

The duration of acupuncture effects and its associated factors in chronic severe functional constipation: secondary analysis of a randomized controlled trial

Yang Wang , Yan Liu, Kehua Zhou, Brent A. Bauer, Baoyan Liu, Tongsheng Su, Qian Mo and Zhishun Liu

Abstract

Background: Electroacupuncture (EA) has been shown to improve complete spontaneous bowel movements (CSBMs), but the duration of its effects remains unknown. The objective of this study was to explore the duration of acupuncture effects after treatment and its associated factors for chronic severe functional constipation (CSFC).

Methods: This was a secondary analysis of a multicenter, randomized, sham-acupuncture (SA) controlled trial that included 1075 participants with CSFC. The primary outcome, the duration of acupuncture effects after treatment, was the number of weeks during the 12-week follow-up period that participants were to meet the weekly CSBM responder criteria. A weekly CSBM responder was defined as a participant who had at least three CSBMs for a given week and an increase from baseline of at least one CSBM for that same week. We performed a retrospective multivariate analysis to explore potential factors associated with sustained acupuncture effects.

Results: The duration of acupuncture effects in the EA group (5.5 weeks) was significantly higher than the duration of SA effects in the SA group (2.2 weeks) with a between-group difference of 3.2 weeks (95% CI, 2.77–3.78; $p < 0.001$). A younger age and higher baseline CSBMs per week [regression coefficient (RC) -0.06 , 95% confidence interval (CI) $(-0.06$ to $-0.04)$; RC 2.43, 95% CI 1.78–3.60; respectively] were associated with longer durations of acupuncture effects.

Conclusions: EA had sustained post-treatment effects for CFSC. A significant association among a younger age, higher baseline CSBMs and sustained acupuncture effects was observed. Further research is needed to confirm the association.

Trial registration: ClinicalTrials.gov (NCT01726504). Registered on 26 August 2012.

Keywords: acupuncture, associated factors, constipation, duration of effects, secondary analysis

Received: 9 June 2019; revised manuscript accepted: 18 September 2019.

Introduction

Constipation is one of the most common gastrointestinal complaints in the general population. Chronic constipation is characterized by difficult, infrequent, or perceived incomplete evacuation of bowel movements.¹ Chronic severe constipation is defined as two or fewer complete spontaneous bowel movements (CSBMs) per week, hard stool,

and a sensation of straining during defecation.² Constipation affects 2% to 35% of adults³ in North America and 11.6% in Asia,⁴ accounts for more than 2.5 million doctor visits and is associated with substantial economic costs.⁵

Causes of chronic constipation include neurologic and metabolic disorders, obstructing lesions of the

Ther Adv Gastroenterol

2019, Vol. 12: 1–9

DOI: 10.1177/
1756284819881859

© The Author(s), 2019.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:
Zhishun Liu
Acupuncture Department,
Guang'anmen Hospital,
China Academy of Chinese
Medical Sciences, No.5,
Beixiang Street, Xicheng
District, Beijing 100053,
China
zhishunjournals@163.com

Yang Wang
Acupuncture Department,
Guang'anmen Hospital,
China Academy of Chinese
Medical Sciences, Beijing,
China

Yan Liu
Key Laboratory of Chinese
Internal Medicine of
Ministry of Education,
Dongzhimen Hospital,
Beijing University of
Chinese Medicine, Beijing,
China

Kehua Zhou
Catholic Health System
Internal Medicine Training
Program, University at
Buffalo, Buffalo, NY, USA

Brent A. Bauer
Division of General
Internal Medicine Mayo
Clinic, Rochester, MN, USA

Baoyan Liu
Institute of Basic Research
in Clinical Medicine, China
Academy of Chinese
Medical Sciences, Beijing,
China

Tongsheng Su
Shanxi TCM Hospital, Xian,
China

Qian Mo
Guiyang University
of Chinese Medicine,
Guiyang, China

gastrointestinal tract, psychiatric disorders, and medication use. Functional constipation, known as chronic idiopathic constipation, is constipation not caused by anorectal defecation disorders or other conditions (endocrine and metabolic disease, medication, or central nervous system disease).^{6,7} The pathophysiology of chronic constipation, especially functional constipation, typically includes slow or dyssynergic defecation.⁶ Treatments of chronic constipation usually target the etiology and relevant pathophysiological changes, including dietary changes, bulk-forming laxatives, surfactants, osmotic agents, and stimulant laxatives.⁶ Severe cases may require suppositories, disimpaction, enema, and even surgery. Additional medications including linaclotide, plecanatide, and lubiprostone have been approved by the US Food and Drug Administration for the treatment of chronic idiopathic constipation.⁶ Nonetheless, effects of all these interventions are nonsatisfactory in many situations, and are usually transitory and accompanied with side effects. Nearly half of patients are dissatisfied with their traditional therapies, such as laxatives.⁸

Available data indicates that acupuncture may be effective and have persisting effects for chronic constipation. The main findings of the multicenter randomized controlled trial on acupuncture (the acupuncture constipation trial) for chronic severe functional constipation (CSFC, defined as having CSBMs no more than twice per week, with hard stools, frequent straining, and the sensation of incomplete evacuation) showed that electroacupuncture (EA) increased mean CSBMs during weeks 1–8.^{2,9,10} Because the original study examined mainly whether acupuncture is effective for chronic constipation, the duration of acupuncture effects and its associated factors remains unknown.

To address the limitations of previous research, a secondary analysis of data from the acupuncture constipation trial was performed to explore the duration of acupuncture effects, defined as the duration of participants meeting the criteria as a CSBM responder, and its associated factors in CSFC.

Methods

Trial design

The acupuncture constipation trial was a multicenter, randomized, controlled trial conducted at 15 hospitals in China from 8 October 2012 to

4 May 2014. It was designed to compare the effectiveness of EA *versus* sham electroacupuncture (SA) in participants with CSFC (ClinicalTrials.gov: NCT01726504). This article presents the results of a secondary analysis that was not pre-specified in the original trial protocol and has not been published previously. The rationale, design, and methods of the acupuncture constipation trial were presented previously. The study protocol was approved by the ethics committees of 15 hospitals and written informed consent was obtained from all participants.

Participants

Participants were described elsewhere.⁹ Briefly, participants with chronic functional constipation with two or fewer mean weekly CSBMs for more than 3 months were eligible if they were between the ages of 18 and 75 years and had not taken constipation medication for a minimum of 2 weeks before enrollment.

Randomization and interventions

Participants were randomly assigned to receive EA or SA using stratified block randomization. The interventions consisted of 28 sessions of EA or SA over 8 weeks (5 sessions per week in the first 2 weeks, and 3 sessions per week in the remaining 6 weeks), each session for 30 min. Huatuo disposable needles and the SDZ-V EA apparatus (Suzhou Medical Appliance Factory, Suzhou, China) were used. Participants in the EA group received EA at bilateral acupoints with EA stimulation. Participants in the SA group received shallow needling at bilateral sham acupoints with sham EA apparatus (no electric stimulation).

Secondary analysis design

We explored the duration and its associated factors in acupuncture effects on CFSC. According to the European Medicines Agency's guideline,⁷ a weekly CSBM responder was defined as a participant who had at least three CSBMs for a given week and an increase from baseline of at least one CSBM for that same week. An overall CSBM responder was defined as participants meeting the weekly responder criteria for at least 75% of the duration of a certain time period.⁷

The primary outcome, duration of acupuncture effects (after last acupuncture treatment), was the

number of total weeks during the 12-week follow up that participants met weekly CSBM responder criteria. We compared the duration of acupuncture effects in the EA group with the duration of SA effects in the SA group. The numbers of participants with different durations of treatment effects (1–2 weeks, 3–4 weeks, 5–6 weeks, 7–8 weeks, 9–10 weeks, and 11–12 weeks) over the follow-up period were counted as a secondary outcome. Additional secondary outcomes include the proportion of the overall CSBM responders over weeks 1–8 and 9–20 in the two groups; mean duration of treatment effects (after last treatment) in treatment-period overall CSBM responders; the proportion of weekly responders from weeks 1–20. We also explored potential factors associated with the duration of acupuncture effects in the EA group.

Statistical design

Descriptive statistics were used for demographics and baseline characteristics. The primary outcome was analyzed using a standard analysis of covariance (ANCOVA) model, including baseline value, treatment and sites as covariates. The same approach was used for the duration of treatment effects (after last treatment) in treatment period overall CSBM responders. The analyses of overall responders, participants who met the responder criteria for at least 6 of 8 treatment- or 9 of 12 follow-up-periods were performed using a generalized linear model with a binomial distribution, adjusted for sites.⁷ All outcomes were performed on the intention-to-treat population, without imputation of missing data.

To identify baseline variables associated with the duration of acupuncture effects, a full model with no interactions was fitted, then a backwards step-down variable selection procedure was performed in the EA group.¹¹ The backward elimination model-building with a bootstrap approach (using 1000 bootstrap samples of all the data) was used to select independent variables to be retained in the final model.¹¹ Before the regression analyses, the presence of collinearity among the predictor variables was checked using the variance inflation factor (VIF). We considered collinearity to be present if the VIFs of the variables were greater than five.

Analyses were performed using SAS (Version 9.4, The SAS institute, Cary, NC, USA) with a

2-sided *p* value of less than 0.05 considered significant.

Results

After a 2-week run-in period, 1075 participants were enrolled and randomized (536 in the EA group and 539 in the SA group); 50 participants dropped out by the end of 8-week treatment period; an additional 4 participants dropped out during the 12-week follow-up period. Participants' baseline characteristics including age, sex, body mass index (BMI), constipation duration, PAC-QOL score, and coexisting illness are presented in Table 1.

The results of the primary outcome and secondary outcomes are summarized in Table 2. For the primary outcome, the duration of acupuncture effects after last acupuncture treatment in the EA group over the follow-up period was significantly longer than the duration of SA effects in the SA group with a between-group difference of 3.2 weeks (95% CI, 2.77–3.78; $p < 0.001$).

The numbers of participants with different durations of treatment effects (1–2 weeks, 3–4 weeks, 5–6 weeks, 7–8 weeks, 9–10 weeks, and 11–12 weeks) over the follow-up period are presented in Table 2. More participants had treatment effects of 1–2 weeks' duration in the SA group, whereas more participants had treatment effects of 5–6 weeks', 7–8 weeks', 9–10 weeks', and 11–12 weeks' duration in the EA group. The proportions of overall CSBM responders over both the treatment (weeks 1–8) and follow-up periods (weeks 9–20) were higher in the EA group than the SA group with between-group differences of 14.43% (95% CI, 10.0–18.89%; $p < 0.001$) during treatment and 24.63% (95% CI, 19.38–29.89%; $p < 0.001$) during follow-up periods.

For the treatment-period overall CSBM responders, the duration of acupuncture effects after last treatment was 9.69 [standard deviation (SD) 3.05] weeks in the EA group, compared with the duration of SA effects after last treatment of 6.92 (SD, 4.23) weeks in the SA group ($p < 0.001$). The proportions of weekly CSBM responders over weeks 1–20 were presented in Figure 1, with higher proportions in the EA group than the SA group at every week, with p values < 0.05 for weeks 2–20. The proportions of weekly CSBM responders in the EA group peaked at week 8.

Table 1. Baseline characteristics of the randomized participants.

Characteristics	EA (n=536)	SA (n=539)	Total (n=1075)	p value
Age, mean (SD), years	47.0 (16.45)	47.3 (15.78)	47.2 (16.11)	0.743
Sex				0.459
Male	121 (22.6)	132 (24.5)	253 (23.5)	
Female	415 (77.4)	407 (75.5)	822 (76.5)	
Race				0.073
Han	519 (96.8)	526 (97.6)	1045 (97.2)	
Minorities	17 (3.2)	13 (2.4)	30 (2.8)	
BMI				0.073
≤18.5	43 (8.0)	25 (4.6)	68 (6.3)	
>18.5 to ≤23.9	349 (65.1)	344 (63.8)	693 (64.5)	
>23.9 to ≤27.9	123 (22.9)	146 (27.1)	269 (25.0)	
>27.9	21 (3.9)	24 (4.5)	45 (4.2)	
Constipation duration, years				0.797
≤10	346 (64.6)	353 (65.5)	699 (65.0)	
>10 to ≤20	113 (21.1)	115 (21.3)	228 (21.2)	
>20 to ≤30	53 (9.9)	45 (8.3)	98 (9.1)	
>30 to ≤40	18 (3.4)	17 (3.2)	35 (3.3)	
>40 to ≤50	5 (0.9)	5 (0.9)	10 (0.9)	
>50	1 (0.2)	4 (0.7)	5 (0.5)	
CSBMs				0.141
≤1	488 (91.0)	476 (88.3)	964 (89.7)	
>1 to ≤2	48 (9.0)	63 (11.7)	111 (10.3)	
PAC-QOL score				0.211
≤2	79 (14.7)	99 (18.4)	178 (16.6)	
>2 to ≤3	269 (50.2)	279 (51.8)	548 (51.0)	
>3 to ≤4	164 (30.6)	141 (26.2)	305 (28.4)	
>4 to ≤5	24 (4.5)	20 (3.7)	44 (4.1)	
Coexisting illness	118 (22.0)	114 (21.2)	232 (21.6)	0.730
Data are n (%) unless otherwise stated. BMI, body mass index; CSBMs, complete spontaneous bowel movements; EA, electro-acupuncture; PAC-QOL, Patient Assessment of Constipation Quality of Life questionnaire; SA, sham electro-acupuncture; SD, standard deviation. More details can be found in the original study. ⁸				

Table 2. Outcome measures of the intention-to-treat population.

Outcomes	EA (n=536)	SA (n=539)	Between-group difference value (95% CI)	p value
Primary outcome				
Duration of treatment effects during 12-week follow-up period, mean(SD), weeks ^a	5.5 (4.93)	2.2 (3.63)	3.2 (2.77–3.78)	<0.001
Secondary outcomes				
Overall CSBM responders for ≥ 9 of 12 follow-up weeks, n (%) ^b	201 (39.0)	57 (11.3)	24.63% (19.38–29.89)	<0.001
Overall CSBM responders for ≥ 6 of 8 treatment weeks, n (%) ^c	138 (26.6)	49 (9.7)	14.43% (10.0–18.89)	<0.001
Duration of treatment effects during the follow-up period, mean(SD), weeks ^d	9.69 (3.05)	6.92 (4.23)	3.42 (2.33–4.51)	<0.001
Patients with different durations of treatment effects during the 12-week follow-up period, n (%) ^a				<0.001
1–2 weeks	50 (9.7)	73 (14.4)		
3–4 weeks	37 (7.1)	35 (6.9)		
5–6 weeks	35 (6.8)	23 (4.5)		
7–8 weeks	30 (5.8)	21 (4.2)		
9–10 weeks	53 (10.2)	22 (4.3)		
11–12 weeks	148 (28.6)	35 (6.9)		
Patients with no duration of treatment effect	165 (31.9)	297 (58.7)		0.024
Overall CSBM nonresponders during the treatment period, n (%) ^e	149 (90.30)	284 (95.62)		
CSBMs, complete spontaneous bowel movements; EA, electro-acupuncture; SA, sham electro-acupuncture; SD, standard deviation.				
^a Number of participants: 515 in the EA group and 506 in the SA group; duration of treatment effects was defined as the number of total weeks during the 12-week follow up that participants were to meet the weekly CSBM responder criteria.				
^b Number of participants: 515 in the EA group and 506 in the SA group; according to the guideline of European Medicines Agency ⁷ , overall CSBM responders were defined as patients who fulfilled both at least three CSBMs/week and an increase of at least one CSBM/week from baseline, in the same week, for at least 9 of the 12 follow-up weeks.				
^c Number of participants: 518 in the EA group and 507 in the SA group; according to the guideline of European Medicines Agency ⁷ , overall CSBM responders were defined as patients who fulfilled both at least three CSBMs/week and an increase of at least one CSBM/week from baseline, in the same week, for at least 6 of the 8 treatment weeks.				
^d Only assessed in the patients who were overall CSBM responders of the treatment period.				
^e Only assessed in the patients without duration of treatment effects during the 12-week follow-up period.				

At week 20, the proportion of weekly CSBM responders in the EA group was similar to the proportion at week 9, and was still much higher than that of the SA group ($p < 0.01$).

Factors associated with sustained acupuncture effects. Multiple regression analysis with backward elimination identified two of eight factors as significantly associated with the duration of acupuncture effects in the EA group: age and the baseline CSBMs (Table 3). A younger age was

associated with longer durations of acupuncture effects over the follow-up period [regression coefficient (RC) -0.06 , 95% confidence interval (CI) $(-0.06$ to $-0.04)$]. Participants with baseline CSBMs between 1 and 2 per week had a longer duration of acupuncture effects than those with less than one CSBM/week (RC 2.43, 95% CI 1.78–3.60). Sex, race, BMI, constipation duration, PAC-QOL score, and coexisting illness did not affect the duration of acupuncture effects.

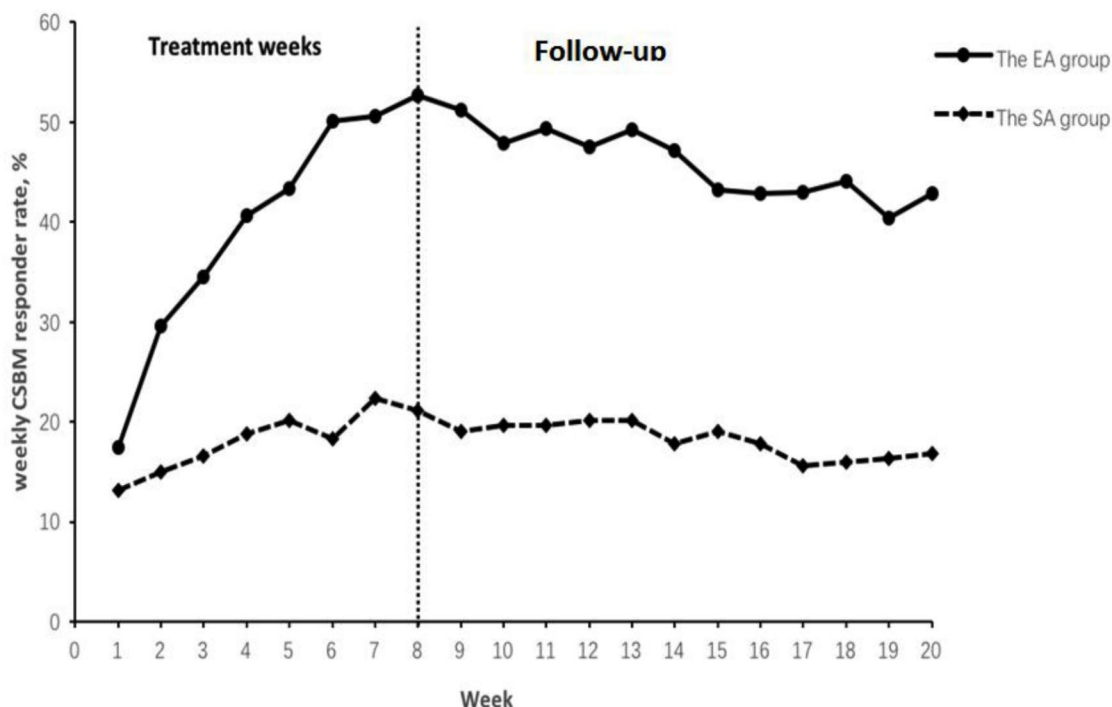


Figure 1. Weekly CSBM responder rate in the EA and the SA groups from week 1 to week 20. A Weekly CSBM responder was defined as a participant achieving at least three CSBMs/week and an increase of at least one CSBM compared with the baseline in a week, according to the guideline of the European Medicines Agency 7. The differences in the weekly CSBM responder rate between the two groups were significant from week 2 to week 20. ($p < 0.01$ for all). CSBM, complete spontaneous bowel movement; EA, electro-acupuncture; SA, sham electro-acupuncture.

Discussion

In this study, we analyzed the data of the acupuncture constipation trial to explore the duration of acupuncture effects after last treatment and its associated factors. The results showed that EA effects lasted longer than SA effects for CSFC with the duration of effects of 5.5 weeks in the EA group as compared with 2.2 weeks in the SA group. Besides, the proportions of overall CSBM responders during treatment and follow-up periods, and weekly CSBM responder proportions from week 2–20 were all higher in the EA group than the SA group.

Based on these results, the sustained acupuncture effects seems promising in chronic constipation as compared with conventional therapy of laxatives which only provided transient symptomatic relief. For example, 30 days after last treatment, 29 of the 47 participants (61.7%) who took polyethylene glycol 3350 required additional constipation treatment interventions.¹² In a study on Linaclotide for chronic constipation,¹³ when participants in

the two groups (linaclotide 290 µg and linaclotide 145 µg) stopped treatment and started to use placebo, the mean weekly CSBM frequency decreased quickly and was similar to the placebo group within 1 week. Similar findings were reported in another trial on plecanatide.¹⁴ Discontinuation of plecanatide 3 mg or 6 mg (once daily) caused a sharp decrease in the percentage of weekly CSBM responders within 2 weeks to the point comparable with the placebo. In this study, the proportion of weekly CSBM responders at week 20 was still much higher than that at baseline and in the SA group. And, for the treatment-period overall CSBM responders, the duration of acupuncture effects was 9.69 weeks. Though EA had a good long-lasting effect, 165 participants in the EA group did not enjoy a durable effect after treatment (Table 2). But, of the 165 participants, only 16 were overall CSBM responders during the treatment period and the rest 149 were nonresponders. Participants with poor response in the treatment period were prone to have no sustained effect in the follow-up period.

Table 3. Full model and backward regression with bootstrap method for the EA group.

Variables	Full model			Backward elimination ^a		
	RC	SE	p value	RC	SD	95% CI
Intercept	7.36	1.74	<0.0001	7.79	0.56	
Age	-0.04	0.01	0.0061	-0.06	0.01	-0.06 to -0.04
Sex	0.25	0.51	0.6192			
Race	-0.71	1.19	0.5510			
BMI	0.30	0.34	0.3745			
Constipation duration	-0.55	0.25	0.0296			
CSBMs	2.06	0.73	0.0052	2.43	0.47	1.78–3.60
PAC-QOL score	0.05	0.28	0.8634			
Coexisting illness	-1.04	0.54	0.0536			

BMI, body mass index; CSBMs, complete spontaneous bowel movements; EA, electro-acupuncture; PAC-QOL, Patient Assessment of Constipation Quality of Life questionnaire; RC, Regression coefficient; SD, standard deviation; SE, standard Error.
^aRegression coefficient, standard deviation, 95% confidence interval after bootstrapping.

The long-lasting effects of acupuncture after treatment and comparison of acupuncture with conventional care have been reported in previous trials. Our results are consistent with a recent study on acupuncture for chronic functional constipation in which Zheng and colleagues reported that acupuncture increased spontaneous bowel movements after 4 weeks treatment, and efficacy lasted for 4 weeks after treatment.¹⁵ Additionally, Zheng and colleagues also found better and longer therapeutic efficacy of acupuncture than mosapride.¹⁵ In the study of acupuncture for irritable bowel disease, MacPherson and colleagues compared 10-week-long acupuncture treatment plus usual care *versus* usual care alone, and found that acupuncture plus usual care significantly improved irritable bowel symptoms, and that the effect persisted during the follow-up periods (at 6, 9, and 12 months).¹⁶ In the study of acupuncture for chronic neck pain,¹⁷ an average of 10 sessions of acupuncture plus usual care over an average of 18 weeks led to significant reductions in neck pain and associated disability compared with usual care at 12 months. Acupuncture may be better than conventional care in its duration of effects.

Another secondary analysis of the same trial published in 2017 explored factors related to

acupuncture response in patients with CSFC.¹⁸ This paper intended to explore the duration of acupuncture effects and the related factors. The results of this secondary analysis showed that EA had a longer duration of effects than SA during the follow-up period. Factors contributing to the therapeutic effects of acupuncture are widely known to acupuncturists, including acupuncture specificity, needle manipulation, and treatment duration.¹⁹ Participants' expectation and belief also contribute to the therapeutic efficacy of acupuncture, which was supposedly minimized by blinding.²⁰ In this trial, we used sham EA as control and randomly selected 140 participants to test the blinding efficacy. No between-group difference was found in the credibility of the intervention participants received. Thus, factors related with patients' expectation and belief were similar in the two groups, and differences in effect durations between the two groups came mainly from the intervention itself. Similar results comparing the effects of the true acupuncture and SA have been seen for migraine prophylaxis, low back pain and stress urinary incontinence.^{21–23} In our analysis, a younger age and more baseline CSBMs/week were associated with longer durations of acupuncture effects in the EA group. We found no reports on the relationship between age and any sustained effect of acupuncture, but we

speculate that, with the reduction of the somatic function, seniors' response to acupuncture might also decrease. Elderly participants were more prone to develop constipation complications and had a greater degree of self-reported symptoms.²⁴ Treating constipation in the elderly was a challenge.²⁵ The results in the present secondary analysis provided additional evidence for the difficulties in treating seniors with chronic constipation. Baseline constipation severity, which may be represented by CSBM/week, is another factor related to the duration of acupuncture effects. Severe participants were less likely to have a good long-lasting response to EA treatment. This result was partly similar with a recent *post hoc* analysis of two drug trials performed in Japan.²⁶ The latter analysis found participants in more severe condition needed a high dose of elobixibat and the treatment duration increased.

Though the sustained effect of acupuncture was reported in many trials, the mechanism is not yet clear. In an editorial about acupuncture for chronic constipation, Tjen-A-Looi speculated that acupuncture stimulated somatic sensory nerves to modify the central neuronal pathways and regions in the brain.²⁷ And like other gastrointestinal disease, functional constipation is also associated with psychological factors.^{28,29} Acupuncture might be effective for emotional issues.³⁰ Thus, the sustained effect of acupuncture for constipation might be achieved partly by improving emotional problems.

Strengths of this study include a large sample size, successful blinding, and high retention rates. However, our findings should be interpreted in light of its limitations. First, the main limitation of our study is the *post hoc* nature of the analysis. Some potential risk factors may not have been captured in this analysis and caution in the interpretation of results is required. Second, the follow-up period is limited and we cannot estimate the real duration of acupuncture effects. Third, potential factors associated with sustained acupuncture effects are not limited to the variables reported in this study.

Conclusion

EA had sustained post-treatment effects for CSFC. EA had longer effect duration than the sham EA. A significant association among a younger age, higher baseline CSBMs, and sustained acupuncture

effects was observed. Further research is needed to confirm the association.

Acknowledgements

Yang Wang and Yan Liu are co-first authors of this study.

Author contributions

ZSL and BYL conceived the study, YW and YL wrote the manuscript, BAB, KZ, QM, and TSS revised the paper.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and publication of this article: This study was supported by the Ministry of Science and Technology of the People's Republic of China through the Twelfth Five-Year National Science and Technology Pillar Program (grant number 2012BAI24B01).

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Yang Wang  <https://orcid.org/0000-0003-2402-5862>

Availability of data and material

The datasets analyzed during the current study are available from Shiyang Yan (E-mail: yanshiyan0927@sina.com)

References

1. Gray JR. What is chronic constipation? Definition and diagnosis. *Can J Gastroenterol* 2011; 25(Suppl. B): 7B–10B.
2. Camilleri M, Kerstens R, Ryck A, *et al.* A Placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; 358: 2344–2355.
3. Higgins PD and Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; 99: 750–759.
4. Wei YJ, Bian HL and Zhao F. Internal progress of epidemiology study on constipation [Chinese]. *Chinese J Dis Control Prev* 2004; 8: 449–451.
5. Sanchez MI and Bercik P. Epidemiology and burden of chronic constipation. *Can J Gastroenterol* 2011; 25(Suppl. B): 11B–15B.

6. Wald A and Talley NJ. Management of chronic constipation in adults. UpToDate, www.uptodate.com/contents/management-of-chronic-constipation-in-adults?source=search_result&selectedTitle=1%7E150 (accessed 6 May 2018).
7. European Medicines Agency. *Guidelines on the evaluation for medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing*. EMA/CHMP/336243/2013, 25 June 2015. London: European Medicines Agency.
8. Johanson JF and Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* 2007; 25: 599–608.
9. Zhishun Liu, Shiyun Yan, Jiani Wu, *et al.* Acupuncture for chronic severe functional constipation: a randomized controlled trial. *Ann Intern Med* 2016; 6: 155: 761–769.
10. Guillermo BC. Management of chronic severe constipation. *Rev Med Chile* 2002; 130: 803–808.
11. Harrell F. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. 2nd ed. Basel: Springer, 2015.
12. Tran LC and Di Palma JA. Lack of lasting effectiveness of PEG 3350 laxative treatment of constipation. *J Clin Gastroenterol* 2005; 39: 600–602.
13. Lembo AJ, Schneier HA, Shiff SJ, *et al.* Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 2011; 365: 527–536.
14. Miner PB Jr, Koltun WD, Wiener GJ, *et al.* A randomized phase iii clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. *Am J Gastroenterol* 2017; 112: 613–621.
15. Zheng H, Liu ZS, Zhang W, *et al.* Acupuncture for patients with chronic functional constipation: a randomized controlled trial. *Neurogastroenterol Motil* 2018; 30: e13307.
16. MacPherson H, Tilbrook H, Bland JM, *et al.* Acupuncture for irritable bowel syndrome: primary care based pragmatic randomised controlled trial. *BMC Gastroenterol* 2012; 12: 150.
17. Macpherson H, Tilbrook H, Richmond S, *et al.* Alexander technique lessons or acupuncture sessions for persons with chronic neck pain: a randomized trial. *Ann Intern Med* 2015; 163: 653–662.
18. Yang X, Liu Y, Liu B, *et al.* Factors related to acupuncture response in patients with chronic severe functional constipation: secondary analysis of a randomized controlled trial. *PLoS One* 2017; 12: e0187723.
19. Shi GX, Yang XM, Liu CZ, *et al.* Factors contributing to therapeutic effects evaluated in acupuncture clinical trials. *Trials* 2012; 13: 42.
20. Pariente J, White P, Frackowiak RS, *et al.* Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. *Neuroimage* 2005; 25: 1161–1167.
21. Zhao L, Chen J, Li Y, *et al.* The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med* 2017; 177: 508–515.
22. Cho YJ, Song YK, Cha YY, *et al.* Acupuncture for chronic low back pain. *Spine* 2013; 38: 549–557.
23. Liu Z, Liu Y, Xu H, *et al.* Effect of electroacupuncture on urinary leakage among women with stress urinary incontinence: a randomized clinical trial. *JAMA* 2017; 317: 2493–2501.
24. Sbahi H and Cash BD. Chronic constipation: a review of current literature. *Curr Gastroenterol Rep* 2015; 17: 47.
25. Martínez-Martínez MI, Calabuig-Tolsá R and Cauli O. The effect of probiotics as a treatment for constipation in elderly people: a systematic review. *Arch Gerontol Geriatr* 2017; 71: 142–149.
26. Nakajima A, Taniguchi S, Kurosu S, *et al.* Efficacy, long-term safety, and impact on quality of life of elobixibat in more severe constipation: post hoc analysis of two phase 3 trials in Japan. *Neurogastroenterol Motil* 2019; 31: e13571.
27. Tjen-A-Looi SC and Fu LW. Sustained effects of acupuncture in treatment of chronic constipation. *Ann Palliat Med* 2017; 6(Suppl. 2): S124–S127.
28. Dore MO, Pes GM, Bibbò S, *et al.* Constipation in the elderly from Northern Sardinia is positively associated with depression, malnutrition and female gender. *Scand J Gastroenterol* 2018; 53: 797–802.
29. Liu ML, Liang FR, Zeng F, *et al.* Cortical-limbic regions modulate depression and anxiety factors in functional dyspepsia: a PET-CT study. *Ann Nucl Med* 2012; 26: 35–40.
30. Li M, Xing X, Yao L, *et al.* Acupuncture for treatment of anxiety, an overview of systematic reviews. *Complement Ther Med* 2019; 43: 247–252.