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Acupuncture for Chronic Severe Functional Constipation

A Randomized, Controlled Trial

Zhishun Liu, MD, PhD; Shiyan Yan, PhD; Jiani Wu, MD; Liyun He, MD, PhD; Ning Li, MD; Guirong Dong, MD; Jianqiao Fang, MD, PhD; Wenbin Fu, MD; Lixin Fu, MD, PhD; Jianhua Sun, MD, PhD; Linpeng Wang, MD; Shun Wang, MD; Jun Yang, MD; Hongxing Zhang, MD; Jianbin Zhang, MD, PhD; Jiping Zhao, MD; Wei Zhou, MD; Zhongyu Zhou, MD; Yanke Ai, PhD; Kehua Zhou, MD, DPT; Jia Liu, MD, PhD; Huanfang Xu, MD, PhD; Yuying Cai, MD, PhD; and Baoyan Liu, MD

Background: Acupuncture has been used for chronic constipation, but evidence for its effectiveness remains scarce.

Objective: To determine the efficacy of electroacupuncture (EA) for chronic severe functional constipation (CSFC).

Design: Randomized, parallel, sham-controlled trial. (Clinical Trials.gov: NCT01726504)

Setting: 15 hospitals in China.

Participants: Patients with CSFC and no serious underlying pathologic cause for constipation.

Intervention: 28 sessions of EA at traditional acupoints or sham EA (SA) at nonacupoints over 8 weeks.

Measurements: The primary outcome was the change from baseline in mean weekly complete spontaneous bowel movements (CSBMs) during weeks 1 to 8. Participants were followed until week 20.

Results: 1075 patients (536 and 539 in the EA and SA groups, respectively) were enrolled. The increase from baseline in mean weekly CSBMs during weeks 1 to 8 was 1.76 (95% CI, 1.61 to 1.89) in the EA group and 0.87 (CI, 0.73 to 0.97) in the SA group (between-group difference, 0.90 [CI, 0.74 to 1.10]; $P < 0.001$). The change from baseline in mean weekly CSBMs during weeks 9 to 20 was 1.96 (CI, 1.78 to 2.11) in the EA group and 0.89 (CI, 0.69 to 0.95) in the SA group (between-group difference, 1.09 [CI, 0.94 to 1.31]; $P < 0.001$). The proportion of patients having 3 or more mean weekly CSBMs in the EA group was 31.3% and 37.7% over the treatment and follow-up periods, respectively, compared with 12.1% and 14.1% in the SA group ($P < 0.001$). Acupuncture-related adverse events during treatment were infrequent in both groups, and all were mild or transient.

Limitations: Longer-term follow-up was not assessed. Acupuncturists could not be blinded.

Conclusion: Eight weeks of EA increases CSBMs and is safe for the treatment of CSFC. Additional study is warranted to evaluate a longer-term treatment and follow-up.

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For author affiliations, see end of text.
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Chronic constipation affects approximately 16% of the world's population (1), 17.1% of persons in Europe (2), 12% to 19% of those in North America (3), and 10.8% of those in Asia (1). Patients with severe chronic constipation have complete spontaneous bowel movements (CSBMs) no more than twice per week, with hard stools, frequent straining, and the sensation of incomplete evacuation (4). Most chronic constipation is functional and is associated with decreased quality of life (5).

Laxatives produce only temporary relief, and constipation tends to reoccur after discontinuing medication (6, 7). Nearly half of patients are dissatisfied with their traditional therapies, such as laxatives (8). Other treatment options may include prokinetic agents. In a trial, 1 to 2 mg of prucalopride (an agonist for 5-hydroxytryptamine receptor 4) per day was reported to normalize BMs in 37.9% of patients with severe chronic constipation (9). However, the adverse cardiac effects induced by some prokinetic agents cannot be ignored (10), and their long-term effects remain unknown.

A systematic review supports the use of acupuncture for chronic constipation (11), and our previous study indicates that electroacupuncture (EA) might have some sustained effects (12). However, the evidence for the therapeutic effects of acupuncture is limited because many randomized, controlled trials have had small sample sizes or other methodological limitations (11).

Our goal was to determine the efficacy of EA for the treatment of chronic severe functional constipation (CSFC) over an 8-week treatment period and evaluate the maintenance of effects throughout the 12-week follow-up. We hypothesized that EA would be superior to sham EA (SA) at both end points.

Methods

Design Overview

We conducted a multicenter, randomized, parallel, sham-controlled trial at 15 sites in China. The study duration per patient was 22 weeks: 2 weeks before randomization (baseline assessment); 8 weeks of treatment; and 12 weeks of follow-up without treatment. Researchers screened candidates for study participation, and experienced physicians at digestive or anorectal departments made diagnoses.

See also:

Summary for Patients 1

Web-Only

Supplement

Participants

Participants were included if they met the diagnosis of functional constipation based on the Rome III diagnostic criteria for functional gastrointestinal disorders (13), had CSFC with 2 or fewer mean weekly CSBMs for more than 3 months, were aged between 18 and 75 years, had not taken constipation medication for a minimum of 2 weeks before enrollment except for rescue medicine (glycerol or sorbitol anal enema), had not received acupuncture for constipation, and had not participated in any other trial in the previous 3 months. The exclusion criteria were constipation caused by irritable bowel syndrome or drugs or that was secondary to endocrine, metabolic, neurologic, or postoperative diseases; severe cardiovascular, hepatic, or renal diseases; cognitive dysfunction, aphasia, mental disorders, or illness that could affect patient cooperation; pregnant or lactating women; abdominal aortic aneurysm or hepatosplenomegaly; blood coagulation disorders or regular anticoagulant use, including warfarin or heparin (an exception was antiplatelet treatment using aspirin or clopidogrel); and cardiac pacemaker implantation. Candidates signed informed consent. After the 2-week baseline assessment, eligible participants were randomly assigned and received their first treatment on the same day. The study was performed according to common guidelines for clinical trials (Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice E6 guidance). The study protocol (14) adhered to the Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines and was approved by the ethics committees of each responsible site.

Randomization and Blinding

Participants were allocated to the EA or SA group using stratified block randomization. The randomization sequences were generated by using PROC PLAN in SAS, version 9.4 (SAS Institute), with the study site as the stratification factor and the block length as 4. Acupuncturists obtained each patient's random number and assignment through the central randomization system (Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences). All participants were treated separately to prevent communication. Except for acupuncturists, all relevant parties were blinded to the intervention (EA vs. SA) groups. Participants were informed that they had an equal chance of allocation to the EA or SA group before study participation. To test the success of blinding, we randomly selected 140 participants (70 from each group, with 9 to 10 participants at each site) for the blinding assessment; the acupuncturists asked them to guess whether they received EA or SA after treatments in weeks 4 and 8.

Intervention

Study interventions were developed by the consensus of acupuncture experts and per the results of our pilot study (Cai Y, Wu J, Liu Z. Electroacupuncture versus sham electroacupuncture for chronic severe functional constipation: a randomized controlled pilot study. 2012. Unpublished data.). Fifteen acupuncturists with 2 to 3 years of experience at the 15 sites administered the EA and SA treatments. All acupuncturists had at least a 5-year undergraduate education and were registered practitioners of traditional Chinese medicine. All research assistants and acupuncturists received a 2-day training session before study initiation. Both treatments consisted of 28 sessions, each for 30 minutes, and were administered over 8 weeks (5 sessions in each of the first 2 weeks, and 3 sessions in each of the remaining 6 weeks). Disposable needles (Huatuo) and the SDZ-V EA apparatus (Suzhou Medical Appliance) were used.

Participants in the EA group received EA at the bilateral acupoints of Tianshu (ST25), Fujie (SP14), and Shangjuxu (ST37) (15). When participants were supine, 0.30 × 50–mm or 0.35 × 75–mm needles were inserted approximately 30 to 70 mm into ST25 and SP14 slowly and vertically, without manipulation, until they pierced the muscle layer of the abdominal wall. Paired alligator clips from the EA apparatus were attached transversely to the needle holders at bilateral ST25 and SP14. The EA stimulation lasted for 30 minutes with a dilatational wave of 10/50 Hz and a current intensity of 0.1 to 1 mA depending on the participant's comfort level (preferably with skin around the acupoints shivering mildly without pain). In addition, 0.30 × 40–mm needles were inserted vertically about 30 mm into ST37 and 3 small, equal manipulations of twirling, lifting, and thrusting (once every 10 minutes) were performed to reach acupuncture de qi—a soreness, heaviness, and distension sensation when needling (16).

Participants in the SA group received shallow needling at bilateral sham ST25, sham SP14, and sham ST37 (nonacupoints that were located at different physical locations than ST25, SP14, and ST37 for EA) (**Supplement**, available at www.annals.org). Specifically, 0.30 × 25–mm needles were inserted vertically about 3 to 5 mm into nonacupoints without manipulation. Similar to EA, paired alligator clips from the specially constructed EA apparatus were attached to the needle holders of sham ST25 and sham SP14. When switched on, the EA apparatus in the SA group had the same working power indicator and sound without actual current output.

In both groups, participants without BMs for 3 or more consecutive days were allowed to use 110-mL glycerol or 40- to 60-mL sorbitol anal enema as rescue medicine with documentation in the stool diary.

Outcomes and Follow-up

Participants completed a stool diary during the 22-week study period and the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) (17) at baseline and weeks 4 and 8. The main components of the stool diary included BMs, SBMs, CSBMs, stool consistency, straining, and medication use. Participants documented their stool consistency according to the Bristol Stool Form Scale (18) (scored from 1 to 7 for stool types 1 to 7, respectively). Straining was rated with scores of 0, 1, 2, and 3 indicating not difficult; a

little difficult, need some straining to defecate; difficult, need straining to defecate; and very difficult, need hard straining to defecate, respectively. An SBM was defined as a BM that occurred without use of any medication or other methods to assist defecation in the previous 24 hours (4). A BM was not considered as an SBM when it occurred within 24 hours after the use of any assisted method for defecation. The PAC-QOL allowed participants to score the effects of constipation on physical discomfort, psychosocial discomfort, worriedness and concerns, and satisfaction in their daily lives. Higher scores indicate greater impairment or dissatisfaction.

The primary outcome was the change from baseline in mean CSBMs per week, calculated as the total number of CSBMs divided by the number of weeks in the assessment period, during weeks 1 to 8. Secondary outcomes included the changes from baseline in mean CSBMs per week during weeks 9 to 20, mean SBMs per week during weeks 1 to 8, mean scores for stool consistency and straining of SBMs during weeks 1 to 8, and health-related quality of life via PAC-QOL score at weeks 4 and 8; the proportion of participants with 3 or more mean CSBMs per week (4); the proportion of participants using rescue medicine and other defecation measures; and the mean weekly frequency of using rescue medicine and other defecation aids during weeks 1 to 4, 1 to 8, and 9 to 20. We also assessed the CSBMs per week and their change from baseline during treatment and follow-up (not prespecified). Adverse events (AEs) were appropriately assessed, managed, and categorized by the acupuncturists and related clinical specialists within 24 hours. Severe AEs had to be reported to the principal investigator and the independent data and safety monitoring board (**Supplement Table 1**) within 24 hours after their occurrence.

Statistical Analysis

The null hypothesis was that the change from baseline in mean CSBMs per week during weeks 1 to 8 would be the same for EA and SA, and the alternative hypothesis was that the change would differ. In our pilot study, the change from baseline in mean CSBMs per week during weeks 1 to 8 was 1.49 (SD, 1.77) in the EA group and 1.01 (SD, 1.61) in the SA group (Cai Y, Wu J, Liu Z. Electroacupuncture versus sham electroacupuncture for chronic severe functional constipation: a randomized controlled pilot study. 2012. Unpublished data.). Considering the variation among sites, we assumed the pooled variance to be 4.58. We used PROC POWER in SAS to calculate that 862 patients would be needed to provide 95% power to detect a difference of 0.5 in the change from baseline in mean CSBMs per week between groups (19–23) at a 1-sided significance level of 5% (per analysis of variance). If we assume that 20% of patients would be lost to follow-up, 1034 would need to be enrolled.

The statistical analysis plan was completed and approved by the data and safety monitoring board. No interim analysis was done. Analyses were based on the intention-to-treat principle, with all randomly assigned participants included.

We analyzed the change from baseline in mean CSBMs per week during weeks 1 to 8 with a general linear model, with group and site as fixed effects and baseline CSBMs, age, and rescue medicine and other defecation aids used as covariates. We also assessed CSBMs per week, change from baseline in CSBMs per week, and changes from baseline in PAC-QOL score at weeks 4 and 8 by setting group, site, and time as fixed effects and baseline CSBMs, age, and rescue medicine and other defecation aids used as covariates.

We used the same approach to obtain the changes from baseline in mean SBMs per week, mean stool consistency, and mean straining scores. For the proportion of participants having 3 or more mean CSBMs per week and using rescue medicine and other defecation aids, we used a generalized log-linear model with the same covariates (except for rescue medicine and other defecation aids used) as the primary outcome. For mean weekly frequency of rescue medicine and other defecation aids used, the Wilcoxon rank-sum test was used. The incidence of AEs in both groups was compared with a Poisson regression model in which the number of participants with AEs was an independent variable and group was a dependent variable.

Missing data (**Supplement Table 2**) were assumed to be missing at random and were imputed using multiple imputation (24); a sensitivity analysis (25) using a pattern-mixture model was conducted to assess the robustness of the results and address the missing-at-random assumption for the primary outcome (**Supplement**).

Chi-square tests were used to assess the success of blinding. We compared the proportions of participants who guessed that they had received EA between groups. A prespecified subgroup analysis for age (<65 and ≥65 years) was conducted for the primary outcome by adding an interaction term of age × group into the general linear model.

We used 2-sided tests at a significance level of 0.05 for all analyses. To obtain robust 95% CIs, we used the bootstrap method (26). All analyses were done with SAS software.

Role of the Funding Source

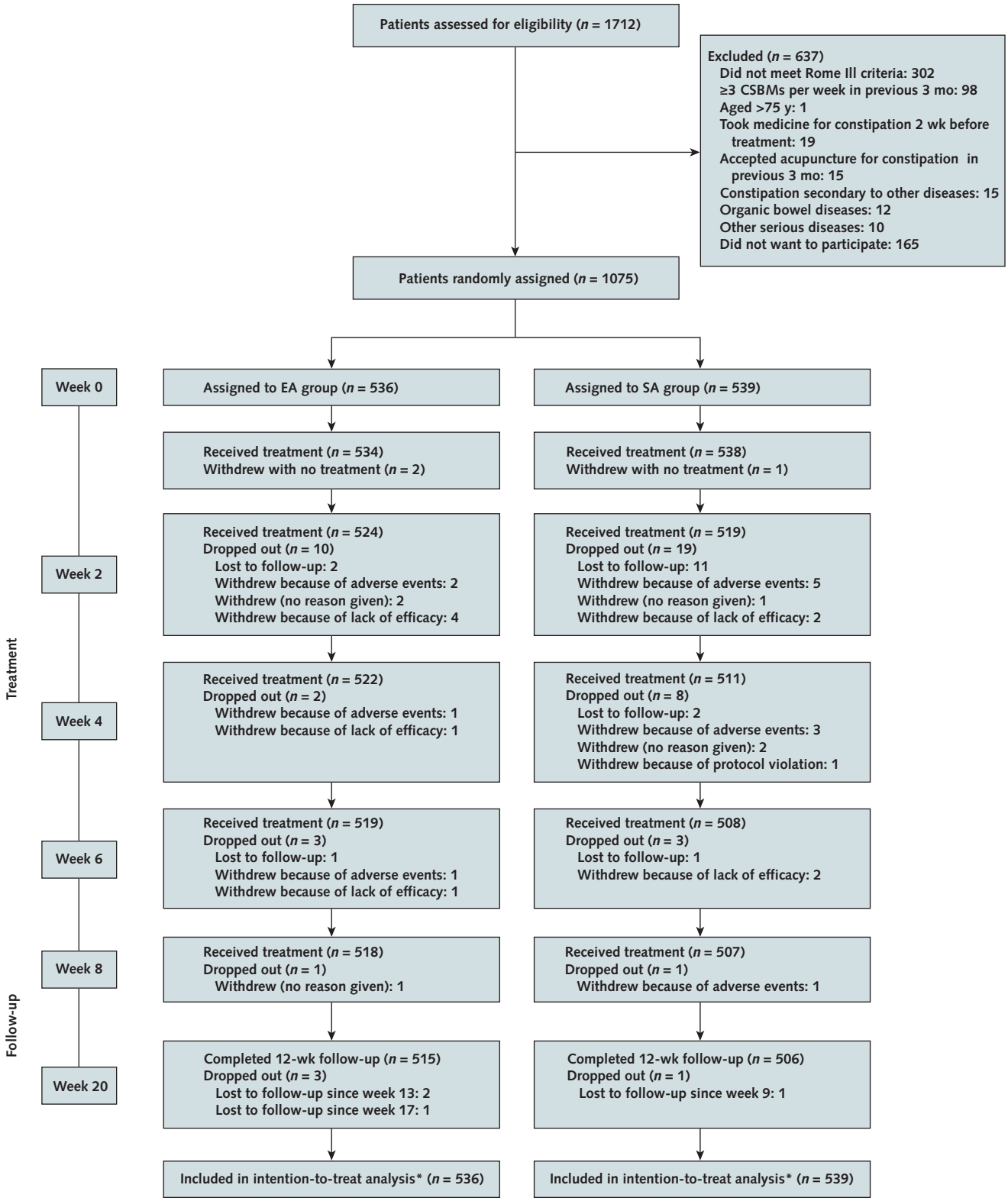
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (B.L.) had full access to all of the data in the study and final responsibility for the decision to submit the manuscript for publication.

RESULTS

Participant Flow

Between 8 October 2012 and 4 May 2014, there were 1712 patients screened from 15 sites. After 637 patients were excluded, 1075 (last recruited on 4 May 2014) were enrolled: 536 in the EA group and 539 in the SA group. A total of 54 (5.0%) patients dropped out during the study: 21 (3.9%) in the EA group and 33 (6.1%) in the SA group (**Figure 1**). The median (25th,

Figure 1. Trial flow diagram.



CSBM = complete spontaneous bowel movement; EA = electroacupuncture; SA = sham electroacupuncture.
* The intention-to-treat analyses consisted of all randomly assigned patients, including 3 who received no treatment. All participants had baseline data.

Table 1. Baseline Characteristics of the Randomly Assigned Population*

Characteristic	EA Group (*n* = 536)	SA Group (*n* = 539)
Age		
Mean age (SD), *y*	47.01 (16.5)	47.33 (15.8)
Participants aged <65 y, *n (%)*	447 (83.4)	457 (84.8)
Participants aged ≥65 y, *n (%)*	89 (16.6)	82 (15.2)
Sex, *n (%)*		
Male	121 (22.6)	132 (24.5)
Female	415 (77.4)	407 (75.5)
Race, *n (%)*		
Han	519 (96.8)	526 (97.6)
Man	5 (0.9)	2 (0.4)
Hui	8 (1.5)	9 (1.7)
Zhuang	1 (0.2)	2 (0.4)
Other	3 (0.6)	0 (0)
Mean body mass index (SD), kg/m^2	22.3 (3.0)	22.8 (3.0)
Mean constipation duration (SD), *mo*	130.8 (122.6)	132.7 (127.0)
Coexisting illness, *n (%)*		
Diabetes	11 (2.1)	10 (1.9)
Hypertension	41 (7.7)	39 (7.2)
Digestive system disease	11 (2.1)	16 (3.0)
Other	78 (14.6)	71 (13.2)
Mean CSBMs per week (SD), *n*	0.39 (0.62)	0.42 (0.62)
Mean SBMs per week (SD), *n*	1.90 (1.34)	2.02 (1.45)
Mean Bristol Stool Form Scale score for stool consistency of SBMs (SD)†	2.58 (1.14)	2.59 (1.09)
Mean straining score of SBMs (SD)†	1.68 (0.65)	1.69 (0.61)
Mean PAC-QOL score (SD)	2.75 (0.69)	2.68 (0.68)
Patients who used other measures, *n (%)*		
Rescue medicine	170 (31.7)	147 (27.3)
Other	17 (3.2)	19 (3.5)
Median frequency of other measures used per week (IQR), *n*‡		
Rescue medicine	1.50 (1.00–2.00)	1.00 (1.00–2.00)
Other	1.00 (0.50–4.00)	1.00 (0.50–3.00)

CSBM = complete spontaneous bowel movement; EA = electroacupuncture; IQR = interquartile range; PAC-QOL = Patient Assessment of Constipation Quality of Life; SA = sham electroacupuncture; SBM = spontaneous bowel movement.
* Percentages may not sum to 100 due to rounding.
† Evaluated on the basis of the stools from SBMs. We could not obtain data from participants who had no SBMs during the baseline period (49 participants in the EA group and 51 in the SA group). Therefore, data for this outcome were from 487 participants in the EA group and 488 in the SA group.
‡ Assessed in the patients who used other measures for constipation.

75th percentiles) length of follow-up was 141 (139, 144) days in the EA group and 140 (139, 144) days in the SA group. Table 1 shows participants' baseline demographic and clinical characteristics.

Figure 2 shows the number of weekly CSBMs in the groups. Compared with the SA group, participants in the EA group had a greater increase in weekly CSBMs throughout weeks 1 to 20. The difference in change from baseline for CSBMs per week between groups was greater than 0.5 since week 2 and greater than 1 since week 5 ($P < 0.001$) (Supplement Table 3).

Table 2 summarizes the results of primary and secondary outcomes. The change from baseline in mean CSBMs per week during weeks 1 to 8 was 1.76 (95% CI, 1.61 to 1.89) in the EA group and 0.87 (CI, 0.73 to 0.97) in the SA group (between-group difference, 0.90 [CI, 0.74 to 1.10]; $P < 0.001$). The change from baseline during weeks 9 to 20 was 1.96 (CI, 1.78 to 2.11) in the EA group and 0.89 (CI, 0.69 to 0.95) in the SA group (between-group difference, 1.09 [CI, 0.94 to 1.31]; $P < 0.001$). The interaction between age (<65 and ≥65 years) and treatment was not significant ($P = 0.71$) (Supplement Figure 1). The results of the pattern-mixture model sensitivity analysis for the primary outcome were similar between groups (Supplement Figure 2). The proportions of participants having 3 or more mean CSBMs per week in the EA group were 31.3% and 37.7% over weeks 1 to 8 and 9 to 20, respectively, compared with 12.1% and 14.1% in the SA group (between-group difference, 19.3 percentage points [CI, 14.3 to 24.2 percentage points] during weeks 1 to 8 and 23.6 percentage points [CI, 18.5 to 28.7 percentage points] during weeks 9 to 20 [$P < 0.001$]). Over the 8-week treatment, the EA group had greater improvement in mean SBMs per week, stool consistency and straining, and the PAC-QOL score ($P < 0.001$). No significant between-group difference was noted in the proportion of patients using rescue medicine over weeks 1 to 4, 1 to 8, and 9 to 20 ($P = 0.21$, 0.071, and 0.28, respectively). The weekly frequency of using rescue medicine in the EA group was lower than that in the SA group during weeks 1 to 8 ($P = 0.042$) but not during other assessment periods.

As for the credibility of blinding, no statistical difference was found between groups in the proportion of participants who guessed that they received EA at week 4 only, week 8 only, and both weeks 4 and 8 ($P = 0.56$, 0.91, and 0.42, respectively) (Supplement Table 4).

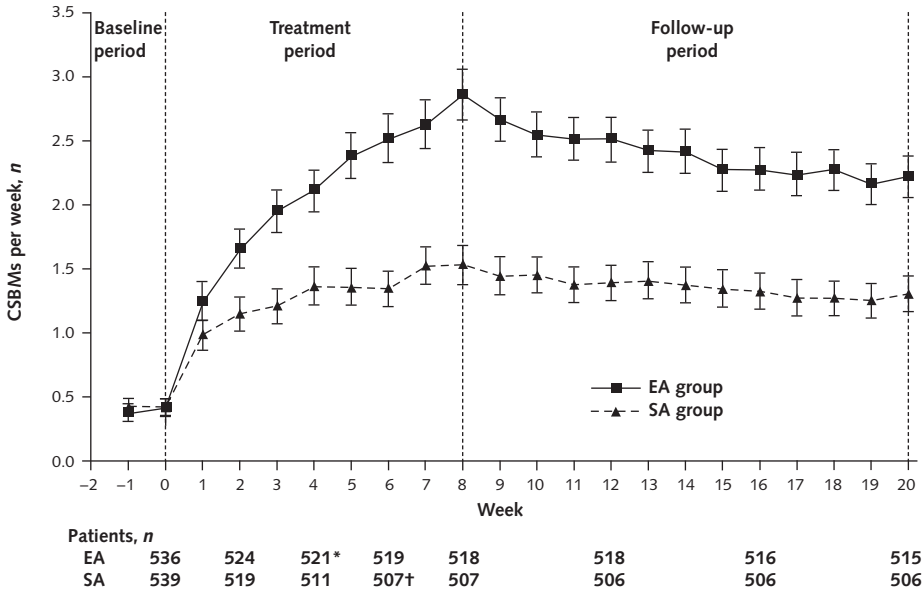
Acupuncture-related AEs occurred in 5.8% of participants in the EA group and 4.5% in the SA group ($P = 0.32$). No significant difference was found between groups for the proportion of patients with specific AEs ($P > 0.05$ for all AEs), except those with other discomforts after acupuncture (more common in the EA group; $P = 0.04$). Neither group had severe AEs. The most commonly reported acupuncture-related AEs were hematoma, sleeplessness, and sharp pain (Table 3). Non–acupuncture-related AEs occurred infrequently (Supplement Table 5). Thirteen participants (4 from the EA group and 9 from the SA group) withdrew from the study because of AEs.

DISCUSSION

This multicenter trial with 1075 participants showed that EA alleviated symptoms and improved quality of life in patients with CSFC during the 8-week treatment; these effects persisted throughout the 12-week follow-up. Thus, EA might be recommended as a valuable and promising new therapeutic option for patients with CSFC.

The main physiopathologic mechanism of SFC is insufficient bowel motility (27). Previous basic research reported that acupuncture stimulation facilitates gastro-

Figure 2. Weekly CSBMs during the study.



Data are observed values of weekly CSBMs; error bars represent 95% CIs. The EA group had more than 2 CSBMs per week from weeks 4 to 20, and the SA group had 1.52 or fewer CSBMs per week throughout weeks 1 to 20. The differences between the EA and SA groups in repeatedly measured CSBMs per week were tested through the general linear model; the differences of the change from baseline in mean weekly CSBMs between groups were significant for the treatment and follow-up periods ($P < 0.001$). CSBM = complete spontaneous bowel movement; EA = electroacupuncture; SA = sham electroacupuncture.

* At 4 weeks, 1 patient in EA group missed the 2-week defecation diaries but completed all other defecation diaries.

† At 6 weeks, 1 patient in SA group missed the 2-week defecation diaries but completed all other defecation diaries.

intestinal motility (28, 29). The distal colon is stimulated via parasympathetic activation at acupoints ST25, SP14, and ST37 (28, 29).

In previous pharmaceutical trials about chronic constipation, the differences between active intervention and placebo in the change from baseline in mean CSBMs per week ranged from 0.48 to 1.8 (19–23). The between-group differences in this study (0.90 [CI, 0.74 to 1.10] and 1.09 [CI, 0.94 to 1.31] during treatment and follow-up, respectively) are within this range. The mean weekly CSBMs can better capture the overall severity of constipation, and thus the change in mean weekly CSBMs provides better objective measurement of EA's effect on CSFC. A 1-unit increase in mean CSBMs per week has been considered clinically meaningful for the relief of severe constipation and indicates enhanced general well-being (19). The change from baseline in mean CSBMs per week of 1.76 (CI, 1.61 to 1.89) and 1.96 (CI, 1.78 to 2.11) during treatment and follow-up, respectively, in the EA group supports the clinical effect of EA.

Yiannakou and colleagues (9) reported that 37.9% of patients with severe constipation had 3 or more mean weekly CSBMs when receiving 1 to 2 mg of prucalopride for 12 weeks. In our study, 31.3% (during treatment) and 37.7% (during follow-up) in the EA group had 3 or more mean CSBMs per week. Patients with CSFC have 2 or fewer CSBMs per week. Because 3 or more CSBMs per week indicates normalization of bowel function (4, 19), our results show that EA may normalize bowel function in some patients. Therapeutic efficacy of EA for severe constipation is further supported by increased weekly SBMs, improved stool consistency, less defecation straining, lower PAC-QOL score, and less frequent rescue medicine use (during treatment). In an integrated analysis of prucalopride for chronic constipation, the overall PAC-QOL score decreased by 0.74 with 2 mg of prucalopride (30). Our study had a similar result (PAC-QOL score decreased by 0.50 and 0.87 at weeks 4 and 8, respectively) with EA. A 0.5-point decrease in the overall PAC-QOL score is recommended as the minimum important difference (17). Our results may thus add to the evidence that EA improves general well-being and quality of life in patients. In addition, we searched for randomized, controlled trials in PubMed from 1 January 2010 to February 2016 using the keywords "acupuncture" and "constipation" in the abstract and title screening and identified 4 suitable publications. These 4 clinical trials (each with sample size of 128, 475, 111, and 104 participants) reported similar findings of EA in relieving functional constipation, although none used the outcomes of CSBMs and PAC-QOL score for constipation evaluation (12, 31–33).

To improve blinding and participant adherence, we used shallow needling at nonacupoints as the control. Although an ideal acupuncture placebo would be noninvasive, acupuncture blinding with Chinese participants is difficult if they do not perceive any needling during treatment. The blinding assessment results and

Table 2. Constipation-Related Primary and Secondary Outcome Measures in All Randomly Assigned Participants

Outcome	EA Group (n = 536)	SA Group (n = 539)	Between-Group Difference (95% CI)*	*P* Value
Change from baseline in mean CSBMs per week (95% CI), *n*				
Weeks 1–8	1.76 (1.61 to 1.89)	0.87 (0.73 to 0.97)	0.90 (0.74 to 1.10)†	<0.001
Weeks 9–20	1.96 (1.78 to 2.11)	0.89 (0.69 to 0.95)	1.09 (0.94 to 1.31)†	<0.001
Participants with ≥3 CSBMs per week, *n (%)*				
Weeks 1–8	168 (31.3)	65 (12.1)	19.3 (14.3 to 24.2)	<0.001
Weeks 9–20	202 (37.7)	76 (14.1)	23.6 (18.5 to 28.7)	<0.001
Change in mean SBMs per week during weeks 1–8 (95% CI), *n*‡	2.27 (2.22 to 2.58)	1.27 (1.23 to 1.55)	1.00 (0.81 to 1.21)†	<0.001
Change in mean Bristol Stool Form Scale score for stool consistency during weeks 1–8 (95% CI)‡	0.87 (0.75 to 0.93)	0.63 (0.54 to 0.70)	0.24 (0.12 to 0.31)†	<0.001
Change in mean score for straining during weeks 1–8 (95% CI)‡	−0.73 (−0.76 to −0.64)	−0.50 (−0.53 to −0.42)	−0.24 (−0.29 to −0.15)†	<0.001
Change in PAC-QOL score (95% CI)				
At week 4§	−0.50 (−0.54 to −0.46)	−0.36 (−0.40 to −0.32)	−0.14 (−0.20 to −0.09)†	<0.001
At week 8	−0.87 (−0.91 to −0.83)	−0.56 (−0.60 to −0.52)	−0.31 (−0.37 to −0.25)†	<0.001
Patients using other measures for constipation, *n (%)*				
Weeks 1–4§				
Rescue medicine	170 (31.7)	147 (27.3)	3.8 (−2.1 to 9.8)	0.21
Other	17 (3.2)	19 (3.5)	−0.1 (−5.8 to 5.6)	0.97
Weeks 1–8				
Rescue medicine	155 (28.9)	183 (34.0)	−5.7 (−11.8 to 0.5)	0.071
Other	15 (2.8)	17 (3.2)	0.8 (−6.5 to 8.0)	0.84
Weeks 9–20				
Rescue medicine	104 (19.4)	124 (23.0)	−3.7 (−10.3 to 2.9)	0.28
Other	12 (2.2)	17 (3.2)	−0.3 (−7.2 to 6.7)	0.94
Median frequency of other measures used per week (IQR), *n*‖				
Weeks 1–4§				
Rescue medicine	1.50 (1.00 to 2.00)	1.00 (1.00 to 2.00)	–¶	0.62
Other	1.00 (0.50 to 4.00)	1.00 (0.50 to 3.00)	–¶	0.48
Weeks 1–8				
Rescue medicine	0.63 (0.25 to 1.25)	0.75 (0.25 to 1.63)	–¶	0.042
Other	0.38 (0.13 to 0.75)	0.38 (0.13 to 0.88)	–¶	0.76
Weeks 9–20				
Rescue medicine	0.83 (0.33 to 1.50)	1.00 (0.38 to 1.83)	–¶	0.30
Other	0.29 (0.17 to 0.42)	1.08 (0.17 to 2.50)	–¶	0.34

CSBM = complete spontaneous bowel movement; EA = electroacupuncture; IQR = interquartile range; PAC-QOL = Patient Assessment of Constipation Quality of Life; SA = sham electroacupuncture; SBM = spontaneous bowel movement.
* Values are percentage points unless otherwise indicated and are rounded.
† Values are numbers.
‡ Evaluated on the basis of the stools from SBMs. Data could not be obtained from participants who had no SBMs during the baseline and/or treatment period (53 participants in the EA group and 53 in the SA group). Therefore, the changes from baseline between baseline and weeks 1–8 for this outcome were from 483 participants in the EA group and 486 in the SA group.
§ Post hoc analysis.
‖ Assessed in the patients who used other measures for constipation.
¶ Wilcoxon rank-sum test was used for comparing the distribution of the weekly frequency of other measures used; thus, differences between 2 groups were not provided.

low dropout rate suggest that blinding was successful. Shallow needling at nonacupoints may have some biological effects (34) in addition to a placebo effect. Our results revealed that EA might have greater benefits than SA for CSFC, which is consistent with prior studies for gastrointestinal symptoms using shallow needling at nonacupoints (control) that showed EA's superiority over SA (35, 36).

In our study, the proportions of participants having acupuncture-related AEs in the EA and SA groups were low, and the specific AEs were mild or transient. These results are similar to those reported in a previous acupuncture study (37). Our study provided additional reassurance of the safety of acupuncture in the treatment of CSFC.

Our study has several limitations. Longer-term follow-up has not been assessed. Our EA treatment session was based on expert consensus in China; however, 28 sessions of EA may be burdensome for some patients. A clear minimal clinically important difference of the change in CSBMs per week has not been established. A few patients with constipation-predominant irritable bowel syndrome may have been mistakenly recruited because its symptoms overlap with those of functional constipation. Acupuncturists could not be blinded, and the blinding assessment was performed on only 9 to 10 of the 70 participants at each site. We did not control for patients' and acupuncturists' expectations of effectiveness, which may affect the results of the blinding assessment and the effects of EA.

Future clinical trials may need a comparison to standard care or a waiting list. The optimal variables, including frequency, duration, and selection of acupoints in EA treatment, deserve further investigation.

In conclusion, we found that 8-week EA treatment increased CSBMs and was safe for the treatment of CSFC. The effect persisted for 12 weeks after treatment. Electroacupuncture could provide an alternative

Table 3. Acupuncture-Related Adverse Events*

Adverse Event	EA (*n* = 534)		SA (*n* = 538)		*P* Value†
	Participants, *n* (%)	Events, *n*	Participants, *n* (%)	Events, *n*	
Total	31 (5.8)	90	24 (4.5)	43	0.32
Needle left in participant	0 (0)	0	1 (0.2)	1	1.00
Nausea during acupuncture	1 (0.2)	1	0 (0)	0	0.50
Fainted during acupuncture	1 (0.2)	1	0 (0)	0	0.50
Severe sharp pain‡	3 (0.6)	5	5 (0.9)	6	0.73
Sharp pain lasting >0.5 h	2 (0.4)	5	1 (0.2)	3	0.62
Hematoma around the site of needling	19 (3.6)	40	17 (3.2)	31	0.72
Bleeding/numbness/infection around the site of needling	0 (0)	0	0 (0)	0	NA
Sleeplessness after acupuncture	1 (0.2)	27	0 (0)	0	0.50
Dizziness after acupuncture	2 (0.4)	2	0 (0)	0	0.25
Other discomforts after acupuncture	7 (1.3)	9	1 (0.2)	2	0.04

EA = electroacupuncture; NA = not available; SA = sham electroacupuncture.
* Data on safety evaluation for 3 participants were not available (2 participants in the EA group and 1 in the SA group).
† For the comparison of the number of participants with that of the adverse events.
‡ Visual analogue scale score ≥7.

to conventional medications for the management of CSFC. Additional study is warranted to evaluate a longer-term treatment and follow-up.

From Guang'anmen Hospital, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing Traditional Chinese Medicine Hospital of Capital Medical University, Dongzhimen Hospital of Beijing University of Chinese Medicine, Huguosi Hospital of Chinese Medicine of Beijing University of Chinese Medicine, Beijing; West China Hospital of Sichuan University, Chengdu, Sichuan; Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine, Shanghai; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang; Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, Guangdong; The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin; Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu; Heilongjiang Province Academy of Chinese Medical Science, Ha'erbin, Heilongjiang; The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, Anhui; Wuhan Integrated Traditional Chinese Medicine and Western Medical Hospital, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China; and Daemen College, Physical Therapy Wound Care Clinic, Amherst, New York.

Note: Of the 15 sites involved in this work, 13 were hospitals of traditional Chinese medicine: Guang'anmen Hospital, Beijing Traditional Chinese Medicine Hospital, Huguosi Hospital of Chinese Medicine, and Dongzhimen Hospital in Beijing; The Third Affiliated Hospital of Zhejiang Chinese Medical University in Hangzhou; The First Affiliated Hospital of Anhui University of Chinese Medicine in Hefei; Jiangsu Province Hospital of Traditional Chinese Medicine, and Nanjing University of Chinese Medicine in Nanjing; Guangdong Province Hospital of Traditional Chinese Medicine in Guangzhou; Wuhan Integrated Traditional Chinese Medicine and Western Medical Hospital in Wuhan; Heilongjiang Province Hospital of Chinese Medical Science in Ha'erbin; The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine in Tianjin; and Yueyang Hospital of Integrated Traditional Chinese and Western Medicine in Shanghai, China. The other 2 sites were Western medicine hospitals: the Chinese People's Liberation Army General Hospital (301 Hospital) in Beijing and West China Hospital in Chengdu, China.

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Requests for Single Reprints: Baoyan Liu, MD, China Academy of Chinese Medical Sciences, 16 Nanxiaojie Dongzhimennei, Dongcheng, Beijing, China 100700; e-mail, 13601180524@139.com.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Z. Liu, Wu, Xu, and Cai: Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 Beixian'ge Street, Xicheng, Beijing, China 100053.
Drs. Yan, He, Ai, and J. Liu: Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, 16 Nanxiaojie Dongzhimennei, Dongcheng, Beijing, China 100700.
Dr. Li: West China Hospital of Sichuan University, Chengdu, Sichuan, 37 Guoxuexiang, Wuhou, Chengdu, Sichuan, China 610041.
Dr. Dong: Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine, 110 Ganhe Road, Hongkou, Shanghai, China 200437.
Dr. Fang: The Third Affiliated Hospital of Zhejiang Chinese Medical University, 219 Moganshan Road, Gongshu, Hangzhou, Zhejiang, China 310005.
Dr. W. Fu: Guangdong Province Hospital of Traditional Chinese Medicine, 111 Dade Road, Yuexiu, Guangzhou, Guangdong, China 510120.
Dr. L. Fu: The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, 314, Anshan West Road, Nankai, Tianjin, China 300000.
Dr. Sun: Jiangsu Province Hospital of Traditional Chinese Medicine, 155 Hanzhong Road, Qinhuai, Nanjing, Jiangsu, China 210029.
Dr. L. Wang: Beijing Traditional Chinese Medicine Hospital of Capital Medical University, 23 Meishuguan Houjie, Dongcheng, Beijing, China 100010.
Dr. S. Wang: Heilongjiang Province Academy of Chinese Medical Science, 33 Xidazhi Street, Nangang, Ha'erbin, Heilongjiang, China 150080.
Dr. Yang: The First Affiliated Hospital of Anhui University of Chinese Medicine, 117 Meishan Road, Hefei, Anhui, China 230031.
Dr. H. Zhang: Wuhan Integrated Traditional Chinese Medicine and Western Medical Hospital, 215 Zhongshan Avenue, Qiaokou, Wuhan, Hubei, China 430022.
Dr. J. Zhang: Nanjing University of Chinese Medicine, 282 Hanzhong Road, Gulou, Nanjing, Jiangsu, China 210029.
Dr. J. Zhao: Dongzhimen Hospital of Beijing University of Chinese Medicine, 5 Haiyuncang, Dongcheng, Beijing, China 100700.
Dr. W. Zhao: Huguosi Hospital of Chinese Medicine of Beijing University of Chinese Medicine, 83 Mianhua Hutong, Xicheng, Beijing, China 100035.
Dr. Z. Zhou: Hubei Provincial Hospital of Traditional Chinese Medicine, 4 Huayuanshan Street, Wuhan, Hubei, China 430061.
Dr. K. Zhou: Daemen College, Physical Therapy Wound Care Clinic, 4380 Main Street, Amherst, NY 14226.
Dr. B. Liu: China Academy of Chinese Medical Sciences, 16 Nanxiaojie Dongzhimennei, Dongcheng, Beijing, China 100700.

Author Contributions: Conception and design: Z. Liu, L. He, B. Liu.
Analysis and interpretation of the data: S. Yan, K. Zhou, H. Xu.
Drafting of the article: Z. Liu, S. Yan, J. Wu, K. Zhou.
Critical revision of the article for important intellectual content: Z. Liu, J. Wu, L. He, K. Zhou, B. Liu.
Final approval of the article: Z. Liu, S. Yan, J. Wu, L. He, N. Li, G. Dong, J. Fang, L. Fu, J. Sun, L. Weng, S. Wang, J. Yang, H. Zhang, J. Zhang, J. Zhao, W. Zhou, Z. Zhou, Y. Ai, K. Zhou, J. Liu, Y. Cai, B. Liu.
Provision of study materials or patients: N. Li, G. Dong, J. Fang, L. Fu, J. Sun, L. Wang, S. Wang, J. Yang, H. Zhang, J. Zhang, J. Zhao, W. Zhou, Z. Zhou, Y. Cai.
Statistical expertise: S. Yan.
Obtaining of funding: Z. Liu, B. Liu.
Administrative, technical, or logistic support: L. He, N. Li, W. Fu, B. Liu.
Collection and assembly of data: Y. Ai, J. Liu, H. Xu.