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Original Article

Comparison of Electroacupuncture and Mild-Warm Moxibustion on Brain-Gut Function in Patients with Constipation-Predominant Irritable Bowel Syndrome: A Randomized Controlled Trial*

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ABSTRACT **Objective:** To compare the effects of electroacupuncture (EA) and mild-warm moxibustion (Mox) therapies for constipation-predominant irritable bowel syndrome (C-IBS) patients. **Methods:** Sixty C-IBS patients were assigned to 2 groups by simple randomized method, i.e. EA group (30 cases) and Mox group (30 cases). Both EA and Mox treatments were performed on bilateral Tianshu (ST 25) and Shangjuxu (ST 37) for 30 min each time, 6 times per week, for 4 consecutive weeks. The gastrointestinal symptoms and psychological symptoms of the two groups were scored before and after treatment. The effects on the corresponding functional brain areas, namely the anterior cingulate cortex (ACC), insular cortex (IC) and prefrontal cortex (PFC) were observed by functional magnetic resonance imaging (fMRI) before and after treatment. **Results:** Compared with the Mox group, greater improvements in abdominal distension, defecation frequency, difficulty in defecation and stool features were observed in the EA group (all $P<0.01$), both Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores were significantly decreased in the EA group (all $P<0.01$). Finally, decreased activated voxel values were observed in the ACC, right IC and PFC brain regions of EA group with 150 mL colorectal distension stimulation ($P<0.05$ or $P<0.01$). **Conclusions:** Both EA and Mox could significantly improve some of the most intrusive symptoms of C-IBS patients, and EA was more effective than Mox. The therapeutic effect of these two therapies might through modulating of the brain-gut axis function. (Registration No. ChiCTR-TRC-11001349).

KEYWORDS irritable bowel syndrome, constipation, electroacupuncture, moxibustion, randomized controlled trial

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by changes in bowel habits or stool features, continuous or intermittent abdominal pain, bloating or abdominal discomfort, etc.[1] Visceral hypersensitivity has been identified as one of crucial neurological evidences underlying the pathogenesis of abdominal pain in IBS.[2] Both central nervous system (CNS) and enteric nervous system (ENS) involved in the development of the altered endogenous pain processing via their interaction through brain-gut axis.[3] Either central or peripheral alteration in visceral pain processing may cause a dysregulation of the brain-gut axis and result in allodynia and/or hyperalgesia.[4]

Blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) was widely used to measure subtle alterations of blood oxygen level responding to rectal balloon distension,[5,6] therefore can be adopted to identify corresponding brain regions associated with subliminal or supraliminal stimulus.[7]

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Previous studies have observed that abnormal activities in anterior cingulate cortex (ACC), insular cortex (IC) and prefrontal cortex (PFC) are closely related to abdominal pain signaling in IBS patients,[7-9] and by proper managements, those abnormalities could be largely improved along with IBS symptoms.[10]

In China, both electroacupuncture (EA) and moxibustion (Mox) are receiving increasing attention as effective treatments for IBS,[11,12] and our previous study has confirmed the effectiveness of EA and Mox in regulating the abnormal brain activities and improving visceral hypersensitivity in diarrhea-predominant IBS (D-IBS) patients.[13] The current research was to explore whether EA and Mox can also modulate brain-gut function in patients with constipation-predominant IBS (C-IBS). Furthermore, it compares the effects of these two treatments on the primary symptoms of the digestive tract, psychological symptoms, and relevant functional areas of the brain in patients with C-IBS, with the aim of identifying suitable treatments.

METHODS

Diagnostic Criteria

IBS was diagnosed in accordance with Rome Ⅲ diagnostic criteria: recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more of the following symptoms: (1) improvement with defecation; (2) onset associated with a change in frequency of stool; (3) onset associated with a change in form (appearance) of stool. The appearance of symptoms 6 months before the diagnosis and the onset of symptoms in recent 3 months meet the diagnostic criteria.[14,15]

The following symptoms can support the diagnosis of C-IBS: (1) defecation of less than 3 times a week; (2) lumpy or hard stools: a. straining during at least 25% of defecation, b. lumpy or hard stools in at least 25% of defecation; (3) difficulty in defecation; (4) abdominal painor discomfort.[14,15]

Inclusion Criteria

Patients were included when they (1) complied with Rome Ⅲ diagnostic criteria of C-IBS; (2) were 18–65 years old; (3) communicated well with doctors and signed the written informed consents.

Exclusion Criteria

The exclusion criteria were as follows: (1) patients with intestinal organic disease; (2) patients with alternating D-IBS and mixed-IBS; (3) simultaneous application of tegaserod hydrogen maleate, trimebutine free base or Chinese medicine; (4) patients with combined heart, liver, kidney and mental illness; (5) pregnant or lactating women.

Termination Criteria

The termination criteria were as follows: (1) subjects were unable to adhere to treatment; (2) subjects failed to implement treatment program; (3) serious adverse events occurred; (4) serious complications or worsening disease occurred during treatment.

Patients

All C-IBS patients were outpatients of the Department of Gastroenterology in Jinhua Central Hospital from October 2011 to September 2012.[15] The study protocol was approved by the Ethics Committee of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Approved No. 2010-08), and was registered at the Chinese Clinical Trial Register Center (registration No. ChiCTR-TRC-11001349). Before and after treatment, 7 patients in the EA group and 6 patients in the Mox group underwent fMRI examination voluntarily. Another 7 healthy volunteers from Jinhua Municipal Central Hospital staff and college interns, 22–45 years old, were selected to serve as controls.

Sample Size Calculation

Previous studies showed that the effective rates of the acupuncture group was 96.5%[16] and the placebo group was 62%.[17] Based on these values, the sample size in this study was estimated as follows: $n=(U\alpha+U\beta)^2(1+1/k)P(1-P)/(Pe-Pc)$.

The significant level is 0.05; the power of test is $1-\beta=0.9$, $k=1$; and the sample loss rate is 15%. The required sample size was 28 by calculation, and no less than 56 cases should be included in the two groups.

Randomization

A simple random sampling method was used by generating a random number table using the SPSS software, and then random assignment cards were created and sealed in envelops. The envelopes were numbered (the same number as the sequence number of the card inside) kept by a dedicated person. When

a qualified participant was enrolled into the trial, researchers then asked this dedicated person for a random number by telephone, text message, or e-mail, and assigned the participant to EA or Mox group.

Treatment

In the EA group, the acupoints Tianshu (ST 25, bilateral) and Shangjuxu (ST 37, bilateral) were selected. Sterile acupuncture needles (0.30 mm in diameter, 40 mm long, Hwatuo, Suzhou, China) were inserted 20–25 mm into the skin of patients. After twisting and Deqi (patients experience soreness, numbness, distension or heaviness sensation), each acupuncture needle was connected to the electrical leads of the HAN Acupoint Nerve Stimulator (HANS, Model LH 100A TENS, Nanjing Jisheng Medical Technology Co., Ltd., China) for 30 min, with a stimulation frequency of 2 Hz and a stimulation intensity of 3.0 mA.

In the Mox group, the same acupoints were selected, and patients were treated with mild-warm Mox according to the following procedure. The lit moxa (planted in Nanyang, China, moxa cone of 1.5 cm in diameter) was placed 1–2 cm above the acupoints, and the surface temperature of the acupoints was maintained at 46±1 ℃ for 30 min.

Both EA and Mox treatments were applied once per day, 6 times per week, for 4 consecutive weeks. The acupoints were located based on the national GB-12346-90 acupoints standard.[18] All the operators were doctors majored in acupuncture and Mox, and have worked more than 5 years and received unified training before the experiment.

Outcome Measurement

Visual Analogue Scale

The Visual Analogue Scale for IBS (VAS-IBS)[19] was adopted to assess the major gastrointestinal symptoms of C-IBS patients. The monitored symptoms included abdominal pain, abdominal distension and difficulty in defecation. Using the VAS-IBS, patients were instructed to record the overall severity of each item on a 100-mm-long line, which was later converted to a 10-point scale ranging from 0 to 10 (no pain, VAS=0; severe, VAS=8 to 10).

Bristol Stool Form Scale

The Bristol Stool Form Scale[20] was adopted to assess C-IBS feces. The scale is descriptive and visual and consists of 7 types of stool, including images and their respective definitions as follows: 1=separate hard lumps, such as nuts (hard to pass); 2=sausage-shaped but lumpy; 3=sausage-shaped but with cracks on the surface; 4=like an Italian sausage or snake, smooth and soft; 5=soft blobs with clear-cut edges (passed easily); 6=fluffy pieces with ragged edges, a mushy stool; 7=watery, no solid pieces, entirely liquid.

Defecation Frequency per Week

A measure of defecation frequency per week was generated for C-IBS patients.[21] The daily number of stools were calculated and registered at each visit. At the end of treatment period, both the patients' and the practitioners' opinions about the overall efficacy of the treatment were recorded.

Mental and Psychological Assessment

The Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD) were adopted for the assessment of mental and psychological status of C-IBS patients. Scores on the HAMA were graded as follows: ⩾14–20, mild anxiety, 1 point; ⩾21–28, moderate anxiety, 2 points; ⩾29, severe anxiety, 3 points. Scores on the HAMD were graded as follows: ⩾8–19, mild depression, 1 point; ⩾20–34, moderate depression, 2 points; ⩾35, severe depression, 3 points.[22,23]

All the measurements mentioned above were taken before treatment as well as directly, 1 and 3 month(s) after treatment.

Rectal Distensions

All subjects with colorectal distension (CRD) were stimulated. Fasting participants were instructed to relax and lie on the MRI examination bed. A volume-controlled plastic balloon (50 mm in length; 20 mm in diameter; with a maximum volume of 320 mL, Hefei Austrian Bio-technology Co. Ltd.) was placed in the rectum, 10–15 cm from the anal margin. Gas was progressively injected. The amount of gas injected when subjects first reported various sensations, including initial perception threshold, urgent defecation threshold and maximum pain threshold, was recorded. Gas was again injected progressively, and the subjects' responses on the feeling scale were again recorded as the balloon reached 50, 100 and 150 mL dilatation. VAS was adopted for the feeling scale (no pain=0 and

pain or defecation that could not be tolerated=10). An fMRI imaging was performed using a block design in which 30 s of distension alternated with 30 s of balloon inflation, with 3 cycles of repeated distension as a sequence. The stimulation volumes were 50, 100 and 150 mL, resulting in a total of 3 sequences. Each manual gas injection was completed within 6 s.

fMRI Scanning

The structural and functional images were acquired on a Siemens 1.5 T MRI system (MagnetomAvanto, Siemens Healthcare, Germany) with a standard head coil. Three-dimensional structural images of participants were obtained by T1-weighted magnetization-prepared rapid-acquisition gradient echo pulse sequence [repetition time (TR), 1900 ms; echo time (TE), 2.91 ms; flip angle, 15° ; data matrix, 256 $mm^2 \times 256$ mm^2; field of view (FOV), 250 $mm^2 \times 250$ mm^2; thickness of slices, 2 mm]. BOLD contrast functional images were obtained by T2-weighted gradient-recalled echo-planar sequence (TR = 3560 ms; TE = 50 ms; data matrix, 64 $mm^2 \times 64$ mm^2; FOV, 192 $mm^2 \times 192$ mm^2; thickness of slices, 3 mm). Transversal images of ACC, IC and PFC regions with a slice thickness of 3 mm and a 0.3-mm slice gap were recorded for further analysis.

Safety Assessment

In this study, possible adverse events during EA and Mox included dizziness, nausea, sweating, pale skin, skin burns, blisters, pruritus, and respiratory symptoms. All adverse events and adverse reactions were accurately recorded. If an adverse event occurred after treatment, a necessary treatment was provided as appropriate for the circumstances of the event in question.

Statistical Analyses

The statistical software SPSS 16.0 (Chicago, USA) was used for statistical analysis. All data were expressed as mean ± standard deviation ($\bar{x} \pm s$). For normally distributed variables, the two independent sample *t* test was used to test differences between the groups before treatment and repeated measures were used to test differences within and between groups after treatment. For abnormally distributed variables, a non-parametric test was used, and the Wilcoxon rank sum test was used for comparison between the two groups and paired tests. $P<0.05$ was considered significant.

RESULTS

Baseline Characteristics

A total of 63 C-IBS patients were randomly assigned to either EA group (31 cases) or Mox group (32 cases), 1 patient in the EA group and 2 patients in the Mox group did not complete the study. Finally 60 patients (30 in each group) completed the study and were included in the statistical analysis (Figure 1). There were no significant differences in age (40.40 ± 12.67 *vs.* 42.33 ± 8.68, year) or disease duration (9.14 ± 7.35 *vs.* 6.96 ± 5.23, year) between the two groups ($P>0.05$).

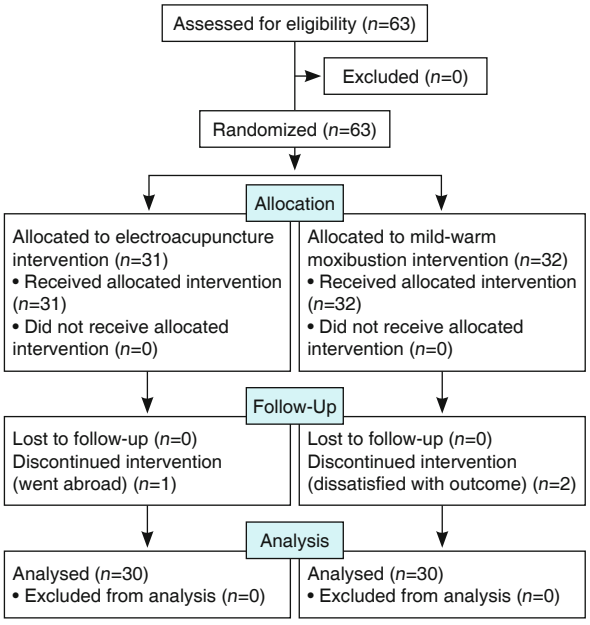

Figure 1. Flow Chart of the Trial for C-IBS Patients

Scale Observation of Main Gastrointestinal Symptoms

The main gastrointestinal symptoms were not significantly different between EA and Mox groups before treatment ($P>0.05$). Compared with before treatment, both the EA and Mox groups reported significant improvements in abdominal pain, abdominal distention directly, 1 and 3 month(s) after treatment ($P<0.05$ or $P<0.01$), and the EA group reporting significantly greater improvements in abdominal distention than the Mox group directly after treatment ($P<0.01$). Compared with before treatment, the EA group reported significant improvements in defecation frequency, reduced difficulty in defecation and improvements in stool form directly, 1 and 3 month(s) after treatment ($P<0.05$ or $P<0.01$). And improvements in the EA group were significantly greater than those in the Mox group directly and 1 month after treatment ($P<0.01$, Table 1).

Chin J Integr Med 2018 May;24(5):328-335

Table 1. Comparison of Therapeutic Effects of EA and Mox on Main Gastrointestinal Symptoms before and after Treatment (Score, $\bar{x} \pm s$)

Group	Symptom	Case	Before treatment	Directly after treatment	One month after treatment	Three months after treatment
EA	Abdominal pain	21	3.79 ± 1.85	1.43 ± 1.23**	1.94 ± 1.74**	2.93 ± 2.73*
	Abdominal distension	29	6.27 ± 2.33	1.78 ± 1.51**△	3.72 ± 3.03**	4.86 ± 2.79**
	Defecation per week (Frequency)	30	2.77 ± 0.77	5.37 ± 1.13**△	5.20 ± 1.10**△	3.10 ± 0.84*
	Difficulty in defecation	30	6.41 ± 2.23	2.28 ± 1.25**△	3.11 ± 1.98**△	5.61 ± 2.32*
	Stool form	30	1.50 ± 0.73	3.37 ± 0.67**△	3.03 ± 0.61**△	2.83 ± 0.65**△
Mox	Abdominal pain	21	3.90 ± 1.89	1.61 ± 1.32**	2.22 ± 2.09**	3.16 ± 2.25*
	Abdominal distension	29	5.94 ± 1.78	3.15 ± 1.62**	3.53 ± 2.34**	4.74 ± 2.36**
	Defecation per week (Frequency)	30	2.73 ± 0.94	3.03 ± 1.07	2.97 ± 1.00	2.87 ± 0.97
	Difficulty in defecation	30	6.65 ± 1.91	5.81 ± 1.98*	5.76 ± 2.11*	5.98 ± 2.15
	Stool form	30	1.70 ± 0.79	1.93 ± 0.83	1.86 ± 0.78	1.80 ± 0.81

Notes: *P<0.05, **P<0.01 *vs*. before treatment; △P<0.01 *vs*. Mox group at the same time. EA: electroacupuncture; Mox: moxibustion

HAMA and HAMD Scores

There were no significant differences in HAMA and HAMD scores between the two groups before treatment (P>0.05). Compared with before treatment, C-IBS patients in the EA group reported significant improvements in anxiety and depression directly, 1 and 3 month(s) after treatment (P<0.01), and the EA group reported significantly greater improvements than the Mox group (P<0.01, Figure 2).

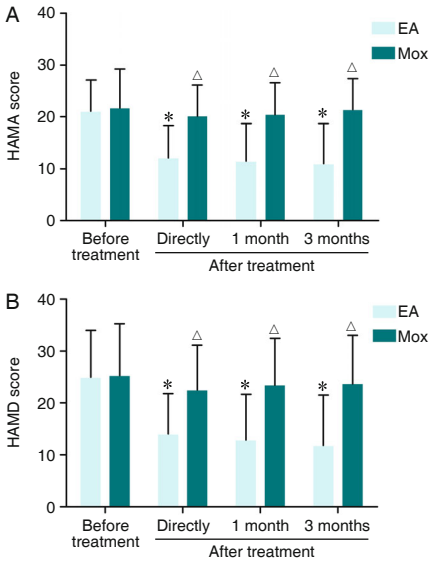

Figure 2. Comparison of HAMA and HAMD Scores in EA and Mox Groups before and after Treatment ($\bar{x} \pm s$)

Notes: *P<0.01 *vs*. before treatment; △P<0.01 *vs*. EA group at the same time. EA: electroacupuncture; Mox: moxibustion; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale

Rectal Sensory Thresholds and VAS Scores

Before treatment, there were significant decreases in urgent defecation thresholds and maximum pain thresholds as well as increases in VAS scores under 100 and 150 mL CRD for both groups compared with healthy controls (P<0.05 or P<0.01). Compared with before treatment, significant increases in the urgent defecation threshold and maximum pain threshold as well as decreases in VAS scores under 100 and 150 mL CRD were observed in the EA group after treatment (P<0.05 or P<0.01). Improvements in the EA group were significantly greater than those in the Mox group (P<0.05, Figure 3).

fMRI Activation Brain Relative Functional Areas

Before treatment, compared with healthy controls,

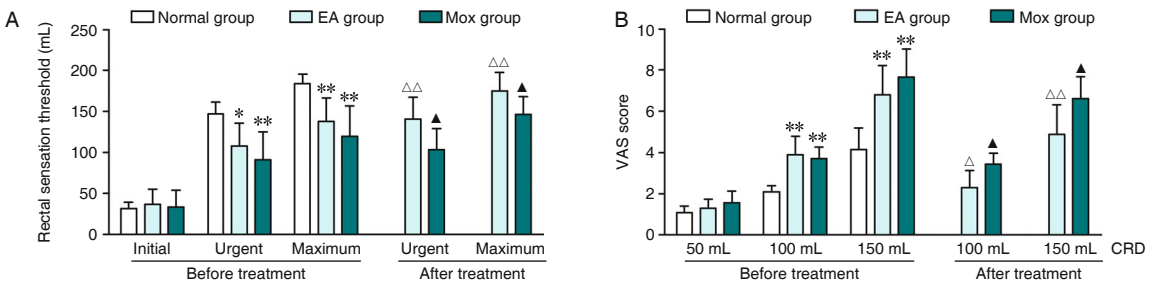

Figure 3. Rectal Sensation Thresholds and VAS Scores ($\bar{x} \pm s$)

Notes: *P<0.05, **P<0.01 *vs*. normal group; △P<0.05, △△P<0.01 *vs*. before treatment; ▲P<0.05 *vs*. EA group after treatment. EA: electroacupuncture; Mox: moxibustion; VAS: Visual Analogue Scale; CRD: colorectal distension

the ACC, right IC and PFC in patients of EA and Mox groups were significantly activated under 150 mL CRD (P<0.05 or P<0.01). Significantly lower voxel values for the activation of relative functional areas of the brain were observed in patients of the EA group after treatment, with decreased ACC, right IC and PFC under 150 mL CRD (P<0.05, Figure 4).

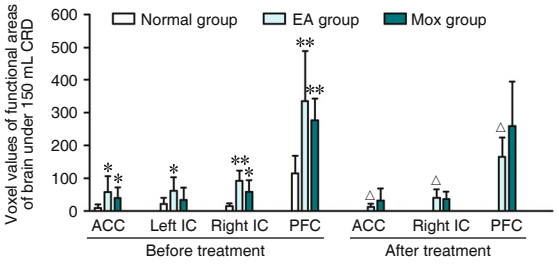

Figure 4. fMRI Activation Brain Relative Functional Areas ($\bar{x} \pm s$)

Notes: $^{*}P$<0.05, $^{**}P$<0.01 *vs*. normal group; $^{\triangle}P$<0.05 *vs*. before treatment. EA: electroacupuncture; Mox: moxibustion; CRD: colorectal distension; ACC: anterior cingulate cortex; IC: insular cortex; PFC: prefrontal cortex

Function brain map of fMRI activation area at the rectal distension of 150 mL are showed in Figure 5.

Safety

There was no serious adverse event during this clinical trial. One patient in the Mox group experienced a mild burn during Mox treatment, no special treatment was required except for topical ointment.

DISSCUSSION

Previous studies have confirmed that acupuncture and Mox are effective treatments for IBS, as they can regulate brain-gut axis and improve visceral hyperactivity.[12,24] But the difference in their mechanism between EA and Mox is unclear.

In the IBS patients, abdominal pain may result from increased afferent input from the gut to the brain, central alterations in the signals from the gut ("central pain amplification") or both.[7,25,26] The application of technologies such as fMRI has shown that the activation of brain areas related to pain and emotion in the IBS patients significantly differs from that of healthy controls, with enhanced or reduced activation of ACC, IC and PFC.[8,27,28] Our research found that before treatment, the defecation urgency threshold and maximum pain thresholds of C-IBS patients were significantly reduced compared with those of healthy controls. Moreover, under 100 and 150 mL CRD stimulation, the VAS scores increased significantly, suggesting decreased intestinal pain threshold and visceral hypersensitivity in IBS patients. Using fMRI, we also observed that the ACC, right IC and PFC were activated under 150 mL CRD stimulation among C-IBS patients (P<0.05), indicating an association between visceral hypersensitivity and the central nervous system. This further confirms the abnormal brain-gut function in IBS. After treatment, significant improvements were observed for the EA group with regard to VAS scores at 100 and 150 mL CRD and defecation urgency threshold. These data suggest that EA therapy can alleviate visceral hypersensitivity in C-IBS patients. Although there were no significant differences with regard to fMRI data between EA and Mox groups, it is not entirely clear that EA and Mox have the same effects on the ACC, right IC and PFC areas of the brain. It is possible that the lack of a significant difference is due to the

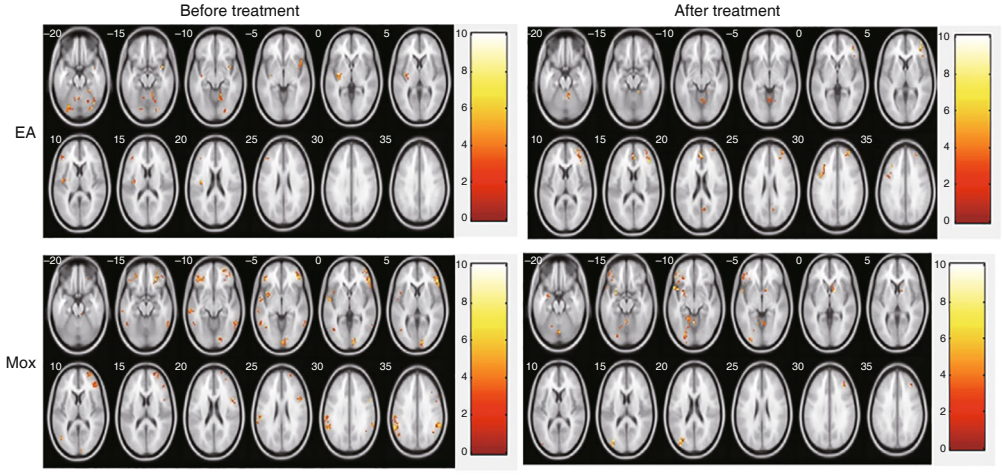

Figure 5. Functional Brain Map in C-IBS Patients

Note: fMRI activation area at the rectal distension of 150 mL

limited sample size. Therefore, an expanded pool of participants is needed for future in-depth research.

In the present research, C-IBS patients in both groups reported apparent abdominal discomfort and pain for CRD of approximately 100 mL and increased abdominal discomfort and pain following CRD stimulation. For this reason, the current research used 100 mL as the cut-off point for the threshold in IBS patients. We found that there were significantly more activated voxels in the ACC area of the brain in patients in both groups compared with healthy controls. Furthermore, this activation was coupled with increased abdominal discomfort and pain when participants under 150 mL CRD, which was above the threshold. This proves the involvement of the ACC area of the brain in the processing of pain signals. Only patients in the EA group exhibited significantly decreased activated voxels in the ACC area compared with before treatment, suggesting that EA therapy is more effective than Mox in improving pain signals.

Additionally, we found that C-IBS patients exhibited increased activated voxels in the right IC compared with healthy controls at 150 mL CRD. From the perspective of imaging anatomy, when the functional connectivity of the insular cortex of two sides is different, the functional connection area of the right lobe is broader than the left.[29] Therefore, unilateral right lobe activation in C-IBS patients may be associated with altered functional connectivity between the lobes of the two sides. The EA treatment group exhibited decreased activated voxels in the right IC following 150 mL CRD compared with before treatment, and the Mox treatment group exhibited no significant changes. At the same time, we observed an increase in PFC activated voxels in C-IBS patients before treatment compared with healthy controls following 150 mL CRD. This result may be due to a projection to the PFC via increased ACC and IC stimulation signals. The EA group exhibited a significant reduction in the number of PFC-activated voxels following 150 mL CRD compared with before treatment, whereas the Mox group exhibited no significant difference.

In addition, some scholars have focused on IBS patients with depression or anxiety and other psychological conditions and found a correlation between gastrointestinal symptoms, the severity of mental states and the altered activation of certain brain regions in these patients.[30,31] Improvements in emotional state reduce brain activation, providing objective evidence for the influence of psychological factors on the pathogenesis of IBS.[10] Clinically, a small emotional stimulation can aggravate or induce gastrointestinal symptoms in IBS patients. The repetition of this phenomenon causes anxiety or depression and other psychological symptoms of varying degrees in a considerable number of IBS patients. These experiences can further aggravate the patients' gastrointestinal symptoms through brain-gut interactions.[32] The two reinforce each other, resulting in patients' experience of tremendous mental suffering and economic pressure and additional challenges for the treatment of IBS. In the current research, we found that EA therapy not only more effectively relieved the major gastrointestinal symptoms of C-IBS patients than Mox, but it also effectively treated patients' anxiety, depression and other psychological symptoms. Therefore, once IBS patients' abdominal pain, bloating or discomfort, stool features, difficulty and abnormal frequency in defecation and other gastrointestinal symptoms are significantly or continually improved, their anxiety, depression and other psychological symptoms also decrease or disappear.

In conclusion, our findings demonstrated that both EA and Mox had good therapeutic effects on C-IBS abdominal pain, bloating or abdominal discomfort, whereas EA is more effective than Mox in improving defecation frequency, constipation, difficulty in defecation and other main gastrointestinal symptoms, alleviating depression or anxiety and other psychological symptoms, as well as affecting brain-related functional areas.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Wu HG and Shi Y were responsible for the conception and design of this study. Zhao JM, Yin XJ, Lu JH and Chen YH recruited the participants and acquired data. Lu JH, Chen XK and Chen YH performed acupuncture and moxibustion treatment. Tang WJ performed fMRI data collection and analysis. Zhao JM, Lu JH, Yin XJ, Wu LY, and Bao CH performed further data acquisition and extraction, re-analyzed the data. Zhao JM drafted the manuscript. Jin XM, Shi Y and Wu HG revised the manuscript. All authors reviewed and approved the final manuscript.

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