

Electroacupuncture for patients with diarrhea-predominant irritable bowel syndrome or functional diarrhea

A randomized controlled trial

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Abstract

Diarrhea-predominant irritable bowel syndrome (IBS-D) and functional diarrhea (FD) are highly prevalent, and the effectiveness of acupuncture for managing IBS-D and FD is still unknown.

The aim of this study was to compare the effectiveness of electroacupuncture with loperamide.

It was a prospective, randomized, parallel group controlled trial.

A total of 448 participants were randomly assigned to He electroacupuncture group (n = 113), Shu-Mu electroacupuncture group (n = 111), He-Shu-Mu electroacupuncture group (n = 112), or loperamide group (n = 112). Participants in the 3 acupuncture groups received 16 sessions of electroacupuncture during a 4-week treatment phase, whereas participants in the loperamide group received oral loperamide 2 mg thrice daily. The primary outcome was the change from baseline in stool frequency at the end of the 4-weeks treatment. The secondary outcomes were the Bristol scale, the MOS 36-item short form health survey (SF-36), the weekly average number of days with normal defecations and the proportion of adverse events.

Stool frequency was significantly reduced at the end of the 4-week treatment in the 4 groups (mean change from baseline, 5.35 times/week). No significant difference was found between the 3 electroacupuncture groups and the loperamide group in the primary outcome (He vs. loperamide group [mean difference 0.6, 95% CI, -1.2 to 2.4]; Shu-Mu vs. loperamide group [0.4, 95% CI, -1.4 to 2.3]; He-Shu-Mu vs. loperamide group [0.0, 95% CI, -1.8 to 1.8]). Both electroacupuncture and loperamide significantly improved the mean score of Bristol scale and increased the weekly average number of days with normal defecations and the mean scores of SF-36; they were equivalent in these outcomes. However, the participants in electroacupuncture groups did not report fewer adverse events than those in the loperamide group. Similar results were found in a subgroup analysis of separating patients with IBS-D and FD patients.

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HZ, YL, and WZ contributed equally to this study.

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Authorship: ZSL and BZ have full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. They have control of the decision to publish this study. YL, ZSL, and BZ contributed to the study concept and design. Methodological advice and statistical analysis were given by FZ and HZ. Data were acquired by SYZ, HBZ, WZZ, CZT, FCW, ZBL, SJW, and MQZ. PJR managed the clinical monitoring. Study implementation and supervision were managed by XHJ. HZ, YL, and WZ drafted the manuscript and made revisions. Critical revisions of the manuscript for important content were performed by all the authors.

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Electroacupuncture is equivalent to loperamide for reducing stool frequency in IBS-D and FD patients. Further studies on cost effectiveness of acupuncture are warranted.

Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, CEC-CACMS = Clinical Evaluation Center of China Academy of Chinese Medical Science, FD = functional diarrhea, IBS = irritable bowel syndrome, IBS-D = Diarrhea-predominant irritable bowel syndrome, ITT = intention-to-treat, MI = multiple imputation, PP = per-protocol, SF-36 = The MOS 36-item short form health survey, TCM = Traditional Chinese medicine.

Keywords: diarrhea-predominant irritable bowel syndrome, electroacupuncture, functional diarrhea, randomized controlled trial

1. Introduction

Diarrhea is defined as 3 or more loose or watery stools per day.^[1] In average, an individual has an episode of acute diarrhea every 18 months, and most of the cases with acute diarrhea are usually caused by bacterial or viral infections. Acute diarrhea is easily treated by a 2-week treatment with antimicrobials.^[2] And diarrhea symptoms caused by viral infections are self-limited and need no specific treatments.^[2] Patients who have diarrhea over 4 weeks are normally diagnosed with chronic diarrhea, which is usually caused by complicated pathogens.^[2,3] The most common types of chronic diarrhea are diarrhea-predominant irritable bowel syndrome (IBS-D) or functional diarrhea (FD).^[2,4] Irritable bowel syndrome (IBS) affects 11% of the global population^[5] and 5 to 11% of the Chinese population.^[6,7] The prevalence of FD is still unclear.^[4] Unspecified diarrhea is found in 9.6% of Minnesota residents^[8] and 4.8% of the individuals in the United States.^[9] These data might be viewed as indirect evidence for the prevalence of FD. The principle of the management for chronic diarrhea is to mitigate diarrhea symptoms and find out the causes.^[2] Significant increase in stool frequency, abdominal pain, and bloating are the main symptoms in patients with FD and IBS-D; however, few strategies are developed to effectively reduce stool frequency in these patients.^[2] Several studies examined the effectiveness of interventions for IBS, but they focused on the global improvement of IBS or quality of life.^[10–12] Additionally, effective strategies for FD are rarely studied.

Acupuncture is used to treat functional bowel disorders.^[13] It promotes the bowel motility of patients with functional constipation and improves spontaneous bowel movements.^[14] Although managing diarrhea with acupuncture is also common in China, there is still a lack of evidence for the effectiveness of acupuncture in treating diarrhea.^[14] Several studies indicated that acupuncture is beneficial for patients with IBS in relieving the abdominal pain and defecation urgency and improving quality of life.^[15–19] However, the effectiveness of acupuncture for IBS-D patients has not been fully studied. This assumption is made on the grounds that: first, IBS-D patients were not separately studied, instead, they were recruited along with patients with constipation-predominant IBS^[16]; second, subjective outcomes were used as in assessing global improvement of IBS, instead of objective outcomes such as stool frequency^[20]; third, benefits in acupuncture treatment for patients with IBS could not be confirmed because of a high risk of bias in trials comparing acupuncture with pharmacological therapies.^[15] In addition, effectiveness of acupuncture for patients with FD has not been studied. Based on the aforementioned facts, a randomized controlled trial was performed to compare the effectiveness of acupuncture with loperamide, as the loperamide is a conventional medication for reducing stool frequency in IBS-D and FD patients.^[21,22]

In traditional Chinese medicine,^[23] the basic acupuncture points for relieving diarrhea symptoms are He and Shu-Mu points. The He points refer to those that specifically treat the

diseases caused by dysfunction of an internal organ and are usually located at lower limbs. The Shu-Mu points are similar to the He points in treating gastrointestinal disease, but they are usually located on the back (Shu points) or the abdomen (Mu points). Based on this background information, we hypothesized that 3 different acupuncture protocols (using He points alone, using Shu-Mu points alone or using both He and Shu-Mu points) are equivalent in treating diarrhea.

2. Materials and methods

2.1. Trial design

We performed a prospective, randomized and parallel group controlled trial. Figure 1 shows the study design. The trial was performed in 8 hospitals across 8 provinces in China: Teaching Hospital of Chengdu University of Traditional Chinese Medicine (TCM), Guanganmen Hospital, the First Affiliated Hospital of Hunan University of TCM, the First Affiliated Hospital of Anhui University of TCM, the First Affiliated Hospital of Guangzhou University of TCM, the Affiliated Hospital of Changchun University of TCM, the Affiliated Hospital of Shandong University of TCM, the Affiliated Hospital of Shanxi University of TCM. From October 2011 to September 2014, a total of 448 participants were randomly allocated to 3 electroacupuncture groups and 1 loperamide group in a 1:1:1:1 ratio. These participants recorded weekly diarrhea diaries in a 10-week research period that is composed of a 2-week baseline phase, a 4-week treatment phase, and a 4-week follow-up phase. Items in the diarrhea diaries include stool frequency and consistency, number of days with normal defecations in a week, whether special food was taken today and whether drugs for diarrhea were taken today. Before being randomized, the participants received baseline evaluation. The participants received 16 sessions of electroacupuncture or oral administration of loperamide daily during the 4-week treatment. Then, the participants were followed up for 4 weeks after treatment. Independent research assistants who were not aware of group assignment assessed clinical outcomes at baseline, the end of treatment (week 4), and follow-up (week 8). Statistical analysis was performed by a statistician in the clinical evaluation center of China academy of Chinese medical science (CEC-CACMS), who was not involved in the trial design and performance. The trial was performed in

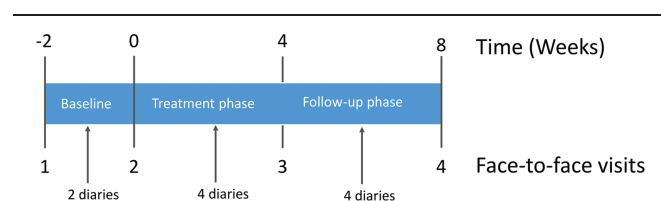


Figure 1. Study design.

accordance with Helsinki declaration and approved by regional institutional review board of Sichuan province for conducting research of Traditional Chinese Medicine (Approval ID: 2011-KL004). The trial was registered at clinicaltrials.gov (registration ID: NCT01350570).

2.2. Participants

Patients who had diarrhea symptoms for at least 6 months were recruited from outpatient settings in the 8 hospitals. Eligibility criteria were: meeting the Rome III criteria for IBS-D or FD^[24]; patients with IBS-D reporting a stool frequency ≥ 3 times/day for ≥ 2 days/week and $\geq 25\%$ stools to be of type 5 to 7 (evaluated with Bristol stool scale); patients with FD reporting the same stool frequency with $\geq 75\%$ stools to be of type 5 to 7. The other eligible criteria were: 18 to 65 years of age; taking no medications that affect stool frequency; not in the middle of other clinical trial; providing signed informed consents. To rule out organic bowel diseases, we asked the participants to provide negative results of colonoscopy, full blood counts, and stool occult blood tests in routine evaluation in the last 12 months; otherwise, they were asked to take the examinations provided by the 8 hospitals. The participants were asked to consume a package of milk (190 mL) after an overnight fast to rule out the possibility of lactose intolerance. Participants were excluded for: mental illness, liver or kidney impairment, malignant neoplasm or pregnancy. Participants who were on long-term depressants were included only if they administered at a stable dose and agreed to remain at the dose during the study period.

2.3. Randomization and masking

Randomization sequence was generated by a computer system in the CEC-CACMS. Permuted block randomization with changing block size was used, and the randomization was stratified according to the type of diarrhea (IBS-D or FD) and duration of diarrhea. The study coordinator in each hospital obtained a randomization code and group assignment through an internet-based randomization system or a message delivering system developed by the CEC-CACMS in a cell phone. The randomization sequence was concealed in the secure server in the CEC-CACMS until all the follow-up visits and data collection were finished and study files were locked. The data manager in the CEC-CACMS who was not aware of the study design had access to the randomization sequence. Performance of the trial was supervised by a monitor group. The group met regularly to discuss and solve the problems that were found during the trial. As participants receive loperamide alone in the control group, the participants, acupuncturists, and doctors in charge were not blinded from the group assignment. The statisticians were masked from the group assignments.

2.4. Interventions

The participants received 1 of the 3 acupuncture treatments or oral administration of loperamide. Diarrhea is commonly classified as a dysfunction in large intestine in traditional Chinese medicine, so acupuncture points selected for managing diarrhea are He points and Shu-Mu points of the large intestine.^[25] In this trial, participants in the He group were needled at Quchi (LI11) and Shangjuxu (ST37) bilaterally, as LI11 and ST37 are the He point of the large intestine. Participants in the Shu-Mu group were needled at Tianshu (ST25) and Dachangshu (BL25)

bilaterally. ST25 is the Mu point of the large intestine meridian, whereas BL25 is the Shu point. Participants in the He-Shu-Mu group were needled at LI11, ST37, ST25, and BL25 in one side of body alternatively (to ensure that patients in this group received also 4 needle insertions and the 4 points), which is a combination of the He and Shu-Mu points. We used disposable acupuncture needles (0.25 mm in diameter and 25 mm long, Hwato, Suzhou, China). Every participant received 4 needle insertions each time, with each acupuncture point being needled to a depth whenever deqi sensation was achieved. The deqi sensation was defined as numbness, distension, or electrical tingling at the needling site. After the needle insertions, the acupuncture points were stimulated electrically for 30 minutes in each acupuncture session. The frequency of electroacupuncture was 15 Hz in continuous-wave mode. The intensity was gradually increased until the nociceptive flexion reflex was achieved in a patient. The LI11 and ST37 were connected to a pair of electrodes and the ST25 and BL25 were connected to another pair. Sixteen sessions of electroacupuncture were given to each participant; 10 sessions of electroacupuncture were given in 2 weeks, whereas 6 sessions were given in the rest 2 weeks. In the 3 electroacupuncture groups, concomitant treatments (moxibustion, cupping, herbs and conventional medications other than loperamide) were not allowed. Patients with acute diarrhea symptoms during the treatment or follow-up period were asked to visit gastroenterologists to determine if rescue medications were needed. Participants were told that they received 1 of the 3 types of electroacupuncture, which were all effective for diarrhea. Acupuncturists were asked to conform to the standardized procedure in providing electroacupuncture treatment, after they were qualified by a test that examined the knowledge of acupuncture performance.

According to the guidelines and previous evidence,^[21,22,26] we used loperamide (2-mg tablet, Xian Janssen Pharmaceuticals Ltd., China) as a positive drug control. Loperamide was administered orally for 2 mg thrice daily in a 4-week treatment. We asked participants to stop loperamide treatment if they reported normal defecation for at least 3 days. The normal defecation was defined as 1 bowel movement daily with a stool consistency to be type 4 in the Bristol scale.

2.5. Outcome measurements

The primary outcome was the primary outcome was the change from baseline in stool frequency at the end of the 4-weeks treatment. The secondary outcomes included the Bristol scale, the weekly average number of days with normal defecations, quality of life, and incidence of adverse events. The Bristol scale^[27] classifies stool consistency into 7 types. Type 5, 6, and 7 in the scale indicate diarrhea, and type 4 indicates normal stool consistency. A normal defecation was defined as a daily stool frequency ≤ 3 times and stool consistency to be type 4. The participants were asked to record the number of days with normal defecations in a week. The quality of life was evaluated with the MOS 36-item short-form health survey (SF-36).^[28] All these outcomes were assessed and recorded weekly in the diarrhea diaries except SF-36, which was assessed at baseline and the end of treatment through a face-to-face interview. Research assistants guided the participants on how to fill in the diarrhea diaries, to ensure the fidelity of the outcome data. The outcome assessors extracted the information from the diaries into calculable variables and entered the data into a server in CEC-CACMS.

2.6. Statistical analysis

Our primary analysis was to test the equivalence between acupuncture and loperamide, so we chose the sample size calculation based on the comparison of acupuncture and loperamide. However, acupuncture was not compared with loperamide for managing diarrhea in previous studies. On the basis of consultations to gastroenterologists and a literature review, we determined that a between-group difference in stool frequency < 1 time/week indicated electroacupuncture is equivalent to loperamide. The comparison between the 3 acupuncture groups was treated as explorative analysis. Considering a between-group difference margin of 1 time/week and a pooled standard deviation of 2 times/week, we decided that a total sample size of 424 was able to reject the H_0 hypothesis (H_0 : acupuncture = loperamide, H_1 : acupuncture \neq loperamide) at a significant level of 0.05 with a power of 0.95 in a 2-sided test. Estimating a 10% dropout rate, we needed at least 466 participants in this trial. The sample size was calculated with the package “TrialSize” in R software (version 3.0.1, www.r-project.org).

All analyses were performed on the basis of intention-to-treat (ITT) population, in which we included participants who received baseline assessment of primary outcome and at least 1 acupuncture session or 1 loperamide administration. We handled missing values through multiple imputation (MI) performed with the package “Amelia” in the R software. We also ran analyses basing on the per-protocol (PP) population, in which the participants accepted the assigned treatment and finished at least 80% of the treatment protocol.

The primary analysis was to reject H_0 through an analysis of covariance (ANCOVA) of the primary outcome. The ANCOVA was adjusted for the following covariates: corresponding baseline variable (stool frequency, the Bristol score, the number of days with normal defecation or the score of each domain in SF-36), age and duration of diarrhea. We ran pairwise comparisons of the 4 groups and adjusted P values through the Tukey method in a post-hoc analysis. The secondary outcomes were analyzed with the same ANCOVA model. The items in SF-36 were summarized into 8 domains (physical functioning, role-physical function, bodily pain, general health, vitality, social functioning, role-emotional function, mental health, reported health transition),

and the score of each domain was compared between the 4 groups in the ANCOVA model. The incidence of adverse events was compared between groups using the chi-square test. A subgroup analysis was performed with patients subdivided into IBS-D and FD subgroups, and the hypothesis testing was rerun to ensure robustness of the result. All these analyses were done in the R software.

3. Results

3.1. Baseline characteristics

After screening 495 possible candidates, we included 448 patients with IBS-D or FD. The reasons for exclusion were violation of the inclusion criteria or decline to participate. The 448 participants were randomly allocated to He (n = 113), Shu-Mu (n = 111), He-Shu-Mu (n = 112), and loperamide group (n = 112). All these participants were from 8 hospitals in 8 provinces in China (113 participants from Chengdu province, 97 from Hunan province, 68 from Beijing province, 55 from Shandong province, 48 from Shanxi province, 42 from Changchun province, 20 from Guangzhou province, 5 from Anhui province). All participants in the 3 acupuncture groups received at least 1 acupuncture treatment, whereas 2 participants in the loperamide group declined to participate after randomization. Five participants did not report primary outcome at baseline, 11 participants were lost to follow-up at week 4, and 19 participants at week 8. A total of 441 participants were included in the ITT population and 411 in the PP population. Figure 2 shows more details.

The age of all participants was 40.5 years, and 253 (57.3%) of them were females. The body mass index (BMI) and duration of diarrhea were 21.8 kg/m² and 3.1 years, respectively. Thirty-five (8%) participants had experience of acupuncture, whereas 161 (36.7%) had experience of traditional Chinese medicine. The participants presented a stool frequency of 16.0 times/week and a Bristol score of 6.1 at baseline. Table 1 shows these variables separately in the 4 groups.

3.2. Stool frequency

The stool frequency reduced to 10.6 times/week at week 4 and slightly increased to 11.1 times/week at week 8. The change from

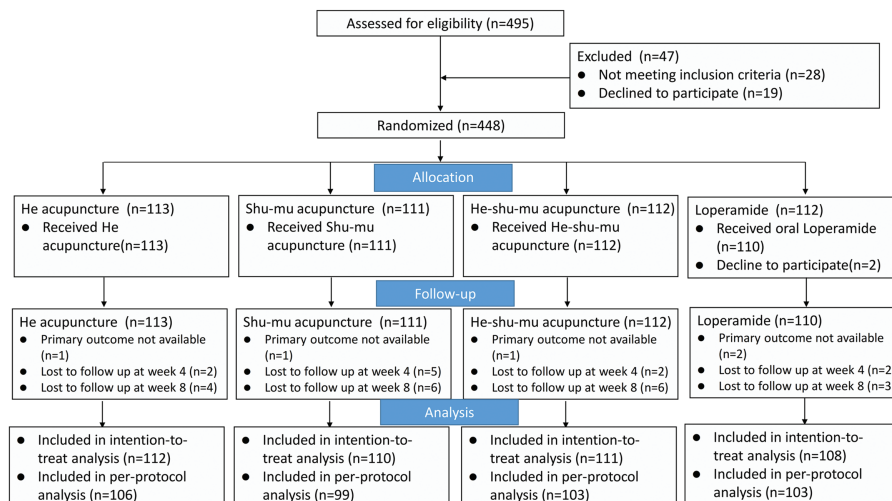


Figure 2. Trial flowchart.

Table 1**Baseline characteristics.**

Variables	He group (n=112)	Shu-Mu group (n=110)	He-Shu-Mu group (n=111)	Loperamide group (n=108)
Age, year	38.6 (16.7)	41.2 (16.5)	41.7 (17.5)	40.6 (16.7)
Sex, n (%)				
Female	69 (61.6)	60 (54.6)	59 (53.2)	65 (60.2)
Male	43 (38.4)	50 (45.4)	52 (46.8)	43 (39.8)
BMI index, kg/m ²	22.1 (3.2)	21.77 (2.96)	21.7 (2.9)	21.8 (3.1)
Duration of the diarrhea, year	2.0 (1.0–30.8)	1.7 (0.8–20.2)	1.5 (0.9–49.6)	1.6 (0.9–12.5)
Received acupuncture before, n (%)				
Yes	9 (8.0)	7 (6.4)	10 (9.0)	9 (8.3)
No	103 (92.0)	103 (93.6)	101 (91.0)	99 (91.7)
Received traditional Chinese medicine before, n (%)				
Yes	42 (37.5)	35 (31.8)	48 (43.2)	36 (33.3)
No	70 (62.5)	75 (68.2)	63 (56.8)	72 (66.7)
Type of diarrhea, n (%)				
IBS-D	46 (41.4)	31 (28.2)	45 (40.5)	44 (41.0)
Functional diarrhea	66 (59.6)	79 (71.8)	66 (59.5)	64 (59.0)
Average weekly stool frequency n (%) [*]	16.4 (6.1)	16.6 (8.8)	16.2 (7.2)	14.6 (6.5)
Bristol score	6.1 (0.7)	6.1 (1.1)	6.2 (0.9)	6.0 (0.9)
Number of days with normal stool per week, day	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
SF-36				
Physical functioning	93.5 (9.9)	93.2 (12.2)	93.2 (10.5)	93.6 (10.5)
Role-Physical	76.1 (37.6)	79.3 (35.0)	78.2 (36.5)	80.3 (33.5)
Bodily pain	75.8 (15.1)	76.1 (14.6)	74.4 (14.8)	74.3 (15.5)
General health	56.1 (21.7)	57.7 (21.8)	54.0 (21.5)	56.9 (19.0)
Vitality	67.8 (18.5)	66.9 (19.0)	67.6 (18.4)	67.1 (20.1)
Social Functioning	93.8 (18.9)	94.3 (17.7)	96.4 (14.7)	93.3 (18.1)
Role-emotional	72.6 (39.8)	73.0 (38.2)	71.8 (39.5)	70.1 (41.0)
Mental health	71.1 (17.1)	72.6 (18.4)	74.8 (16.7)	72.0 (17.5)
Reported Health transition	53.6 (21.5)	53.6 (23.2)	52.3 (23.7)	50.0 (22.4)

BMI=body mass index, IBS-D=diarrhea-predominant irritable bowel syndrome, SF-36=the MOS 36-item short form health survey.

^{*}The average weekly stool frequency was assessed at baseline, week 4 and 8. From baseline evaluation period (week -2~0) to week 8, patients were asked to keep weekly diaries and the stool frequency was calculated from the diaries.

baseline in stool frequency was 5.4 times/week at week 4 and 4.8 times/week at week 8. The change in stool frequency at week 4 was comparable between the 4 groups ($P=0.80$), even after adjusted for baseline variables ($P=0.76$). In pairwise comparisons, all the 3 electroacupuncture treatments were equivalent to loperamide (He vs. loperamide, [mean difference 0.6, 95% CI, -1.2 to 2.4], $P=0.857$; Shu-Mu vs. loperamide, [0.4, 95% CI, -1.4 to 2.3], $P=0.933$; He-Shu-Mu vs. loperamide [0.0, 95% CI, -1.8 to 1.8], $P=1.000$). In an exploratory analysis, all the 3 electroacupuncture groups were comparable in pairwise comparisons (He vs. Shu-Mu [mean difference 0.1, 95% CI, -1.7 to 2.0], $P=0.997$; He vs. He-Shu-Mu [0.6, 95% CI, -1.2 to 2.4], $P=0.858$; Shu-Mu vs. He-Shu-Mu [0.5, 95% CI, -1.4 to 2.3], $P=0.935$). Figure 3 shows the details.

The 4 groups were equivalent in the change in stool frequency at week 8 (He vs. loperamide [mean difference, 1.1, 95% CI, 0.1–2.1], $P=0.02$; Shu-Mu vs. loperamide [0.6, 95% CI, -0.5 to 1.6], $P=0.64$; He-Shu-Mu vs. loperamide [0.8, 95% CI, -0.2 to 1.7], $P=0.14$; He vs. Shu-Mu [-0.6, 95% CI, -0.5 to 1.6], $P=0.472$; He vs. He-Shu-Mu [0.3, 95% CI, -0.7 to 1.2], $P=0.87$; Shu-Mu vs. He-Shu-Mu [-0.3, 95% CI, -1.4 to 0.7], $P=0.88$).

We used the PP and MI dataset to rerun the analysis, the results were consistent with the ITT analysis. Table 2 shows more details.

3.3. Bristol scale

The Bristol score decreased to 5.2 units at the week 4, with an improvement of 0.9 units compared with baseline. The 4 groups

were comparable in scores of the Bristol scale assessed at week 4 ($P=0.17$) and week 8 ($P=0.07$). To test the reliability of this result, we ran the Kruskal–Wallis rank sum test and found the results consistent with the ANCOVA analysis (Kruskal–Wallis chi-square=2.25, $P=0.52$). Table 2 shows more details.

3.4. Weekly average number of days with normal defecations

The number of days with normal defecation significantly increased (baseline, 0.4 days; week 4, 2.5 days; week 8, 2.4

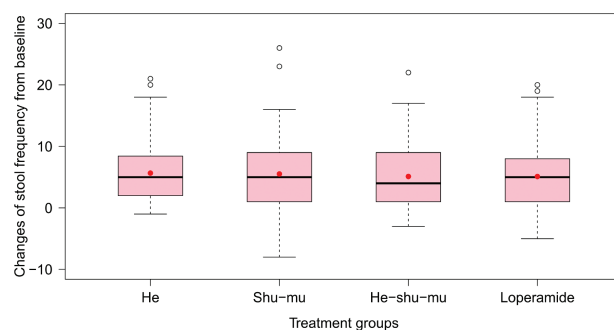


Figure 3. Change from baseline in stool frequency. The mean change from baseline in stool frequency at week 4 is shown. The He, Shu-Mu, He-Shu-Mu, and loperamide groups were comparable in this outcome ($P=0.82$). The red dots show the mean changes in stool frequency in the 4 groups, which were 5.66, 5.52, 5.11, and 5.11 times/week, respectively.

Table 2**Outcome measurements.**

Outcome measurements (95% CI)	Time points	He group (n=112)	Shu-Mu group (n=110)	He-Shu-Mu group (n=111)	Loperamide group (n=108)	P value*
Change in stool frequency from baseline	Week 4	5.7 (4.8–6.5)	5.5 (4.5–6.6)	5.1 (4.2–6.0)	5.1 (4.1–6.1)	0.76
	Week 8	5.3 (4.3–6.3)	5.6 (4.2–7.0)	4.8 (3.8–5.8)	3.6 (2.6–4.5)	0.03
Bristol score	Week 4	5.3 (5.1–5.5)	5.1 (4.8–5.3)	5.3 (5.2–5.5)	5.1 (4.9–5.3)	0.17
	Week 8	5.1 (4.9–5.3)	5.0 (4.7–5.2)	5.2 (5.0–5.4)	5.3 (5.1–5.6)	0.07
The weekly average number of days with normal defecations	Week 4	2.6 (2.1–3.0)	2.5 (2.0–3.0)	2.0 (1.6–2.4)	2.9 (2.4–3.3)	0.06
	Week 8	2.6 (2.1–3.1)	2.6 (2.0–3.1)	2.2 (1.7–2.7)	2.2 (1.7–2.8)	0.59

95% CI, 95% confidence interval.

* The P value was calculated with analysis of covariates (ANCOVA) and was adjusted for age, sex, body mass index (BMI), duration of diarrhea, study sites, and history of receiving acupuncture or TCM treatments.

days). The 4 groups were equivalent in this outcome (week 4, $P=0.06$; week 8, $P=0.59$). Table 2 shows more details.

3.5. SF-36

The scores in 6 domains in SF-36 increased after the 4-weeks treatment. Two decreased domains were physical functioning and reported health transition. We used ANCOVA models to test the equivalence of the 4 groups in the 8 domains, and the results showed the groups were comparable. Table 3 shows the details.

3.6. Adverse events

Eleven adverse events were reported by 11 participants. The events were abdominal pain (1 event in the He-Shu-Mu group), cold limbs (1 event in the Shu-Mu group), faint (3 events in the 3 electroacupuncture groups), hot flush (1 event in the loperamide group), insomnia (1 in the He group, 1 in the He-Shu-Mu group and 2 in the Shu-Mu group), weakness (1 in the He-Shu-Mu group). Between-group difference of the incidence of adverse events was not statistically significant (chi-square=14.21, $P=0.51$).

3.7. Subgroup analysis

Of the 441 participants, 166 (37.6%) were diagnosed with IBS-D and 275 (62.4%) were with FD. We split these 2 populations into 2 subgroups and reran the analyses of the primary outcome and secondary outcomes. The 3 electroacupuncture treatments and loperamide were still comparable in these 2 subgroups. Table 4 shows the details.

Table 3**The MOS 36-item short form health survey (SF-36).**

Domains (95% CI)	He group (n=112)	Shu-Mu group (n=110)	He-Shu-Mu group (n=111)	Loperamide group (n=108)	P value*
Physical functioning	94.0 (91.9–96.0)	94.4 (92.7–96.2)	94.1 (92.4–95.8)	94.5 (92.7–96.3)	0.96
Role-physical function	79.2 (72.9–85.6)	77.7 (71.1–84.2)	79.7 (73.2–86.2)	80.1 (73.9–86.4)	0.95
Bodily pain	74.3 (71.3–77.3)	74.3 (71.2–77.4)	73.5 (70.6–76.3)	74.1 (70.9–77.3)	0.97
General health	59.6 (55.9–63.3)	59.8 (55.8–63.8)	55.7 (51.9–59.5)	61.7 (58.1–65.3)	0.10
Vitality	71.1 (67.7–74.4)	70.0 (66.6–73.5)	70.1 (67.0–73.1)	70.4 (66.6–74.1)	0.96
Social functioning	93.4 (90.1–96.6)	95.5 (92.0–99.0)	96.0 (92.9–99.1)	93.3 (89.6–96.9)	0.58
Role-emotional function	76.3 (69.6–83.0)	69.7 (61.8–77.6)	75.9 (68.9–82.9)	69.8 (62.1–77.6)	0.46
Mental health	74.0 (71.0–77.1)	74.3 (70.8–77.8)	76.3 (73.5–79.0)	75.4 (72.3–78.4)	0.74
Reported health transition	46.4 (42.1–50.6)	48.8 (44.2–53.3)	48.7 (44.5–53.0)	45.6 (41.2–50.1)	0.59

This table shows the assessments of the SF-36 at week 4.

* $P<0.05$ was recognized as significant difference between groups.**4. Discussion**

To the best of our knowledge, this is the first multicenter randomized controlled trial to test the effectiveness of electroacupuncture for patients with IBS-D or FD. Our study result showed that electroacupuncture was equivalent to loperamide in reducing stool frequency in patients with IBS-D or FD. Additionally, electroacupuncture improved stool consistency, the number of days with normal defecation, and quality of life. So our study adds the knowledge that electroacupuncture could be used as a symptom-control modality in patients with chronic functional diarrhea.

In the designing stage of this trial, one of our major concerns was how to confirm the effectiveness of electroacupuncture in reducing stool frequency. We selected loperamide as a positive drug control, as it is recommended as a first-line symptom-control modality for therapy-induced diarrhea^[21,22] and loperamide is also advocated for the treatment of IBS-D.^[29] The major side effect of loperamide is constipation, leading to abdominal distention, which might worsen the symptom of patients with IBS-D.^[30] After consulting gastroenterologists and reviewing the literatures, we suggested participants to stop loperamide if stool consistency was classified as type 4 by the Bristol scale and stool frequency was once daily.^[31] Loperamide would be used again if the diarrhea symptom collapsed.

The treatment regimen of acupuncture is labor-intensive; however, we developed the regimen because: first, this treatment regimen was developed through a review of acupuncture textbooks and literatures; second, the regimen was reviewed by the acupuncturists in China and they strongly recommended a treatment frequency of 5 days/week; third, the practitioners usually provide acupuncture treatment in a frequency of 3 to 5

Table 4
Subgroup analysis.

Outcomes (95% CI)	Time points	He group	Shu-Mu group	He-Shu-Mu group	Loperamide group	P value*
The participants with functional diarrhea Change in stool frequency from baseline		(n=66)	(n=79)	(n=66)	(n=64)	
	Week 4	5.4 (4.3–6.6)	5.8 (4.5–7.1)	5.5 (4.3–6.6)	5.8 (4.4–7.1)	0.90
Bristol score	Week 8	4.6 (3.3–5.9)	5.1 (3.7–6.5)	4.5 (3.1–5.8)	3.6 (2.3–5.0)	0.34
	Week 4	5.2 (5.1–5.4)	5.1 (4.9–5.4)	5.3 (5.1–5.5)	4.9 (4.6–5.2)	0.05
The weekly average number of days with normal defecations	Week 8	5.2 (4.9–5.4)	5.1 (4.9–5.3)	5.3 (5.0–5.5)	5.2 (4.8–5.5)	0.90
	Week 4	3.0 (2.4–3.5)	2.7 (2.1–3.3)	2.1 (1.6–2.6)	3.4 (2.8–4.0)	0.01
The participants with IBS-D Change in stool frequency from baseline	Week 8	2.6 (2.0–3.3)	2.3 (1.8–2.8)	2.2 (1.6–2.8)	2.6 (1.7–3.4)	0.72
		(n=46)	(n=31)	(n=45)	(n=44)	
Bristol score	Week 4	6.0 (4.6–7.3)	4.8 (3.1–6.5)	4.6 (3.1–6.1)	4.1 (2.8–5.5)	0.28
	Week 8	6.2 (4.5–7.9)	6.9 (3.3–10.5)	5.3 (3.7–6.9)	3.5 (2.3–4.8)	0.07
The weekly average number of days with normal defecations	Week 4	5.4 (5.0–5.7)	5.0 (4.4–5.6)	5.4 (5.1–5.6)	5.4 (5.1–5.6)	0.56
	Week 8	5.1 (4.7–5.4)	4.5 (3.9–5.2)	5.1 (4.8–5.5)	5.6 (5.3–5.8)	0.003
	Week 4	2.0 (1.3–2.7)	2.0 (1.1–3.0)	1.9 (1.3–2.6)	2.1 (1.4–2.7)	0.99
	Week 8	2.5 (1.7–3.3)	3.3 (1.8–4.7)	2.3 (1.5–3.1)	1.8 (1.1–2.4)	0.99

95% CI, 95% confidence interval.

* $P < 0.05$ was recognized as significant difference between groups.

times/week in China, so if we provided a treatment frequency lower than 3 times/week, patients might not be compliant to our acupuncture treatment. We assume that acupuncture may not be cost-effective in this treatment frequency of 16 times/month. And in future studies, we will consider a treatment frequency of 2 times/week or less.

There are several explanations for the effect of electroacupuncture on improving stool frequency. First, it is a specific acupuncture therapeutic effect, working through a positive regulation of gastrointestinal motility, brain-gut axis, and visceral hypersensitivity.^[32] Functional bowel disorders are closely related to a dysfunction in brain-gut axis.^[4] Patients with IBS-D were found with dysfunction in the visceral sensory center by positron emission tomography (PET), and acupuncture corrected this dysfunction.^[33] Additionally, activation of neurons in the locus ceruleus contributes to colonic dysfunction, and acupuncture may inhibit the hyper-excitability of the neurons through expression of *N*-methyl-D-aspartate receptor 1 (NR1) in rostral ventromedial medulla.^[32] However, all these mechanisms partly explain the acupuncture effect on diarrhea modulation, so further studies are needed to reveal how acupuncture works. Second, it might be a placebo effect, which plays an important role in functional bowel disorders.^[34] The response rate of functional bowel disorders to placebo varied from 3% to 84%,^[34] which is similar to pain conditions.^[35] A response rate to placebo in patients with IBS ranges from 16.0 to 71.4%,^[36] whereas the response rate to complementary therapies is 42.6%.^[37] Additionally, antidepressants are effective for managing IBS symptoms.^[38] The response to placebo in patients with FD is not clearly studied. Regarding the similar effect of acupuncture in treating IBS-D and FD in our subgroup analysis, we assumed a similar placebo effect in FD patients. The strong placebo effect of acupuncture was reported in treating pain conditions,^[39–41] IBS,^[15] menopausal vasomotor symptoms,^[42] for that clinical relevant difference between true and sham acupuncture was not found. We, therefore, assumed that the acupuncture effect on diarrhea might also be placebo effect. We did not set up a sham control group, because clarifying placebo effect of acupuncture in FD and IBS-D patients was not our primary aim. Third, the effect might be a regression to the mean. Although chronic diarrhea is not self-limited,^[2] there also might be a possible reduction of stool frequency without any treatment.

We found it interesting that the incidence of adverse events was lower in the loperamide group than in the electroacupuncture groups, although significantly between-group difference was not found. Adverse events related to loperamide were constipation (1.7–5.3%), dizziness (1.4%), nausea (0.7–3.2%), and abdominal cramps (0.5–3.0%).^[26] Our study reported only 1 adverse event (hot flush, 0.9%) related to loperamide usage. Regarding that electroacupuncture is equivalent to loperamide in treatment effect but with more adverse events, whether we should use electroacupuncture to treat diarrhea will largely depend on cost-effectiveness.

This study had several limitations. First, we included both FD and IBS-D patients, which caused the risk of imbalance between groups. We used a stratified randomization with the type of diarrhea as a stratification factor, and the result showed that the proportion of participants with IBS-D or FD was comparable between groups. Second, only 8% of the included participants had the experience of acupuncture, which may introduce bias to the study results. However, the proportion of these participants is comparable in the 4 groups, which minimizes the performance bias. Third, 16 sessions of electroacupuncture in this trial is labor intensive and likely to have significant cost implications. The design of this acupuncture protocol is on the basis of a literature review and expert consensus. In addition, patients in China usually receive acupuncture in a frequency of 5 times/week,^[43] so they might not have been compliant to the treatment protocol if we gave acupuncture in a frequency lower than what they expected. Therefore, these acupuncture protocols may be limited to the Chinese population.

In summary, our study confirmed that electroacupuncture was equivalent to loperamide in reducing stool frequency in patients with IBS-D or FD. However, participants using loperamide did not report more adverse events than those using electroacupuncture, so whether electroacupuncture should be recommended for managing IBS-D and FD needs cost-effectiveness studies.

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