Efficacy of acupuncture based on acupoint combination theory for irritable bowel syndrome: study protocol for a multicenter randomized controlled trial

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Abstract

Background: Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain, diarrhea or constipation, and changes in defecation patterns. No organic disease has been found to explain these symptoms by routine clinical examination. This study aims to investigate the efficacy and safety of acupuncture therapy for IBS patients based on conventional treatments. We also want to explore the optimal acupoint combination recommended for IBS and clarify the clinical advantage of "multi-acupoint co-effect and synergistic effect".

Methods and analysis: A total of 204 eligible patients who meet the Rome IV criteria for IBS will be randomly allocated to receive different acupuncture. Each patient will receive 12 acupuncture treatments over four weeks and will be followed up for four weeks. The primary outcome is the IBS-symptom severity score (IBS-SSS). The secondary outcomes include the Bristol stool form scale (BSFS), the work and social adjustment score (WSAS), the IBS-quality of life (IBS-QOL), self-rating anxiety scale (SAS), and the self-rating depression scale (SDS). Both the primary outcome and the secondary outcomes measures are collected at baseline, 2 weeks, and 4 weeks of the intervention, 6 weeks, and 8 weeks after the intervention.

Ethics and dissemination: The entire project has been approved by the ethics committee of Beijing University of Chinese Medicine (2020BZYLL0903) .

Discussion: This is a multicenter randomized controlled trial for IBS in China. This may shed light on the efficacy of acupuncture as an alternative to IBS. The results of the trial will be disseminated in peer-reviewed publications.

Trial registration: Chinese Clinical Trials Register, ID: ChiCTR2000041215. First registered on 12 December 2020. <http://www.chictr.org.cn/>.

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain, associated with stool abnormalities and changes in stool consistency[1]. Epidemiological data shows that the prevalence of IBS is approximately 11.2% in the world[2], 5-6% in China[3], approximately 10-20% of adults in Western countries[4] and the incidence is increasing year by year, which indicates that IBS is a major public health issue. The main symptoms of IBS are abdominal pain, abdominal distension or abdominal discomfort, which are related to bowel movements or associated with changes in bowel habits such as frequency and/or fecal traits. Irritable bowel syndrome is a common medical condition that significantly alters patient quality of life and presents a series of diagnostic and treatment challenges to the treating provider[5].

It is currently believed that genetic susceptibility, diet, abnormal intestinal motility, visceral hypersensitivity, intestinal inflammation and infection, intestinal flora disorders, neurological and

neuroimmunology, and mental and psychological factors, etc. are all related to the pathogenesis of IBS[6]. Despite many findings and advances in IBS research, the pathophysiology of IBS is still poorly understood with no definitive biomarker, thereby hampering the development of effective therapies for IBS.

Recent studies have shown that there has been a rise in the use of non-pharmacological therapies, including acupuncture[7]. As a traditional Chinese medicine treatment, acupuncture has been widely used to alleviate the resulting pain from IBS. Besides, it is widely accepted as an effective treatment option for gastrointestinal disorders in clinical practice. Acupuncture could be used as an adjunct in clinical settings to improve efficacy. Relative to sham controls, acupuncture showed no superiority for treating IBS, while the advantage over western medicine was significant[8]. Although there has been an increasing number of randomized controlled trials on traditional Chinese medicine treatment of IBS in recent years, few of them have observed adverse reactions, and meta-analysis shows that there is a large heterogeneity among the studies, and no significant difference conclusions can be obtained[9]. Therefore, future high-quality and large-sample-size studies with adequate quantity-effect design need to be conducted. As a result, our team design a multi-center, large-sample, double-blind randomized controlled trial to explore a relatively suitable acupoint combination and provide certain clinical evidence for the optimization of acupuncture treatment of IBS.

Methods/design

This multi-center randomized controlled trial will be conducted at 6 hospitals in China: Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine; Dongfang Hospital Affiliated to Beijing University of Chinese Medicine; Third Hospital Affiliated to Beijing University of Chinese Medicine; Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University; Clinical Medicine College/Teaching Hospital Affiliated to Chengdu University of Traditional Chinese Medicine, and Third Hospital/Acupuncture and Tuina School Affiliated to the Chengdu University of Chinese Medicine. The study has been approved by ethics committees and registered at www.chictr.org.cn on 14 December 2020 (Registration number: ChiCTR2000041215). The eligible patients will be randomly divided into three groups, among participants who will receive 1 week of a wash-out, 12 sessions over 4 weeks of treatment, and 4 weeks of post-treatment follow-up. Outcomes will be assessed at baseline, during the treatment, and at the end of the follow-up. Figure 1 illustrates the flow diagram of the trial.

Patient recruitment

Patients meeting the Rome IV IBS criteria will be primarily recruited from the outpatient centers of the 6 participating hospitals and their surrounding communities. Besides, the mode of recruitments includes advertisements on hospital social Internet media (WeChat subscription, Tik Tok, etc), posters, flyers about this trial, and outpatient clinics. Clinicians will primarily select the patients with suspected IBS for further detailed assessment. One clinical research assistant will identify eligible participants for this trial

according to the following rigorous inclusion and exclusion criteria. All patients will voluntarily agree to participate and sign an informed consent document before randomization.

The Rome IV criteria[10]: (1) Diagnostic time frame: ≥ 3 months of persistent symptoms with symptom onset at least 6 months before diagnosis, ≥ 1 day per week, (2) Symptom description: Abdominal pain, (3) Recurrent association (2 or more) of the following criteria: $\geq$ Related to defecation, $\geq$ Associated with a change in the form of stool, $\geq$ Associated with a change in the frequency of stool.

The following inclusion criteria will be used: (1) adults aged 18–70 years, (2) fulfilled Rome IV criteria for IBS, (3) symptoms are present for ≥ 6 months, (4) baseline IBS-Symptom Severity Score (IBS-SSS) score of 75 points or greater, (5) there was no abnormal occult blood in the past one month, (6) no acupuncture treatment for 3 months preceding the trial, and (7) agreement to participate and signing of the informed consent document.

The exclusion criteria are: (1) past colonoscopy, barium meal fluoroscopy, abdominal ultrasound and other examinations have found organic intestinal diseases (including but not limited to patients with ulcerative colitis and colorectal cancer), (2) the following warning symptoms (one or more): blood in the stool, fecal occult blood test positive, anemia, abdominal mass, ascites, fever, weight loss, (3) those with serious diseases of cardiovascular system, endocrine system and rheumatic immune system that affect the judgment of the condition, (4) those who are unconscious, unable to express subjective symptoms of discomfort and severe mental disorders with a clear diagnosis, (5) pregnancy, lactation, and post-partum period of less than 12 months, and (6) patients who have received acupuncture for IBS in the past three months. Physical examination will be conducted at the time of recruitment to exclude participants with serious diseases not suitable for this trial.

Randomization and Blinding

A blocked randomization sequence for multicenter will be generated by an independent professional statistician (Linkermed Tech Co., Ltd), using Statistical Analysis System software. And all eligible participants will be randomly stratified into acupuncture group A or acupuncture group B or the control group in a 1:1:1 ratio with a central web-based randomization system. Outcome evaluators and statisticians will not participate in the treatment and conduct outcome evaluation and statistical analysis independently. Both patients and assistants will be blind to group assignments. However, due to the nature of acupuncture, the acupuncturist who provides the intervention is not blinded. To minimize the known bias sources, the location of the acupuncture points and manipulation of needles are similar in acupuncture group A or acupuncture group B or the control group, thereby optimizing the blinding of subjects.

Interventions

In order to ensure the safety and proper operation of acupuncture, all the acupuncturists will participate in the standard operation process (SOP) of the skin disinfection, location acupoints, fundamental puncture and needles manipulations before the trials.

And treatments will be performed by licensed acupuncturists who have at least 3 years of experience in acupuncture. Acupuncture will be discontinued if the patients suffer from any cases of adverse event (AE) after acupuncture. The stages of research is shown in figure 2. The schedule of enrolment, interventions, assessments, and participant visits is shown in figure 3.

Treatment as usual (TAU)

TAU is defined as the continuation of current therapeutic agents prescribed by a general practitioner or gastroenterologist. All patients will continue treatment as usual during the study period. Any changes in personal medication will be recorded on a diary card.

The experimental group and the control group

Patients allocated to either the experimental group or the control group will be taken acupuncture treatment three times a week for 4 weeks for a total of 12 treatment sessions, with disposable and sterile acupuncture needles (length:25-40mm, diameter:0.30mm; Huatuo, Suzhou, China). Based on traditional Chinese medicine theory and our clinical experience, the prespecified acupoints used in the control group include bilateral *Tianshu (ST25)*, *Shangjuxu (ST37)*, *Neiguan (PC6)*, *Zusanli (ST36)*.The prespecified acupoints used in experimental group A included bilateral *Tianshu (ST25)*, *Shangjuxu (ST37)*, *Neiguan (PC6)*. The prespecified acupoints used in experimental group B included bilateral *Tianshu (ST25)*, *Shangjuxu (ST37)* , *Zusanli (ST36)* (see table 1-3 and figure 4).

The exact location and depth of needling for each point will be determined based on the 2006 People’s Republic of China National Standard: The Name and Location of Acupoints (GB/T 12346-2006)[11]. After insertion, all points will be manually stimulated by twirling and lifting the needle every 10-min to elicit “deqi”, which is characterized by distention, soreness, numbness, etc. And the needles will be retained for 30-min.

Table 1 Locations of acupoints in the control group.

Acupoints	Locations
Tianshu (ST25)	On the same level of the umbilicus, and 2 cun* lateral to the anterior midline
Shangjuxu (ST37)	6 cun directly below Dubi (ST35), and one finger-breadth lateral to the anterior border of the tibia
Neiguan (PC6)	On the line joining Daling (PC7) and Quze (PC3), between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist
Zusanli (ST36)	3 cun directly below Dubi (ST35), and one finger-breadth lateral to the anterior border of the tibia

*1 cun (≈ 20 mm) is defined as the width of the interphalangeal joint of the patient's thumb

Table 2 Locations of acupoints in experiment group A.

Acupoints	Locations
Tianshu (ST25)	On the same level of the umbilicus, and 2 cun* lateral to the anterior midline
Shangjuxu (ST37)	6 cun directly below Dubi (ST35), and one finger-breadth lateral to the anterior border of the tibia
Neiguan (PC6)	On the line joining Daling (PC7) and Quze (PC3), between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist

*1 cun (≈ 20 mm) is defined as the width of the interphalangeal joint of the patient's thumb

Table 3 Locations of acupoints in experiment group B.

Acupoints	Locations
Tianshu (ST25)	On the same level of the umbilicus, and 2 cun* lateral to the anterior midline
Shangjuxu (ST37)	6 cun directly below Dubi (ST35), and one finger-breadth lateral to the anterior border of the tibia
Zusanli (ST36)	3 cun directly below Dubi (ST35), and one finger-breadth lateral to the anterior border of the tibia

*1 cun (≈ 20 mm) is defined as the width of the interphalangeal joint of the patient's thumb

Outcomes

Primary outcome

IBS symptom severity score (IBS-SSS)

A number of questionnaires exist to assist diagnosis and assessment of severity of the disease. One of these is the irritable bowel syndrome-severity scoring system (IBS-SSS). The IBS-SSS was validated 1997 in its English version[12]. The questionnaire is scored from 0 to 500 and is composed of five 100-point scales that measure the severity of pain (IBS-SSS1), frequency of abdominal pain (IBS-SSS2), the severity of abdominal distention (IBS-SSS3), satisfaction with bowel habits (IBS-SSS4), and disruption in life quality (IBS-SSS5). The scores are classified into normal (< 75), mild IBS case (75–175), moderate IBS case (175–300), and severe IBS case (> 300), which will be used as the primary outcome of this trial. IBS-SSS is assessed at baseline, 2, 4, 6 and 8 weeks.

Secondary outcomes

Bristol Stool Form Scale

The Bristol Stool Form Scale (BSFS) is a 7-point scale used extensively in clinical practice and research for stool form measurement[13]. In this trial, participants will be asked to record the type and score of defecations in a week. The scores obtained from Bristol scale will be assessed at baseline, weeks 2, 4, 6 and 8.

Work and Social Adjustment Scale (WSAS)

The Work and Social Adjustment Scale (WSAS) is designed to measure patients' perceived functional impairment associated with a health problem[14]. The WSAS will be assessed at baseline, weeks 2, 4, 6 and 8 using 5-domain scale with a total possible score of 40, of each item scores 0 (not affected) to 8 (severely affected), respectively.

IBS-Quality of Life (IBS-QOL)

The IBS-QOL items demonstrate very good construct validity and the ability to detect changes due to treatment effects[15]. The questionnaire consists of 34 items. Each item includes a 5-point response scale. Patients will complete questionnaires at baseline, 2 weeks, and 4 weeks after treatment. Then total scores of each item will be calculated and analyzed with higher scores suggestive of better QOL.

Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS)

Self-rating Anxiety Scale (SAS) is a norm-referenced scale that enjoys widespread use as a screener for anxiety disorders[16]. Self-rating Depression Scale (SDS) is an established norm-referenced screening

measure used to identify the presence of depressive disorders in adults[17]. IBS-M is more likely to be associated with a higher level of depression and anxiety, and the prevalence of depression and anxiety in IBS-C is highest. Psychological screening and appropriate psychotherapy are needed for patients with IBS-C, IBS-D, and IBS-M[18]. Therefore, anxiety and depression symptoms will be assessed using SAS and SDS at baseline, Week 2, and Week 4. Higher scores indicate higher levels of anxiety and depression.

Blinding assessment

To test the patient-blinding effects, all patients will be asked to guess which group they have received at the end of the first treatment session and the twelfth treatment session.

Safety evaluation

The research assistant is required to document all the AEs on the Case Report Form (CRF), including information such as time of occurrence, severity, duration, measurement, management, and outcome. During the trial, adverse events will be monitored during the 4 weeks of treatment and next 4 weeks follow-up. The common side effects of acupuncture include subcutaneous hematoma, local bleeding, skin bruising, pruritus or persistent pain at the acupuncture site, muscle spasm, dizziness, and so on. In the event of a serious adverse event (SAE), the necessary action will be taken immediately for the subject's safety. The Department of Acupuncture and Moxibustion of the six above-mentioned hospitals will be responsible for the treatment of all AES respectively.

Sample size and statistical analysis

Based on previous clinical experience, we anticipate an improvement of 30 points in experiment group A and experiment group B, 15 points in the control group on the IBS-SSS. The standard deviation is set at 10, and the ratio among the experiment group A, experiment group B and control group C is 1:1:1. The sample size is calculated with 15% type II error rate (80% power) and 5% type I error. The superiority trial will be adopted to minimize of the three groups' difference, and a 10-point is expected. In total, 177 (59 patients in each group) is estimated. Allowing for 10% loss to follow-up, the sample size expands to 68 patients in each group.

All analyses will be performed using the intent-to-treat (ITT) and the per-protocol (PP) population. ITT requires all participants who receives baseline assessment of primary outcome and at least 1 acupuncture session. Missing values will be imputed through the multiple imputation method. Whereas the PP population is usually defined as patients who completing at least 80% of the treatment protocol without major protocol violations. The primary outcome will be assessed using analysis of covariance (ANCOVA) and adjusted for baseline total IBS-SSS. For other secondary outcomes: continuous variables will be analyzed using the Student's t-test or Wilcoxon rank-sum test, and data will be represented as the mean $\pm$ SD or median; Categorical variables will be calculated using Fisher's exact test or Wilcoxon rank-

sum test, and data will be represented by frequency (percentage). In terms of efficacy factors, other covariates such as age, gender, disease duration, conventional pharmacological agent classification and so on will be considered for further revision. The differences in blinding and adverse events between the groups will be compared using the chi-square test. Meanwhile, we decide to carry out subgroup analysis based on patients with IBS subtypes, avoiding a heterogeneous patient population which may affect the efficacy results.

Statistical analysis of all data in this study will be performed by a specialized third-party statistician evaluation. SAS, version 8.2 statistical software (SAS Institute Inc) will be used for data analysis. A two-sided $P < 0.05$ is considered statistically significant.

Data management and quality control

To ensure the objectivity of the data, the data of individual participants will not be disclosed externally. All researchers will receive training on data management. Data input and management will be carried out by the data management staff of the Chinese Academy of Chinese Medical Sciences using the database software clinical trial data management system. The electronic case report form (e CRF) will be designed to collect all clinical observations of each participant before recruitment. The research assistant is responsible for verifying the accuracy and completeness of the data to prevent any errors, omissions or items that need to be changed or clarified. After the research is completed, the data administrator will implement data lock. All paper documents and electronic data will be kept for 5 years after publication and will be destroyed afterwards.

In order to ensure the quality of the trial, prespecified SOP including recruitment and screening of participants, randomization, laboratory detection results, intervention, details in filling CRF, assessment of outcomes, data management, and AEs of acupuncture will be unified trained through multi-centers internal study for consistency of results, respectively. In addition, we will set up a data and security monitoring board, an independent advisory group to review and explain the data generated by the research, and will hold meetings every three months to report on the progress of the research. Each amendment of the protocol conforms to the GCP principles and maintains ethical standards of the RCT.

Patients and public involvement

Patients in this trial will not be involved in the design or conduct of the study or the outcome assessments. However, we are planning to disseminate our research to the participants and the public, such as publicizing our research in hospital social Internet media (WeChat subscription, Tik Tok app) and various academic lectures.

Ethics and dissemination

This study complies with the principles of the Declaration of Helsinki and relevant ethical guidelines. The entire project has been approved by the ethics committee of Beijing University of Chinese Medicine (ID:2020BZYL0903). Written informed consent will be obtained from patients before enrolment in the study. The outcomes of the trial will be disseminated through peer-reviewed publications.

Discussion

Irritable bowel syndrome (IBS) is a common non-organic gastrointestinal disorder. However, the etiology of the disease is indefinite and there is no effective treatment. IBS is a large economic burden to both the patients themselves and society which could adversely affect the living quality, even though it does not increase mortality.

As a traditional Chinese medicine external treatment method, acupuncture is characterized by simple operation, significant treatment effect, and few side effects. Acupuncture has been widely used in treating Diarrhea Predominant Irritable Bowel Syndrome (IBS-D)[19]. Compared with routine pharmacotherapies and placebo, acupuncture and cognitive-behavioral therapy (CBT) had better efficacy in relieving IBS symptoms. Based on the SUCRA values, acupuncture ranked first in improving overall clinical efficacy and avoiding adverse effects[20]. Acupuncture produced a more significant effect than loperamide in weekly defecation. Compared with dicetel, acupuncture showed more effectiveness in the IBS Symptom Severity Scale. Besides, compared to dicetel and trimebutine maleate, acupuncture also showed more effectiveness at total efficiency. Acupuncture treatment can improve the clinical effectiveness of IBS-D or FD, with great safety, but the conclusions need to be further verified through the higher quality of evidence[21]. Acupuncture and electro-acupuncture (low/very low-level evidence) may have a benefit for constipation. The next 20 years should be exciting in the field as higher-level studies are performed[22].

Acupoint combination, which is based on traditional Chinese medicine theories, is now widely used in clinical treatment. From the perspective of traditional Chinese medicine, the combination of acupoints based on syndrome differentiation can integrate the specific effects of different acupoints to produce synergistic effects for better clinical efficacy. Hence, acupoint combination is considered to be an important part of acupuncture prescription and the basis of acupuncture manipulation.

The use of acupoints in combination rather than a single acupoint is often the preferred treatment. Acupoint combination therapy based on clinical experience has a better curative effect and wider therapeutic scope. As the classic acupoint combination, the combination of the He and Mu acupoints has been proven effective and has a synergistic effect on functional dyspepsia[23]. Different acupoint combinations have specific synergistic effects that can be applied to relevant diseases. Therefore, the use of the most appropriate acupoint combination plays a critical role in the therapeutic effects of acupuncture. However, the efficacy of the acupoint combination should be investigated further in clinical trials due to the lack of a clear scientific explanation. As a consequence, we believe that a multicenter randomized controlled clinical trial that describes the different acupoint combination of treating IBS is needed to find some clues for providing clinical acupoint combination [24].

Based on previous research and our previous review, the basic acupoints that play an important role in relieving diarrhea symptoms are *Tianshu (ST25)*, *Zusanli (ST36)*, and *Shangjuxu (ST37)*[25]. Acupuncture highlights the specific functions of acupoints in the treatment of psychosomatic diseases. Clinical evidence shows that *Neiguan (PC6)* can improve anxiety symptoms very well[26]. Therefore, the selected acupoints of *Tianshu (ST25)*, *Zusanli (ST36)*, *Shangjuxu (ST37)*, and *Neiguan (PC6)* in this experiment not only accord with the principle of "treatment based on syndrome differentiation" in traditional Chinese medicine, but also accord with the clinical practice guidelines in China. Therefore, there is an urgent need for a large sample, multi-center randomized controlled trial to evaluate the efficacy of acupoint combination in improving IBS symptoms within an evidence-based medicine framework.

This study aims to evaluate the efficacy and safety of acupuncture treatment for IBS by comparing different groups of acupoints. Based on conventional treatment, with *Tianshu (ST25)* and *Shangjuxu (ST37)* as the basic prescriptions, comparing *Tianshu (ST25)* and *Shangjuxu (ST37)* with *Neiguan (PC6)* or *Tianshu (ST25)* and *Shangjuxu (ST37)* with *Zusanli (ST36)* for the treatment of IBS clinical effect value, we want to clarify the clinical advantage of "multi-acupoint co-effect and synergistic effect". The findings of the study will provide the optimal acupoint combination and high quality clinical evidence for the compatibility of different acupoints in the treatment of IBS, facilitating clinical practice and further scientific studies.

Nevertheless, there are still limitations in this study that are worth noting. Firstly, the primary outcome measure is the subjective rating scale, which lacks objective evidence to directly support the effectiveness of a particular treatment. Secondly, the drop-out rate is likely to be higher at the end of the 6-week treatment followed by a 3-month follow-up. To reduce potential dropouts, we developed guidelines and training for researchers and established good communication relationships with participants.

In conclusion, we hope that the results of this study not only provide more reliable clinical evidence for the efficacy and safety of acupuncture in the treatment of irritable bowel syndrome but also explore the value of clinical acupoint combination guidelines in irritable bowel syndrome.

Abbreviations

IBS: Irritable bowel syndrome; IBS-SSS: IBS-symptom severity score; BSFS: Bristol stool form scale; WSAS: the work and social adjustment score; IBS-QOL: the IBS-quality of life; SAS: self-rating anxiety scale; SDS : the self-rating depression scale; AE : adverse event; SOP: standard operation process; TAU: Treatment as usual; CRF: Case Report Form; SAE: serious adverse event; IBS-D: Diarrhea Predominant Irritable Bowel syndrome; CBT: cognitive-behavioral therapy; FD: functional disease.

Declarations

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Availability of data and materials

After the study is completed, all relevant data will be shared from the corresponding author on a reasonable request.

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Ethics approval and consent to participate

This study protocol and informed consent materials have been approved by the Ethics Committee of Beijing University of Chinese Medicine; Approved No. of the Ethics Committee: 2020BZYLL0903.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Authors' contributions

ZGL is the principal investigator and takes responsibility for the study and the manuscript. JWS, MLS, and DL are co-first authors. JWS, MLS, DL, HZ, SGY, and JZ were involved in the conception, design, and critical revision for this study protocol. HML, JXG, RDX, XW, YH, HXL, XF and SHS are responsible for recruiting subjects and assessment. ZGL sought funding and ethical approval and helped with its implementation. ZGL is responsible for revising the manuscript. All authors read and approved the final manuscript.

Trial Status

This trial is currently in the preparation phase. No patient was involved.

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Figures

Figure 1

Flow Diagram

Figure 2

Stages of research *0, 2, 4, 6 and 8 respectively represent the first, second and third evaluation time points and the data of the week before this time point is used for each evaluation time point.

The research phase	baseline	Treatment period					follow-up period	
assessment	first	second	third	fourth	fifth	sixth	seventh	
time	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	
Clinical therapy								
confirmed case inclusion	√							
sign informed Consent	√							
vital signs	√							
past medical history/ treatment history	√							
concomitant disease/medication	√		√		√	√	√	
evaluation of acupuncture and moxibustion expectation value	√							
Safety check								
blood routine tests	√							
urine routines	√							
stool routine examination	√							
electrocardiograph	√							
hepatic and renal function	√							
Therapeutic effect evaluation								
IBS-SSS	√		√		√	√	√	
assessment of adequate relief of IBS symptoms		√	√	√	√			
the frequency of defecation weekly	√		√		√	√	√	
Bristol Stool form Scale	√		√		√	√	√	
WSAS	√		√		√	√	√	
IBS-QOL	√		√		√			
SAS	√		√		√			
SDS	√		√		√			
Test evaluation								
blinded evaluation		√			√			
evaluation of treatment satisfaction					√			
safety assessment of acupuncture			√		√			
adverse event assessment					√			
safety evaluation								√
compliance evaluation					√			√
Work after completion of test cases								
the person in charge of the sub-center reviews the medical records	Within one week after the observation, the observation contents shall be reviewed and signed by the person in charge and recorded electronically							
the inspector reviews medical records	The supervisor set up by the project undertaking unit regularly monitors and reviews the project							
inspectors review medical records	The project quality supervision Committee shall set up inspectors to audit all CRFS							

Figure 3

Schedule of enrollment, intervention, and assessments of this study protocol.

Figure 4

Locations of acupoints (from 3Dbody anatomy).