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Transcutaneous Electrical Acustimulation Improves Irritable Bowel Syndrome With Constipation by Accelerating Colon Transit and Reducing Rectal Sensation Using Autonomic Mechanisms

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INTRODUCTION: **Slow colon transit and visceral hypersensitivity are recognized as major pathophysiological mechanisms in irritable bowel syndrome with constipation (IBS-C). However, there is a lack of therapies targeting both abdominal pain and colonic motility. This study was designed to investigate the long-term effects and possible mechanisms of transcutaneous electrical acustimulation (TEA) in patients with IBS-C.**

METHODS: **Fifty-two patients with IBS-C were randomized into 2 groups: daily TEA for 4 weeks (n = 26) and daily sham-TEA for 4 weeks (n = 26). The number of complete spontaneous bowel movements per week (CSBMs/week, primary outcome), Irritable Bowel Syndrome Severity Scoring System, Patient Assessment of Constipation Quality of Life, visual analog scale (VAS) pain score, colonic transit time, and anorectal physiology were evaluated before treatment and at the end of the treatment. Colonic transit was assessed with radiopaque markers. Electrocardiograms were recorded for assessing autonomic functions.**

RESULTS: **(i) TEA improved constipation and abdominal pain. After the treatment, the number of CSBMs/week during the last week in the TEA group was higher than that in the sham-TEA group (3.5 ± 1.6 vs 2.3 ± 0.6, $P = 0.002$). Similar effects were also noted in the visual analog scale pain score ($P = 0.002$) and Irritable Bowel Syndrome Severity Scoring System score ($P = 0.025$). In addition, there was a significant improvement in the quality of life of patients with constipation. The Patient Assessment of Constipation Quality of Life total score was significantly decreased in the TEA group ($P = 0.004$). (ii) Compared with sham-TEA, TEA improved colon transit ($P = 0.002$) and increased the threshold of rectal sensation (desire to defecate, $P = 0.004$; maximum tolerability, $P < 0.001$). (iii) TEA increased vagal activity, compared with sham-TEA ($P < 0.05$); at the end of the treatment, the vagal activity was significantly correlated with colon transit and the CSBMs/week.**

DISCUSSION: **TEA improves constipation and symptoms of IBS by accelerating colon transit and reducing rectal sensation, possibly mediated by using the autonomic mechanisms.**

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with symptoms including abdominal pain and altered bowel habits in the absence of detectable structural abnormalities (1). IBS is estimated to affect up to 20% of the US population according to a recent survey conducted by the American Gastroenterology Association and results in reduced quality of life and high healthcare costs (2). IBS can be categorized into 4 subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits, and IBS unclassified (3).

IBS-C includes a wide range of symptoms, and its pathophysiology is complex and not fully understood. Visceral hypersensitivity (increased sensation in response to stimuli) and delayed gut transit are recognized as major pathophysiological mechanisms in IBS-C (4). Visceral hypersensitivity may account for symptoms of abdominal pain, bloating, and discomfort. Delayed gut transit causes constipation. The conventional management for IBS-C

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includes dietary fiber, a fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, laxatives, linaclotide, lubiprostone, tegaserod, cognitive behavioral therapy, peppermint oil, and selective serotonin reuptake inhibitor antidepressant (1). However, the treatment of IBS-C is still unsatisfactory; it is particularly difficult to concurrently treat constipation and abdominal pain because most of pain medications worsen constipation.

Acupuncture has been applied for treating functional gastrointestinal diseases (5). PC6 (Neiguan) and ST36 (Zusanli) are the most commonly used acupuncture points. Electroacupuncture (EA) is a combination of acupuncture and electrical stimulation. In the past few years, transcutaneous electrical acustimulation (TEA), a noninvasive method that replaces needles by surface electrodes, has been found to improve chronic constipation, postoperative recovery, abdominal pain, and functional dyspepsia (6–8). However, it is unknown whether TEA is capable of concurrently improving constipation and abdominal pain.

With the replacement of acupuncture needles by surface electrodes, TEA can be performed at home daily or even a few times daily, which improves therapeutic outcomes. In addition, TEA only uses a few acupuncture points that are near peripheral nerves; for example, it uses ST36 that is near peroneal, sciatic, and tibial nerves and PC6 that coincides with the medial nerve. By stimulating these specific acupoints with optimized parameters, TEA has been consistently shown to improve autonomic functions (7,9). However, it is unknown whether TEA is able to improve autonomic functions in patients with IBS who have been reported to exhibit low vagal tone and greater sympathetic drive.

Based on published studies and pathophysiological mechanisms of IBS-C, TEA at ST36 and PC6 using the previously established parameters is hypothesized to improve both constipation and abdominal pain by accelerating colon transit and reducing rectal sensation mediated using the autonomic pathway. A placebo-controlled randomized clinical trial was performed to investigate the effects of TEA on constipation and abdominal pain, physiological effects of TEA on colon transit and rectal sensation, and mechanisms involving autonomic functions in patients with IBS-C.

MATERIALS AND METHODS

Study subjects

This study was conducted from August 2018 to July 2019 at Sir Run Run Shaw Hospital. Fifty-two patients with IBS-C (34 women, mean age 50.5 ± 16.7 years) were enrolled in this study. This study was approved by the Ethical Review Committee of Sir Run Run Shaw Hospital, and consent was obtained from the subjects before the experiment.

Men and women aged 18–75 years who met the Rome IV diagnostic criteria for IBS-C were eligible for study enrollment (10). Exclusion criteria were as follows: (i) took medications known to cause constipation; (ii) any organic diseases that might induce constipation such as colorectal cancer, metabolic disorders, multiple sclerosis, or neurological disorders; (iii) organic diseases of the small or large intestine such as ulcerative colitis and Crohn's disease; (iv) had a history of gastrointestinal surgery (other than appendectomy or cholecystectomy); (v) mechanical obstruction; (vi) had a serious concomitant disease of the heart, liver, or kidney or diabetes; (vii) pregnant or lactating women; (viii) severe psychiatric disorders or any medical condition associated with IBS-C; (ix) allergic to surface electrodes; or (x) knowledgeable of acupoints and meridians that might unblind the treatment.

Study design and protocol

This was a single-center, single-blind, randomized controlled trial. After a 2-week run-in period, patients were randomly divided into 2 groups: TEA and sham-TEA. The patients were trained by an unblinded study team member for placing stimulation electrodes in the right locations. Randomization of sham and real TEA treatment with a ratio of 1:1 was determined by a computer-generated random digital table. The sample size was estimated based on a previous study (7,11,12) in which TEA was used for treating functional constipation. This resulted in a sample size of 42 patients with 80% power and an α value of 0.05 with the use of the number of spontaneous bowel movements per week as the primary outcome. With a titration of 20% for noncompliance, the total estimated sample size was 52 patients.

During the run-in and treatment periods, patients with weekly bowel movements less than 3 were allowed to use polyethylene glycol as rescue medicine and the dosage was recorded. The patients were asked to record a stool diary and visual analog scale (VAS) every day during the 4-week study period and to complete the IBS Severity Scoring System (IBS-SSS) and IBS-QOL scores every week. The stool diary included bowel movement, stool quality, time of defecation, degree of difficulty of defecation, sensation of complete emptying, manual manipulation, and medication use.

At the end of the run-in period but before the treatment and at the end of the 4-week treatment, electrocardiogram (ECG), colonic transit, and high-resolution anorectal manometry were performed. Six months after the termination of the treatment, the patients were requested to complete a stool diary for 1 week; the IBS-SSS and VAS were assessed again. The study protocol is detailed in Figure 1.

TEA and sham-TEA treatment

Acupoints PC6 (Neiguan) and ST36 (Zusanli) were chosen for the TEA therapy based on several previous studies (7,9). The location of ST36 is at the depression inferior to the tibia tubercle and 1-finger breadth (the patient's thumb finger) from the anterior of the crest of the tibia. ST36 is near peroneal, sciatic, and tibial nerves. PC6 is located on the inner side of the wrist, at the place of one-sixth of the distance from the cubital crease to the palmar wrist crease. PC6 coincides with the medial nerve. Sham-TEA was the same as TEA except that stimulation was applied at the non-acupoints (not on any meridian). The sham point for PC6 was 10 cm away from PC6 (upper to the elbow) at non-acupoints, and the sham point for ST36 was 2–4 cm lateral and 10 cm below ST36. A watch-size digital stimulator (SNM-FDC01, Ningbo MedKinetic, Ningbo, China) was used to deliver electrical stimulation (Figure 2). The stimulation parameters were set as follows: a train on-time of 2 seconds and off-time of 3 seconds, pulse width of 0.5 ms, pulse frequency of 25 Hz, and amplitude of 2–10 mA (at the maximum level tolerated by the subject). This set of parameters was previously shown to improve gastrointestinal motility and enhance vagal activity (6,9). TEA or sham-TEA was performed for 1 hour, twice daily (8 AM and 8 PM), lasting for 4 weeks (7,11).

Symptom assessment

Primary outcome measurements. 1. The number of CSBMs per week: A spontaneous bowel movement (SBM) was defined as a

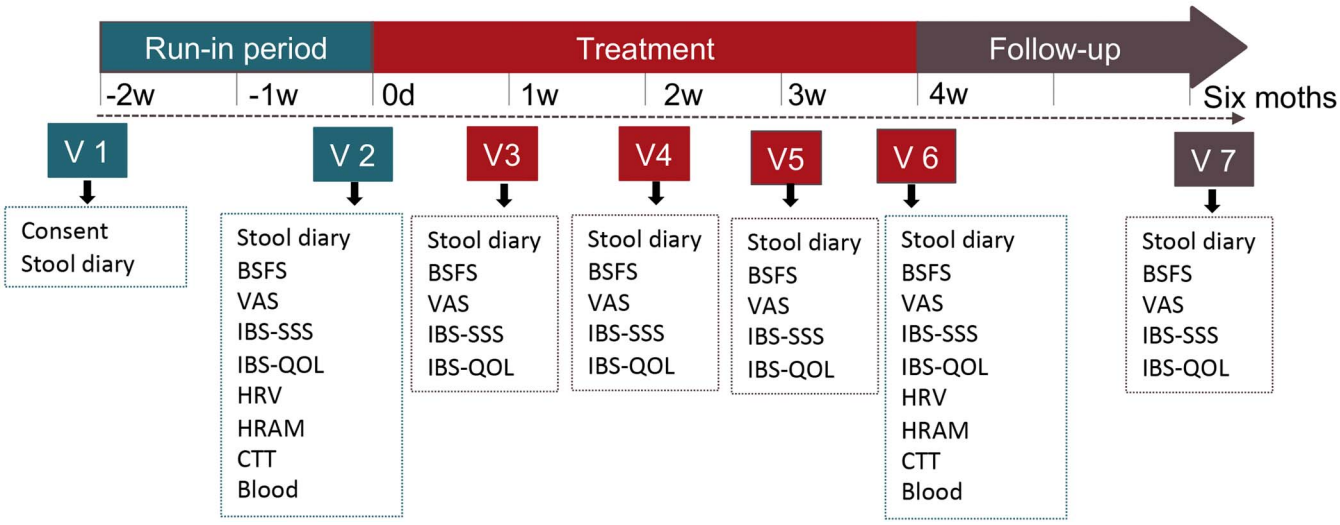

Figure 1. Study schedule. BSFS, Bristol Stool Form Scale; CTT, colonic transit time; HRAM, high-resolution anorectal manometry; HRV, heart rate variability; IBS-QOL, IBS Quality of Life questionnaire; IBS-SSS, IBS Symptom Severity Scale; VAS, visual analog scale.

bowel movement not induced by laxatives or manual manipulation; a CSBM was defined as an SBM with a sensation of complete evacuation. This measurement was obtained from the stool diary.

Secondary outcome measures

1. Stool quality (Bristol Stool Form Scale), straining severity, sensation of anorectal obstruction, and time of defecation were documented in the bowel diary. Straining and the sensation of anorectal obstruction were scored on a 5-point severity scale (0 [absent] to 4 [very severe]). This information was retrieved from the stool diary.
2. Abdominal pain was assessed by a VAS questionnaire, from 0 (normal) to 10 (most intolerable). The average pain scores during 1 week before the treatment and during the last week of the treatment were used for analysis.
3. IBS-SSS: The IBS-SSS is a reliable scale for evaluating the severity of IBS, which covers the degree of abdominal pain, frequency of abdominal pain, degree of abdominal distention, defecation satisfaction, and degree of disturbance in life. The full score for each item was 100 points, summing to a total score of 500 points. The higher the score, the more severe the symptoms. According to the IBS-SSS, the severity of IBS was divided into mild (75–175), moderate (175–300), and severe (>300) (13). The IBS-SSS during the 10 days before the treatment and the IBS-SSS during the last 10 days of the treatment were used in statistical analysis.
4. IBS Quality of Life (IBS-QOL): The IBS-QOL questionnaire was used to assess the quality of life of patients with IBS. The scale consisted of 8 dimensions (irritability, interference with activities, body image, health concerns, food avoidance, social response, sex, and interpersonal relationship), which were subdivided into 34 items. The total IBS-QOL score ranged from 34 to 170, with a higher score indicating a better quality of life. The score of each field was converted into a score of 0–100 using the following formula: converted score = (original score − possible lowest score)/possible score range * 100 (14). The IBS-QOL during the 7 days before the treatment and the IBS-QOL during the last 7 days of the treatment were used for analysis.

High-resolution anorectal manometry

High-resolution anorectal manometry (Sierra Scientific Instruments, Los Angeles) was performed to evaluate anorectal sensory and motor functions. Rectoanal pressures were measured at rest, during squeezing, and during simulated evacuation. The analyzed high-resolution anorectal manometry parameters included anal canal length, resting anal pressure, anal squeeze pressure, anal endurance squeeze pressure, push maneuver, rectoanal inhibitory reflex, and rectal sensations. The initial sensory volume, defecation desire threshold, and maximum tolerance were measured by continuous balloon distention (15).

Heart rate variability

A heart rate variability (HRV) signal was derived from the ECG. The ECG was recorded using a 1-channel amplifier (Ningbo

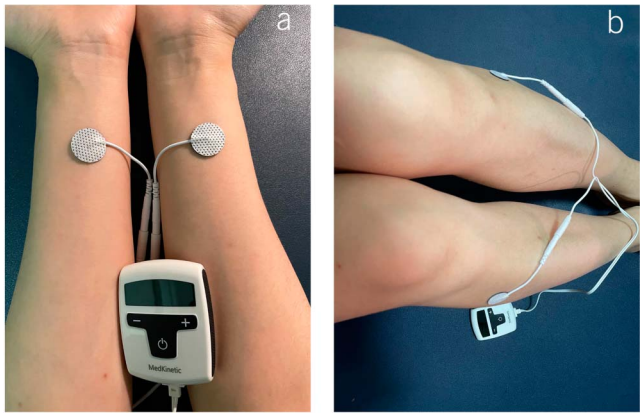

Figure 2. Transcutaneous electrical acustimulation. Two pairs of surface electrocardiogram electrodes were applied at bilateral PC6 (**a**) and ST36 (**b**), respectively. Two watch-size digital stimulators were used to deliver electrical stimulation.

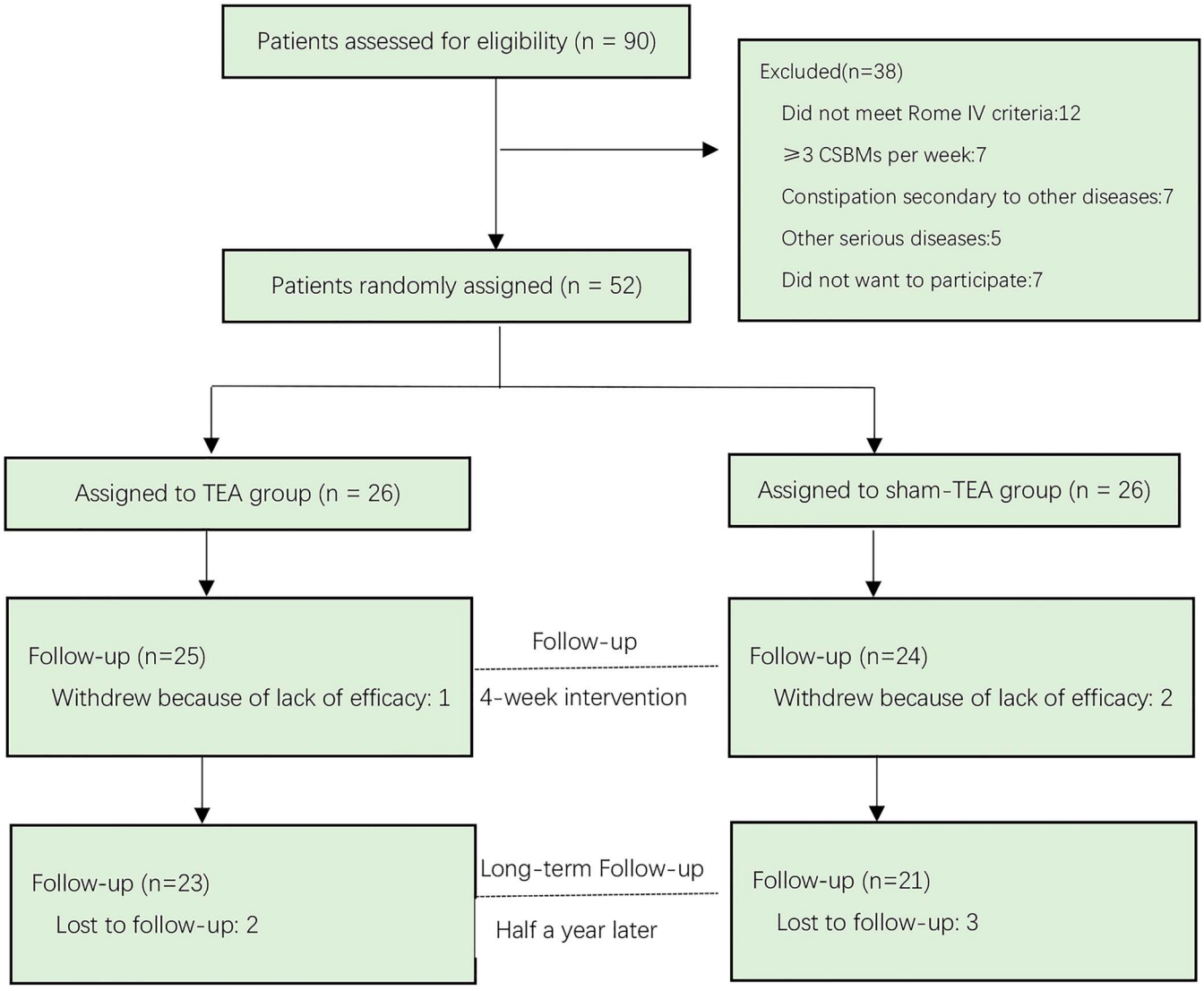

Figure 3. Flowchart of the study design.

Maida Medical Device, Ningbo, China). Three ECG electrodes were placed on the abdomen: 1 at the apex area of the heart, 1 at the right edge of the sternum, and a reference electrode at the right side of the abdomen (11).

The following frequency domain parameters were calculated using the power spectral analysis of the HRV signal: low-frequency power (LF power, 0.04–0.15 Hz) reflecting mainly sympathetic activity, high-frequency power (HF power, 0.15–0.50 Hz) reflecting purely vagal activity, and the LF/HF ratio (8). The ratio of LF/HF reflects the balance between sympathetic and parasympathetic activities (16,17).

Colonic transit study

Colonic transit was assessed by a simplified radiopaque marker method. The patient took a capsule containing 20 radiopaque markers on day 0. Abdominal radiographs were obtained at 72 hours after administration of the capsule, and markers that remained in the gut were counted. The marker excretion rate (MER) = (20-NI)/20, where NI is the sum of the markers present in the entire x-ray film(s) (18,19).

Blood draw and assay

The autonomic function was also assessed by plasma pancreatic polypeptide (PP) and norepinephrine (NE). Blood samples were collected at baseline and at the end of TEA/sham treatment. Human enzyme-linked immunosorbent assay (ELISA) kits (Thermo Fisher Scientific, American, Cat. No. EH357RB, Shanghai Jiya Biological Technology, Ltd., China, Lot. No. YS01685B) were used for the analysis of plasma PP and NE. Absorbance was read at 450 *nm* in a plate reader.

Long-term follow-up

After the termination of the TEA/sham-TEA treatment, the patients were followed up for 6 months. Six months after the treatment, the patients were asked to complete a stool diary for

Table 1. Demographic data and disease characteristics at baseline

	TEA	Sham-TEA	*P* Value
Patient(n)	26	26	
Age, yr	51.4 ± 16.2	49.6 ± 17.5	0.70
Male, n (%)	9 (34.6%)	10 (38.5%)	0.77
BMI (kg/m2)	21.2 ± 2.8	22.5 ± 2.5	0.07
Disease duration (mo)	16.65 ± 9.74	12.2 ± 7.1	0.07
CSBMs/week	1.5 ± 0.7	1.8 ± 0.6	0.11
Bristol Stool Form Scale	1.69 ± 0.5	1.65 ± 0.5	0.84
VAS pain score	3.2 ± 1.2	3.4 ± 1.1	0.65
IBS-SSS score	249.2 ± 89.48	252.9 ± 68.4	0.86
IBS-QOL score	74.1 ± 14.5	74.6 ± 12.1	0.89

CSBMs/week, complete spontaneous bowel movements per week; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; TEA, transcutaneous electrical acustimulation.

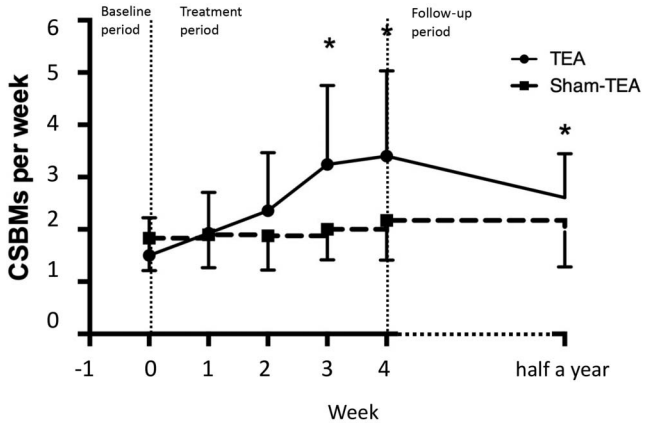

Figure 4. Weekly CSBMs during the study. TEA progressively improved constipation throughout weeks 1–4. The differences in weekly CSBMs between groups were significant for the treatment (from weeks 3–4) and follow-up periods ($P < 0.05$). CSBMs = complete spontaneous bowel movements; TEA, transcutaneous electrical acustimulation.

1 week (the last week of the follow-up period) for the calculation of the complete spontaneous bowel movements per week (CSBMs/week).

Statistical analysis

Quantitative variables are reported as mean ± SD. Categorical data were compared using the χ^2 test. The independent sample Student *t* test was performed to assess the difference in the measurement between the TEA and sham-TEA groups. $P < 0.05$ was considered statistically significant. Pearson correlation analysis was used to determine the correlation of the autonomic functions and CSBMs. Data were analyzed by statistical software SPSS 26.0.

RESULTS

Patient demographics and baseline characteristics

Ninety patients were screened; 52 of them (34 female, mean age 50.5 ± 16.7) were qualified for this study and randomized into sham-TEA (26 patients) and TEA (26 patients) groups. One patient in the TEA group and 2 patients in the sham-TEA group were dropped from this study (Figure 3). Demographic data are summarized in Table 1. There was no significant difference in baseline characteristics between the 2 groups.

Effects of TEA on constipation and symptoms of IBS

As shown in Figure 4, TEA progressively improved constipation throughout weeks 1–4 and this improvement was not noted with sham-TEA. During the fourth week of the treatment, the number of CSBMs/week in the TEA group was significantly higher than that in the sham-TEA group (3.5 ± 1.6 vs 2.3 ± 0.6, $P = 0.002$). At the end of the treatment, 11 patients (44%) in the TEA group reported to have 3 or more CSBMs/week, compared with 1 patient (4.2%) in the sham-TEA group ($P = 0.001$). At the end of the follow-up (6 months after the treatment), the number of CSBMs/week decreased to 2.6 ± 0.7 in the TEA group but was still higher than that in the sham-TEA group (2.1 ± 0.6, $P = 0.011$ vs TEA).

The average BSFS score during the fourth week of the treatment in the TEA group was significantly higher than that in the sham-TEA group (2.9 ± 0.9 vs 1.9 ± 0.7, $P < 0.001$). TEA also decreased the degree of straining compared with that in sham-TEA (1.96 ± 0.7 vs 2.6 ± 0.8, $P < 0.001$). During the entire 4-week treatment period, the percentage of medication usage in the TEA group was lower than that in the sham-TEA group (16.0% vs 37.5%, $P < 0.001$).

The average pain score during the fourth week of the treatment assessed by the daily VAS was significantly lower with the TEA therapy than that with the sham-TEA therapy (1.34 ± 1.1 vs 2.32 ± 1.0, $P = 0.002$); the IBS-SSS score during the last 10 days of the treatment was also lower with the TEA therapy than that with the sham-TEA therapy (161.7 ± 85.8 vs 217.9 ± 83.6, $P = 0.025$). Moreover, the IBS-QOL score during the last 7 days of the treatment was higher in the TEA group than that in the sham-TEA group (86.4 ± 9.5 vs 76.5 ± 12.8, $P = 0.004$) (Figure 5).

Mechanisms of TEA involving colonic motility and anorectal function

Colonic motility was assessed by the radiopaque marker study. The 4-week TEA treatment accelerated colon transit in comparison with the sham treatment (Figure 6). At the end of the treatment, the MER was 71.6% ± 15.7% with TEA but 47.92% ± 31.3 with sham-TEA ($P = 0.002$).

A subgroup analysis was performed in 24 patients with slow transit constipation (13 in the TEA group and 11 in the sham-TEA group). TEA improved both constipation and colon transit in these patients at the end of the 4-week treatment: (i) The number of CSBMs/week in the TEA group was higher than that in the sham-TEA group (3.7 ± 1.8 vs 1.9 ± 0.5, $P = 0.006$) and (ii) the percentage of radiopaque markers expelled from the gut at 72 hours was significantly higher in the TEA group than that in the sham-TEA group (72.5% ± 19.6 vs 23.6% ± 16.9, $P < 0.001$).

The TEA treatment reduced rectal sensitivity to balloon distention. At the end of the treatment, TEA increased the distention threshold volume for desire to defecate (85.0 ± 16.8 vs 73.3 ± 8.2, $P = 0.004$) and for maximum tolerance (204.4 ± 18.3 vs 165.1 ± 43.0, $P < 0.001$) in comparison with sham-TEA (Table 2).

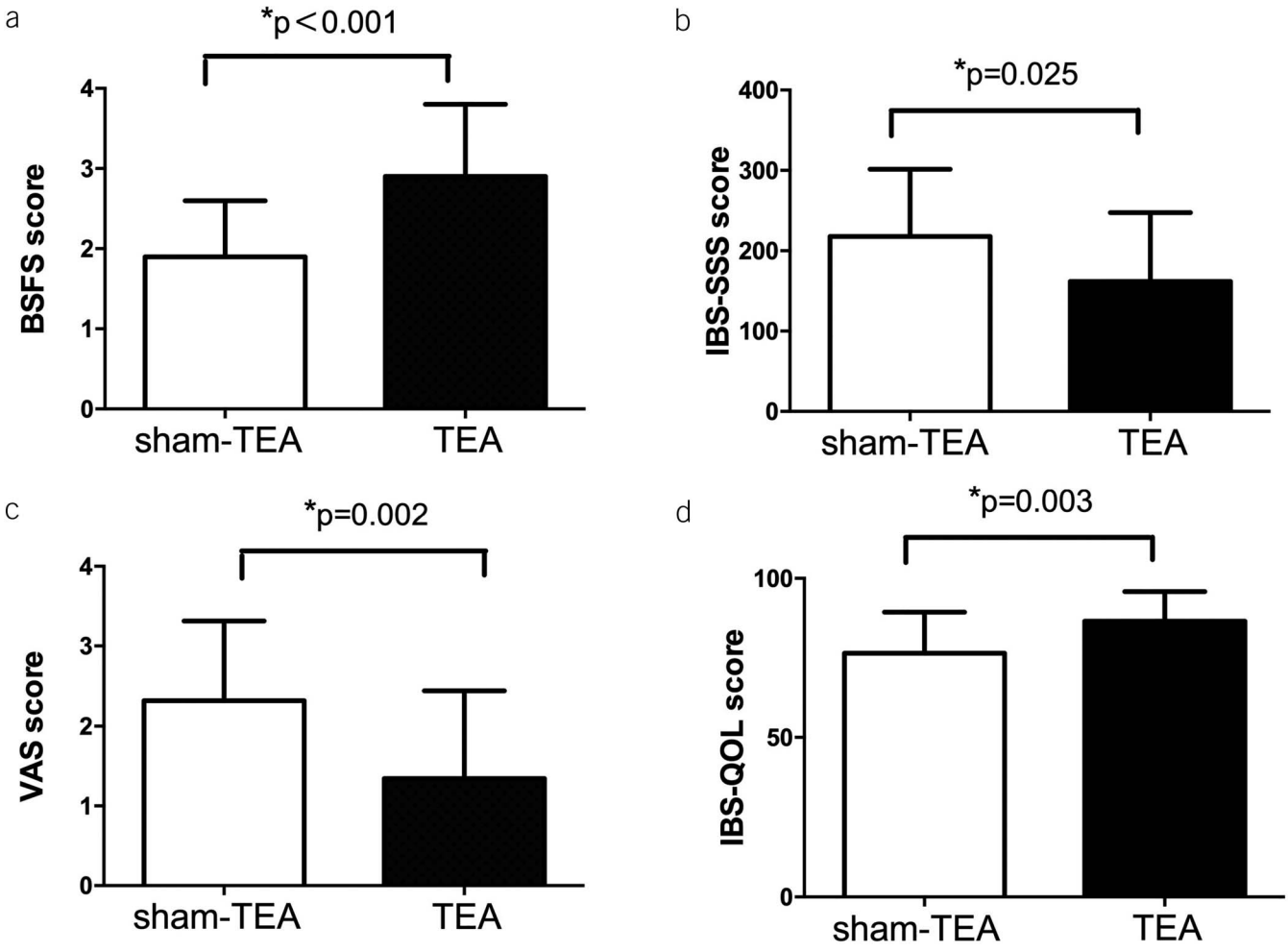

Figure 5. Effects of TEA on symptoms of irritable bowel syndrome with constipation and IBS-QOL. TEA increased the BSFS score (**a**) and IBS-QOL score (**d**). TEA decreased the IBS-SSS (**b**) and VAS scores (**c**). At baseline, both groups n = 26; after treatment, TEA group, n = 25 and sham-TEA group, n = 24. BSFS, Bristol Stool Form Scale; VAS, visual analog scale; IBS-QOL, Irritable Bowel Syndrome Quality of Life; IBS-SSS, IBS Symptom Severity Scale; TEA, transcutaneous electrical acustimulation.

Mechanisms of TEA involving autonomic functions

The 4-week TEA treatment enhanced vagal activity assessed by both spectral analysis of HRV and plasma PP. At the end of the treatment, the vagal activity (HF) in the TEA group was significantly higher than that in the sham-TEA group (0.67 ± 0.13 vs 0.54 ± 0.16, $P = 0.004$). The sympathovagal ratio (LF/HF) was lower with TEA compared with sham-TEA (0.58 ± 0.45 vs 1.01 ± 0.68, $P = 0.013$). Compared with sham-TEA, TEA increased the plasma level of PP (197.1 ± 80.6 vs 128.9 ± 46.3, $P < 0.001$) and decreased the level of NE (278.1 ± 48.6 vs 311.8 ± 70.8, $P = 0.06$) (Figure 7).

Furthermore, the vagal activity was found to be positively correlated with colon transit and CSBMs/week. At the end of the treatment, Pearson correlation analysis was used to determine the correlation of PP and HF with the MER and CSBMs/week in both TEA and sham-TEA groups. The MER was positively correlated with the plasma level of PP ($r = 0.697$; $P < 0.001$) and HF ($r = 0.507$; $P < 0.001$), suggesting that vagal activity was correlated with colonic transit (Figure 6). The CSBMs/week was positively correlated with MER ($r = 0.698$; $P < 0.001$). The average VAS score during the last week of the treatment was weakly correlated with the maximum tolerable volume ($r = -0.295$; $P = 0.04$) (Figure 8).

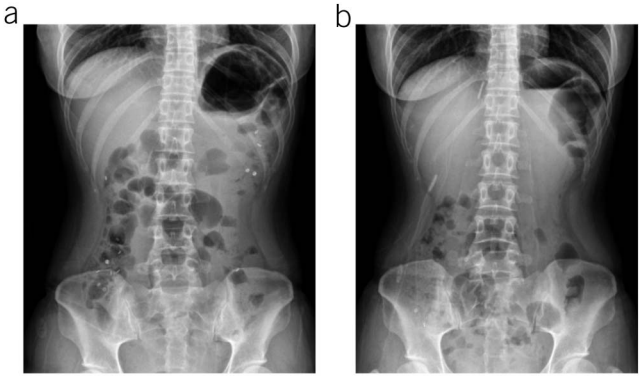

Figure 6. Colonic transit time (CTT) was assessed by radiopaque markers. Abdominal radiographs were obtained at baseline (**a**) and after transcutaneous electrical acustimulation (**b**).

Table 2. Anorectal function before and after TEA/sham-TEA treatment

	TEA		Sham-TEA	
	Baseline	TEA	Baseline	Sham-TEA
Anal sphincter				
Anal rest pressure (mm Hg)	71.0 ± 3.2	69.8 ± 3.6	70.9 ± 2.9	70.8 ± 3.1
Maximal squeeze pressure (mm Hg)	157.4 ± 10.5	162.3 + 8.7	153.2 ± 21.4	159.2 ± 11.4
Duration of anal contraction (s)	11.8 ± 0.6	11.8 + 0.5	12.1 ± 0.6	12.0 ± 0.6
Relaxion during push (%)	21.8 ± 5.3	22.9 ± 4.7	21.5 ± 4.6	21.3 ± 4.8
Sensation to rectal distention				
First sensation (mL)	47.7 ± 7.6	47.2 ± 7.3	45.4 ± 7.0	46.7 ± 7.5
Desire of defecation (mL)	74.2 ± 15.0	85.0 ± 16.8*	71.9 ± 14.9	73.3 ± 8.2
Maximum tolerable volume (mL)	176.1 ± 47.7	204.4 ± 18.3*	171.7 ± 48.1	165.1 ± 43.0
Rectal pressure (mm Hg)	44.9 ± 4.1	47.1 ± 10.0	46.5 ± 3.2	46.2 ± 3.2

TEA, transcutaneous electrical acustimulation.

DISCUSSION

In this study, we found the following: (i) TEA improved constipation symptoms and alleviated abdominal pain in patients with IBS-C. The effect of TEA lasted for 6 months. TEA also improved the quality of life assessed by the Patient Assessment of Constipation Quality of Life. (ii) Physiologically, TEA

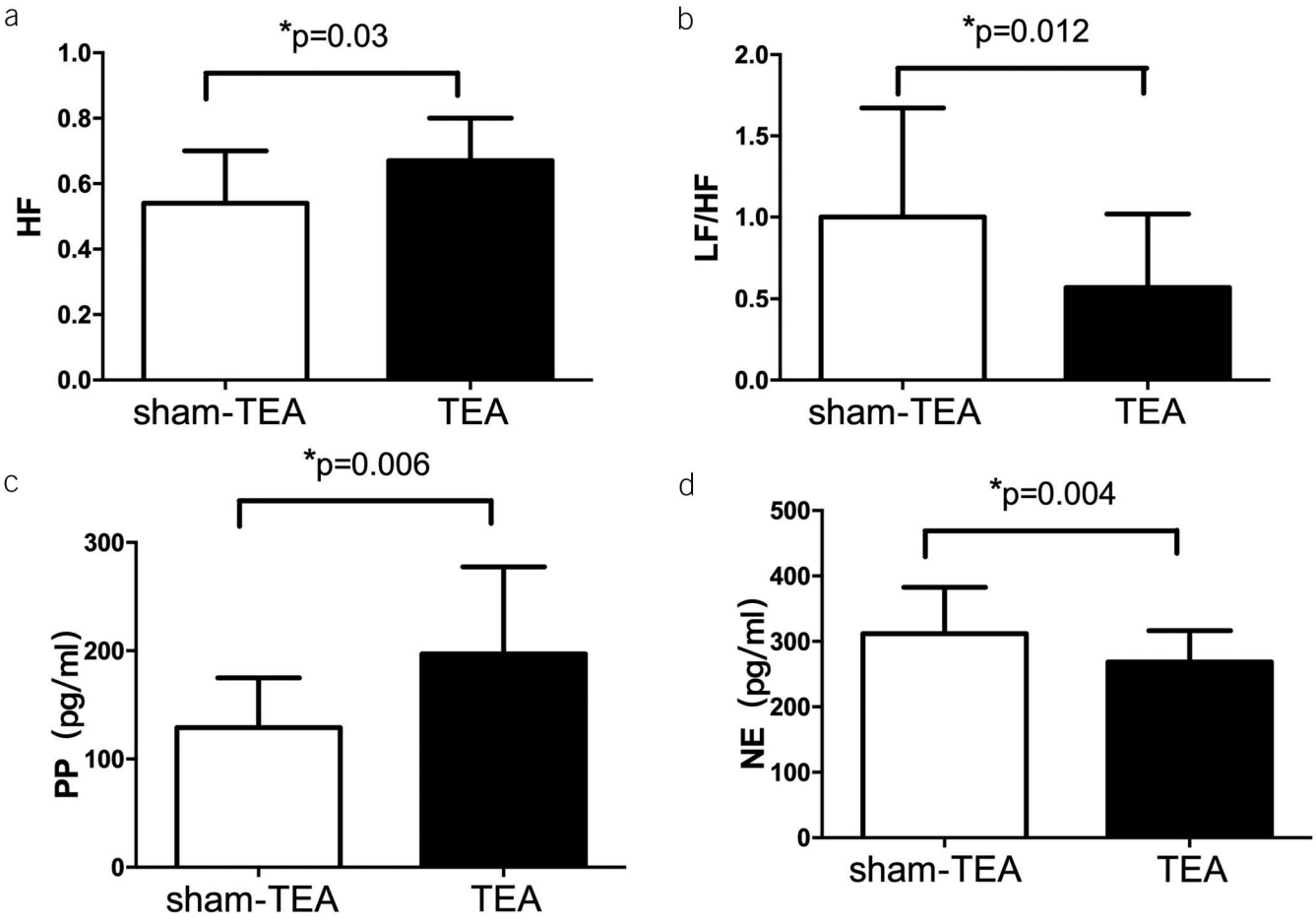

Figure 7. Effects of TEA on autonomic function. (**a**) TEA significantly increased HF ($P = 0.004$). (**b**) TEA significantly decreased sympathetic activity (LF/HF) ($P = 0.013$). (**c**) The TEA group had increased the level of PP ($P < 0.001$). (**d**) The TEA group had increased the level of NE ($P = 0.06$). LF/HF, sympathetic activity; NE, norepinephrine; PP, pancreatic polypeptide; TEA, transcutaneous electrical acustimulation. HF, high-frequency band.

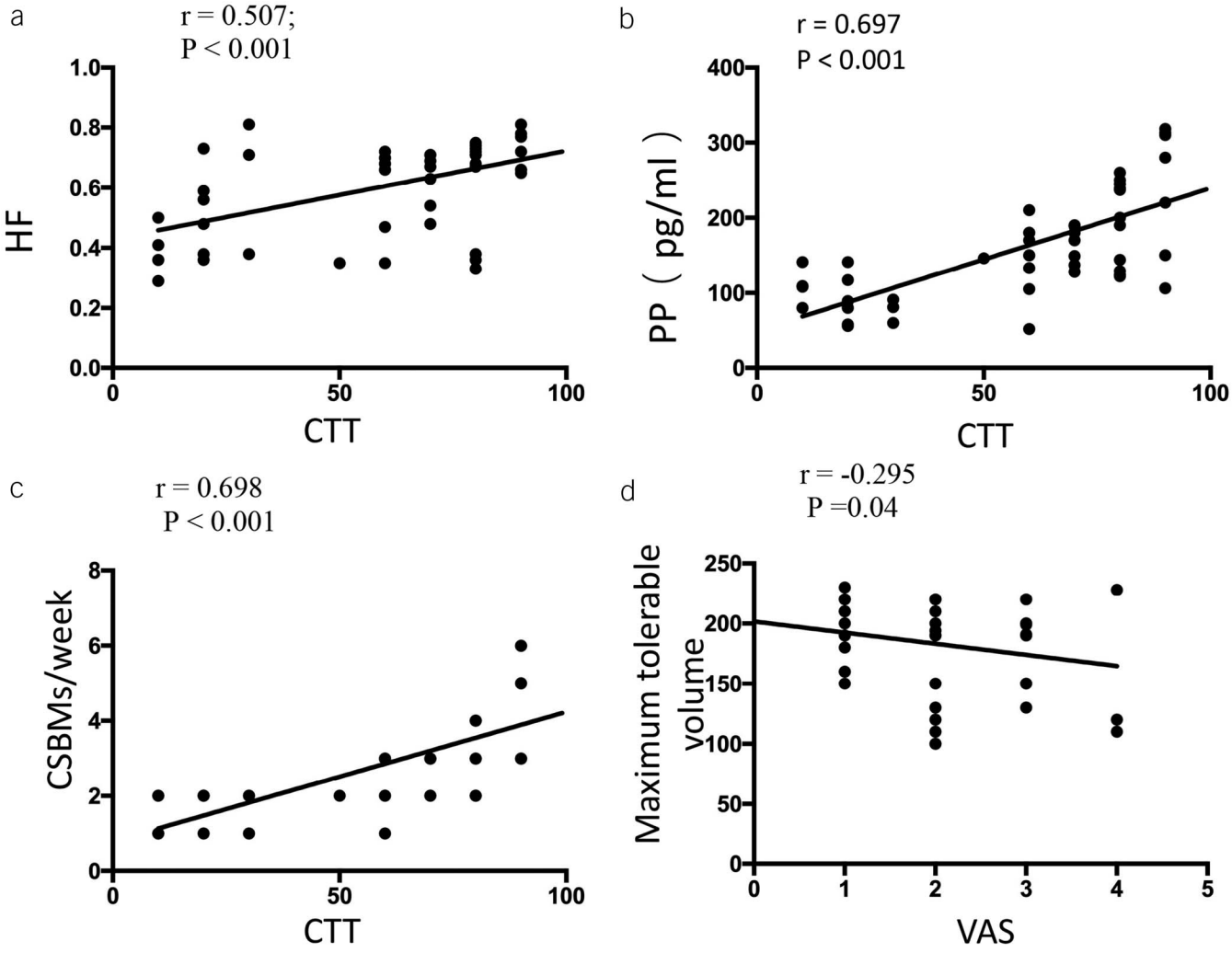

Figure 8. The correlation between autonomic function, CTT, and CSBMs/week. HF (**a**) and PP (**b**) positively correlated with CTT. CTT positively correlated with CSBMs/week (**c**). The VAS score was weakly negatively correlated with the maximum tolerable volume after treatment. CSBMs, complete spontaneous bowel movements; CTT, colon transit time; PP, pancreatic polypeptide; TEA, transcutaneous electrical acustimulation. HF, high-frequency band.

accelerated colon transit and increased the threshold of rectal sensation. (iii) Mechanistically, TEA increased vagal activity assessed by the spectral analysis of HRV and serum level of PP and also decreased sympathetic activity assessed by the serum level of NE. (iv) The Pearson analysis revealed significant correlations between vagal activity and colon transit, between colon transit and the number of CSBMs, and between vagal activity and the number of CSBMs. These findings seemed to suggest that TEA enhanced vagal activity and the enhanced vagal activity led to the acceleration of colon transit, resulting in an increased number of CSBMs.

In this study, TEA improved both constipation and abdominal pain. After the 4-week therapy, TEA substantially increased the number of CSBMs/week and constipation was resolved in 44% (those with CSBMs ≥ 3). These profound effects were in agreement with several previous studies and unlikely attributed to single-blinding. Although this study was single-blinded, the symptom questionnaires were completed by the patients (blinded) independently without any interference from the person who was in contact with the patients; data analysis was performed by an investigator who was blinded to the nature of the treatment. In a previous placebo-controlled, crossover study, TEA at ST36 was also shown to improve the frequency of spontaneous defecation after 2 weeks of therapy (7). Shi et al. (11) found that transcutaneous auricular vagal nerve stimulation (taVNS) increased the number of CSBMs/week by more than 4-folds in comparison with the baseline and reduced the total dosage of emergency laxatives usage. Similar findings were also reported in EA studies. Liu et al. (20) reported that EA increases the number of CSBMs in patients with chronic severe functional constipation compared with sham-EA. In another study, Liu et al. (21) showed that EA was noninferior to prucalopride for the treatment of severe chronic constipation.

In addition to the improvement in the symptoms of constipation, our study also showed that TEA improved the CTT assessed using radiopaque markers. Previously, EA at ST36 was reported to shorten distal colon transit time and whole gut transit time in a rat model of constipation (22). Similar findings were reported in other rodent studies: EA increased contractility of the distal colon measured by manometry (23) and accelerated colonic

motility and whole gut transit time (22). To the best of our knowledge, this study was the first clinical study to demonstrate that TEA increases colonic transit in patients with IBS-C.

Meanwhile, we noted a substantial reduction in the abdominal pain score during the last week of the treatment and IBS-SSS score during the last 10 days of the treatment with TEA in comparison with sham-TEA. A few previous studies have also reported the therapeutic effects of acupuncture/EA on IBS symptoms. In an open-labeled pilot study, Chan et al. (24) reported a significant improvement in symptoms of bloating at the end of acupuncture treatment. In a controlled clinical study in 43 patients with IBS, A Schneider et al. (25) showed that both the acupuncture and sham acupuncture improved the quality of life and suggested purely placebo effects. The authors suggested that 566 patients with IBS were needed to prove the efficacy of acupuncture in comparison with sham acupuncture. The same group later reported that real acupuncture, but not sham acupuncture, increased the parasympathetic tone and improved pain in patients with IBS (26). Recently, in a randomized, placebo-controlled trial, transcutaneous auricular vagal nerve stimulation (taVNS) was reported to improve abdominal pain in patients with IBS-C (11). A meta-analysis of 6 randomized controlled trials showed a significant efficacy of acupuncture for treating IBS (27).

In this study, we found that TEA increased the threshold of rectal sensation and exhibited ameliorating effects on visceral hypersensitivity in IBS-C. Visceral hypersensitivity is a characteristic of patients with IBS and could account for abdominal pain (28). Improvement in visceral hypersensitivity with EA has been reported. In a rat model of IBS, EA attenuated visceral hyperalgesia by inhibiting the enhanced excitability of colon dorsal root ganglion neurons (29). Zhao et al. found that EA improved IBS visceral hypersensitivity by inhibiting the activation of astrocytes in the medial thalamus and anterior cingulate cortex (30). In a controlled clinical study with 7 patients with IBS-D, TEA increased the threshold for rectal sensation of gas, desire to defecate, and pain (31). In another study, TEA increased the rectal sensory thresholds of patients with IBS-D (32). We found that abdominal pain (VAS score) was negatively correlated with rectal sensation, but the correlation was weak. We speculated that TEA increased the threshold of rectal sensation; the improvement in visceral hypersensitivity resulted in improvement in abdominal pain.

One may argue that the reduction in rectal sensation might worsen constipation by decreasing urge in patients with IBS-C. Two major problems with IBS-C include visceral pain (could be attributed to rectal hypersensitivity) and constipation (could be attributed to reduced rectal sensation or urge to defecate). That is, a patient with IBS-C might have increased rectal sensation due to visceral hypersensitivity or reduced rectal sensation associated with constipation. In this study, we found that the distention threshold of desire to defecate was 71.3 mL at baseline and 85 mL after TEA treatment (Table 2). Both of these values were lower than the average value of 90 mL in healthy Chinese volunteers (33). These findings indicated that TEA improved rectal "hypersensitivity" instead of inducing "rectal hyposensitivity". Accordingly, the improvement in rectal sensation would not worsen constipation.

In addition to rectal sensation and colon transit, we also investigated the effect of TEA on pelvic floor dysfunction (PFD) and found that none of the anorectal manometric parameters associated with PFD were altered with TEA (Table 2). Subgroup analysis revealed that 7 patients (4 in the TEA group and 3 in the sham-TEA group) in this study had PFD and that TEA did not improve symptoms in 3 of the 4 patients with PFD. These preliminary findings seemed to suggest that TEA may be ineffective in treating patients with PFD.

Autonomic dysfunction is considered 1 of the major causes of IBS. Previous studies have reported that subjects with IBS are characterized by a reduction in vagal activity (34,35). Vagal activity is difficult to measure directly. In this study, spectral analysis of HRV and the plasma level of PP were used to represent the level of vagal activity. We found that TEA increased the HF and decreased the LF/HF by using spectral analysis of the HRV (36). The effect of EA or TEA on vagal activity and sympathetic activity has been consistently reported in numerous studies. In animals, EA was reported to enhance vagal activity and decrease sympathetic activity (22,37). In humans, EA or TEA at ST36 and PC6 with appropriate parameters was shown to balance the sympathovagal activities in patients with gastrointestinal disorders (7,38,39). However, the exact neural pathway involved in the regulation of the autonomic nervous system is not completely known. Basic and clinical studies have suggested that EA activates peripheral nerves, sending afferent signals to the enteric nervous system, resulting in an enhanced vagal efferent flow to the gastrointestinal tract and leading to improved gastrointestinal motility (40–42). In this study, we found that the vagal nerve activity was correlated with colon transit and colon transit was correlated with the number of CSBMs. Accordingly, we speculated that TEA enhanced vagal activity; the enhanced vagal activity led to acceleration of colon transit and acceleration of colon transit resulted in improvement in constipation. The results suggested that autonomic function plays an important role in constipation.

There were several limitations in this study. This was a single-center study with a relatively small sample size. The patients were followed up for only 6 months and the longer term effect of TEA is still unknown. Thus, further studies are needed to investigate how long the efficacy may last after termination of the TEA treatment. Moreover, the possible analgesic mechanism involving in rectal sensation or rectal hypersensitivity deserves further investigation in patients with more severe pain because the pain severity was mild to moderate in this study.

In conclusion, TEA at ST36 and PC6 with a specific set of parameters improves constipation and abdominal pain in patients with IBS-C and the clinical effect can be partially maintained after termination of the therapy. The improvement in IBS-C symptoms might be attributed to the integrative effects of TEA on colonic motility and rectal sensation mediated by the autonomic mechanism.

CONFLICTS OF INTEREST

Guarantor of the article: Ning Dai, MD.

Specific author contributions: Z.H. and Z.L. contributed equally. Study design: Z.H., J.C., and N.D. Data acquisition: Z.L., Z.H., H.C., and X.Z. Data analysis: B.C., L.D., and Z.L. Manuscript preparation: Z.H., Z.L., J.C., and N.D.

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Study Highlights

WHAT IS KNOWN

- ✓ Slow colon transit and visceral hypersensitivity are recognized as major pathophysiological mechanisms in IBS-C.
- ✓ It is particularly difficult to concurrently treat constipation and abdominal pain.
- ✓ Transcutaneous electrical acustimulation (TEA) has been shown to enhance gastrointestinal motility and improve abdominal pain.

WHAT IS NEW HERE

- ✓ TEA improved constipation symptoms and alleviated abdominal pain in patients with IBS-C. The effect of TEA lasted for six months.
- ✓ TEA accelerated colon transit and increased the threshold of rectal sensation.
- ✓ TEA enhanced vagal activity. The vagal activity was correlated with colon transit and the number of CSBM.

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