Efficacy and safety of mild-warm moxibustion in treating diarrhea-predominant irritable bowel syndrome (spleen deficiency and dampness excess syndrome): a study protocol for a randomized controlled trial

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Author contributions
Yun-Yi Chen and Jing Gu developed the idea for the study. Yun-Yi Chen, Jing Gu, Hua Huang, Yu-Hui Wang and Li-Ying Fang performed the research; Yun-Yi Chen wrote original draft the paper; Qian Fan analyzed the data analysis; Li-Jiang Ji provided assistance in the writing of the article and improved the quality of the paper.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
IBS, Irritable bowel syndrome; IBS-QOL, Irritable Bowel Syndrome-Quality of Life; RCT, randomized controlled trial; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; SP, substance P; IBS-M, mixed-type IBS; IBS-U, unsubtyped IBS; SP, substance P; 5S, somatostatin; 5-HT, 5-hydroxytryptamine; SFDA, State Food and Drug Administration; CRF, case report form; IBS-SSS, Irritable Bowel Syndrome-Symptom Severity Scale.

Citation

Abstract
Background: Irritable bowel syndrome (IBS) is a disorder of bowel function, and diarrhea-predominant irritable bowel syndrome (IBS-D) is the most common. The current treatment for IBS-D is focused on improving patients’ gastrointestinal-related symptoms, but there are limitations such as unstable effects and adverse drug reactions. Acupuncture and moxibustion exerts advantages in treating IBS-D. They include several forms, of which moxibustion is one of the most commonly used. And moxibustion is a common way used in treating IBS-D, but there is a lack of relevant evidence-based medical research data. This protocol aims to compare the efficacy of moxibustion (mild-warm moxibustion) in treating IBS-D (spleen deficiency and dampness excess syndrome) with the first-line treatment.

Methods: In this prospective, parallel, randomized controlled trial (RCT) protocol, patients will be randomly allocated for 4-week treatment or control therapies and then 4-week follow-up in both groups. We will use Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS) score, Irritable Bowel Syndrome-Quality of Life (IBS-QOL) score, serum brain-gut peptide levels, and traditional Chinese medicine (TCM) syndrome scale score to produce more evidence on IBS-D treatment with moxibustion. Finally, we will use SPSS 22.0 software to statistically analyze the data. Discussion: Mild-warm moxibustion is a complementary alternative therapy that fits with the pathogenesis of IBS-D. We hope to see more clinical evidence for mild-warm moxibustion against IBS-D that this RCT supported.

Keywords: IBS-D; mild-warm moxibustion; protocol; complementary alternative therapy; randomized controlled trial
Background

As a disorder of bowel function, irritable bowel syndrome (IBS) mainly causes pain in abdomen, diarrhea, constipation and abdominal distention [1]. Globally, IBS’ prevalence is approximately 11%, ranging from 9% to 23%, but varies widely by country depending on diagnostic criteria, gender and age, 7.0% in Southeast Asia and 21.0% in South America [2], and in Asian countries is 5% to 10% [3]. Subtypes with different symptoms of IBS include: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed-type IBS (IBS-M), and unsubtyped IBS (IBS-U) [4], and IBS-D contributes the most [5], representing about 45% or more of all cases [6], which is about 4.60% to 5.67% in China, with a yearly increasing trend [7].

IBS-D has a long and recurrent course, with no organic changes on ancillary examinations or colonoscopy, and the pathogenesis is associated with altered gastrointestinal dynamics, abnormal brain-gut axis regulation, altered fecal microbiota, bacterial overgrowth, food sensitivities, carbohydrate malabsorption and intestinal inflammation [8]. Clinical treatment of IBS-D is often performed by a combination of antispasmodics, antidiarrheal drugs, probiotics, antidepressants, and other drugs to improve patients’ gastrointestinal-related symptoms [8, 9]. Although traditional Western medicine treatment modalities can alleviate symptoms, they have disadvantages such as varying degrees of side effects and unstable effects [7, 10].

The advantages of Chinese medicine therapies, especially acupuncture and moxibustion, in treating IBS-D are becoming more and more obvious, in addition to alleviating symptoms and improving life quality, it also reduces the financial burden on patients [11]. The effectiveness of acupuncture in treating IBS-D is manifested in regulating intestinal stress response through sympathetic nerves, regulating intestinal function and intestinal motility, and influencing the secretion of other neurotransmitters through neuroendocrine pathways [12]. Meanwhile, acupuncture and moxibustion can regulate brain-gut peptides levels through the brain-gut axis, like substance P (SP), vasoactive intestinal peptide (VIP), 5-hydroxytryptamine (5-HT) and so on to achieve a bidirectional regulation of the organism [13, 14]. Acupuncture and moxibustion include many forms, and moxibustion is one of the most commonly used, and mild-warm moxibustion increases the secretion of the mucus layer of the intestinal wall, improve the viscosity of the mucus layer and reduce bile reflux to play a role in protecting the intestinal mucosa, as well as improve the morphology and function of the intestinal mucosal epithelium and promote its repair and regeneration [15].

Based on TCM theory, spleen and stomach’s weaknes mainly causes IBS-D, and spleen deficiency and dampness excess syndrome can often be seen clinically [16, 17]. Moxa’s burning effect on acupuncture contributes to the effectiveness of moxibustion, and components from moxa leaves also produces chemical stimulation [19, 20], which can achieve the effect of invigorating spleen and dispelling dampness. Although current evidence suggests the advantages of moxibustion on IBS-D, the reliable efficacy and safety of mild-warm moxibustion in spleen deficiency and dampness excess syndrome of IBS-D patients still need to be verified. Therefore, we designed this prospective randomized parallel controlled trial.

Methods

Ethical approval and informed consent

We followed the Declaration of Helsinki and the Clinical Research Ethics Committee of Changshu Hospital of TCM reviewed it (No. 20230539). Registration number in the international platform: TCTR20230523002. Once we will make an amendment or change, the committee (mentioned above) will reApprove it through a formal process. The included patients will first undergo informed consent (sign a form), and patients will have the choice at any time whether to continue with the trial. The privacy of all patients will be strictly protected.

Trial status

Patient recruitment is expected to begin on July 01, 2023, and to be completed by December 31, 024.

Study aims and design

This prospective, parallel, randomized controlled trial (RCT) will confirm mild-warm moxibustion on IBS-D in efficacy and safety. And syndrome combining spleen deficiency and dampness will be observed. Patients will be randomly assigned to receive 4 weeks of mild-warm moxibustion treatment or oral loperamide hydrochloride capsules therapy, followed by 4 weeks of follow-up in both groups. See trial’s flow diagram in Figure 1 and schedule of protocol in Table 1. The Consolidated Standards of Reporting Trials 2017 guided this protocol, and also Standard Protocol Items: Recommendations for Interventional Trials [21] (Table S1).

Figure 1 Trial’s flow diagram.
### Table 1 Schedule of protocol.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screening Period</th>
<th>Treatment Period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project</td>
<td>Baseline</td>
<td>2-week</td>
<td>4-week</td>
</tr>
<tr>
<td>Record fill</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Fulfill inclusion criteria and exclusion criteria</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Informed consent</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Random allocation</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Treatment</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

### Eligibility criteria, Diagnostic criteria

**Western medical diagnostic criteria for IBS-D.** The Western diagnostic criteria for IBS-D referring to the diagnostic description of *Rom IV criteria* [22]: abdominal pain 3 days or more monthly, recently (in three months), at least 2 symptoms: ① change in stool pattern; ② significant improvement in symptoms after defecation; ③ change in frequency of defecation; and ④ symptoms present for six months or more before diagnosed, the above diagnostic criteria were met in the last 3 months and 25% or more of the defecation met the Bristol stool pattern scale for loose (pasty) or watery stools, and less than 25% of the defecation were dry globular or sausage-like [23].

**TCM diagnostic criteria.** IBS-D patients were diagnosed with spleen deficiency and dampness syndrome referring to the Expert Consensus Opinions on the Treatment of IBS in TCM 2017 [16]: primary symptoms: ① loose stools and diarrhea; ② vague abdominal pain; secondary symptoms: ① attacks or worsening after exertion or cold; ② fatigue and lassitude; ③ anorexia. Tongue and pulse: Pale tongue with teeth marks on two sides, white and greasy fur; weak pulse.

**Inclusion Criteria.** ① Patients should meet both TCM and Western diagnostic criteria of IBS-D; ② Patients at age of 18 to 65 years old; ③ No history of relevant treatment before enrollment or with discontinuation of treatment with Chinese medicine, antidiarrheal drugs and antispasmodics for more than 1 month; ④ IBS Severity Scoring System scores(IBS-SSS) more than 75 totally [24]; ⑤ Voluntary participation and informed consent.

**Exclusion Criteria.** ① IBS-C, IBS-M, and IBS-U patients; ② Patients with inflammatory bowel disease, organic intestinal lesions, peptic ulcer, infectious diarrhea; ③ Patients combined with severe cardiovascular, hepatic, renal, endocrine and hematopoietic system diseases; patients with other diseases other than diarrhea that may affect the test results that cannot be discontinued; patients with mental illness; ④ Patients who are pregnant or lactating, and those who have a birth plan from their enrollment to 1 month after the end of the trial; ⑤ Participated in other clinical trials within 1 month.

**Sample size.** IBS-SSS scoring results helped to calculate sample size, which was 97.28 ± 31.72 for the treatment group and 116.63 ± 37.18 for the control group according to pretest results, and the sample size was estimated using PASS 15.0, in which α = 0.05, β = 0.2, test efficacy = 0.8, the study is suitable for difference test. The cases number in treatment group and control group was equal. The sample size was calculated according to the software, and 46 patients per group were required considering the clinical shedding rate of 10%.

**Randomization, allocation and blinding**

A total of 92 patients will be included by a completely randomized method, and an independent statistical analyst will code the 92 patients into numbers 1 to 92 in order; using Excel 2013 software, we entered “ = RANDBetween (11,000)” to make numbers randomly, which were ordered ascend, and 1–46 and 47–92 were into the treatment and control group, respectively. Groups were placed in opaque envelopes beforehand, which were opened after patients had been selected and given informed consent, and corresponding
treatment was administered according to the groups in the envelopes. Due to the limitations of the intervention protocol, double-blinding will be not possible in this study, and at the start of the study, the outcome evaluators and statistical analysts, but not every patient and investigators, will be unaware of the plan.

Interventions

Treatment group. Patients will be placed in supine position, and moxa strips (1.8 × 20 cm, Nanyang Hanyi Moca Co Ltd, Nanyang, China) will be placed on the moxibustion racks with the burning end of the moxa strips perpendicular to the acupoints (Tianning ST25, Zhongwan CV12, and Zusanli ST36) and 3–5 cm from the acupoints, to the extent that the patients felt warm and comfortable. Procedure referring to State Standard of the People’s Republic of China Manipulation of Acupuncture and Moxibustion [25]: 30 minutes every other day, for 4 weeks.

Control group. Oral loperamide hydrochloride capsules (Xi’an Janssen Pharmaceutical Co. Ltd., SFDA approval number H10910085, Product Lot number 20201119, Specification: 2mg/capsule), 2 mg, tid for 4 weeks.

Outcomes

Main Outcome Indicators

The main outcome indicator is the IBS-SSS, which includes five aspects: abdominal pain frequency and degree, abdominal distention degree, defecation volume satisfaction, life disruption, with a score range of 0 to 100 out of 500 for each indicator [24]. The evaluation will be divided: normal (< 75); mild (75–174); moderate (175–300); and severe (> 300). Keep scores at baseline, 2-week treatment, 4-week treatment, 4-week follow-up, respectively.

Secondary outcome indicators

IBS-Quality of Life (IBS-QOL) score. It includes 34 entries in 8 items including emotional status, mental status, sleep status, energy changes, daily exercise, dietary impact, daily socialization, and work impact [26]. Score each item on a 5-point scale. Sum of the points is the total score, and higher scores indicates better health status. The scores will be scored at baseline, 4-week treatment, 4-week follow-up once each.

Serum brain-gut peptide levels. Measure neuropeptide Y, calcitonin-related gene peptide, and vasoactive intestinal peptide at baseline, 4-week treatment, 4-week follow-up once each.

TCM syndrome scale score. The IBS-D TCM symptom scoring criteria refers to the Guidelines for Clinical Research on New Chinese Medicines (Trial) [27]. Higher score indicates more severe symptoms, and the scoring details are shown in Table 2. Perform score at baseline, after 4 weeks of treatment, and at week 4 of follow-up once each.

Safety observation index. Treatment-related adverse reactions, including burns, skin sensitization, dizziness, headache, nausea, and vomiting, will be recorded during the study period. In addition, test function of liver and renal (urea nitrogen and serum creatinine) at baseline, 4-week treatment, 4-week follow-up to assess safety. The case report form (CRF) will record details of all adverse events (time of occurrence, degree, duration-time, cause, useful treatment and outcome). Statistically count adverse reactions when treatment finished.

Data collecting and managing

Data collecting requires 2 researchers. Collect personal information and store it in a separate room to safeguard it all the time. Only authorized researchers have access to the database.

Statistical analysis

We will use SPSS 22.0 for statistical processing and data analysis. We will use mean ± standard deviation to describe the results of primary and secondary outcome measures, and use the t-test or Wilcoxon rank sum test for intergroup comparison. Use generalized linear models or repeated measures analysis for comparisons between repeated measurements. At P < 0.05, we identify significant differences.

Table 2 IBS-D TCM syndrome scale.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mild (2 points)</th>
<th>Moderate (4 points)</th>
<th>Severe (6 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Unshaped stools, 3 to 4 times a day</td>
<td>Loose stools, 5 to 10 times a day</td>
<td>Watery stool, more than 10 times a day</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>Occasional mild abdominal distention and pain</td>
<td>Abdominal distension and abdominal pain</td>
<td>Severe abdominal distension and pain that are unbearable and need to be controlled with medication</td>
</tr>
<tr>
<td>Abdominal fullness</td>
<td>Abdominal fullness after eating, relieved after 0.5h</td>
<td>Abdominal fullness after eating, relieved after 2h</td>
<td>Fullness of the abdomen and stomach all day</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Poor appetite, less than 1/3 reduction in food intake</td>
<td>Poor appetite, food intake reduced by more than 1/3 but less than 1/2</td>
<td>No desire to eat or drink for the whole day, and the amount of food intake is reduced by more than 1/2</td>
</tr>
<tr>
<td>Weariness and weakness</td>
<td>Slight physical fatigue, can maintain light work</td>
<td>Weakness in the limbs, barely able to keep up with daily activities</td>
<td>Weakness all over the body, not working all day</td>
</tr>
</tbody>
</table>
Discussion

IBS-SSS and IBS-QOL are evaluation tools recommended by Chinese guidelines and used internationally to evaluate overall symptom changes and improvement of IBS patients’ life quality [16, 28, 29]. IBS-D may be associated with abnormal brain-gut axis regulation, and acupuncture and moxibustion can regulate brain-gut peptide levels through the brain-gut axis, and monitoring changes in brain-gut peptide levels can help analyze the potential mechanism of action of acupuncture and moxibustion for IBS-D. TCM syndrome scale can monitor changes of patients’ TCM symptoms, and can explain why mild-warm moxibustion is effective for IBS-D in TCM theory. This study attempts to comprehensively and objectively explore the efficacy of mild-warm moxibustion on IBS-D through the above indicators. The main guiding principle of Chinese medicine is to identify and treat different disease types with different treatment plans. To objectively evaluate the clinical efficacy of moxibustion in treating IBS-D, we will observe the common clinical syndrome type, which is a syndrome type with spleen deficiency combined with dampness. How moxibustion acts on IBS-D has not been fully elucidated. Previous studies have found in animal experiments that moxibustion can regulate the abnormal expression of P2X3 receptor protein and mRNA in color-associated dorsal root ganglion (DRG) of IBS rats, which may be the mechanism of moxibustion relieving peripheral sensitization of IBS visceral pain [30]. When treat IBS-D, loperamide hydrochloride capsule is the first-line drug, which inhibits intestinal smooth muscle contraction, reduce intestinal peristalsis, and improve diarrhea [31]. In conclusion, we adopted the prospective RCT method to objectively observe the clinical efficacy of mild-warm moxibustion on IBS-D (spleen deficiency and dampness excess syndrome), using clinical first-line drugs as controls.

References


