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Efficacy of acupuncture at sensitive acupoints for diarrhea-predominant irritable bowel syndrome (IBS-D): protocol of a randomized controlled trial

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ABSTRACT

Introduction While recent research suggests that acupuncture may offer benefits for individuals with diarrhea-predominant irritable bowel syndrome (IBS-D), high-quality studies are scarce in this area. We intend to investigate the efficacy and safety of individualized sensitized acupuncture in IBS-D.

Methods and analysis The study will be designed as a large-scale, multi-center, two-arm, randomized clinical trial, involving 326 patients diagnosed with IBS-D. Participants will be randomly allocated into either the acupuncture or sham acupuncture groups in a 1:1 ratio. Both groups will undergo 15 sessions over 6 weeks. The primary outcome is the composite response rate at week 6, with secondary outcomes including effective response rate at alternative time points, percentage of patients with a 50% reduction in effective response weeks throughout the treatment duration, IBS Symptom Severity Scale, IBS-Quality of Life, Patient Health Questionnaire-9, Adequate Relief of IBS Symptoms Scale, Extraintestinal Symptoms Scale and other symptoms.

Ethics and dissemination This protocol has been approved by the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the ethics committees of other participating institutions. The study results will be submitted for publication in a peer-reviewed journal.

Trial registration The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2300078321. Register date: December 5, 2023. https://www.chictr.org.cn/showproj.html?proj=199310).

Keywords: Acupuncture, Diarrhea-predominant irritable bowel syndrome, Randomized controlled trials, Protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first large-sample clinical trial to evaluate the efficacy and safety of acupuncture at sensitive acupoints in patients with diarrhea-predominant irritable bowel syndrome.
- The treatment program involves a personalized selection of sensitive acupoints based on individual patients' sensitivity levels.
- Methodologic rigor will be applied, including the use of adequate randomization, objective measures, rigorous training of trial personnel, and clear role separation.
- The absence of blinding for the acupuncturists could introduce bias and compromise the validity and reliability of the results.
- Eligible participants will be recruited from five hospitals throughout China, and the findings might have certain limitations when extended to IBS-D patients in other nations.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain with or without abnormal bowel habits. [1] The global prevalence of IBS is estimated to be as high as 11.2%, with a higher prevalence among females and a lower incidence among individuals aged 50 years or older. [2, 3] According to predominant fecal characteristics, IBS can be categorized into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed symptoms (IBS-M), and IBS Unclassified (IBS-U). IBS-D is the most prevalent, accounting for three-quarters of diagnosed cases. [4-6] While IBS is not life-threatening, it significantly impacts patients' quality of life for patients. It imposes a substantial economic and medical burden on society, with costs in the United States reaching 10 billion dollars. [7]

The primary treatment for IBS-D involves pharmacotherapy, utilizing antidiarrheal agents, antispasmodics, and antidepressants as first-line or second-line therapies. However, most medications often only provide temporary relief for specific symptoms and are associated with a high recurrence rate. [8] An escalating number of IBS patients are increasingly seeking out complementary and alternative therapies, with acupuncture being acknowledged as a pivotal alternative therapy for IBS. A meta-analysis [9] of IBS with 27 randomized controlled trials (RCTs) reveals that acupuncture showed notable effectiveness in alleviating symptoms, outperforming certain symptomatic drugs. Recent high-quality RCTs have further substantiated this perspective. Collectively, acupuncture has the potential to alleviate the symptoms and enhance the quality of life for IBS patients compared to both pharmacological interventions and sham acupuncture. [10] Our previous study showed clinically meaningful improvement in IBS-D symptoms. The composite response rates of patients in both the specific acupoints and the nonspecific acupoints group were 46.7%, yet there was no significant difference in the composite response rates when compared with the sham acupuncture group. [11] However, the majority of current studies on acupuncture for IBS-D still yield inconsistent conclusions and lack sufficient methodology. [12-15] We observed that in some clinical

studies in which the efficacy of acupuncture for IBS was not obvious, most of them used standardized acupoint selection programs and did not consider individual patient variation. [15-17] In clinical therapy, acupuncturists typically conduct examinations of acupoints on the patient's body surface before treatment and select sensitive acupoints for acupuncture. Although these patients share the same disease, the acupoint program is not uniform. Thus, we contend that personalized acupuncture therapy could elevate the efficacy of acupuncture in patients afflicted with IBS.

The precise selection of acupoints is crucial for determining the therapeutic efficacy of acupuncture. Historically, acupuncturists targeted highly sensitive acupoints to achieve optimal treatment outcomes. The relationship between the disease condition and acupoints is significant, as lesions in internal viscera or deep tissues can cause changes in specific acupoints related to the affected organs. [18] In the diseased state, specific acupoints will demonstrate sensitive conditions. The sensitivity of acupoints is mainly manifested by local skin swelling, heat, and pain, among which the decrease in the pain threshold is the most common. [19] The sensitive acupoints are linked to the clinical effectiveness of acupuncture. Recently, the efficacy of treating sensitive acupoints has been substantiated by some studies, encompassing chronic neck pain, bronchial asthma, stable angina pectoris, knee osteoarthritis, and other conditions. [20-23] Studies have also shown that patients with gastrointestinal disorders often have sensitive acupoints, particularly those that are sensitive to pain. [24] Pain-sensitive points are regions that react in response to stimulation with the minimum force applied on the skin by external pressure and are characterized by a decrease in the pain threshold. [25]

This study aims to conduct a multicenter randomized controlled clinical trial to investigate the efficacy of personalized sensitive acupoints acupuncture over a 6-week period (15 sessions) in alleviating abdominal pain and the number of days with loose stool in patients with IBS-D. This study aims to investigate the efficacy and safety of sensitive acupoints acupuncture for treating IBS-D, in order to provide high-quality clinical evidence for acupuncture treatment of IBS-D.

METHODS AND ANALYSIS

Study design

This study is a large-scale, multi-center, two-arm, randomized clinical trial designed to testify to the efficacy of sensitive acupoints-acupuncture treatment for patients with IBS-D. The trial will be conducted at five institutions in China: (Ⅰ) Liangxiang Hospital, Fangshan District, Beijing, (Ⅱ) Hospital of the Chengdu University of TCM, (Ⅲ) Affiliated Hospital of Shandong University of Traditional Chinese Medicine, (Ⅳ) Hospital of Jiangxi University of TCM, (Ⅴ) Hebei Provincial Hospital of Traditional Chinese Medicine. Eligible IBS-D patients will be randomly assigned to either the acupuncture group or the sham acupuncture group according to a 1:1 ratio. The trial will consist of three phases: a 2-week screening phase (weeks-2 and-1), a 6-week treatment phase (weeks 1-6), and a 12-week follow-up phase (weeks 7-18), totaling 20 weeks. The flow chart of this study is shown in Figure 1, and the assessment time point is shown in Table 1. The study protocol was approved by the Medical Ethics Committee of the Beijing University of Chinese Medicine and the Ethics Committee of each research center before the study commencement. All test personnel will receive unified training on the implementation of the test. The recruitment commenced on 5 December 2023 and is expected to continue until December 2024.

Participants

The subjects will be recruited via the outpatient clinic of the research center, as well as through recruitment advertisements and WeChat platforms. Participant data will be collected by the REDCap electronic data capture (EDC) system. Participants will be required to maintain a defecation diary throughout a 2-week screening period before enrollment. Each participant will sign an informed consent form before randomization.

Inclusion criteria

(Ⅰ)Age between 18-75 years old (including 18 and 75 years old), both male and female;

(Ⅱ) Fulfilled Rome IV diagnostic criteria for IBS-D;

(Ⅲ) The daily defecation records from the past two weeks indicate that Bristol stool patterns of type 6 or 7 were present for a minimum duration of 4 days, while type 1 or 2 only occurred for a maximum duration of 4 days; Furthermore, the average daily

abdominal pain score was equal to or greater than 3 during the previous week;

(Ⅳ) No treatment of acupuncture in the last 6 months.

Exclusion criteria

(Ⅰ)Other subtypes of IBS: IBS-C/ IBS-U/ IBS-M;

(Ⅱ) Inflammatory bowel disease/microscopic colitis/history of celiac disease/Crohn's disease and other organic bowel diseases (colonoscopy results within 2 years are required for those age 50 or older or with the following alarming signs: unexplained weight loss (weight loss equal to or greater than 10% within 3 months), blood in stool other than from hemorrhoids or anal fissures, nighttime diarrhea, or family history of colorectal cancer)

(Ⅲ)Take antidepressants and medications with therapeutic effects on symptoms of irritable bowel syndrome within 2 weeks before treatment, including traditional Chinese medicine or Chinese patent medicine, antidiarrheal agents, antispasmodic agents, intestinal antibiotics, probiotics, etc;

(Ⅳ)Diabetes, thyroid dysfunction, severe acute/chronic organic disease, and kidney or liver disease;

(Ⅴ)Previous history of abdominal surgery, excluding appendectomy, hemorrhoidectomy, or polypectomy performed more than 3 months ago;

(Ⅵ)During the period of pregnancy or lactation;

(Ⅶ)History of substance abuse, including alcohol and drug use;

(Ⅷ)Patients enrolled in alternative clinical trials.

The exclusion criteria will apply to individuals who meet one or more of the aforementioned requirements.

Randomization and blinding

In this study, patients diagnosed with IBS-D will be randomly allocated to either the acupuncture group or the sham acupuncture group in a 1:1 ratio by the RedCap EDC system. Randomization will be stratified by recruitment site, with a dynamic block size of 4, 6, or 8. The randomization sequences will be generated by an independent statistician and securely stored within the RedCap EDC system. Before the first

acupuncture treatment, the acupuncturist will receive the assigned grouping information through the RedCap EDC system. Different roles within this study will have varying levels of access and permissions to the RedCap EDC system. Only the acupuncturist and their assistant will have access to the participants' grouping information. Participants, recruiters, outcome evaluators, data managers, and statistical analysts will be blinded to the participants' randomization grouping. A sham acupuncture group will be established in this study. Patients will receive treatment in individual cubicles to ensure blinding and are strictly prohibited from engaging in any form of communication during the treatment sessions. A blinding assessment will be performed on participants at the early and mid-treatment stages.

Interventions

The acupuncture group and the sham acupuncture group will be set in this study. Acupuncture interventions will be conducted by licensed acupuncturists with a minimum of 3 years of clinical experience. Participants will undergo a 6-week acupuncture treatment, with sessions scheduled three times per week for the initial 3 weeks and two times per week for the subsequent 3 weeks, totaling 15 sessions lasting 30 minutes each. Before the study commencement, personnel in different roles will receive specialized training, and only those who have completed the training will be eligible to participate.

During treatment, loperamide (Xi'an Janssen Pharmaceutical Co., LTD.) will be provided to the participant as a contingency medication, administered by a gastroenterologist only in cases of severe and intolerable symptoms like acute abdominal pain. Medications used will be carefully documented throughout the trial, including any non-IBS-related medications.

The participant will be discontinued from the study in the event that any of the following circumstances arise: the patient experiences a serious adverse event, other conditions that impede the outcomes assessment, poor compliance, or the subject expresses unwillingness to continue during the course of the clinical trial.

Acupuncture group

In the acupuncture group, acupuncture will be administered at the five high-sensitive acupoints. The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles (Suzhou Huatuo Medical Equipment Co., LTD., 0.30mm×40mm). The manipulation will be performed to achieve *deqi*, with the degree of local acid distension serving as the indicator of successful treatment.

Selection and localization of acupoints repository

After a comprehensive literature review and clinical experience, we have identified 17 acupoints that are frequently used in treating IBS-D. [26-28] (Table 2) The acupoint locations will be determined according to the national standard of the People's Republic of China (GB/T12346-2021), Name and Location of Acupoints.

Assessment of pain threshold at acupoints

The pain threshold will be measured twice at each of the 17 acupoints in a predetermined sequence (upper limbs→abdomen→lower limbs→back) using a Wagner digital force gage (FDX 50; Wagner, Greenwich, CT, USA). If the difference between the two measurements is more than 5 N, a third measurement will be performed, and the pain threshold measured will be averaged.

Identification of intervention acupoints

The acupoints on the abdominal midline, including Zhongwan (CV 12), Xiawan (CV 12), Qihai (CV 6), and Guanyuan (CV 4), will be assessed for pain threshold, with selection of the first two acupoints based on their ranking from low to high.

Bilateral acupoints will be selected based on the ratio of bilateral pain threshold (right/left), with the absolute value of < ratio-1 > being sorted in descending order, and the top 4 acupoints will be chosen.

During the treatment period, the acupoints pain thresholds will be measured once every 3 weeks during the treatment, specifically before the first treatment in the first week and before the first treatment in the fourth week. Acupoints will be adjusted according to the results.

Sham acupuncture group

Five non-acupoints will be selected (Table 3). The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles. The shallow needling method will be used to penetrate the skin of the participants. The needle tip will only penetrate 2-3 mm under the skin, without manipulation and without reaching *deqi*.

The pain thresholds of the 5 non-acupoints will also be measured and recorded before the first treatment in the first week and the first treatment in the fourth week.

Outcomes

primary outcome

The primary outcome will be the composite response rate at week 6. The composite response rate is defined as the percentage of patients with a mean 30% improvement from baseline in the worst abdominal pain and a 50% reduction from baseline in the number of days with loose stools at week 6. These criteria align with the recommended outcomes by the Food and Drug Administration (FDA).

The defecation diary will be used to record the participants ' defecation and abdominal pain, bloating, and other symptoms. The worst abdominal pain score in the past 24 hours will be assessed using a numerical rating scale (NRS, on a scale from 0 to 10, with 0 indicating no pain at all and 10 the worst pain the patient could imagine) and the weekly average will be calculated. Episodes of loose stool will be defined as the presence of at least one stool type 6 or 7 on a given day.

Secondary outcomes

The secondary outcomes will include the composite response rate at other time points, the percentage of patients experiencing 50% reduction in effective response weeks during treatment, IBS Symptom Severity Scale (IBS-SSS), IBS-Quality of Life (IBS-QOL), Patient Health Questionnaire-9 (PHQ-9), Adequate Relief of IBS Symptoms Scale (IBS-AR), Extraintestinal Symptoms Scale, abdominal pain symptoms, bloating, loose stool days, blinding assessment, Credibility/Expectancy Questionnaire.

IBS-SSS

The IBS-SSS [29] is a comprehensive assessment scale that evaluates the overall

symptoms of IBS, encompassing clinical manifestations and their correlation with patients' quality of life. The scale evaluation includes five domains: the severity of abdominal pain, the duration of abdominal pain, the severity of abdominal distension, satisfaction with defecation, and impact on quality of life. Each domain is scored on a scale from 0 to 100, resulting in a total score ranging from 0 to 500. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-QOL

The IBS-QOL [30] scale comprises 34 items and is organized into 8 dimensions: Dysphoria (DY), Health worry (HW), Body image (BI), Interference with activity (IN), Food avoidance (FA), Social reaction (SR), Sexual (SX) and Relationship (RL). The scores range from 0 to 100, with higher total scores indicating a higher quality of life. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

PHQ-9

The PHQ-9 [31] is a diagnostic instrument used to assess common mental disorders, with scores ranging from 0 to 27. A higher total score indicates a more severe psychological condition. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-AR

The IBS-AR [32] scale includes a dichotomous item that asks patients, "Have your IBS symptoms been adequately relieved during the past week?" This scale will be employed to evaluate symptom relief in individuals with irritable bowel syndrome (IBS). The evaluation time points will be at 1, 2, 3, 4, 5, 6, 8, 10,12,14,16, and 18 weeks after the start of treatment.

Extraintestinal Symptoms Scale

The Extraintestinal Symptoms Scale [33] comprises a rating scale for 15 prevalent symptoms frequently reported as adverse events in clinical drug trials. Each symptom is scored on a scale of 0-5, with 0 indicating absence and 5 indicating severity. The severity scores for the 15 symptoms are summed to calculate a composite score for each

participant, resulting in an overall symptom burden score ranging from 0 to 75. The evaluation time points will be baseline and 6 and 18 weeks after the start of treatment.

Blinding Assessment and Credibility/Expectancy Questionnaire

Patients will be asked to guess their treatment at week 1 and week 3 to test patient blinding. Following the initial treatment, participants will be mandated to complete the Credibility/Expectancy Questionnaire to evaluate their perceived credibility of the treatment and their expectations.

Adverse events

Adverse events, both related and unrelated to acupuncture, will be promptly documented in the RedCap EDC system during both the treatment and follow-up periods. All adverse events will be managed symptomatically by acupuncturists and doctors with relevant specialties. The assessment of the incidence and severity of adverse events will be conducted after the treatment period (week 6) and at the end of the follow-up period (week 18).

Data management

Both paper files and electronic documents will be preserved for at least 5 years after publication. Original data can be accessed by contacting the corresponding author. Patient information will remain anonymous, including name, ID number, and mobile phone number. An electronic Case Report Form (eCRF) will be used for data collection during the trial. Paper defecation diary cards will be provided to participants who do not have easy access to electronic devices. Each center will implement a standardized RedCap EDC system and uniformly printed paper test materials. Independent monitors will monitor the eCRF data in real-time to guarantee the completeness and promptness of data collection, without interfering in the trial. Any changes to the data will be traceable through the eCRF.

Quality assurance

Before the initiation of the study, all trial personnel underwent comprehensive training on the study objectives, patient screening, intervention modalities, and evaluation follow-up, as well as familiarization with the operation of the RedCap EDC system.

The trial personnel will maintain all paper documents, such as defecation diary cards and acupuncture record forms. Access permissions for the RedCap EDC system will vary depending on the roles within the study. A team of monitors will be established to monitor the trial data both online and offline. The monitors will conduct random monitoring of study implementation and data collection when 10% and 90% of the participants are included. The monitoring will encompass all trial procedures, including patient recruitment, intervention implementation, assessment, and data input. The contact information and residential addresses of the trial participants will be recorded, and regular communication will be maintained to enhance participant adherence to the protocol. The investigator will actively reach out to the participant to assess their condition in instances when the participant has not undergone treatment multiple times.

Sample size

According to the previous research of our group (the results are still unpublished), the composite response rate will be estimated to be 55.9% in the acupuncture group and 38.8% in the sham acupuncture group. We used a two-sided test with α=0.05 and β=0.2. The sample size calculation indicated that each group should have a minimum of 130 effective cases. Considering a dropout rate of 20%, a total of 163 cases need to be recruited for each group, resulting in a total of 326 cases across both groups.

Statistical analysis

The study will utilize SAS 9.3 software for data analysis. Statistical analysis will be performed by an independent statistician who is blinded to group assignments. Continuous data will be presented as either mean ± standard deviation (M±SD) or median and interquartile range, while categorical data will be reported as frequencies (percentages). A two-sided test level of 0.05, with P values of less than 0.05, will be considered to indicate statistical significance.

All analyses will adhere to the intention-to-treat (ITT) protocol, which includes all randomized patients with available baseline information. Missing data will be imputed using multiple imputations. A per-protocol population analysis (PP) of the primary outcome measure will be conducted for participants who completed no less than 80%

of the treatment. Safety analyses will be based on participants who will receive at least one session of treatment.

For the primary outcome, a logistic generalized linear mixed model will be used to test for differences between groups. The secondary outcomes will be compared between groups using the t-test or Wilcoxon rank-sum for continuous data, and the $\chi 2$ test or Fisher's exact tests for categorical data.

Ethics and dissemination

The protocol has obtained approval from the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the medical ethics committees of five hospitals. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) platform (number: ChiCTR2300078321). Each participant will be required to provide written consent before enrollment. The findings of this study will be submitted for publication in a peer-reviewed journal.

DISCUSSION

IBS-D is the most prevalent subtype of IBS, characterized by chronic, recurring episodes and comorbid mental health conditions like anxiety and depression, which significantly impact patients' quality of life. [34] A large-scale, multi-center, two-arm, randomized clinical trial is currently being designed to assess the efficacy of acupuncture at sensitized acupoints for IBS-D.

The selection of acupoints plays a crucial role in acupuncture treatment. This study will implement a personalized program for acupoint selection based on the level of acupoint sensitization. In the ancient Chinese medical book, the Medical Classic of the Yellow Emperor, it is documented that excellent therapeutic efficacies can be procured by choosing the acupoints featuring sensitive manifestations such as induration and tenderness in the context of acupuncture treatment. In a randomized neuroimaging trial, 99 patients with chronic neck pain were randomized to either true acupuncture or sham acupuncture. The true acupuncture group and the sham acupuncture group were treated with standard acupuncture treatment at the pain sensitive acupoints and shallow acupuncture at non-acupoints, respectively. Both groups received treatment for 4 weeks.

After treatment, sensitive acupoint acupuncture showed a significant improvement in both the severity and duration of pain when compared to the sham acupuncture group. [35] IBS-D is characterized by a range of symptoms, which can vary between individual patients. Therefore, a personalized acupuncture regimen may yield greater efficacy in alleviating IBS symptoms among participants. A study randomly dichotomized 80 patients with IBS-D into a control group and a treatment group. The control group received treatment with Piverium bromide, while the treatment group underwent therapy with Piverium bromide in combination with heat-sensitive moxibustion. [36] The results indicated that the treatment group exhibited a significant improvement in IBS-SSS and quality of life when compared with the control group. Lei C et al [37] identified that the sensitive acupoints of IBS-D model rats was the *Dachangshu* (BL 25). Subsequently, the rats were stratified into sensitive and non-sensitive acupoint groups, revealing a significantly enhanced efficacy of electroacupuncture in the sensitive acupoint group compared to the non-sensitive counterpart. In this study, pain sensitization will be utilized as the criterion for acupoint selection due to its prevalence as a manifestation of sensitization. [23] The degree of change in pain threshold will objectively reflect the intensity of acupoint sensitization and may be correlated with the disease state. [38] Additionally, there is a study that has shown individuals with IBS have a lower acupoint pain threshold compared to healthy individuals. [39] However, the current research on the efficacy of sensitive acupoints in IBS patients is predominantly theoretical, with a notable absence of high-quality clinical studies.

This multi-center, RCT adheres to the CONSORT [40] and STRICTA [41] guidelines, showcasing high-quality methodological standards. One major challenge in clinical acupuncture research is establishing an appropriate sham acupuncture control. Common types of sham acupuncture used in clinical trials include needling insertion at acupuncture points, needling insertion at non-acupuncture points, non-insertion at acupuncture points, and non-insertion at non-acupuncture points. [42] Maintaining blinding in Chinese participants, many of whom have acupuncture experience, is particularly difficult. To address this, the sham acupuncture group will receive shallow

needling at non-acupoints, with pain threshold measurements taken. Participants will be separated during treatment to ensure blinding and compliance. The FDA-recommended composite response rate will serve as the primary outcome, offering a more rigorous assessment than the IBS-SSS used in previous studies. Randomization will be conducted using the RedCap EDC system, with computer-generated sequences and restricted access to allocation information to prevent bias. Additionally, all trial personnel will undergo professional training before the trial commences, with independent supervisors overseeing data monitoring and trial implementation to uphold trial integrity.

This study has several limitations. Firstly, due to the distinctive characteristics of acupuncture intervention, implementing blinding for acupuncturists may not be feasible. Secondly, time and resource constraints will only allow for pain threshold measurements to be taken twice for each acupuncturist. Subsequently, patients will receive treatment at the same acupoints for 3 weeks based on the measured data. The stability of higher sensitized acupoints over 3 weeks cannot be guaranteed. Finally, the generalizability of our findings to IBS-D patients outside of China may be limited.

Trial status

This trial is currently recruiting participants.

Authors' contributions

C-ZL and N-NY proposed and initiated the study; Z-TF, N-NY, C-ZL, J-WY and YW participated in the designing, drafting and revising the manuscript; Q-HZ, L-LC, X-BH, J-HG and Y-WX coordinated the study; C-ZL, Q-HZ, L-LC, X-BH, J-HG and Y-WX sought ethical approval; J-WY, YW ,HZ and Y-DL assisted in manuscript revision.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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Figure legends

Figure 1 Trial flow chart.

IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

Figure 2. Location of acupoints and non-acupuncture points.

Red dots: location of acupoints in the sensitive acupoints group; blue dots: location of non-acupuncture points in the sham acupuncture group. (Note: This figure is modified based on www.3Dbody.com). (A) Ventral view; (B) Dorsal view; (C) View of the upper extremity; (D) Anterior aspect view of the lower extremity; (E) Lateral view of the lower extremity; (F) Medial aspect view of the lower extremity.

Table 1 Time points of treatment assessment

Time point	Screening		Baseline	Treatment							Follow-up				
	Week-2	Week-1	Week 0	Week 1	After first treatment	Week2	Week3	Week4	Week5	Week6	Week8	Week10	Week12	Week14	Week16	Week18
Screening and enrolment																
Eligibility screen	×	×														
Informed consent	×	×														
Randomization			×													
Interventions																
Sensitive acupoints				←						→						
Sham acupuncture				←						→						
Assessments																
The response rate				×		×	×	×	×	×		×	×	×	×	×
Abdominal pain				×		×	×	×	×	×		×	×	×	×	×
Bloating				×		×	×	×	×	×		×	×	×	×	×
Loose stool days				×		×	×	×	×	×		×	×	×	×	×
IBS-AR				×		×	×	×	×	×		×	×	×	×	×
IBS-SSS			×			×		×		×		×		×		×
IBS-QOL			×			×		×		×		×		×		×
PHQ-9			×			×		×		×		×		×		×
Extraintestinal symptoms			×							×						×
Credibility/Expectancy					×											
Blinding assessment				×			×									
Adverse events				×		×	×	×	×	×	×	×	×	×	×	×

Table 2 Acupoints used in the sensitive acupoints group

Acupoint	Location
LI 11 (*Quchi*)	Lateral to the elbow, at the midpoint of the line between LU5(*Chize*) and the lateral epicondyle of the humerus.
LI 4(*Hegu*)	It is located on the dorsum of the hand, between the first and second metacarpal bones, approximately at the midpoint of the radial side of the second metacarpal bone.
ST 25(*Tianshu*)	In the epigastric region, transversely aligned with the umbilicus, 2 cun lateral to the anterior midline.
CV 12(*Zhongwan*)	In the epigastric region, located 4 cun superior to the umbilicus along the anterior midline.
CV 4(*Guanyuan*)	In the hypogastric region, 3 cun below the umbilicus along the anterior midline.
CV 10(*Xiawan*)	In the epigastric region, located 2 cun superior to the umbilicus along the anterior midline.
CV 6(*Qihai*)	In the hypogastric region, 1.5 cun below the umbilicus along the anterior midline.
SP 15(*Daheng*)	In the epigastric region, transversely aligned with the umbilicus, 4 cun lateral to the anterior midline.
SP16(*Fuai*)	In the epigastric region,3 cun above the midpoint of the umbilicus, and 4 cun lateral to the anterior midline.
BL 25(*Dachangshu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the fourth lumbar vertebra.
BL 21(*Weishu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the twelfth thoracic vertebra.
BL 27(*Xiaochangshu*)	The point is located at the sacral region, parallel to the first posterior sacral foramen and 1.5 cun away from the median sacral crest.
ST 36(*Zusanli*)	The point is located on the lateral aspect of the calf, 3 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
ST 37(*Shangjuxu*)	The point is located on the lateral aspect of the calf, 6 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
SP 6(*Sanyinjiao*)	The point is located medially to the calf, 3 cun above the tip of the medial malleolus, and posterior to the medial margin of the tibia.
SP 9(*Yinlingquan*)	The point is located on the medial side of the calf, in the depression formed by the lower margin of the medial condyle of the tibia and the medial margin of the tibia.
ST 39(*Xiajuxu*)	The point is located on the lateral aspect of the calf, 9 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).

Table 3 Acupoints used in the sham acupuncture group

Non-acupoint	Location
Non-acupoint 1	The point is situated on the upper limb, at the midpoint between LU5(*Chize*) and LI7(*Wenliu*).
Non-acupoint 2	The point is located in the abdomen, 2 cun above the anterior superior iliac spine, between the gall bladder meridian and the spleen meridian.
Non-acupoint 3	The point is located in the abdomen, 2 cun below the umbilicus and 1 cun lateral to the anterior midline, between the renal meridian and the gastric meridian.
Non-acupoint 4	The point is located in the lower extremity, on the lateral leg, 3 cun below the GB34 (*Yanglingquan*), between the gall bladder meridian and the bladder meridian.
Non-acupoint 5	The point is located 2 cun above the medial malleolus, on the medial aspect of the tibia, between the liver meridian and the spleen meridian in the lower extremity.

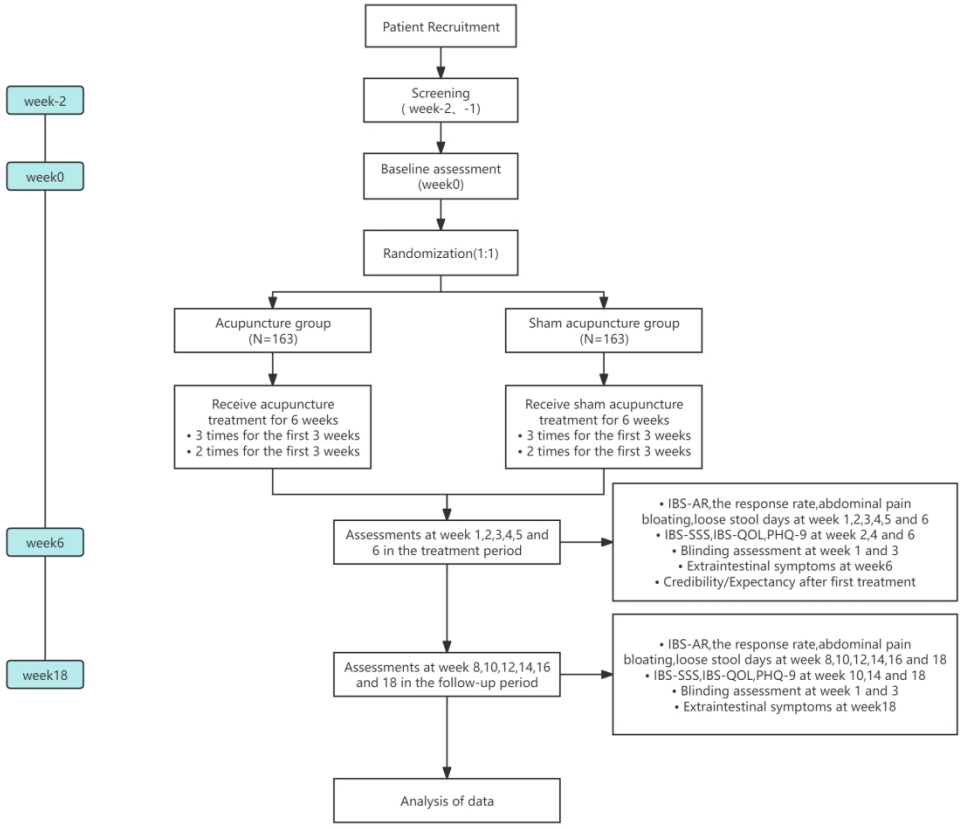

Figure 1 Trial flow chart.
IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

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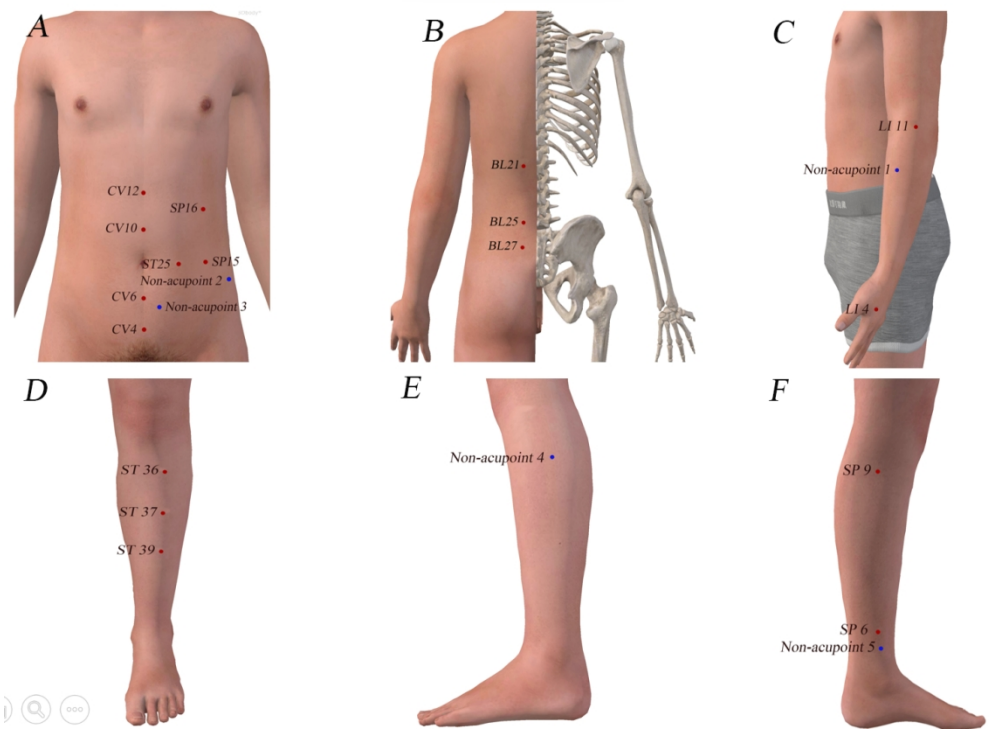

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259x189mm (144 x 144 DPI)

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Efficacy of acupuncture at pain sensitive acupoints for diarrhea-predominant irritable bowel syndrome (IBS-D): protocol of a multicentre, randomized, sham-controlled trial

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Efficacy of acupuncture at pain sensitive acupoints for diarrhea-predominant irritable bowel syndrome (IBS-D): protocol of a multicentre, randomized, sham-controlled trial

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ABSTRACT

Introduction While recent research suggests that acupuncture may offer benefits for individuals with diarrhea-predominant irritable bowel syndrome (IBS-D), high-quality studies are scarce in this area. We intend to investigate the efficacy and safety of individualized sensitized acupuncture in IBS-D.

Methods and analysis The study will be designed as a large-scale, multi-center, two-arm, randomized clinical trial, involving 326 patients diagnosed with IBS-D. Participants will be randomly allocated into either the acupuncture or sham acupuncture groups in a 1:1 ratio. Both groups will undergo 15 sessions over 6 weeks. The primary outcome is the effective response rate at week 6, with secondary outcomes including the effective response rate at alternative time points, the percentage of patients with a 50% reduction in effective response weeks throughout the treatment duration, IBS Symptom Severity Scale, IBS-Quality of Life, Patient Health Questionnaire-9, Adequate Relief of IBS Symptoms Scale, Extraintestinal Symptoms Scale and other symptoms.

Ethics and dissemination This protocol has been approved by the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the ethics committees of other participating institutions. Each participant will be required to provide written consent before enrollment. The study results will be submitted for publication in a peer-reviewed journal.

Trial registration The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2300078321). Register date: December 5, 2023.

Keywords: Acupuncture, Diarrhea-predominant irritable bowel syndrome, Randomized controlled trials, Protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large-sample clinical trial to evaluate the efficacy and safety of acupuncture at sensitive acupoints in patients with diarrhea-predominant irritable bowel syndrome.
- The treatment program involves a personalized selection of sensitive acupoints based on individual patients' sensitivity levels.
- Methodologic rigor will be applied, including the use of adequate randomization, objective measures, rigorous training of trial personnel, and clear role separation.
- The absence of blinding for the acupuncturists could introduce bias and compromise the validity and reliability of the results.
- Eligible participants will be recruited from five hospitals throughout China, and the findings might have certain limitations when extended to IBS-D patients in other nations.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain with or without abnormal bowel habits. [1] The global prevalence of IBS is estimated to be as high as 11.2%, with a higher prevalence among females and a lower incidence among individuals aged 50 years or older. [2, 3] According to predominant fecal characteristics, IBS can be categorized into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed symptoms (IBS-M), and IBS Unclassified (IBS-U). IBS-D is the most prevalent, accounting for three-quarters of diagnosed cases. [4-6] While IBS is not life-threatening, it significantly impacts patients' quality of life for patients. It imposes a substantial economic and medical burden on society, with costs in the United States reaching 10 billion dollars. [7]

The primary treatment for IBS-D involves pharmacotherapy, such as utilizing antidiarrheal agents, antispasmodics, and antidepressants as first-line or second-line therapies. However, most medications often only provide temporary relief for specific symptoms and are associated with a high recurrence rate. [8] An escalating number of IBS patients are seeking out complementary and alternative therapies, with acupuncture being acknowledged as a pivotal alternative therapy for IBS. A meta-analysis [9] of IBS with 27 randomized controlled trials (RCTs) reveals that acupuncture showed notable effectiveness in alleviating symptoms, outperforming certain symptom medications. Recent high-quality RCTs have further substantiated this perspective. Collectively, acupuncture has the potential to alleviate the symptoms and enhance the quality of life for IBS patients compared to both pharmacological interventions and sham acupuncture. [10] Our previous study showed clinically meaningful improvement in IBS-D symptoms. The effective response rates of patients in both the specific acupoints and the nonspecific acupoints group were 46.7%, yet there was no significant difference in the effective response rates when compared with the sham acupuncture group. [11] However, the majority of current studies on acupuncture for IBS-D still yield inconsistent conclusions and lack sufficient methodology. [12-15] MacPherson H et al. [12] randomised 233 IBS participants to receive either a short course of traditional acupuncture

combined with usual care, or usual care alone, with equal distribution between the two groups. The study found that, at three months, the IBS symptom severity (IBS-SSS) scores of participants receiving acupuncture treatment significantly decreased. However, the study has some limitations, including the lack of blinding for participants and the use of the relatively subjective IBS-SSS score as the primary outcome measure. Anthony J. Lembo et al. [14] compared the efficacy of acupuncture and sham acupuncture treatments over six sessions across three weeks in IBS patients. The results indicated that, at the end of the treatment, there were no significant differences in symptom improvement between the acupuncture and sham acupuncture groups. However, both groups showed significant improvements when compared to the waitlist control group. Although this study included a sham acupuncture control group, it still has limitations, such as a relatively short treatment duration and the use of a subjective primary outcome. At the same time, we observed that in some clinical studies in which the efficacy of acupuncture for IBS was not found, most of them used standardized acupoint selection programs and did not consider individual patient variation. [15-17] In clinical therapy, acupuncturists typically conduct examinations of acupoints on the patient's body surface before treatment and select sensitive acupoints for acupuncture. Although these patients share the same disease, the acupoint program is not uniform. Thus, we contend that personalized acupuncture therapy could elevate the efficacy of acupuncture in patients afflicted with IBS.

The precise selection of acupoints is crucial for determining the therapeutic efficacy of acupuncture. Historically, acupuncturists targeted highly sensitive acupoints to achieve optimal treatment outcomes. The relationship between the disease condition and acupoints is significant, as lesions in internal viscera or deep tissues can cause changes in specific acupoints related to the affected organs. [18] In the diseased state, specific acupoints will demonstrate sensitive conditions. The sensitivity of acupoints is mainly manifested by local skin swelling, heat, and pain, among which the decrease in the pain threshold is the most common. [19] The sensitive acupoints are linked to the clinical effectiveness of acupuncture. The efficacy of treating sensitive acupoints has recently been substantiated by studies encompassing chronic neck pain, bronchial asthma, stable

angina pectoris, knee osteoarthritis, and various other conditions. [20-24] Studies have also shown that patients with gastrointestinal disorders often have sensitive acupoints, particularly those that are sensitive to pain. [25] Pain-sensitive points are regions that react in response to stimulation with the minimum force applied on the skin by external pressure and are characterized by a decrease in the pain threshold. [26]

Based on this, we designed a multicenter randomized controlled clinical trial. This study implements personalized sensitive acupoints acupuncture treatment for IBS-D participants. To accommodate the chronic and functional nature of IBS, an appropriate treatment duration and number of sessions have been designed. The primary outcome for evaluating treatment efficacy is the effective response rate, combining both objective and subjective outcome measures. This study aims to investigate the efficacy of personalized sensitive acupoints acupuncture over a 6-week period (15 sessions) in alleviating abdominal pain and the lessening number of days with loose stool in patients with IBS-D. This study aims to investigate the efficacy and safety of sensitive acupoints acupuncture for treating IBS-D, in order to provide high-quality clinical evidence for acupuncture treatment of IBS-D.

METHODS AND ANALYSIS

Study design

This study is a large-scale, multi-center, two-arm, randomized clinical trial designed to test the efficacy of sensitive acupoints-acupuncture treatment for patients with IBS-D. It will test the following hypothesis: 6 weeks of sensitive acupoint acupuncture treatment will result in a better effective response in IBS-D patients compared to sham acupuncture. The trial will be conducted at five institutions in China: (Ⅰ) Liangxiang Hospital, Fangshan District, Beijing, (Ⅱ) Hospital of the Chengdu University of TCM, (Ⅲ) Affiliated Hospital of Shandong University of Traditional Chinese Medicine, (Ⅳ) Hospital of Jiangxi University of TCM, (Ⅴ) Hebei Provincial Hospital of Traditional Chinese Medicine, Eligible IBS-D patients will be randomly assigned to either the acupuncture group or the sham acupuncture group according to a 1:1 ratio. The trial will consist of three phases: a 2-week screening phase (weeks-2 and-1), a 6-week treatment phase (weeks 1-6), and a 12-week follow-up phase (weeks 7-18), totaling 20

weeks. The flow chart of this study is shown in *Figure 1*, and the assessment time point is shown in *Supplement Table 1*. The study protocol was approved by the Medical Ethics Committee of the Beijing University of Chinese Medicine and the Ethics Committee of each research center before the study commencement. All study personnel will receive unified training on the implementation of the test. The recruitment commenced on 5 December 2023 and is expected to continue until December 2024.

Participants

The subjects will be recruited via the outpatient clinic of the research center, as well as through recruitment advertisements and WeChat platforms. Participant data will be collected by the REDCap electronic data capture (EDC) system. Participants will be required to maintain a defecation diary throughout a 2-week screening period before enrollment. Each participant will sign an informed consent form before randomization.

Inclusion criteria

(Ⅰ)Age between 18-75 years old (including 18 and 75 years old), both male and female;

(Ⅱ) Fulfilled Rome IV diagnostic criteria for IBS-D;

(Ⅲ) The daily defecation records from the past two weeks indicate that Bristol stool patterns of type 6 or 7 were present for a minimum duration of 4 days, while type 1 or 2 only occurred for a maximum duration of 4 days; Furthermore, the average daily abdominal pain score was equal to or greater than 3 during the previous week;

(Ⅳ) No treatment of acupuncture in the last 6 months.

Exclusion criteria

(Ⅰ)Other subtypes of IBS: IBS-C/ IBS-U/ IBS-M;

(Ⅱ) Inflammatory bowel disease/microscopic colitis/history of celiac disease/Crohn's disease and other organic bowel diseases (colonoscopy results within 2 years are required for those age 50 or older or with the following alarming signs: unexplained weight loss (weight loss equal to or greater than 10% within 3 months), blood in stool other than from hemorrhoids or anal fissures, nighttime diarrhea, or family history of colorectal cancer)

(Ⅲ)Take antidepressants and medications with therapeutic effects on symptoms of irritable bowel syndrome within 2 weeks before treatment, including traditional Chinese medicine or Chinese patent medicine, antidiarrheal agents, antispasmodic agents, intestinal antibiotics, probiotics, etc;

(Ⅳ)Diabetes, thyroid dysfunction, severe acute/chronic organic disease, and kidney or liver disease;

(Ⅴ)Previous history of abdominal surgery, excluding appendectomy, hemorrhoidectomy, or polypectomy performed more than 3 months ago;

(Ⅵ)During the period of pregnancy or lactation;

(Ⅶ)History of substance abuse, including alcohol and drug use;

(Ⅷ)Patients enrolled in alternative clinical trials.

The exclusion criteria will apply to individuals who meet one or more of the aforementioned requirements.

Randomization and blinding

In this study, patients diagnosed with IBS-D will be randomly allocated to either the acupuncture group or the sham acupuncture group in a 1:1 ratio by the RedCap EDC system. Randomization will be stratified by recruitment site, with a dynamic block size of 4, 6, or 8. The randomization sequences will be generated by an independent statistician and securely stored within the RedCap EDC system. Before the first acupuncture treatment, the acupuncturist will receive the assigned grouping information through the RedCap EDC system. Different roles within this study will have varying levels of access and permissions to the RedCap EDC system. Only the acupuncturist and their assistant will have access to the participants' grouping information. Participants, recruiters, outcome evaluators, data managers, and statistical analysts will be blinded to the participant's randomization grouping. A sham acupuncture group will be established in this study. Patients will receive treatment in individual cubicles to ensure blinding and are strictly prohibited from engaging in any form of communication during the treatment sessions. A blinding assessment will be performed on participants at the early and mid-treatment stages.

Interventions

The acupuncture group and the sham acupuncture group will be set in this study. Acupuncture interventions will be conducted by licensed acupuncturists with a minimum of 3 years of clinical experience. Participants will undergo a 6-week acupuncture treatment, with sessions scheduled three times per week for the initial 3 weeks and two times per week for the subsequent 3 weeks, totaling 15 sessions lasting 30 minutes each. Before the study commencement, personnel in different roles will receive specialized training, and only those who have completed the training will be eligible to participate.

During treatment, loperamide (Xi'an Janssen Pharmaceutical Co., LTD.) will be provided to the participant as a contingency medication, administered by a gastroenterologist only in cases of severe and intolerable symptoms like acute abdominal pain. Medications used will be carefully documented throughout the trial, including any non-IBS-related medications.

The participant will be discontinued from the study in the event that any of the following circumstances arise: the patient experiences a serious adverse event, other conditions that impede the outcomes assessment, poor compliance, or the subject expresses unwillingness to continue during the course of the clinical trial.

Acupuncture group

In the acupuncture group, acupuncture will be administered at the five high-sensitive acupoints. The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles (Suzhou Huatuo Medical Equipment Co., LTD., 0.30mm×40mm). The manipulation will be performed to achieve *deqi*, with the degree of local acid distension serving as the indicator of successful treatment.

Selection and localization of acupoints repository

After a comprehensive literature review and clinical experience, we have identified 17 acupoints that are frequently used in treating IBS-D. [27-29] (*Figure 2, Supplement Table 2*) The acupoint locations will be determined according to the national standard of the People's Republic of China (GB/T12346-2021), Name and Location of Acupoints.

Assessment of pain threshold at acupoints

The pain threshold will be measured twice at each of the 17 acupoints in a predetermined sequence (upper limbs → abdomen → lower limbs → back) using a Wagner digital force gage (FDX 50; Wagner, Greenwich, CT, USA). If the difference between the two measurements is more than 5 N, a third measurement will be performed, and the pain threshold measured will be averaged.

Identification of intervention acupoints

The acupoints on the abdominal midline, including Zhongwan (CV 12), Xiawan (CV 12), Qihai (CV 6), and Guanyuan (CV 4), will be assessed for pain threshold, with selection of the first two acupoints based on their ranking from low to high.

Bilateral acupoints will be selected based on the ratio of bilateral pain threshold (right/left), with the absolute value of < ratio-1 > being sorted in descending order, and the top 4 acupoints will be chosen.

During the treatment period, the acupoint pain thresholds will be measured once every 3 weeks during the treatment, specifically before the first treatment in the first week and before the first treatment in the fourth week. Acupoints will be adjusted according to the results.

Sham acupuncture group

Five non-acupoints will be selected (*Supplement Table 3*). The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles. The shallow needling method will be used to penetrate the skin of the participants. The needle tip will only penetrate 2-3 mm under the skin, without manipulation and without reaching *deqi*.

The pain thresholds of the 5 non-acupoints will also be measured and recorded before the first treatment in the first week and the first treatment in the fourth week.

Outcomes

primary outcome

The primary outcome will be the effective response rate at week 6. The effective response rate is defined as the percentage of patients with a mean 30% improvement from baseline in the worst abdominal pain and a 50% reduction from baseline in the

number of days with loose stools. These criteria align with the recommended outcomes by the Food and Drug Administration (FDA)[30].

The defecation diary will be used to record the participants ' defecation and abdominal pain, bloating, and other symptoms. The worst abdominal pain score in the past 24 hours will be assessed using a numerical rating scale (NRS, on a scale from 0 to 10, with 0 indicating no pain at all and 10 the worst pain the patient could imagine) and the weekly average will be calculated. Episodes of loose stool will be defined as the presence of at least one stool type 6 or 7 on a given day.

Secondary outcomes

The secondary outcomes will include the effective response rate at other time points, the percentage of patients experiencing 50% reduction in effective response weeks during treatment. A 50% reduction in effective response weeks throughout the treatment duration is defined as the proportion of participants who show effective response in more than half of the weeks during the 6-week treatment period. The IBS Symptom Severity Scale (IBS-SSS), IBS-Quality of Life (IBS-QOL), Patient Health Questionnaire-9 (PHQ-9), Adequate Relief of IBS Symptoms Scale (IBS-AR), Extraintestinal Symptoms Scale, abdominal pain symptoms, bloating, loose stool days, blinding assessment, and the Credibility/Expectancy Questionnaire will also be evaluated as secondary outcomes.

IBS-SSS

The IBS-SSS [31] is a comprehensive assessment scale that evaluates the overall symptoms of IBS, encompassing clinical manifestations and their correlation with patients' quality of life. The scale evaluation includes five domains: the severity of abdominal pain, the duration of abdominal pain, the severity of abdominal distension, satisfaction with defecation, and impact on quality of life. Each domain is scored on a scale from 0 to 100, resulting in a total score ranging from 0 to 500, with high scores indicating worse symptoms. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-QOL

The IBS-QOL [32] scale comprises 34 items and is organized into 8 dimensions:

Dysphoria (DY), Health worry (HW), Body image (BI), Interference with activity (IN), Food avoidance (FA), Social reaction (SR), Sexual (SX) and Relationship (RL). The scores range from 0 to 100, with higher total scores indicating a higher quality of life. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

PHQ-9

The PHQ-9 [33] is a diagnostic instrument used to assess common mental disorders, with scores ranging from 0 to 27. A higher total score indicates a more severe psychological condition. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-AR

The IBS-AR [34] scale includes a dichotomous item that asks patients, "Have your IBS symptoms been adequately relieved during the past week?" This scale will be employed to evaluate symptom relief in individuals with irritable bowel syndrome (IBS). The evaluation time points will be at 1, 2, 3, 4, 5, 6, 8, 10,12,14,16, and 18 weeks after the start of treatment.

Extraintestinal Symptoms Scale

The Extraintestinal Symptoms Scale [35] comprises a rating scale for 15 prevalent symptoms frequently reported as adverse events in clinical drug trials. The 15 symptoms include bad dreams, excessive sleepiness, insomnia, fatigue, inability to concentrate, irritability, dry mouth, headache, weakness, dizziness, joint pain, muscle pain, nasal congestion, skin rash, bruising. Each symptom is scored on a scale of 0-5, with 0 indicating absence and 5 indicating severity. The severity scores for the 15 symptoms are summed to calculate a composite score for each participant, resulting in an overall symptom burden score ranging from 0 to 75. The evaluation time points will be baseline and 6 and 18 weeks after the start of treatment.

Blinding Assessment and Credibility/Expectancy Questionnaire

All participants will be asked the question, "Do you believe you have received traditional acupuncture or modern acupuncture?" for blind assessment during week 1 and week 3. Following the initial treatment, participants will be mandated to complete

the Credibility/Expectancy Questionnaire [36] to evaluate their perceived credibility of the treatment and their expectations. The Credibility/Expectancy Questionnaire consists of two components: the credibility of the treatment and the patients' expectations of the treatment. The aim is to assess whether patients' expectations influence the actual effectiveness of the treatment, and whether their confidence in the treatment predicts treatment adherence and outcomes.

Adverse events

Adverse events, both related and unrelated to acupuncture, will be promptly documented in the RedCap EDC system during both the treatment and follow-up periods. All adverse events will be managed symptomatically by acupuncturists and doctors with relevant specialties. The assessment of the incidence and severity of adverse events will be conducted after the treatment period (week 6) and at the end of the follow-up period (week 18).

Data management

Both paper files and electronic documents will be preserved for at least 5 years after publication. Original data can be accessed by contacting the corresponding author. Patient information will remain anonymous, including name, ID number, and mobile phone number. An electronic Case Report Form (eCRF) will be used for data collection during the trial. Paper defecation diary cards will be provided to participants who do not have easy access to electronic devices. Each center will implement a standardized RedCap EDC system and uniformly printed paper test materials. Independent monitors will monitor the eCRF data in real-time to guarantee the completeness and promptness of data collection, without interfering in the trial. Any changes to the data will be traceable through the eCRF.

Quality assurance

Before the initiation of the study, all trial personnel underwent comprehensive training on the study objectives, patient screening, intervention modalities, and evaluation follow-up, as well as familiarization with the operation of the RedCap EDC system. The trial personnel will maintain all paper documents, such as defecation diary cards and acupuncture record forms. Access permissions for the RedCap EDC system will

vary depending on the roles within the study. A team of monitors will be established to monitor the trial data both online and offline. We will conduct one fixed online monitoring session per month, with untimed checks on the completeness and timeliness of data uploads. When 10% and 90% of participants have been recruited, the monitoring team will carry out fixed offline monitoring. Additionally, if any center encounters irregularities in trial implementation or experiences slow recruitment progress, on-site monitoring will be conducted for that center. The monitoring will encompass all trial procedures, including patient recruitment, intervention implementation, assessment, and data input. The contact information and residential addresses of the trial participants will be recorded, and regular communication will be maintained to enhance participant adherence to the protocol. When participants miss multiple appointments, we will contact them to determine the reasons for their absences.

Sample size

According to the previous research of our group (the results are still unpublished), the effective response rate will be estimated to be 55.9% in the acupuncture group and 38.8% in the sham acupuncture group. We used a two-sided test with α=0.05 and β=0.2. The sample size calculation indicated that each group should have a minimum of 130 effective cases. Considering a dropout rate of 20%, a total of 163 cases need to be recruited for each group, resulting in a total of 326 cases across both groups.

Statistical analysis

The study will utilize SAS 9.3 software for data analysis. Statistical analysis will be performed by an independent statistician who is blinded to group assignments. Continuous data will be presented as either mean ± standard deviation (M±SD) or median and interquartile range, while categorical data will be reported as frequencies (percentages). A two-sided test level of 0.05, with P values of less than 0.05, will be considered to indicate statistical significance.

All analyses will adhere to the intention-to-treat (ITT) protocol, which includes all randomized patients with available baseline information. Missing data will be imputed using multiple imputations. A per-protocol population analysis (PP) of the primary outcome measure will be conducted for participants who completed no less than 80%

of the treatment. Safety analyses will be based on participants who will receive at least one session of treatment.

For the primary outcome, a logistic generalized linear mixed model will be used to test for differences between groups. The secondary outcomes will be compared between groups using the t-test or Wilcoxon rank-sum for continuous data, and the $\chi 2$ test or Fisher's exact tests for categorical data.

Patient and public involvement

None.

Ethics and dissemination

The protocol has obtained approval from the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the medical ethics committees of five hospitals. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) platform (number: ChiCTR2300078321). A written informed consent (*details are provided in the Supplement-Informed Consent Document*) will be obtained from each participant before any study procedure is performed, according to good clinical practice. The findings of this study will be submitted for publication in a peer-reviewed journal.

DISCUSSION

IBS-D is the most prevalent subtype of IBS, characterized by chronic, recurring episodes and comorbid mental health conditions like anxiety and depression, which significantly impact patients' quality of life. [37] A large-scale, multi-center, two-arm, randomized clinical trial is currently being designed to assess the efficacy of acupuncture at sensitized acupoints for IBS-D.

The selection of acupoints plays a crucial role in acupuncture treatment. This study will implement a personalized program for acupoint selection based on the level of acupoint sensitization. In the ancient Chinese medical book, the Medical Classic of the Yellow Emperor, it is documented that excellent therapeutic efficacies can be procured by choosing the acupoints featuring sensitive manifestations such as indurated, nodular and tenderness in the context of acupuncture treatment. In a randomized neuroimaging

trial, 99 patients with chronic neck pain were randomized to either true acupuncture or sham acupuncture. The true acupuncture group and the sham acupuncture group were treated with standard acupuncture treatment at the pain sensitive acupoints and shallow acupuncture at non-acupoints, respectively. Both groups received treatment for 4 weeks. After treatment, sensitive acupoint acupuncture showed a significant improvement in both the severity and duration of pain when compared to the sham acupuncture group. [38] IBS-D is characterized by a range of symptoms, which can vary between individual patients. Therefore, a personalized acupuncture regimen may yield greater efficacy in alleviating IBS symptoms among participants. A study randomly dichotomized 80 patients with IBS-D into a control group and a treatment group. The control group received treatment with Piverium bromide, while the treatment group underwent therapy with Piverium bromide in combination with heat-sensitive moxibustion (a novel form of moxibustion that identifies thermally sensitive acupoints through suspended moxibustion). [39] The results indicated that the treatment group exhibited a significant improvement in IBS-SSS and quality of life when compared with the control group. Lei C et al [40] identified that the sensitive acupoints of IBS-D model rats was the *Dachangshu* (BL 25). Subsequently, the rats were stratified into sensitive and non-sensitive acupoint groups, revealing a significantly enhanced efficacy of electroacupuncture in the sensitive acupoint group compared to the non-sensitive counterpart. In this study, pain sensitization will be utilized as the criterion for acupoint selection due to its prevalence as a manifestation of sensitization. [23] The degree of change in pain threshold will objectively reflect the intensity of acupoint sensitization and may be correlated with the disease state. [41] Additionally, there is a study that has shown individuals with IBS have a lower acupoint pain threshold compared to healthy individuals. [42] However, the current research on the efficacy of sensitive acupoints in IBS patients is predominantly theoretical, with a notable absence of high-quality clinical studies.

This multi-center, RCT adheres to the CONSORT [43] and STRICTA [44] guidelines, showcasing high-quality methodological standards. One major challenge in clinical acupuncture research is establishing an appropriate sham acupuncture control.

Common types of sham acupuncture used in clinical trials include needling insertion at acupuncture points, needling insertion at non-acupuncture points, non-insertion at acupuncture points, and non-insertion at non-acupuncture points. [45] Maintaining blinding in Chinese participants, many of whom have acupuncture experience, is particularly difficult. To address this, the sham acupuncture group will receive shallow needling at non-acupoints, with pain threshold measurements taken. Participants will be separated during treatment to ensure blinding and compliance. The FDA-recommended effective response rate will serve as the primary outcome, offering a more rigorous assessment than the IBS-SSS used in previous studies. Randomization will be conducted using the RedCap EDC system, with computer-generated sequences and restricted access to allocation information to prevent bias. Additionally, all trial personnel will undergo professional training before the trial commences, with independent supervisors overseeing data monitoring and trial implementation to uphold trial integrity.

This study has several limitations. Firstly, due to the distinctive characteristics of acupuncture intervention, implementing blinding for acupuncturists may not be feasible. Secondly, time and resource constraints will only allow for pain threshold measurements to be taken twice for each acupuncturist. Subsequently, patients will receive treatment at the same acupoints for 3 weeks based on the measured data. The stability of higher sensitized acupoints over 3 weeks cannot be guaranteed. Finally, the generalizability of our findings to IBS-D patients outside of China may be limited.

Trial status

This trial is currently recruiting participants.

Authors' contributions

Submitting author: Z-TF; Corresponding author: N-NY; Collaborators (group authorship): Cun-Zhi Liu , Qian-Hua Zheng , Li-Li Chi , Xian-Bao Huang , Ji-Hua Gao , Ya-Wei Xi , Yu Wang , Jing-Wen Yang , Hang Zhou , Yi-Duo Liu.

C-ZL and N-NY proposed and initiated the study; Z-TF, N-NY, C-ZL, J-WY and YW participated in the designing, drafting and revising the manuscript; Q-HZ, L-LC, X-BH, J-HG and Y-WX coordinated the study; C-ZL, Q-HZ, L-LC, X-BH, J-HG and Y-WX sought ethical approval; J-WY, YW ,HZ and Y-DL assisted in manuscript revision. Guarantor:Na-Na Yang

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Competing interests statement

The authors declare that they have no competing interests.

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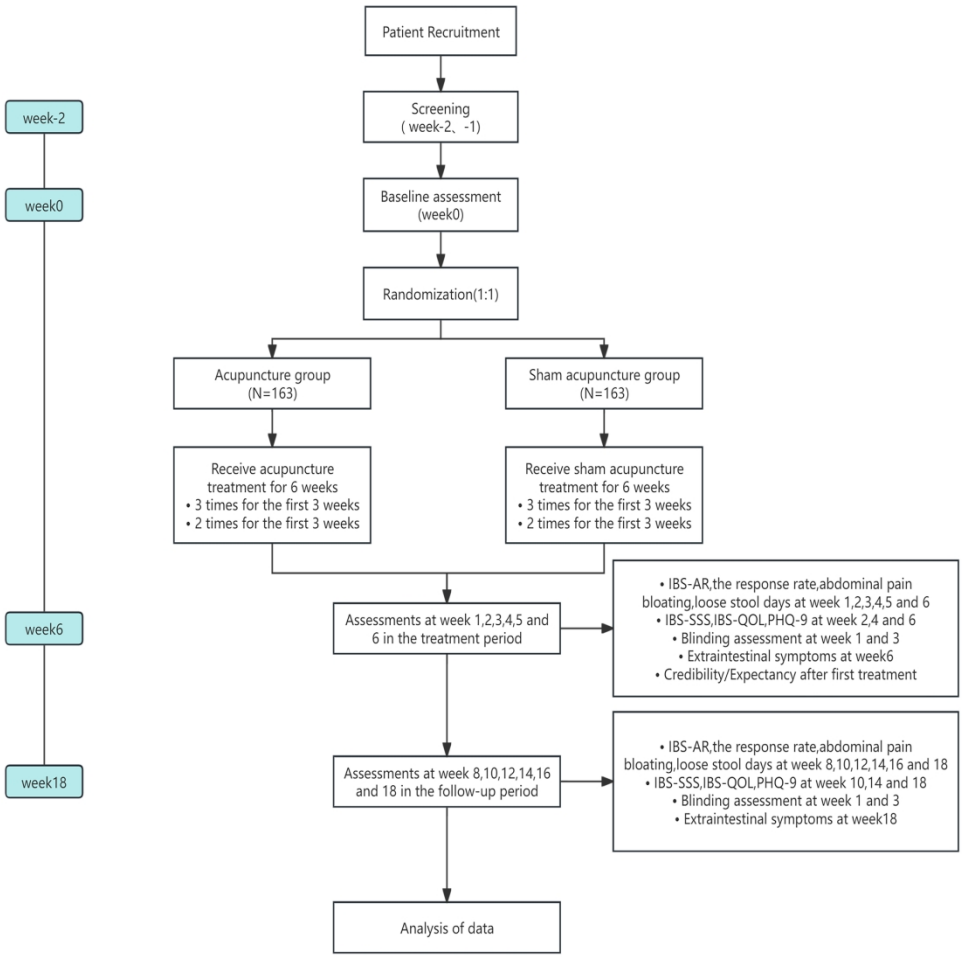
Figure legends

Figure 1 Trial flow chart.

IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

Figure 2. Location of acupoints and non-acupuncture points.

Red dots: location of acupoints in the sensitive acupoints group; blue dots: location of non-acupuncture points in the sham acupuncture group. (Note: This figure is modified based on www.3Dbody.com). (A) Ventral view; (B) Dorsal view; (C) View of the upper extremity; (D) Anterior aspect view of the lower extremity; (E) Lateral view of the lower extremity; (F) Medial aspect view of the lower extremity



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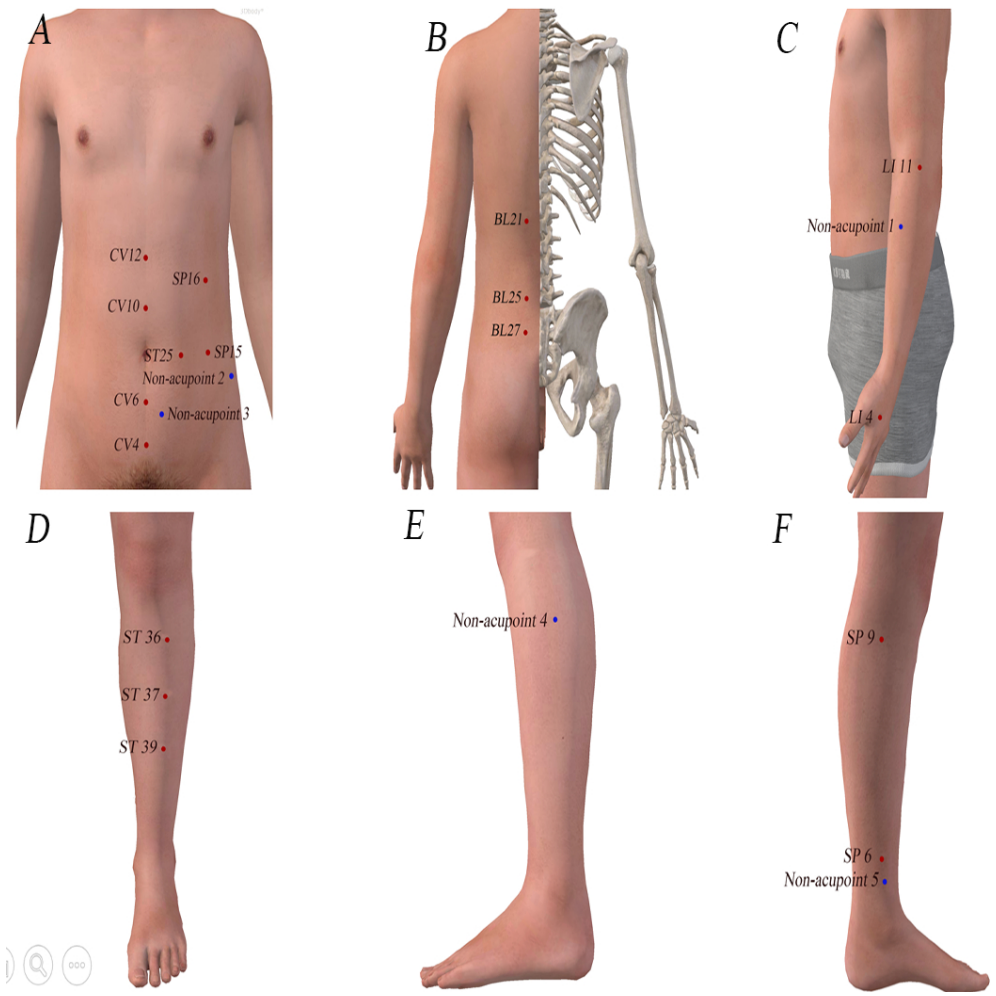
IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

90x90mm (600 x 600 DPI)



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90x90mm (300 x 300 DPI)

Table 1 Time points of treatment assessment

Time point	Screening		Baseline	Treatment							Follow-up				
	Week-2	Week-1	Week 0	Week 1	After first treatment	Week2	Week3	Week4	Week5	Week6	Week8	Week10	Week12	Week14	Week16	Week18
Screening and enrolment																
Eligibility screen	×	×														
Informed consent	×	×														
Randomization			×													
Interventions																
Sensitive acupoints				←						→						
Sham acupuncture				←						→						
Assessments																
The response rate				×		×	×	×	×	×		×	×	×	×	×
Abdominal pain				×		×	×	×	×	×		×	×	×	×	×
Bloating				×		×	×	×	×	×		×	×	×	×	×
Loose stool days				×		×	×	×	×	×		×	×	×	×	×
IBS-AR				×		×	×	×	×	×		×	×	×	×	×
IBS-SSS			×			×		×		×		×		×		×
IBS-QOL			×			×		×		×		×		×		×
PHQ-9			×			×		×		×		×		×		×
Extraintestinal symptoms			×							×						×
Credibility/Expectancy					×											
Blinding assessment				×			×									
Adverse events				×		×	×	×	×	×	×	×	×	×	×	×

Table 2 Acupoints used in the sensitive acupoints group

Acupoint	Location
LI 11 (*Quchi*)	Lateral to the elbow, at the midpoint of the line between LU5(*Chize*) and the lateral epicondyle of the humerus.
LI 4(*Hegu*)	It is located on the dorsum of the hand, between the first and second metacarpal bones, approximately at the midpoint of the radial side of the second metacarpal bone.
ST 25(*Tianshu*)	In the epigastric region, transversely aligned with the umbilicus, 2 cun lateral to the anterior midline.
CV 12(*Zhongwan*)	In the epigastric region, located 4 cun superior to the umbilicus along the anterior midline.
CV 4(*Guanyuan*)	In the hypogastric region, 3 cun below the umbilicus along the anterior midline.
CV 10(*Xiawan*)	In the epigastric region, located 2 cun superior to the umbilicus along the anterior midline.
CV 6(*Qihai*)	In the hypogastric region, 1.5 cun below the umbilicus along the anterior midline.
SP 15(*Daheng*)	In the epigastric region, transversely aligned with the umbilicus, 4 cun lateral to the anterior midline.
SP16(*Fuai*)	In the epigastric region,3 cun above the midpoint of the umbilicus, and 4 cun lateral to the anterior midline.
BL 25(*Dachangshu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the fourth lumbar vertebra.
BL 21(*Weishu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the twelfth thoracic vertebra.
BL 27(*Xiaochangshu*)	The point is located at the sacral region, parallel to the first posterior sacral foramen and 1.5 cun away from the median sacral crest.
ST 36(*Zusanli*)	The point is located on the lateral aspect of the calf, 3 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
ST 37(*Shangjuxu*)	The point is located on the lateral aspect of the calf, 6 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
SP 6(*Sanyinjiao*)	The point is located medially to the calf, 3 cun above the tip of the medial malleolus, and posterior to the medial margin of the tibia.
SP 9(*Yinlingquan*)	The point is located on the medial side of the calf, in the depression formed by the lower margin of the medial condyle of the tibia and the medial margin of the tibia.
ST 39(*Xiajuxu*)	The point is located on the lateral aspect of the calf, 9 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).

Table 3 Acupoints used in the sham acupuncture group

Non-acupoint	Location
Non-acupoint 1	The point is situated on the upper limb, at the midpoint between LU5(*Chize*) and LI7(*Wenliu*).
Non-acupoint 2	The point is located in the abdomen, 2 cun above the anterior superior iliac spine, between the gall bladder meridian and the spleen meridian.
Non-acupoint 3	The point is located in the abdomen, 2 cun below the umbilicus and 1 cun lateral to the anterior midline, between the renal meridian and the gastric meridian.
Non-acupoint 4	The point is located in the lower extremity, on the lateral leg, 3 cun below the GB34 (*Yanglingquan*), between the gall bladder meridian and the bladder meridian.
Non-acupoint 5	The point is located 2 cun above the medial malleolus, on the medial aspect of the tibia, between the liver meridian and the spleen meridian in the lower extremity.

Informed Consent Document • Informed Disclosure Section

Dear Sir/Madam:

You are being invited to participate in a randomized controlled clinical study on ' Optimization of acupuncture acupoint compatibility regimen for irritable bowel syndrome: a randomized controlled clinical trial'. This study aims to optimize the acupoint selection protocol for acupuncture treatment of diarrhea-predominant irritable bowel syndrome.

Before you decide whether to participate in this study, please carefully read the following information, which will help you understand the purpose of the study, the procedures and duration involved, as well as the potential benefits, risks, and discomforts that may result from participation. If you wish, you may also discuss this with your family, friends, or consult your doctor for further clarification to assist you in making an informed decision.

1 Introduction to the Research Project

1.1 Project Title, Researchers, Sponsor, Version Number or Date of Document

We are conducting a trial on acupuncture treatment for diarrhea-predominant irritable bowel syndrome. The principal investigator for this project is Professor Liu Cunzhi from the School of Acupuncture and Tuina, Beijing University of Chinese Medicine. The study is funded by the ' National Key Research and Development Program for the Modernization of Traditional Chinese Medicine (No. 2022YFC3500605)'. (Document Version:, Date:)

1.2 Research Objective

To investigate the therapeutic effect of acupuncture at sensitive acupoints for the treatment of diarrhea-predominant irritable bowel syndrome and to optimize the acupoint selection protocol for acupuncture treatment of this condition.

1.3 Procedures

This study will involve 326 participants with diarrhea-predominant irritable bowel syndrome. A central stratified block randomization method will be used, meaning that after random allocation (similar to a coin toss), you will receive either

traditional acupuncture or modern acupuncture. The selection of acupoints and techniques will differ between the two treatment methods, and the probability of being assigned to either group is the same. Previous studies have shown that both treatment methods are effective. Both groups will receive acupuncture treatment for 6 weeks, with 3 sessions per week during the first 3 weeks and 2 sessions per week during the following 3 weeks. After the treatment period, there will be a 12-week follow-up, making the total duration of the trial 20 weeks. During the trial, participants will need to record their bowel movements and complete periodic assessments using relevant scales. If you experience a severe adverse reaction, significant abdominal pain or diarrhea, use any treatment or medication outside the study protocol, exceed the prescribed emergency medication dosage, or fail to record bowel movements for at least 80% of the scheduled follow-up days, you will be discontinued from the trial. Additionally, if necessary, you may be required to undergo a colonoscopy for a comprehensive understanding of your condition.

1.4 Study Duration and Timeline

Screening will take place over 2 weeks prior to treatment. After the treatment begins, participants will receive 3 sessions per week for the first 3 weeks and 2 sessions per week for the following 3 weeks, for a total of 6 weeks of treatment. There will be a 12-week follow-up, with participants involved in the study for a total of 20 weeks.

1.5 Follow-up Frequency and Procedures

Throughout the trial, in addition to the follow-ups during the treatment period, you will need to attend 6 additional follow-up visits, which will take place during weeks 1 to 12 after the treatment ends. Follow-up will generally involve visits to the hospital for doctor consultations, but can also be conducted via telephone.

1.6 Group Allocation

This project will use a central stratified dynamic block randomization method. After random allocation (similar to a coin toss), you will receive one of two acupuncture treatment protocols, each with distinct methods. The probability of being assigned to either group is the same, and previous studies have shown that both

methods are effective.

2 Research Institution and Personnel Qualifications

The research center include Hebei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Liangxiang Hospital of Fangshan District, Beijing. These institutions are equipped with comprehensive acupuncture treatment platforms and a sufficient team of medical professionals.

The project leader, Professor Liu Cunzhi, has been engaged in acupuncture research and clinical practice for many years. His research focuses on the specific effects of acupoints and their combinations, and he has conducted multi-center clinical trials on conditions such as irritable bowel syndrome, migraine, knee pain, functional dyspepsia, and dementia. Professor Liu has led and participated in several major projects, including the National Key Research and Development Program, the National 973 Program, and the National Natural Science Foundation, and he possesses extensive clinical and research experience. All acupuncturists involved in the trial must hold a Chinese Medicine Practitioner Qualification Certificate issued by the People's Republic of China and have at least 3 years of clinical experience.

3 Potential Benefits of Participating in This Study

This study involves acupuncture intervention, which may help improve abdominal pain and diarrhea symptoms, enhance the participants' quality of life, with minimal adverse reactions. If follow-up completion is satisfactory, you will be offered an additional free acupuncture treatment at the end of the follow-up period. Additionally, we hope that the information gathered from your participation in this study will benefit individuals with similar conditions in the future.

4 Potential Discomforts and Risks to Participants in the Study

Adverse reactions during acupuncture: these may include subcutaneous bruising, hematoma, or a sensation of soreness and fullness after acupuncture treatment. If any of these occur, acupuncture treatment will be paused, and once the adverse reaction

subsides, a decision will be made on whether to continue treatment. A colonoscopy is an invasive procedure that can only be performed if certain conditions are met, and there are risks of infection or damage to the intestinal wall during the procedure.

5 Emergency Procedures in Case of an Urgent Situation During the Trial Treatment

Should you experience any adverse reactions or discomfort during the trial, such as severe abdominal pain or diarrhea, it is crucial that you report them immediately to the research physician. The doctor will provide symptomatic treatment as needed. In the case of fainting due to acupuncture, the treatment will be immediately stopped, all needles will be removed, and you will be asked to lie flat while being kept warm. If minor subcutaneous bleeding occurs, resulting in small bruises, no treatment is generally needed, and the bruising will subside on its own. For more significant local swelling or pain, or larger areas of bruising, cold compresses may be applied to stop the bleeding. If the soreness and fullness after acupuncture is mild, gently massaging the area with your fingers may alleviate it. If severe, aside from massaging, other treatment methods may be used under the guidance of the physician. If either you or your research physician believe you cannot tolerate these adverse reactions, the intervention may be discontinued, and you may be withdrawn from the study. In the case of any study-related injury, you will receive appropriate treatment. All adverse events will be managed symptomatically, and if the acupuncturist is unable to handle the issue, a consultation with the relevant specialist will be arranged.

6 Other Available Treatment Options for the Diseases Involved in the Clinical Trial

You may choose not to participate in this study, and this will not affect your access to standard treatment. Currently, the standard treatment options for your condition include anti- diarrhea medications (such as loperamide), antispasmodics (such as pinaverium bromide), intestinal antibiotics (such as rifaximin), and probiotics (such as lactobacillus). Please take these medications under the guidance of your doctor.

7 Related Costs of Participating in the Trial

The cost of acupuncture treatment and any study-related assessments will be provided by the researchers. Participants who meet the inclusion criteria will receive acupuncture treatment free of charge. Any costs arising from adverse events related to the intervention during the trial will be handled in accordance with relevant laws and regulations. This study does not provide compensation for transportation, lost wages, or other expenses, and no financial rewards will be given.

8 Confidentiality of the Study

All information related to you, including your identity, medical history, condition, physical examination, and laboratory test results, will be kept strictly confidential within the bounds of the law. The researchers, study sponsor's appointed monitors, ethics committee, and the Ministry of Science and Technology project management department are authorized to review your medical records related to this study to verify the authenticity and accuracy of the data collected, but your personal details will not be disclosed. Your name will not appear in any public documents or reports related to this study.

9 Rights of the Participants

Your participation in this study is **completely voluntary**. You have the right to withdraw from the study at any stage without penalty or loss of benefits, and it will not affect the treatment you receive from your doctor. If you decide not to participate in this study or wish to withdraw at any point after the study has begun, please contact your doctor promptly.

Your doctor may terminate your participation in this study without your consent under the following circumstances:

A. For your treatment considerations.

B. If you, as a participant, fail to comply with the study regulations, such as not taking medication as prescribed by the doctor or not attending scheduled assessments.

C. If the study is terminated.

10 Handling of Participant Complaints

If you have any complaints regarding your participation in the study, please contact the Medical Ethics Committee of Beijing University of Chinese Medicine (Phone: 010-53911431).

Informed Consent Form • Consent Signature Page

Participant's Declaration

I have carefully read the 'Participant Information Sheet for Clinical Research' and fully understand the purpose, content, methods, and the potential benefits and risks of participating in this study. The doctor has clearly explained all relevant medical terms, and all the questions I asked have been answered in a clear and understandable manner. I understand that I have the right to refuse participation in the study or to withdraw from it at any time and under any circumstances, and that this will not affect my medical treatment or rights.

My participation in this study is entirely voluntary, and I have given it careful consideration. I understand the therapeutic effects of acupuncture for my condition as well as the potential risks involved. I have received complete and accurate information related to this study. I fully understand and support this clinical research. Without any pressure and with the freedom to make my own choice, I voluntarily agree to participate in this clinical study and cooperate with the research physician, adhering to the prescribed treatment, undergoing physical examinations, and completing this clinical research.

I consent to the Ministry of Science and Technology project management personnel, clinical research auditors, and monitoring staff reviewing my medical records and study data when necessary.

I will receive a signed and dated copy of the informed consent form.

Participant (Signature): Date:

(Or Legal Representative (Signature)) Relationship to the Participant:

Contact Number:

Researcher's Declaration

I declare that I have thoroughly explained the details, procedures, potential risks, and benefits of this study to the participant, and have provided full answers to any questions raised by the participant. The participant has received satisfactory responses and has expressed understanding

Research Physician (Signature): Date:

Contact Number:

BMJ Open

Efficacy of acupuncture at pain sensitive acupoints for diarrhoea-predominant irritable bowel syndrome (IBS-D): protocol of a multicentre, randomized, sham-controlled trial

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Primary Subject Heading:	Gastroenterology and hepatology
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Keywords:	Acupuncture, Irritable Bowel Syndrome, Randomized Controlled Trial

Efficacy of acupuncture at pain sensitive acupoints for diarrhoea-predominant irritable bowel syndrome (IBS-D): protocol of a multicentre, randomized, sham-controlled trial

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ABSTRACT

Introduction: While recent research suggests that acupuncture may offer benefits for individuals with diarrhoea-predominant irritable bowel syndrome (IBS-D), high-quality studies are scarce in this area. We intend to investigate the efficacy and safety of individualized sensitized acupuncture in IBS-D.

Methods and analysis: The study is designed as a large-scale, multicentre, two-arm, randomized clinical trial, involving 326 patients diagnosed with IBS-D. Participants will be randomly allocated into the acupuncture or sham acupuncture groups in a 1:1 ratio. Both groups will undergo 15 sessions over 6 weeks. The primary outcome is the effective response rate at week 6, with secondary outcomes including the effective response rate at alternative time points, the percentage of patients with 3 or more effective response weeks throughout the treatment duration, IBS Symptom Severity Scale, IBS-Quality of Life, Patient Health Questionnaire-9, Adequate Relief of IBS Symptoms Scale, Extraintestinal Symptoms Scale and other symptoms.

Ethics and dissemination: The study protocol has been approved by the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the ethics committees of other participating institutions. Each participant will be required to provide written consent before enrolment. The study results will be submitted for publication in a peer-reviewed journal.

Trial registration: Chinese Clinical Trials Registry, ChiCTR2300078321 (Dec 5, 2023).

Keywords: Acupuncture, Diarrhea-predominant irritable bowel syndrome, Randomized controlled trials, Protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large-sample clinical trial to evaluate the efficacy and safety of acupuncture at sensitive acupoints in patients with diarrhoea-predominant irritable bowel syndrome.
- The treatment program involves a personalized selection of sensitive acupoints based on individual patients' sensitivity levels.
- Methodologic rigor will be applied, including adequate randomization, objective measures, rigorous training of trial personnel, and clear role separation.
- The absence of blinding for the acupuncturists could introduce bias and compromise the validity and reliability of the results.
- Eligible participants will be recruited from five hospitals throughout China, and the findings might have certain limitations when extended to IBS-D patients in other nations.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain with or without abnormal bowel habits. [1] The global prevalence of IBS is estimated to be as high as 11.2%, with a higher prevalence among females and a lower incidence among individuals aged 50 years or older. [2, 3] According to predominant faecal characteristics, IBS can be categorized into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhoea (IBS-D), IBS with mixed symptoms (IBS-M), and IBS Unclassified (IBS-U). IBS-D is the most prevalent, accounting for three-quarters of diagnosed cases. [4-6] Although IBS is not life-threatening, it significantly impacts patients' quality of life and imposes a substantial economic and medical burden on society, with costs in the United States reaching 10 billion dollars. [7]

The primary treatment for IBS-D involves pharmacotherapy, such as utilizing antidiarrheal agents, antispasmodics, and antidepressants as first-line or second-line therapies. However, most medications usually provide only temporary relief for specific symptoms and are associated with a high recurrence rate. [8] An escalating number of IBS patients are seeking out complementary and alternative therapies, and acupuncture is being acknowledged as a pivotal alternative therapy for IBS. A meta-analysis [9] of IBS with 27 randomized controlled trials (RCTs) reveals that acupuncture showed notable effectiveness in alleviating symptoms, superior to certain symptom medications. Recent high-quality RCTs have further substantiated this perspective. Collectively, acupuncture has the potential to alleviate the symptoms and enhance the quality of life for IBS patients compared to both pharmacological interventions and sham acupuncture. [10] Our previous study showed clinically meaningful improvement in IBS-D symptoms. The effective response rates of patients in both the specific acupoints and the nonspecific acupoints group were 46.7%, yet there was no significant difference in the effective response rates when compared with the sham acupuncture group. [11] However, the majority of current studies on acupuncture for IBS-D still yield inconsistent conclusions and lack sufficient methodology. [12-15] MacPherson H [12] randomized 233 IBS participants to receive either a short course of traditional

acupuncture combined with usual care, or usual care alone, with equal distribution between the two groups. The study found that, at three months, the IBS symptom severity (IBS-SSS) scores of participants receiving acupuncture treatment significantly decreased. However, the study has some limitations, including the lack of blinding for participants and the use of the relatively subjective IBS-SSS score as the primary outcome measure. Anthony J. Lembo [14] compared the efficacy of acupuncture and sham acupuncture treatments over six sessions across three weeks in IBS patients. The results indicated no significant differences in symptom improvement between the acupuncture and sham acupuncture groups at the end of the treatment. However, compared to the waitlist control group, both groups showed significant improvements. Although this study included a sham acupuncture control group, it still has limitations, such as a relatively short treatment duration and the use of a subjective primary outcome. At the same time, we observed that in some clinical studies in which the efficacy of acupuncture for IBS was not found, most of them used standardized acupoint selection programs without considering individual patient variation. [15-17] In clinical therapy, acupuncturists typically conduct examinations of acupoints on the patient's body surface before treatment and select sensitive acupoints for acupuncture. Although these patients share the same disease, the acupoint program may be various. Thus, we contend that personalized acupuncture therapy could elevate the efficacy of acupuncture in patients afflicted with IBS.

The precise selection of acupoints is crucial for determining the therapeutic efficacy of acupuncture. Historically, acupuncturists targeted highly sensitive acupoints to achieve optimal clinical effectiveness. The relationship between the disease condition and acupoints is significant, as lesions in internal viscera or deep tissues can cause changes in specific acupoints related to the affected organs. [18] In the diseased state, specific acupoints will demonstrate sensitive conditions. The sensitivity of acupoints is mainly manifested by local skin swelling, heat, and pain, among which the decrease in the pain threshold is the most common. [19] The sensitive acupoints are linked to the clinical effectiveness of acupuncture. The efficacy of treating sensitive acupoints has recently been substantiated by studies encompassing chronic neck pain, bronchial asthma, stable

angina pectoris, knee osteoarthritis, and various other conditions. [20-24] Studies have also shown that patients with gastrointestinal disorders often have sensitive acupoints, particularly those that are sensitive to pain. [25] Pain-sensitive points are regions that react in response to stimulation with the minimum force applied on the skin by external pressure and are characterized by a decrease in the pain threshold. [26]

Based on this, we designed a multicentre randomized controlled clinical trial. This study implements personalized sensitive acupoints acupuncture treatment for IBS-D participants. To adapt to the chronic and functional nature of IBS, an appropriate treatment duration and number of sessions have been designed. The primary outcome for evaluating treatment efficacy is the effective response rate, combining both objective and subjective outcome measures. This study aims to investigate the efficacy of personalized sensitive acupoints acupuncture over 6 weeks (15 sessions) in alleviating abdominal pain and reducing the number of days with loose stool in patients with IBS-D. This study aims to investigate the efficacy and safety of sensitive acupoints acupuncture for treating IBS-D, in order to provide high-quality clinical evidence for acupuncture treatment of IBS-D.

METHODS AND ANALYSIS

Study design

This study is a large-scale, multicentre, two-arm, randomized clinical trial designed to test the efficacy of sensitive acupoint acupuncture treatment for patients with IBS-D. It will test the following hypothesis: 6 weeks of sensitive acupoint acupuncture treatment will result in a better effective response in IBS-D patients compared to sham acupuncture. The trial will be conducted at seven institutions in China: (Ⅰ) Liangxiang Hospital, Fangshan District, Beijing, (Ⅱ) Hospital of the Chengdu University of TCM, (Ⅲ) Affiliated Hospital of Shandong University of Traditional Chinese Medicine, (Ⅳ) Hospital of Jiangxi University of TCM, (Ⅴ) Hebei Provincial Hospital of Traditional Chinese Medicine, (Ⅵ) Yunnan Provincial Hospital of Traditional Chinese Medicine, (Ⅶ) The Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine. Eligible IBS-D patients will be randomly assigned to either the acupuncture group or the sham acupuncture group according to a 1:1 ratio. The trial will consist of

three phases: a 2-week screening phase (weeks 2 and 1), a 6-week treatment phase (weeks 1 to 6), and a 12-week follow-up phase (weeks 7 to 18), totalling 20 weeks. The flow chart of this study is shown in *Figure 1*, and the assessment time point is shown in *Supplement Table 1*. The study protocol was approved by the Medical Ethics Committee of the Beijing University of Chinese Medicine and the Ethics Committee of each research centre before the study commencement. All study personnel will receive unified training on the implementation of the test. The recruitment commenced on 5 December 2023 and is expected to continue until December 2025.

Participants

The subjects will be recruited via the outpatient clinic of the research centre, recruitment advertisements, and WeChat platforms. Participant data will be collected by the REDCap electronic data capture (EDC) system. Participants will be required to maintain a defecation diary throughout a 2-week screening period prior to enrolment. Each participant will sign an informed consent form before randomization.

Inclusion criteria

(Ⅰ)Aged between 18 and 75 years old (including 18 and 75 years old), both male and female;

(Ⅱ) Fulfilled Rome IV diagnostic criteria for IBS-D;

(Ⅲ) The daily defecation diary from the past two weeks indicate that Bristol stool patterns of type 6 or 7 were present for a minimum duration of 4 days, while type 1 or 2 only occurred for a maximum duration of 4 days; Furthermore, the average daily abdominal pain score was equal to or greater than 3 during the previous week;

(Ⅳ) No treatment of acupuncture in the last 6 months.

Exclusion criteria

(Ⅰ)Other subtypes of IBS: IBS-C/ IBS-U/ IBS-M;

(Ⅱ) Inflammatory bowel disease/microscopic colitis/history of celiac disease/Crohn's disease and other organic bowel diseases (a normal results of endoscopy within 2 years are required for those age 50 or older or with the following alarming signs: unexplained weight loss (weight loss equal to or greater than 10% within 3 months), haematochezia other than from haemorrhoids or anal fissures, nocturnal diarrhoea, or family history of

colorectal cancer)

(Ⅲ)Take antidepressants and medications with therapeutic effects on symptoms of irritable bowel syndrome within 2 weeks before treatment, including traditional Chinese medicine or Chinese patent medicine, antidiarrheal agents, antispasmodic agents, intestinal antibiotics, probiotics, etc;

(Ⅳ)Diabetes, thyroid dysfunction, severe acute/chronic organic disease, and kidney or liver disease;

(Ⅴ)History of previous abdominal surgery, excluding appendectomy, haemorrhoidectomy, or polypectomy performed more than 3 months ago;

(Ⅵ)During the period of pregnancy or lactation;

(Ⅶ)History of substance abuse, including alcohol and drug use;

(Ⅷ)Patients enrolled in alternative clinical trials.

The exclusion criteria will apply to individuals who meet one or more of the aforementioned requirements.

Randomization and blinding

In this study, eligible IBS-D patients will be randomly allocated to either the acupuncture group or the sham acupuncture group in a 1:1 ratio by the RedCap EDC system. Randomization will be stratified by recruitment site, with a dynamic block size of 4, 6, or 8. The randomization sequences will be generated by an independent statistician and securely stored within the RedCap EDC system. Before the first acupuncture treatment, the acupuncturist will receive the assigned grouping information through the RedCap EDC system. Different roles within this study will have varying levels of access and permissions to the RedCap EDC system. Only the acupuncturist and their assistant will have access to the participants' allocation information. Participants, recruiters, outcome evaluators, data managers, and statistical analysts will be blinded to the participant's randomization grouping. A sham acupuncture group will be established in this study. Patients will receive treatment in individual cubicles to ensure blinding and are strictly prohibited from engaging in any form of communication during the treatment sessions. A blinding assessment will be performed on participants at the early and mid-treatment stages.

Interventions

The acupuncture group and the sham acupuncture group will be set in this study. Interventions will be conducted by licensed acupuncturists with a minimum of 3 years of clinical experience. Participants will undergo a 6-week acupuncture treatment, with sessions scheduled three times per week for the initial 3 weeks and two times per week for the subsequent 3 weeks, totalling 15 sessions lasting 30 minutes each. Before the study commencement, personnel in different roles will receive specialized training, and only those who have completed the training will be eligible to participate.

During treatment, loperamide (Xi'an Janssen Pharmaceutical Co., LTD.) will be provided to the participant as a contingency medication, administered by a gastroenterologist only in cases of severe and intolerable symptoms like acute abdominal pain. The medications used will be carefully documented throughout the trial, including any non-IBS-related medications.

The participant will be discontinued from the study if any of the following circumstances arise: the patient experiences a serious adverse event, other conditions that impede the outcomes assessment, poor compliance, or the subject expresses unwillingness to continue during the course of the clinical trial. Poor compliance is defined as the use of non-protocol treatments or medications, exceeding the prescribed dosage of rescue medication, or repeatedly missing treatment sessions, which constitutes a serious deviation from the study protocol.

Acupuncture group

In the acupuncture group, acupuncture will be administered at the five high-sensitive acupoints. The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles (Suzhou Huatuo Medical Equipment Co., LTD., 0.30mm×40mm). The manipulation will be performed to achieve *deqi*, with the degree of local acid distension serving as the indicator of successful treatment.

Selection and localization of acupoints repository

After a comprehensive literature review and clinical experience, we have identified 17 acupoints that are frequently used in treating IBS-D(*Figure 2, Supplement Table 2*). [27-9]

[29] The acupoint locations will be determined according to the national standard of the People's Republic of China (GB/T12346-2021), Name and Location of Acupoints.

Assessment of pain threshold at acupoints

The pain threshold will be measured twice at each of the 17 acupoints in a predetermined sequence (upper limbs→abdomen→lower limbs→back) using a Wagner digital force gage (FDX 50; Wagner, Greenwich, CT, USA). If the difference between the two measurements is more than 5 N, a third measurement will be performed, and the pain threshold measured will be averaged.

Identification of intervention acupoints

The acupoints on the abdominal midline, including Zhongwan (CV 12), Xiawan (CV 12), Qihai (CV 6), and Guanyuan (CV 4), will be assessed for pain threshold, with selection of the first two acupoints based on their ranking from low to high.

Bilateral acupoints will be selected based on the ratio of bilateral pain threshold (right/left), with the absolute value of < ratio-1 > being sorted in descending order, and the top 4 acupoints will be chosen.

During the treatment period, the acupoint pain thresholds will be measured once every 3 weeks during the treatment, specifically before the first treatment in the first week and before the first treatment in the fourth week. Acupoints will be adjusted according to the results.

Sham acupuncture group

Five non-acupoints will be selected (*Supplement Table 3*). The acupuncture sites and the hands of the acupuncturist must undergo strict sterilization with 75% alcohol. Acupuncture treatment will utilize disposable sterile acupuncture needles. The shallow needling method will be used to penetrate the skin of the participants. The needle tip will only penetrate 2-3 mm under the skin, without manipulation and without reaching *deqi*.

The pain thresholds of the 5 non-acupoints will also be measured and recorded before the first treatment in the first week and the first treatment in the fourth week.

Outcomes

Primary outcome

The primary outcome will be the effective response rate at week 6. The effective response rate is defined as the percentage of patients with a mean 30% improvement from baseline in the worst abdominal pain and a 50% reduction from baseline in the number of days with loose stools. These criteria align with the recommended outcomes by the Food and Drug Administration (FDA)[30].

The defecation diary will be used to record the participants ' defecation and abdominal pain, bloating, and other symptoms. The worst abdominal pain score in the past 24 hours will be assessed using a numerical rating scale (NRS, on a scale from 0 to 10, with 0 indicating no pain at all and 10 indicating the worst pain the patient could imagine) and the weekly average will be calculated. Episodes of loose stool will be defined as the presence of at least one stool type 6 or 7 on a given day.

Secondary outcomes

The secondary outcomes will include the effective response rate at other time points, and the percentage of patients experiencing 3 or more effective response weeks during treatment. The IBS Symptom Severity Scale (IBS-SSS), IBS-Quality of Life (IBS-QOL), Patient Health Questionnaire-9 (PHQ-9), Adequate Relief of IBS Symptoms Scale (IBS-AR), Extraintestinal Symptoms Scale, abdominal pain symptoms, bloating, loose stool days, blinding assessment, and the Credibility/Expectancy Questionnaire will also be evaluated as secondary outcomes.

IBS-SSS

The IBS-SSS [31] is a comprehensive assessment scale that evaluates the overall symptoms of IBS, encompassing clinical manifestations and their correlation with patients' quality of life. The scale evaluation includes five domains: the severity of abdominal pain, the duration of abdominal pain, the severity of abdominal distension, satisfaction with defecation, and impact on quality of life. Each domain is scored on a scale from 0 to 100, resulting in a total score ranging from 0 to 500, with high scores indicating worse symptoms. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-QOL

The IBS-QOL [32] scale comprises 34 items and is organized into 8 dimensions:

Dysphoria (DY), Health worry (HW), Body image (BI), Interference with activity (IN), Food avoidance (FA), Social reaction (SR), Sexual (SX) and Relationship (RL). The scores range from 0 to 100, with higher total scores indicating a higher quality of life. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

PHQ-9

The PHQ-9 [33] is a diagnostic instrument used to assess common mental disorders, with scores ranging from 0 to 27. A higher total score indicates a more severe psychological condition. The evaluation time points will be baseline and 2, 4, 6, 10, 14, and 18 weeks after the start of treatment.

IBS-AR

The IBS-AR [34] scale includes a dichotomous item that asks patients, "Have your IBS symptoms been adequately relieved during the past week?" This scale will be employed to evaluate symptom relief in individuals with irritable bowel syndrome (IBS). The evaluation time points will be at 1, 2, 3, 4, 5, 6, 8, 10,12,14,16, and 18 weeks after the start of treatment.

Extraintestinal Symptoms Scale

The Extraintestinal Symptoms Scale [35] comprises a rating scale for 15 prevalent symptoms frequently reported as adverse events in clinical drug trials. The 15 symptoms include bad dreams, excessive sleepiness, insomnia, fatigue, inability to concentrate, irritability, dry mouth, headache, weakness, dizziness, joint pain, muscle pain, nasal congestion, skin rash, and bruising. Each symptom is scored on a scale of 0-5, with 0 indicating absence and 5 indicating severity. The severity scores for the 15 symptoms are summed to calculate a composite score for each participant, resulting in an overall symptom burden score ranging from 0 to 75. The evaluation time points will be baseline and 6 and 18 weeks after the start of treatment.

Blinding assessment and Credibility/Expectancy Questionnaire

All participants will be asked the question, "Do you believe you have received traditional acupuncture or modern acupuncture?" for blind assessment during week 1 and week 3. Following the initial treatment, participants will be mandated to complete

the Credibility/Expectancy Questionnaire [36] to evaluate their perceived credibility of the treatment and their expectations. The Credibility/Expectancy Questionnaire consists of two components: the credibility of the treatment and the patients' expectations of the treatment. The aim is to assess whether patients' expectations influence the actual effectiveness of the treatment, and whether their confidence in the treatment predicts treatment adherence and outcomes.

Adverse events

Adverse events, both related and unrelated to acupuncture, will be promptly documented in the RedCap EDC system during both the treatment and follow-up periods. All adverse events will be managed symptomatically by acupuncturists and doctors with relevant specialties. The assessment of the incidence and severity of adverse events will be conducted after the treatment period (week 6) and at the end of the follow-up period (week 18).

Data management

Both paper files and electronic documents will be preserved for at least 5 years after publication. Original data can be accessed by contacting the corresponding author. Patient information will remain anonymous, including name, ID number, and mobile phone number. An electronic Case Report Form (eCRF) will be used for data collection during the trial. Paper defecation diary cards will be provided to participants who do not have easy access to electronic devices. Each centre will implement a standardized RedCap EDC system and uniformly printed paper test materials. Independent monitors will monitor the eCRF data in real time to guarantee the completeness and promptness of data collection, without interfering in the trial. Any changes to the data will be traceable through the eCRF.

Quality assurance

Before the initiation of the study, all trial personnel underwent comprehensive training on the study objectives, patient screening, intervention modalities, and evaluation follow-up, as well as familiarization with the operation of the RedCap EDC system. The trial personnel will maintain all paper documents, such as defecation diary cards and acupuncture record forms. Access permissions for the RedCap EDC system will

vary depending on the roles within the study. A team of monitors will be established to monitor the trial data both online and offline. We will conduct one fixed online monitoring session per month, with untimed checks on the completeness and timeliness of data uploads. When 10% and 90% of participants have been recruited, the monitoring team will carry out fixed offline monitoring. Additionally, if any centre encounters irregularities in trial implementation or experiences slow recruitment progress, on-site monitoring will be conducted for that centre. The monitoring will encompass all trial procedures, including patient recruitment, intervention implementation, assessment, and data input. The contact information and residential addresses of the trial participants will be recorded, and regular communication will be maintained to enhance participant adherence to the protocol. When participants miss multiple appointments, we will contact them to determine the reasons for their absences.

Sample size

According to the previous research of our group (unpublished), the effective response rate will be estimated to be 55.9% in the acupuncture group and 38.8% in the sham acupuncture group. We used a two-sided test with α=0.05 and β=0.2. The sample size calculation indicated that each group should have a minimum of 130 effective cases. Considering a dropout rate of 20%, a total of 163 cases to be recruited for each group, resulting in a total of 326 cases across both groups.

Statistical analysis

The study will utilize SAS 9.3 software for data analysis. Statistical analysis will be performed by an independent statistician who is blinded to group assignments. Continuous data will be presented as either mean ± standard deviation (M±SD) or median and interquartile range, while categorical data will be reported as frequencies (percentages). A two-sided test level of 0.05, with P values of less than 0.05, will be considered to indicate statistical significance.

All analyses will adhere to the intention-to-treat (ITT) protocol, which includes all randomized patients with available baseline information. Missing data will be imputed using multiple imputations. A per-protocol population analysis (PP) of the primary outcome measure will be conducted for participants who completed no less than 80%

of the treatment. Safety analyses will be based on participants who will receive at least one session of treatment.

For the primary outcome, a logistic generalized linear mixed model will be used to test for differences between groups. The secondary outcomes will be compared between groups using the t-test or Wilcoxon rank-sum for continuous data, and the $\chi 2$ test or Fisher's exact tests for categorical data.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

The protocol has obtained approval from the Medical Ethics Committee of Beijing University of Chinese Medicine (project number: 2023BZYLL0102) and the medical ethics committees of five hospitals. This study has been registered on the Chinese Clinical Trial Registry (ChiCTR) platform (number: ChiCTR2300078321). A written informed consent (*Supplement-Informed Consent Document*) will be obtained from each participant before any study procedure is performed, according to good clinical practice. The findings of this study will be submitted for publication in a peer-reviewed journal.

Trial status

This trial is currently recruiting participants. The recruitment commenced on 5 December 2023 and is expected to continue until December 2025.

DISCUSSION

IBS-D is the most prevalent subtype of IBS, characterized by chronic, recurring episodes and comorbid mental health conditions like anxiety and depression, which significantly impact patients' quality of life. [37] A large-scale, multicentre, two-arm, randomized clinical trial is currently being designed to assess the efficacy of acupuncture at sensitized acupoints for IBS-D.

The selection of acupoints plays a crucial role in acupuncture treatment. This study will

implement a personalized program for acupoint selection based on the level of acupoint sensitization. In the ancient Chinese medical book, the Medical Classic of the Yellow Emperor, it is documented that excellent therapeutic efficacies can be procured by choosing the acupoints featuring sensitive manifestations such as induration, nodular and tenderness in the context of acupuncture treatment. In a randomized neuroimaging trial, 99 patients with chronic neck pain were randomized to either true acupuncture or sham acupuncture. The true acupuncture group and the sham acupuncture group were treated with standard acupuncture treatment at the pain-sensitive acupoints and shallow acupuncture at non-acupoints, respectively. Both groups received treatment for 4 weeks. After treatment, sensitive acupoint acupuncture showed a significant improvement in both the severity and duration of pain when compared to the sham acupuncture group. [38] IBS-D is characterized by a range of symptoms, which can vary between individual patients. Therefore, a personalized acupuncture regimen may yield greater efficacy in alleviating IBS symptoms among participants. A study randomly dichotomized 80 patients with IBS-D into a control group and a treatment group. The control group received treatment with Piverium bromide, while the treatment group underwent therapy with Piverium bromide in combination with heat-sensitive moxibustion (a novel form of moxibustion that identifies thermally sensitive acupoints through suspended moxibustion). [39] The results indicated that the treatment group exhibited a significant improvement in IBS-SSS and quality of life when compared with the control group. Lei C [40] identified that the sensitive acupoints of IBS-D model rats was the *Dachangshu* (BL 25). Subsequently, the rats were stratified into sensitive and non-sensitive acupoint groups, revealing a significantly enhanced efficacy of electroacupuncture in the sensitive acupoint group compared to the non-sensitive counterpart. In this study, pain sensitization will be utilized as the criterion for acupoint selection due to its prevalence as a manifestation of sensitization. [23] The degree of change in pain threshold will objectively reflect the intensity of acupoint sensitization and may be correlated with the disease state. [41] Additionally, a study has shown that individuals with IBS have a lower acupoint pain threshold compared to healthy individuals. [42] However, the current research on the efficacy of sensitive acupoints in

IBS patients is predominantly theoretical, with a notable absence of high-quality clinical studies.

The reporting of this multicentre RCT will adhere to the CONSORT [43] and STRICTA [44] guidelines. One major challenge in clinical acupuncture research is establishing an appropriate sham acupuncture control. Common types of sham acupuncture used in clinical trials include needling insertion at acupuncture points, needling insertion at non-acupuncture points, non-insertion at acupuncture points, and non-insertion at non-acupuncture points. [45] Maintaining blinding in Chinese participants, many of whom have acupuncture experience, is particularly difficult. To address this, the sham acupuncture group will receive shallow needling at non-acupoints, with pain threshold measurements taken. Participants will be separated during treatment to ensure blinding and compliance. The FDA-recommended effective response rate will serve as the primary outcome, offering a more rigorous assessment than the IBS-SSS used in previous studies. Randomization will be conducted using the RedCap EDC system, with computer-generated sequences and restricted access to allocation information to prevent bias. Additionally, all trial personnel will undergo professional training before the trial commences, with independent supervisors overseeing data monitoring and trial implementation to uphold trial integrity.

This study has several limitations. Firstly, due to the distinctive characteristics of acupuncture intervention, implementing blinding for acupuncturists may not be feasible. Secondly, time and resource constraints will only allow for pain threshold measurements to be taken twice for each acupuncturist. Subsequently, patients will receive treatment at the same acupoints for 3 weeks based on the measured data. The stability of higher sensitized acupoints over 3 weeks cannot be guaranteed. Finally, the generalizability of our findings to IBS-D patients outside of China may be limited.

Contributors

Submitting author: Z-TF; Corresponding author: N-NY; Collaborators (group authorship): Cun-Zhi Liu , Qian-Hua Zheng , Li-Li Chi , Xian-Bao Huang , Ji-Hua Gao , Ya-Wei Xi , Yu Wang , Jing-Wen Yang , Hang Zhou , Yi-Duo Liu.

C-ZL and N-NY proposed and initiated the study; Z-TF, N-NY, C-ZL, J-WY and YW participated in the designing, drafting and revising the manuscript; Q-HZ, L-LC, X-BH, J-HG and Y-WX coordinated the study; C-ZL, Q-HZ, L-LC, X-BH, J-HG and Y-WX sought ethical approval; J-WY, YW ,HZ and Y-DL assisted in manuscript revision. Guarantor: Na-Na Yang.

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Competing interests

The authors declare that they have no competing interests.

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FIGURE LEGENDS

Figure 1. Trial flowchart

IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

Figure 2. Location of acupoints and non-acupuncture points

Red dots: location of acupoints in the sensitive acupoints group; blue dots: location of non-acupuncture points in the sham acupuncture group. (Note: This figure is modified based on www.3Dbody.com). (A) Ventral view; (B) Dorsal view; (C) View of the upper extremity; (D) Anterior aspect view of the lower extremity; (E) Lateral view of the lower extremity; (F) Medial aspect view of the lower extremity

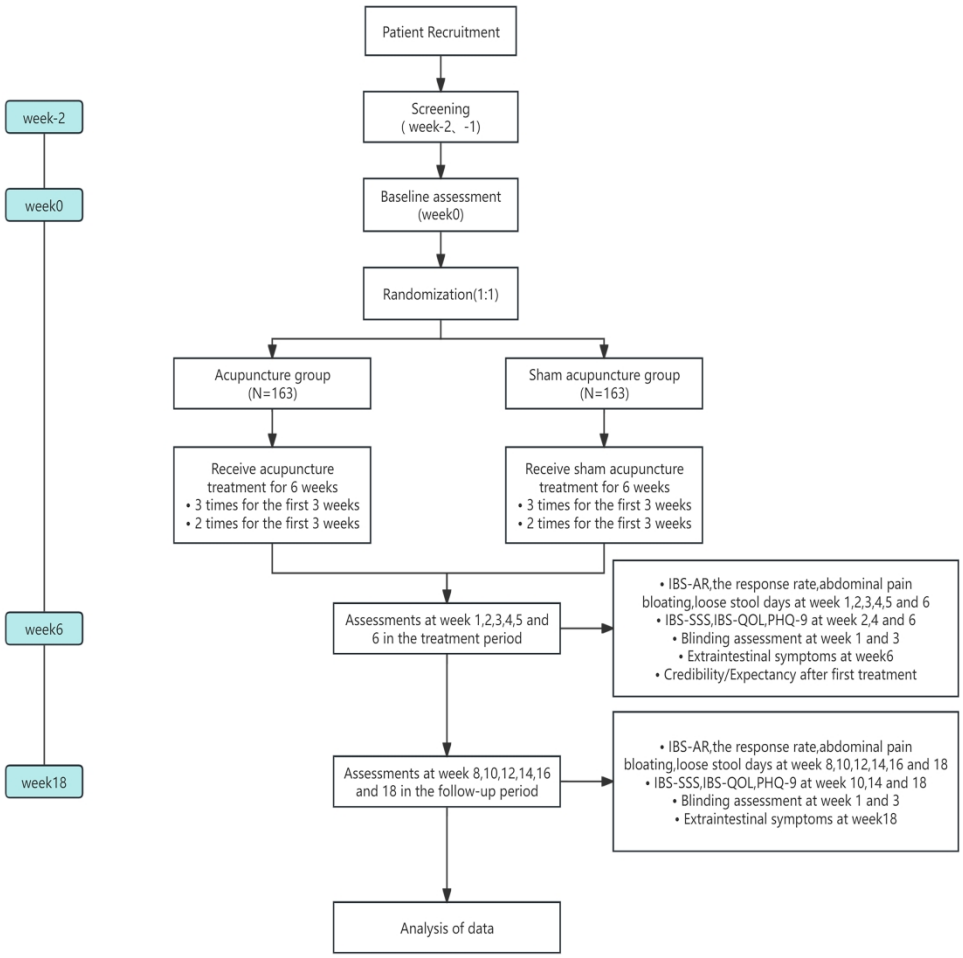

Figure 1 Trial flow chart.
IBS-AR, Adequate Relief of IBS Symptoms Scale; IBS-SSS, IBS Symptom Severity Scale; IBS-QOL, IBS-Quality of Life; PHQ-9, Patient Health Questionnaire-9.

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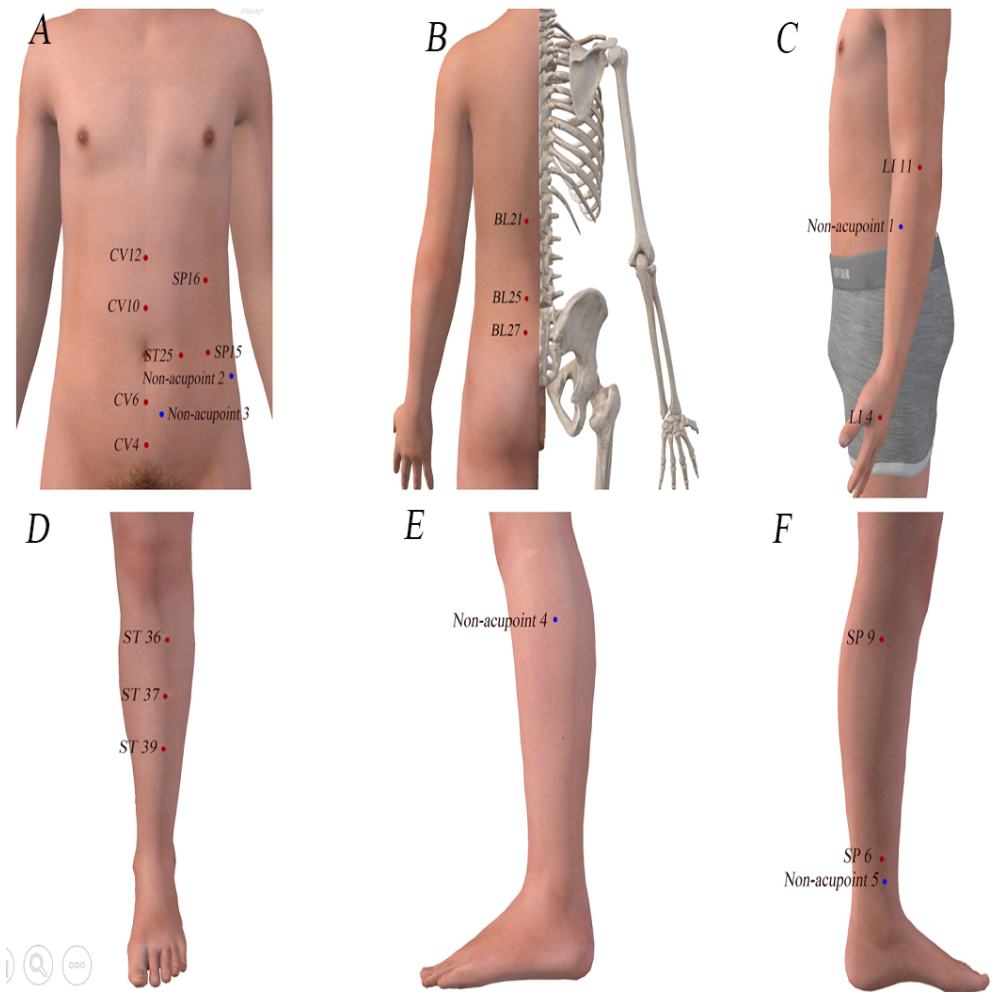

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90x90mm (300 x 300 DPI)

Table 1 Time points of treatment assessment

Time point	Screening		Baseline	Treatment							Follow-up				
	Week-2	Week-1	Week 0	Week 1	After first treatment	Week2	Week3	Week4	Week5	Week6	Week8	Week10	Week12	Week14	Week16	Week18
Screening and enrolment																
Eligibility screen	×	×														
Informed consent	×	×														
Randomization			×													
Interventions																
Sensitive acupoints				←						→						
Sham acupuncture				←						→						
Assessments																
The response rate				×		×	×	×	×	×		×	×	×	×	×
Abdominal pain				×		×	×	×	×	×		×	×	×	×	×
Bloating				×		×	×	×	×	×		×	×	×	×	×
Loose stool days				×		×	×	×	×	×		×	×	×	×	×
IBS-AR				×		×	×	×	×	×		×	×	×	×	×
IBS-SSS			×			×		×		×		×		×		×
IBS-QOL			×			×		×		×		×		×		×
PHQ-9			×			×		×		×		×		×		×
Extraintestinal symptoms			×							×						×
Credibility/Expectancy					×											
Blinding assessment				×			×									
Adverse events				×		×	×	×	×	×	×	×	×	×	×	×

Table 2 Acupoints used in the sensitive acupoints group

Acupoint	Location
LI 11 (*Quchi*)	Lateral to the elbow, at the midpoint of the line between LU5(*Chize*) and the lateral epicondyle of the humerus.
LI 4(*Hegu*)	It is located on the dorsum of the hand, between the first and second metacarpal bones, approximately at the midpoint of the radial side of the second metacarpal bone.
ST 25(*Tianshu*)	In the epigastric region, transversely aligned with the umbilicus, 2 cun lateral to the anterior midline.
CV 12(*Zhongwan*)	In the epigastric region, located 4 cun superior to the umbilicus along the anterior midline.
CV 4(*Guanyuan*)	In the hypogastric region, 3 cun below the umbilicus along the anterior midline.
CV 10(*Xiawan*)	In the epigastric region, located 2 cun superior to the umbilicus along the anterior midline.
CV 6(*Qihai*)	In the hypogastric region, 1.5 cun below the umbilicus along the anterior midline.
SP 15(*Daheng*)	In the epigastric region, transversely aligned with the umbilicus, 4 cun lateral to the anterior midline.
SP16(*Fuai*)	In the epigastric region,3 cun above the midpoint of the umbilicus, and 4 cun lateral to the anterior midline.
BL 25(*Dachangshu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the fourth lumbar vertebra.
BL 21(*Weishu*)	The point is located at the waist, 1.5 cun lateral to the posterior midline, under the spinous process of the twelfth thoracic vertebra.
BL 27(*Xiaochangshu*)	The point is located at the sacral region, parallel to the first posterior sacral foramen and 1.5 cun away from the median sacral crest.
ST 36(*Zusanli*)	The point is located on the lateral aspect of the calf, 3 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
ST 37(*Shangjuxu*)	The point is located on the lateral aspect of the calf, 6 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).
SP 6(*Sanyinjiao*)	The point is located medially to the calf, 3 cun above the tip of the medial malleolus, and posterior to the medial margin of the tibia.
SP 9(*Yinlingquan*)	The point is located on the medial side of the calf, in the depression formed by the lower margin of the medial condyle of the tibia and the medial margin of the tibia.
ST 39(*Xiajuxu*)	The point is located on the lateral aspect of the calf, 9 cun below ST35 (*Dubi*), and along the trajectory between ST35 (*Dubi*) and ST41 (*Jiexi*).

Table 3 Acupoints used in the sham acupuncture group

Non-acupoint	Location
Non-acupoint 1	The point is situated on the upper limb, at the midpoint between LU5(*Chize*) and LI7(*Wenliu*).
Non-acupoint 2	The point is located in the abdomen, 2 cun above the anterior superior iliac spine, between the gall bladder meridian and the spleen meridian.
Non-acupoint 3	The point is located in the abdomen, 2 cun below the umbilicus and 1 cun lateral to the anterior midline, between the renal meridian and the gastric meridian.
Non-acupoint 4	The point is located in the lower extremity, on the lateral leg, 3 cun below the GB34 (*Yanglingquan*), between the gall bladder meridian and the bladder meridian.
Non-acupoint 5	The point is located 2 cun above the medial malleolus, on the medial aspect of the tibia, between the liver meridian and the spleen meridian in the lower extremity.

Informed Consent Document • Informed Disclosure Section

Dear Sir/Madam:

You are being invited to participate in a randomized controlled clinical study on ' Optimization of acupuncture acupoint compatibility regimen for irritable bowel syndrome: a randomized controlled clinical trial'. This study aims to optimize the acupoint selection protocol for acupuncture treatment of diarrhea-predominant irritable bowel syndrome.

Before you decide whether to participate in this study, please carefully read the following information, which will help you understand the purpose of the study, the procedures and duration involved, as well as the potential benefits, risks, and discomforts that may result from participation. If you wish, you may also discuss this with your family, friends, or consult your doctor for further clarification to assist you in making an informed decision.

1 Introduction to the Research Project

1.1 Project Title, Researchers, Sponsor, Version Number or Date of Document

We are conducting a trial on acupuncture treatment for diarrhea-predominant irritable bowel syndrome. The principal investigator for this project is Professor Liu Cunzhi from the School of Acupuncture and Tuina, Beijing University of Chinese Medicine. The study is funded by the ' National Key Research and Development Program for the Modernization of Traditional Chinese Medicine (No. 2022YFC3500605)'. (Document Version:, Date:)

1.2 Research Objective

To investigate the therapeutic effect of acupuncture at sensitive acupoints for the treatment of diarrhea-predominant irritable bowel syndrome and to optimize the acupoint selection protocol for acupuncture treatment of this condition.

1.3 Procedures

This study will involve 326 participants with diarrhea-predominant irritable bowel syndrome. A central stratified block randomization method will be used, meaning that after random allocation (similar to a coin toss), you will receive either

traditional acupuncture or modern acupuncture. The selection of acupoints and techniques will differ between the two treatment methods, and the probability of being assigned to either group is the same. Previous studies have shown that both treatment methods are effective. Both groups will receive acupuncture treatment for 6 weeks, with 3 sessions per week during the first 3 weeks and 2 sessions per week during the following 3 weeks. After the treatment period, there will be a 12-week follow-up, making the total duration of the trial 20 weeks. During the trial, participants will need to record their bowel movements and complete periodic assessments using relevant scales. If you experience a severe adverse reaction, significant abdominal pain or diarrhea, use any treatment or medication outside the study protocol, exceed the prescribed emergency medication dosage, or fail to record bowel movements for at least 80% of the scheduled follow-up days, you will be discontinued from the trial. Additionally, if necessary, you may be required to undergo a colonoscopy for a comprehensive understanding of your condition.

1.4 Study Duration and Timeline

Screening will take place over 2 weeks prior to treatment. After the treatment begins, participants will receive 3 sessions per week for the first 3 weeks and 2 sessions per week for the following 3 weeks, for a total of 6 weeks of treatment. There will be a 12-week follow-up, with participants involved in the study for a total of 20 weeks.

1.5 Follow-up Frequency and Procedures

Throughout the trial, in addition to the follow-ups during the treatment period, you will need to attend 6 additional follow-up visits, which will take place during weeks 1 to 12 after the treatment ends. Follow-up will generally involve visits to the hospital for doctor consultations, but can also be conducted via telephone.

1.6 Group Allocation

This project will use a central stratified dynamic block randomization method. After random allocation (similar to a coin toss), you will receive one of two acupuncture treatment protocols, each with distinct methods. The probability of being assigned to either group is the same, and previous studies have shown that both

methods are effective.

2 Research Institution and Personnel Qualifications

The research center include Hebei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Liangxiang Hospital of Fangshan District, Beijing. These institutions are equipped with comprehensive acupuncture treatment platforms and a sufficient team of medical professionals.

The project leader, Professor Liu Cunzhi, has been engaged in acupuncture research and clinical practice for many years. His research focuses on the specific effects of acupoints and their combinations, and he has conducted multi-center clinical trials on conditions such as irritable bowel syndrome, migraine, knee pain, functional dyspepsia, and dementia. Professor Liu has led and participated in several major projects, including the National Key Research and Development Program, the National 973 Program, and the National Natural Science Foundation, and he possesses extensive clinical and research experience. All acupuncturists involved in the trial must hold a Chinese Medicine Practitioner Qualification Certificate issued by the People's Republic of China and have at least 3 years of clinical experience.

3 Potential Benefits of Participating in This Study

This study involves acupuncture intervention, which may help improve abdominal pain and diarrhea symptoms, enhance the participants' quality of life, with minimal adverse reactions. If follow-up completion is satisfactory, you will be offered an additional free acupuncture treatment at the end of the follow-up period. Additionally, we hope that the information gathered from your participation in this study will benefit individuals with similar conditions in the future.

4 Potential Discomforts and Risks to Participants in the Study

Adverse reactions during acupuncture: these may include subcutaneous bruising, hematoma, or a sensation of soreness and fullness after acupuncture treatment. If any of these occur, acupuncture treatment will be paused, and once the adverse reaction

subsides, a decision will be made on whether to continue treatment. A colonoscopy is an invasive procedure that can only be performed if certain conditions are met, and there are risks of infection or damage to the intestinal wall during the procedure.

5 Emergency Procedures in Case of an Urgent Situation During the Trial Treatment

Should you experience any adverse reactions or discomfort during the trial, such as severe abdominal pain or diarrhea, it is crucial that you report them immediately to the research physician. The doctor will provide symptomatic treatment as needed. In the case of fainting due to acupuncture, the treatment will be immediately stopped, all needles will be removed, and you will be asked to lie flat while being kept warm. If minor subcutaneous bleeding occurs, resulting in small bruises, no treatment is generally needed, and the bruising will subside on its own. For more significant local swelling or pain, or larger areas of bruising, cold compresses may be applied to stop the bleeding. If the soreness and fullness after acupuncture is mild, gently massaging the area with your fingers may alleviate it. If severe, aside from massaging, other treatment methods may be used under the guidance of the physician. If either you or your research physician believe you cannot tolerate these adverse reactions, the intervention may be discontinued, and you may be withdrawn from the study. In the case of any study-related injury, you will receive appropriate treatment. All adverse events will be managed symptomatically, and if the acupuncturist is unable to handle the issue, a consultation with the relevant specialist will be arranged.

6 Other Available Treatment Options for the Diseases Involved in the Clinical Trial

You may choose not to participate in this study, and this will not affect your access to standard treatment. Currently, the standard treatment options for your condition include anti- diarrhea medications (such as loperamide), antispasmodics (such as pinaverium bromide), intestinal antibiotics (such as rifaximin), and probiotics (such as lactobacillus). Please take these medications under the guidance of your doctor.

7 Related Costs of Participating in the Trial

The cost of acupuncture treatment and any study-related assessments will be provided by the researchers. Participants who meet the inclusion criteria will receive acupuncture treatment free of charge. Any costs arising from adverse events related to the intervention during the trial will be handled in accordance with relevant laws and regulations. This study does not provide compensation for transportation, lost wages, or other expenses, and no financial rewards will be given.

8 Confidentiality of the Study

All information related to you, including your identity, medical history, condition, physical examination, and laboratory test results, will be kept strictly confidential within the bounds of the law. The researchers, study sponsor's appointed monitors, ethics committee, and the Ministry of Science and Technology project management department are authorized to review your medical records related to this study to verify the authenticity and accuracy of the data collected, but your personal details will not be disclosed. Your name will not appear in any public documents or reports related to this study.

9 Rights of the Participants

Your participation in this study is **completely voluntary**. You have the right to withdraw from the study at any stage without penalty or loss of benefits, and it will not affect the treatment you receive from your doctor. If you decide not to participate in this study or wish to withdraw at any point after the study has begun, please contact your doctor promptly.

Your doctor may terminate your participation in this study without your consent under the following circumstances:

A. For your treatment considerations.

B. If you, as a participant, fail to comply with the study regulations, such as not taking medication as prescribed by the doctor or not attending scheduled assessments.

C. If the study is terminated.

10 Handling of Participant Complaints

If you have any complaints regarding your participation in the study, please contact the Medical Ethics Committee of Beijing University of Chinese Medicine (Phone: 010-53911431).

Informed Consent Form • Consent Signature Page

Participant's Declaration

I have carefully read the 'Participant Information Sheet for Clinical Research' and fully understand the purpose, content, methods, and the potential benefits and risks of participating in this study. The doctor has clearly explained all relevant medical terms, and all the questions I asked have been answered in a clear and understandable manner. I understand that I have the right to refuse participation in the study or to withdraw from it at any time and under any circumstances, and that this will not affect my medical treatment or rights.

My participation in this study is entirely voluntary, and I have given it careful consideration. I understand the therapeutic effects of acupuncture for my condition as well as the potential risks involved. I have received complete and accurate information related to this study. I fully understand and support this clinical research. Without any pressure and with the freedom to make my own choice, I voluntarily agree to participate in this clinical study and cooperate with the research physician, adhering to the prescribed treatment, undergoing physical examinations, and completing this clinical research.

I consent to the Ministry of Science and Technology project management personnel, clinical research auditors, and monitoring staff reviewing my medical records and study data when necessary.

I will receive a signed and dated copy of the informed consent form.

Participant (Signature): Date:

(Or Legal Representative (Signature)) Relationship to the Participant:

Contact Number:

Researcher's Declaration

I declare that I have thoroughly explained the details, procedures, potential risks, and benefits of this study to the participant, and have provided full answers to any questions raised by the participant. The participant has received satisfactory responses and has expressed understanding

Research Physician (Signature): Date:

Contact Number: