ZhiGang Li served as the reviewers of grant proposals for the National Natural Science Foundation of China.

Informed consent was obtained from all the patients, in which their identifying information is included in this article. Other ethical board approval is not applicable in this manuscript.

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