Acupuncture For The Treatment of Diarrhoea-Predominant Irritable Bowel Syndrome (ATIBS-D): A Pilot Randomized Controlled Trial

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Research

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Abstract

Background: Diarrhoea-predominant irritable bowel syndrome (IBS-D) is a common disease without an established optimal treatment. Acupuncture has promising effects on IBS-D, but high-quality evidence is scarce.

Methods: In this parallel, multicenter, randomized controlled trial, participants with IBS-D were assigned to three groups: specific acupoints (SA), non-specific acupoints (NSA) and non-acupoints (NA). Participants received 12 sessions (3 sessions per week) treatment over 4 weeks. The primary endpoint was a composite response rate at week 4 of treatment. An eligible composite responder was responded in both abdominal pain intensity and stool consistency, defined as at least 30% decrease in the weekly average of worst abdominal pain score and 50% or greater reduction in the number of Type 6 or 7 stool days weekly compared with baseline.

Results: Of 201 screened patients with IBS-D, 90 (44.8%) patients were enrolled, and 88.9% patients completed this study (26 in NSA; 27 in SA and NA). The composite response rates at week 4 were 46.7%, 46.7% and 26.7% (P 0.05) of the participants who received SA, NSA and NA acupuncture, respectively. Adverse events were reported in 2 (6.7%) patients in SA, 3 (10%) patients in NSA and NA. There were no serious adverse events.

Conclusions: The present study suggests that acupuncture treatment is feasible and safe for IBS-D patients. The further adequately powered trials can be achieved by recruiting more patients, increasing treatment dose, prolonging follow-up, choosing specific acupoints, setting up sham-acupuncture control, or a combination thereof.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2000030670. Registered on 9 March 2020. https://www.chictr.org.cn/edit.aspx?pid=50167&htm=4

Background

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain associated with changes in stool form or frequency. Due to the absence of universally recognized disease biomarkers, the diagnosis of IBS relies on past medical history and self-reported symptom, and the treatment of IBS aims to improve the most troublesome symptom without a cure. Global prevalence of IBS has a wide variation, and the condition affects approximately 5–10% individuals in most geographical regions [1]. Although IBS is not a fatal disease, it has a substantial impact on quality of life and social functioning. The annual direct and indirect costs associate with IBS are estimated to be up to billions or more in several countries [2–4]. Patients even are willing to accept a 1% median risk of sudden death in exchange for a 99% chance of using hypothetical medications to cure symptoms [5].

IBS with diarrhoea (IBS-D) was the most common subtype with the Rome IV criteria [6]. Antidiarrhoeals, antispasmodics and antidepressants are used as first/second-line therapies in IBS-D, but the efficacy of

the above medications is limited due to their frequent side-effects [7, 8]. In case of low satisfaction with current therapies, patients' demand for complementary and alternative therapies has increased [9]. Acupuncture is considered a beneficial alternative treatment for functional gastrointestinal disorders (FGIDs) [10–12]. Although the increasing amount of randomized clinical trials (RCTs) investigating the acupuncture efficacy of acupuncture, high-quality evidences are still too few to draw sound conclusions. Furthermore, primary efficacy outcomes of some related studies do not as strict as current recommendations from the US Food and Drug Administration (FDA) or the European Medicines Agency, which may exaggerate the actual efficacy of acupuncture.

Additionally, acupoint is considered to be the most determined factor on the efficacy of acupuncture [13]. Based on traditional meridian and acupoint theories, there is a specific effect of acupoint (including specific acupoint (SA) and non-specific acupoint (NSA)) compared with non-acupoint (NA), and acupoint selection programs according to the principle of matching specific points for *He-acupoint* and *Mu-acupoint* are regarded as being more effective than other [14–16]. However, there are still no clinical studies to explore the difference in efficacy among SA, NSA and NA, which may limit the optimization of acupoint selection programs and the maximization curative effect of acupuncture for IBS-D. Considering the cost of economy and time on implementing a pivotal trial, we suggest that it is necessary to conduct a pilot trial firstly. Therefore, the present study aims to preliminarily explore the feasibility, efficacy and safety of acupuncture in the treatment of IBS-D (ATIBS-D) and compare the therapeutic effects of different programs of acupoint selection.

Methods

Study design

ATIBS-D was a parallel three-group, multicenter randomized trial with 2-week screening, 4-week treatment, and 8-week follow-up for patients with IBS-D. The study protocol has been published on *Trials* (see Additional file 1). We recruited patients from 4 tertiary hospitals in North and Southwest China, March 2020 to December 2020, and fourteen-week data collection completed in March 2021. Recruitment strategies included posting recruitment advertisements on social media (such as WeChat, which is similar to Facebook) and at hospital clinics (such as flyers in physician offices and posters in the public area of hospitals). This study was approved by the Ethics Committee of the coordinating center (see Material 1 and 2 of Additional file 2) and each study site, and informed consent were provided for all participants before randomization. The study was registered in Chinese Clinical Trial Registry under the number ChiCTR2000030670.

Participants

Rome IV criteria for IBS-D was main criteria for eligibility assessment, participants were eligible if they fulfilled following criteria at 2-week screening, defined as: (I) Patients of IBS-D aged between 18 and 75

years (either sex); (II) Type 6 or 7 of the Bristol Stool Form Scale appeared for at least 4 days and type 1 or 2 appeared for less than 4 days in last 2 weeks; (III) The average score of daily abdominal pain was ≥ 3 in the last week.

Exclusion criteria: (I) Patients with the following diseases: inflammatory bowel disease, microscopic colitis, celiac disease, Crohn's disease and other organic bowel diseases (age ≥ 50 years or have the following alarm signs will be required to provide colonoscopy report within nearly 2 years: unexplained weight loss [weight loss > 10% within 3 months]; hematochezia caused by non-hemorrhoids or anal fissure; nocturnal diarrhea; family history of colorectal cancer); diabetes mellitus and abnormal thyroid function; severe acute or chronic organic diseases, kidney or liver diseases; (II) History of previous abdominal surgery (appendectomy, hemorrhoidectomy, or polypectomy greater than 3 months post-surgery are allowed.); (III) Pregnancy or lactation, or history of alcohol and drug abuse; (IV) Treated with acupuncture in the last 6 months, or participating in other clinical trials; (V) Usage of antidepressant or IBS medication within 2 weeks before treatment, including Traditional Chinese Medicine (TCM) or proprietary Chinese medicine, antidiarrheal, antispasmodic, intestinal antibiotics, probiotics and so on.

Randomization And Blinding

After completing baseline questionnaires, participants were randomized to one of the three trial arms (SA group, NSA group and NA group) according to the ratio of 1:1:1. Randomization was stratified by recruitment site, with fixed block size of 6. An independent statistician who was not involved in the implementation or statistical analysis of this trial generated the blocked randomization sequence by using the software SAS 9.3. As with any therapy trial, acupuncturists and her/his assistants could not be masked to treatment allocation. Participants, clinical recruiters, outcome assessors, data managers, and statisticians were blinded.

Study Procedures

All researchers in different divisions of labor have undergone rigorous training to standardized procedures of trial. They also received researcher manuals to remind them of inclusion criteria, details of assessment and treatment and so on. Participants recorded defecation diary (see Figure 1 of Additional file 2) throughout the trial. Before receiving the first treatment, all participants received baseline assessments, including assessments of IBS-D related symptoms via defecation diary of 2-week screening, IBS Symptom Severity Scale (IBS-SSS), and IBS-Quality of Life scale (IBS-QoL) [17, 18]. For IBS-SSS, a decrease of 50 points is adequate to reliably indicate clinical improvement [17]. For IBS-QoL, higher scores indicate better QoL, and a meaningful clinical response is represented by an increase of at least 14 points [19]. Anxiety and depression were assessed via Patient Health Questionnaire-9 depression scale (PHQ-9) [20]. After the first treatment, patients were asked to complete the credibility and expectancy questionnaire in 5 minutes [21]. During the 4-week treatment and 8-week posttreatment follow-up, we completed comprehensive assessments of patients by IBS-SSS, IBS-QoL, PHQ-9, IBS

Adequate Relief (IBS-AR) and related IBS-D individual symptoms (abdominal pain, bloating, loose stool day and stool frequency) [22]. To test the implementation of blinding, patients were asked to guess which kind of acupuncture they received after the last treatment. Adverse events and usage of rescue medicine were monitored and recorded at assessment time points during the treatment and follow-up phases of trial.

Interventions

Participants received 12 sessions (3 sessions per week) of 30-minute treatment overall 4-week treatment phase. Single-use sterile needles (length: 25 to 40 mm; diameter: 0.30 mm; Hwatuo, Suzhou, China) were used in SA group and NSA group. Blunt-tipped placebo needles (similar to the Streitberger design) with a similar appearance to conventional needles but no skin penetration, were used in NA group [23, 24]. Adhesive pads were placed on puncture points in all groups which is to help maximize blinding of participants in NA group and to fix blunt-tipped placebo needles. The treatments were administered by certified acupuncturists who had 5 years of undergraduate education on acupuncture and at least 3 years of clinical experience. Each acupuncturists received a 2-day training who could perform treatments of all group, with priority given to the same acupuncturist delivering treatment to a specific participant throughout the trial whenever possible.

Participants in SA group received acupuncture at 6 acupoints (5 fixed acupoints and one of 3 optional acupoints) according to the syndrome diagnosis and the principle of matching specific points for *He-acupoint* and *Mu-acupoint*. The six fixed acupoints of NSA group were chose based on the usage frequency of acupoints. Insertion was followed by stimulation performed by lifting and thrusting the needle combined with twirling and rotating the needle sheath to produce the sensation known as *deqi* (sensation of soreness, numbness, distention, or radiating, which is considered to indicate effective needling) [25]. Five non-acupoints which away from meridians or conventional acupoints were selected in NA group without manipulations. The location of acupoints in each group was described in our study protocol [26].

Outcomes

For primary endpoint, a composite response rate at week 4 of treatment phase were used in accordance with FDA recommendations. An eligible composite responder was responded in both abdominal pain intensity and stool consistency, defined as at least a 30% decrease in the weekly average of worst abdominal pain in the past 24 hours score compared with baseline and a 50 percent or greater reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline. For secondary endpoints, IBS-SSS, IBS-QoL, and PHQ-9 were assessed at weeks 2, 4, 8 and 12, and the response rates at other time points (without week 4), IBS-AR, and IBS-D individual symptoms were assessed at weeks 1, 2, 3, 4, 8 and 12 after randomization. Regard to individual symptoms of IBS-D,

abdominal pain and bloating were assessed by 0-10 numerical rating scale (NRS), and Bristol stool score (BBS) were used to record loose stool day and stool frequency of participants.

Statistical analysis

This exploratory study aimed to assess the efficacy of SA, NSA, and NA for IBS and determine the feasibility of a further large-scale clinical trial. According to Provisions for Drug Registration in China, the minimum sample size for exploratory trials is 20-30 per group, and 90 participants (30 patients for each group) were randomized eventually. Intention-to-treat (ITT) set was used in all efficacy analysis, which consisted of all patients who had been randomized, and the missing data was imputed using last observation carried forward (LOCF). Relevant data were summarized with counts and percentages for categorical data, whereas with mean ± standard deviation (M ± SD) for continuous data.

The differences among the three groups in primary endpoint (composite response rate at week 4) were analyzed using the χ^2 test. Additionally, a logistic generalized linear mixed model included baseline abdominal pain score and stool consistency as covariates was used, with time, and group as fixed factors; patient as a random factor; and logit function set as the link function. A per-protocol analysis was used for primary outcome as sensitivity analysis covering patients who complete ≥10 sessions and have no major protocol violations (taking other drugs during the trial, etc.) [25].

For change scores of IBS-SSS, IBS-QoL, PHQ-9 and IBS-D individual symptoms (abdominal pain, abdominal bloating, loose stool days, and stool frequency), the Analysis of Variance (ANOVA) was used for comparison among the three groups. The response rates at other time points, IBS-AR, blinding assessment, the credibility and expectancy, and adverse event rates were analyzed using the χ^2 test or Fisher's exact test. We concentrated on the overall comparison among three groups, and provided comparative descriptions for the results of pairwise comparisons merely. All reported *P* values are two-sided with a significance level less than 0.05.

Results

Patients and characteristics

During May 2020 to March 2021, a total of 201 patients with IBS-D were screened. Of these, 111 (55.2%) were excluded for various reasons (Figure 1), and 90 (44.8%) were enrolled and underwent randomization in SA group, NSA group, and NA group, respectively. A total of 10 (11.1%) patients dropped out of this study (4 in NSA, 3 in SA and NA; 7 during the 4-week treatment and 3 during the 8-week follow-up). All clinical characteristics and baseline demographics randomize were similar in the three groups (Table 1). The credibility and expectancy of paints assessed after the first treatment in three groups were also found no difference (*P*=0.862, *P*=0.292, respectively) (see Table 1 of Additional file 2).

Table 1: Characteristics of patients at the trial baseline.

Characteristics	SA group (n=30)	NSA group (n=30)	NA group (n=30)	P
Age, years, (SD)	36.7 (12.2)	31.0 (9.9)	35.7 (11.1)	0.11
Sex, female/male	11/19	10/20	15/15	0.45
BMI, (SD)	24.0 (4.1)	22.9 (3.7)	22.3 (3.4)	0.22
IBS-D course, years, (SD)	6.5 (2.9)	8.2 (4.1)	7.7 (3.6)	0.17
Occupation, mental/manual	26/4	27/3	27/3	0.89
IBS-SSS, (SD)	271.5 (63.0)	281.0 (77.7)	274.5 (84.1)	0.88
IBS-QoL, (SD)	74.0 (13.9)	68.5 (18.2)	73.9 (14.3)	0.30
PHQ-9, (SD)	8.2 (5.5)	8.0 (4.7)	7.5 (4.6)	0.84
Loose stool days, (SD)	5.3 (1.4)	5.4 (1.7)	5.3 (1.6)	0.98
Abdominal pain score, (SD)	4.6 (1.6)	4.3 (1.3)	4.3 (1.4)	0.59
Bloating score, (SD)	3.3 (2.1)	3.5 (1.9)	3.6 (2.0)	0.86
Stool frequency, (SD)	2.5 (1.2)	2.5 (1.7)	2.6 (1.3)	0.99

SA: specific acupoint; NSA: non-specific acupoint; NA: non-acupoint; SD: Standard Deviation.

Primary Efficacy Parameter

The composite response rate at week 4 was 46.7% with true acupuncture (SA and NSA group) and 26.7% with sham acupuncture (NA group), and no significant difference among the three groups (*P*=0.221) (Table 2). The per-protocol analysis set excluded the 10 patients dropped out trial, of whose results is similar with results of the ITT analysis (*P*=0.494, 51.9%, 50.0% and 30.8% of SA, NSA and NA, respectively). Covariate analysis was performed on the primary endpoint via a logistic generalized linear mixed model including baseline covariates for both abdominal pain score and stool consistency, which showed that the baseline abdominal pain score and stool consistency did not affect the composite response rate at week 4 (see Table 2 of Additional file 2).

Table 2
Efficacy parameters, differences between groups, and changes over time.

Efficacy parameters	SA group (n=30)	NSA group (n=30)	NA group (n=30)	P
Primary efficacy parameter				
Response rates at week 4, (95%CI), %	46.7 (28.8-64.6)	46.7 (28.8-64.6)	26.7 (10.9-42.5)	0.24
Secondary efficacy parameters				
Response rates at other time points, (95%CI), %				
Week 1	26.7 (10.9-42.5)	20.0 (5.7-34.3)	26.7 (10.9-42.5)	0.86
Week 2	30.0 (13.6-46.4)	36.7 (19.5-53.9)	30.0 (13.6-46.4)	0.88
Week 3	36.7 (19.5-53.9)	46.7 (28.8-64.6)	33.3 (16.4-50.2)	0.63
Week 8	53.3 (35.4-71.2)	46.7 (28.8-64.6)	53.3 (35.4-71.2)	0.90
Week 12	60.0 (42.5-77.5)	66.7 (48.8-83.6)	50.0 (32.1-67.9)	0.46
changes of IBS-SSS score, (SD)				
Week 2	74.8 (76.2)	79.5 (71.4)	72.0 (82.3)	0.93
Week 4	107.8 (83.8)	109.1 (80.6)	102.6 (89.7)	0.95
Week 8	121.0 (109.6)	95.5 (89.4)	104.1 (75.6)	0.56
Week 12	129.3 (102.8)	126.0 (90.8)	112.0 (86.6)	0.75
changes of IBS-QoL score, (SD)				
Week 2	45.2 (77.5)	32.3 (62.7)	24.4 (61.5)	0.49
Week 4	58.2 (89.7)	36.4 (66.7)	28.7 (66.0)	0.29
Week 8	76.1 (109.5)	39.3 (80.8)	37.1 (71.8)	0.17
Week 12	74.1 (111.2)	51.8 (88.4)	43.8 (84.0)	0.45
changes of PHQ-9 score, (SD)				

SA: specific acupoint; NSA: non-specific acupoint; NA: non-acupoint; SD: Standard Deviation; IBS: irritable bowel syndrome; IBS-Symptom Severity Scale: IBS-SSS; IBS-Quality of Life scale: IBS-QoL; Patient Health Questionnaire-9 depression scale: PHQ-9; IBS Adequate Relief: IBS-AR.

Efficacy parameters	SA group (n=30)	NSA group (n=30)	NA group (n=30)	P
Week 2	1.3 (3.9)	1.3 (2.2)	0.4 (2.9)	0.45
Week 4	2.7 (4.2)	2.0 (2.8)	1.4 (3.7)	0.38
Week 8	3.1 (4.8)	1.9 (3.5)	2.1 (4.0)	0.45
Week 12	3.6 (5.4)	2.1 (5.2)	2.5 (3.5)	0.42
AR response rates, (95%CI), %				
Week 1	39.3 (21.8-56.8)	34.5 (17.5-51.5)	55.2 (37.4-73.0)	0.27
Week 2	53.6 (35.8-71.4)	51.7 (33.8-69.6)	55.2 (37.4-73.0)	0.97
Week 3	53.6 (35.8-71.4)	55.2 (37.4-73.0)	44.8 (27.0-62.6)	0.74
Week 4	64.3 (47.2-81.4)	62.1 (44.7-79.5)	55.2 (37.4-73.0)	0.79
Week 8	60.7 (43.2-78.2)	41.4 (23.8-59.0)	46.4 (28.6-64.2)	0.33
Week 12	60.7 (43.2-78.2)	48.3 (30.4-66.2)	46.4 (28.6-64.2)	0.54
changes of abdominal pain score, (SD)				
Week 1	1.2 (2.0)	1.0 (1.1)	1.2 (1.4)	0.85
Week 2	1.6 (2.1)	1.3 (1.2)	1.4 (1.3)	0.75
Week 3	2.0 (2.1)	1.5 (1.2)	1.7 (1.4)	0.44
Week 4	2.2 (2.4)	1.7 (1.2)	1.6 (1.5)	0.36
Week 8	2.5 (2.2)	2.1 (1.3)	2.2 (1.3)	0.61
Week 12	2.7 (2.2)	2.4 (1.5)	2.5 (1.6)	0.82
changes of loose stool day, (SD)				
Week 1	2.2 (2.5)	1.3 (2.1)	1.7 (2.5)	0.31
Week 2	2.2 (2.6)	2.0 (2.3)	2.1 (2.4)	0.93
Week 3	2.7 (2.4)	2.4 (2.1)	2.7 (2.9)	0.83

SA: specific acupoint; NSA: non-specific acupoint; NA: non-acupoint; SD: Standard Deviation; IBS: irritable bowel syndrome; IBS-Symptom Severity Scale: IBS-SSS; IBS-Quality of Life scale: IBS-QoL; Patient Health Questionnaire-9 depression scale: PHQ-9; IBS Adequate Relief: IBS-AR.

Efficacy parameters	SA group (n=30)	NSA group (n=30)	NA group (n=30)	P
Week 4	3.1 (2.6)	2.7 (2.6)	2.5 (2.6)	0.60
Week 8	3.3 (2.5)	2.6 (2.5)	3.2 (2.9)	0.52
Week 12	3.4 (2.6)	3.3 (2.5)	3.2 (2.7)	0.96
changes of bloating score, (SD)				
Week 1	0.7 (1.8)	0.9 (1.3)	1.1 (1.5)	0.50
Week 2	1.1 (1.8)	1.1 (1.3)	1.5 (1.5)	0.51
Week 3	1.3 (1.7)	1.1 (1.3)	1.3 (1.7)	0.85
Week 4	1.7 (2.1)	1.4 (1.6)	1.9 (1.5)	0.50
Week 8	1.6 (2.1)	1.7 (1.8)	2.1 (1.6)	0.62
Week 12	3.3 (2.1)	3.5 (1.9)	3.6 (2.0)	0.86
changes of stool frequency, (SD)				
Week 1	0.3 (0.8)	0.2 (0.6)	0.2 (0.5)	0.72
Week 2	0.3 (0.7)	0.2 (0.6)	0.1 (0.4)	0.42
Week 3	0.4 (0.8)	0.2 (0.5)	0.3 (0.4)	0.73
Week 4	0.4 (0.8)	0.3 (0.6)	0.4 (0.5)	0.83
Week 8	0.5 (0.8)	0.3 (0.7)	0.4 (0.8)	0.56
Week 12	0.5 (1.0)	0.6 (1.0)	0.6 (1.0)	0.93

SA: specific acupoint; NSA: non-specific acupoint; NA: non-acupoint; SD: Standard Deviation; IBS: irritable bowel syndrome; IBS-Symptom Severity Scale: IBS-SSS; IBS-Quality of Life scale: IBS-QoL; Patient Health Questionnaire-9 depression scale: PHQ-9; IBS Adequate Relief: IBS-AR.

Secondary Efficacy Parameters

Secondary outcomes have no significant difference among the three groups whether immediately after the 12 treatments or follow-up (P 0.05) (see Table 2, Figure 2 of Additional file 2). Nevertheless, there were several worth mentioning findings in scores and trends among three groups: (I) for overall syndrome severity of patients, the decrease score from baseline of IBS-SSS in three groups all exceeded 50 points at the whole treatment and follow-up phases, and the response rates of AR scale in SA group were reached more than 60.0% both in immediately after the 4-week treatment and follow-up; (II) for quality life of patients, the significant increase score of 14 points for IBS-QoL was reached by three groups at assessment times during whole trial, and the increase score in the SA group was approximately twice that

of the NA group at weeks 4 and 8; (III) in terms of depression of patients, the change score of PHQ-9 exceeded 3 points at weeks 8 and 12 in SA group; (IV) for individual symptom of IBS-D, loose stool days all decreased more than 3 days from the baseline at weeks 4, 8, and 12 in SA group.

As for the success of blinding, no difference was found among groups in the proportion of patients who guessed that they received acupuncture immediately after the 12th sessions (P=0.880) (see Table 3 of Additional file 2).

Table 3
Adverse events.

	SA group (n=30)	NSA group (n=30)	NA group (n=30)
Hematoma	0	1(3.3%)	1(3.3%)
Sensation after needle removal	1 (3.3%)	2(6.6%)	1(3.3%)
Residual needling	1(3.3%)	0	1(3.3%)
SA: specific acupoint; NSA: non-specific acupoint; NA: non-acupoint.			

Adverse Events

Adverse events were reported in 2 (6.7%) patients in SA group, 3 (10%) patients in NSA group and NA group. The most frequently reported adverse events was residual needling sensation after needle removal (Table 3). No serious adverse events were reported.

Discussion

As there is likely considerable uncertainty when preparing a large-scale trial of an intervention that is not widely adopted, feasibility, efficacy and safety need to be tested and demonstrated prior to committing considerable human and monetary resources preliminarily [27]. Based on findings of this pilot trial, we suggested that acupuncture treatment is feasible and safe for patients with IBS-D. Although there were no significant differences on treatment efficacy among the SA, NSA and NA groups, it is necessary and worthy to commit to larger and more comprehensive trials. We summarized that the following full-scale trials should be optimized and upgraded from the following aspects: recruiting more patients, increasing treatment dose, prolonging follow-up, choosing specific acupoints, setting up sham-acupuncture control, or a combination thereof.

To our knowledge, ATIBS-D is the first parallel three-group, multicenter, randomized controlled pilot trial that used the pre-specified primary outcome as defined by FDA guideline, which explored the difference in efficacy among SA, NSA and NA of acupuncture treatment for IBS-D. Moreover, the 2-week screening

phase can better distinguish IBS-D from other FGIDs (e.g., functional diarrhea) to ensure the accuracy of the study population and eliminate the effect of previous medications that may affect the results of the trial. In ATIBS-D, the enrollment rate of 55.2% and the dropout rate of 11.1% (4 in NSA, 3 in SA and NA) are approximately to previous studies [28, 29]. and even higher completion rate (92.2%) of 4-week treatment phase in present study, which suggests that participants have good compliance and acceptance for acupuncture treatment of IBS-D [30, 31]. Furthermore, in previous trials of IBS, the differences in response rate between active pharmaceutical interventions and placebo ranged from 5.5–28% [32, 33]. The difference between true acupuncture and sham acupuncture in this study (20%) is within this range, which may suggest that although there is no significantly statistical difference, it has constituted a clinically meaningful outcome. Furthermore, the changes from baseline in global scores of IBS-SSS and IBS-QoL both satisfied a meaningful clinical response that is not equivalent to statistical differences but should not be ignored. We speculate that there were two objective reasons resulted in the negative results between the true acupuncture group and sham acupuncture group. First, the minimum sample size increased type 2 error (that is, insufficient power will weaken the true effect of enhanced acupuncture). Second, we found the composite response rates and most scores of secondary endpoints among groups tended to produce a greater difference at week 8 rather than week 4, which may indicate the effective dose or treatment duration of acupuncture for IBS-D in present study is insufficient. By reviewing current clinical researches, 16-18 acupuncture sessions in more than 4 weeks are common in IBS-related clinical researches [31, 34, 35]. Therefore, the effective threshold of dose and duration for acupuncture treatment of IBS-D may be higher than in the present trial. And we suggest that recruiting more patients (280 patients would be necessary to prove efficacy according to results of ATIBS-D), increasing treatment dose and duration, and prolonging follow-up are desirable ways to optimize future trials.

Additionally, we speculate that the lack of significant findings between SA and NSA were due to the acupoints in both groups are effective for IBS-D. Acupoints in NSA group located in stomach meridian of *foot-yangming* and *Ren* meridian that the two most commonly used meridians for the treatment of IBS in Chinese clinical practice [36–38]. From the point of TCM, abdominal pain, bloating, and diarrhea, the main syndromes of IBS-D belong to the common treatment area of acupoints in NSA group [39, 40]. Therefore, the NSA group and the SA group had the same composite response rates at week 4, which is understandable to a certain extent. It is worth noting that although differences in primary endpoint and secondary endpoints are not statistical significance, the trends of assessment time points in SA group are more consistent and stable than NSA and NA group (see Figure 2 of Additional file 2), which may indicate that SA may provide patients with a better treatment experience in future trials with sufficient power. We have the following findings as support for the above speculation. First, although there is no statistical difference compared with NA group, the IBS-QoL change scores of SA group has nearly doubled. Second, the change score of PHQ-9 exceeded 3 points in SA group, which is more likely to bring about changes in patient's depression assessment level [20]. Third, the response rates of AR scale in SA group (more than 60.0% both in immediately after the 4-week treatment and follow-up) are similar to several studies that concluded intervention medications can effectively improve the symptoms of IBS [41, 42]. Last but not the least, loose stool days in SA group decreased more than 3 days at weeks 4, 8, and 12 compared with

baseline, which means that patients may not meet the IBS-D diagnostic criteria of Rome IV due to improved bowel conditions, and then become "non-IBS-D patients". For the above content, trials as to further explore the efficacy of acupuncture in the treatment of IBS-D are necessary and we recommend that acupoints in SA group should be chosen as intervention acupoints. And this may be a strength of our study that provides a basis for the selection of acupoints for subsequent trials.

An ideal acupuncture placebo would be noninvasive, however, blinding of Chinese patients is difficult with a noninvasive acupuncture placebo when they do not perceive any needling. To improve blinding and participant adherence, we chose blunt-tipped placebo needles as the sham control in the present trial, which can make the patients have the feeling of acupuncture under the premise that the needle tip does not penetrate the skin. We evaluated that there was no statistical difference in the blinding evaluation results among the three groups. In view of the fact that patients' expectancy of the treatment to be received may affect the efficacy of acupuncture, we conducted an evaluation of credibility and expectancy and the results showed that there was no difference between the three groups [43, 44]. Additionally, the drop-out rate and adverse event rate were low in each group, which suggested that these treatments can be achieved with minimal difficulty and did not produce any serious adverse effects. Based on the dropout rate of 11.1% and the good compliance of patients in the entire trial, we suggest that the use of blunt-tipped placebo needles ensure the better adherence of patients.

The present study has limitations. First, the exploratory nature of the pilot trial is restricted to a small sample size [45]. Consequently, the inclusion of too few patients in the present study may increase the risk that a significant treatment benefit will not be shown (a type 2 error), even if such an effect exists [46]. A sample size of 280 patients was estimated to have at least 80% power to detect a 2-sided significance level of 5% based on the composite response rate. Second, although we used FDA approved dichotomous and composite end points for this trial, defecation diaries as the data sources are subjective and susceptible to interference from potential biases of self-reporting [47]. To avoid it, recruitment and outcome evaluators maintained continuous contact with patients and supervised the correct filling of defecation diary, which aimed to ensure that defecation diaries of patients are filled out every day as much as possible. Third, acupuncturists could not be blinded which may affect the effect of interventions between groups.

In summary, the present study suggests that acupuncture (3 sessions per week for 4 weeks) intervention is feasible and safe for patients with IBS-D. Compared with patients who received NA acupuncture, IBS-D patients who received SA or NSA acupuncture have a beneficial trend of improving symptoms to a certain extent. Although there were no statistical differences between the true acupuncture and the sham acupuncture group, the 20% difference of composite response rate between them should not be ignored. Note that the findings may be appropriate to describe as inconclusive rather than negative because the present trial is a pilot study of which the power is too small to detect modest treatment effects [46]. We suggest that large-scale randomized trials would be necessary to prove efficacy of acupuncture for IBS-D.

Abbreviations

ATIBS-D: acupuncture for the treatment of diarrhoea-predominant irritable bowel syndrome; IBS-D: diarrhoea-predominant irritable bowel syndrome; SA: specific acupoints; NSA: non-specific acupoints; NA: non-acupoints; IBS: irritable bowel syndrome; FGIDs: functional gastrointestinal disorders; RCTs: randomized clinical trials; FDA: the US Food and Drug Administration; IBS-SSS: IBS Symptom Severity Scale; IBS-QoL: IBS-Quality of Life scale; PHQ-9: Patient Health Questionnaire-9 depression scale; IBS-AR: IBS Adequate Relief; NRS: numerical rating scale; BBS: Bristol stool score; ITT: Intention-to-treat; LOCF: last observation carried forward; M ± SD: mean ± standard deviation; ANOVA: Analysis of Variance.

Declarations

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Authors' contributions

LYQ, JWY, SYY, JFT and CZL planned and designed the study. LYQ, JWY, YFS, YL, LLC and BQW conducted the study. LYQ and SSY performed the statistical analyses. LYQ and JWY wrote the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Beijing University of Chinese Medicine (Project Number: 2020BZHYLL0117). Written informed consent was obtained from all eligible participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

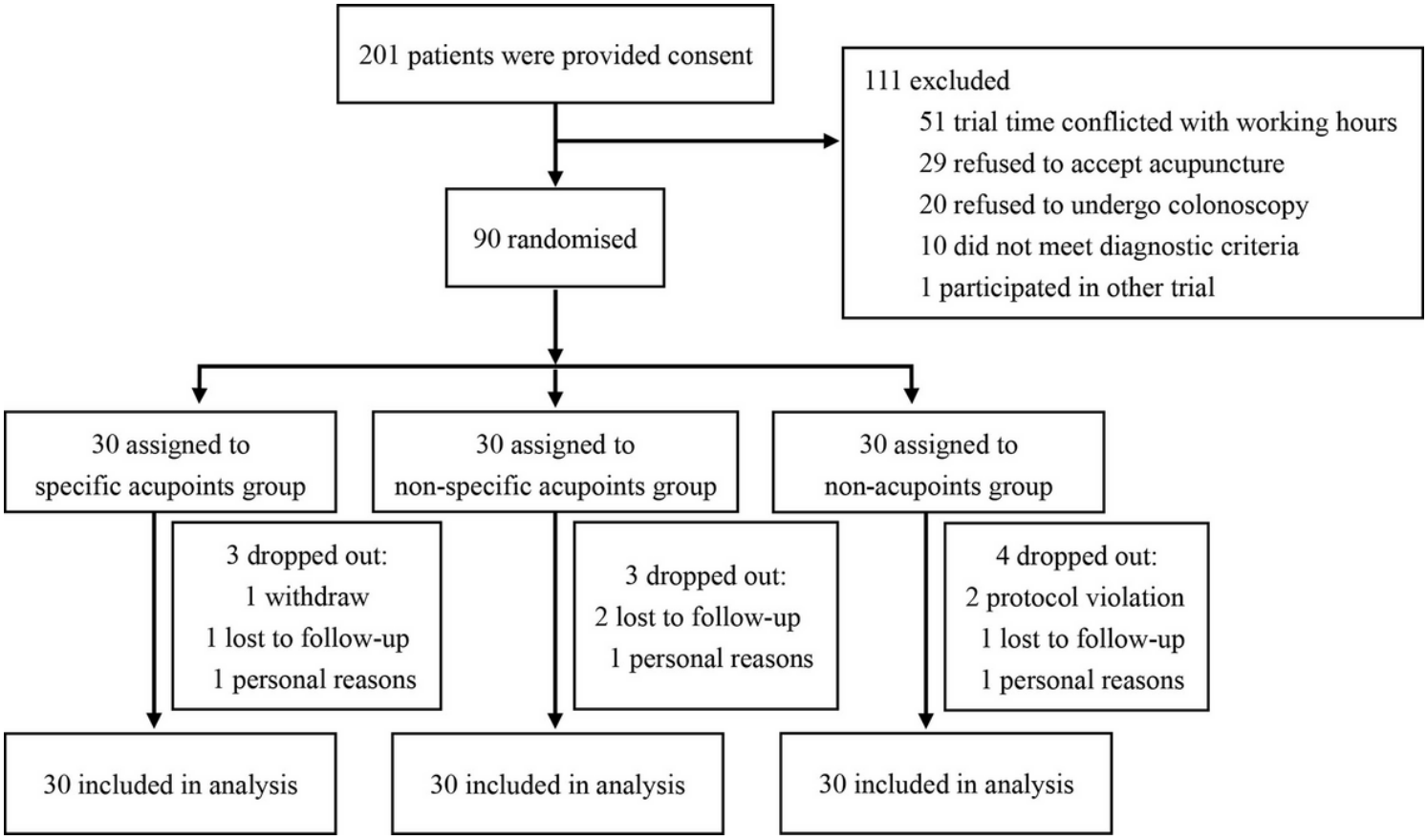

Figure 1

The flow diagram of this trial.

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