

# Transcutaneous electric nerve stimulation over acupoints for patients with diarrhea-predominant irritable bowel syndrome

## Protocol for systematic review and meta-analysis

Bo-yu Han, MD<sup>a,b</sup>, Qian-Feng Shao, MD<sup>b</sup>, Yu Cong, MD<sup>b</sup>, Song Guo, MD<sup>b</sup>, Xin-Yong Mao, MD<sup>b</sup>, Ru-Han Wei, MD<sup>c</sup>, Wei Wei, PhD<sup>b,\*</sup>

### Abstract

**Background:** At present, drug therapy for diarrhea-predominant irritable bowel syndrome (IBS-D) has made great progress; however, it does not often produce a satisfying curative effect. Transcutaneous electric nerve stimulation over acupoints (Acu-TENS) might be more effective in improving patient's symptoms and producing fewer side-effects as a result.

Although with a great progress of the drug therapy for IBS-D, it is often hard to achieve its satisfactory curative effect. Acu-TENS that may be effective to improve patients' symptoms and fewer side-effects will be sought. There is no systematic review concerning the efficacy of Acu-TENS for IBS-D published. Therefore, this review aims to systematically evaluate the efficacy of Acu-TENS on IBS-D.

**Methods:** Four English (PubMed, EMBASE, The Cochrane Library, Web of Science) and 4 Chinese electronic databases (Biomedical Literature Database, CNKI, VIP, Wanfang Database) will be searched from their inception to November 26, 2018. Randomized controlled trials that evaluated the effect of Acu-TENS on patients with IBS-D will be included. The primary outcome measures will include average weekly stool frequency, visual analog scale (VAS), and the Bristol scale. The secondary outcome measures will include the MOS 36-item short-form health survey (SF-36), IBS Quality of Life Questionnaire (IBS-QOL), severity of IBS symptoms (IBS-SSS), and rectal perception. Quality evaluation and data extraction will be independently undertaken, respectively. The data from the eligible trials will be analyzed by RevMan5.3.

**Results:** For patients with IBS-D, this systematic review will provide evidences related to the efficacy of Acu-TENS in these evaluation aspects, stool frequency, VAS and the Bristol scale, SF-36, IBS-QOL, IBS-SSS, and rectal perception.

**Conclusion:** This evidence may be useful to medical workers with regard to the use of Acu-TENS in the treatment of IBS-D. PROSPERO registration number: PROSPERO CRD442018109294.

**Abbreviations:** Acu-TENS = transcutaneous electric nerve stimulation over acupoints, CI = confidence interval, IBS = irritable bowel syndrome, IBS-QOL = IBS Quality of Life Questionnaire, IBS-SSS = severity of IBS symptoms, RRs = the relative risks, SF-36 = MOS 36-item short-form health survey, VAS = visual analog scale.

**Keywords:** irritable bowel syndrome with diarrhea, meta-analysis, protocol, systematic review, transcutaneous electric nerve stimulation over acupoints

*Ethics and dissemination:* This review will not gather original data. All data used in this meta-analysis are fully available in the public domain; hence, ethical approval is not required.

This research was supported by the National Natural Science Foundation of China (Grant nos. 81774066 and 81503439).

The authors have no conflicts of interest to disclose.

<sup>a</sup> Dongzhimen Hospital, Beijing University of Chinese Medicine, <sup>b</sup> Beijing Key Laboratory of Functional Gastrointestinal Disorders Diagnosis and Treatment of Traditional Chinese Medicine, Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing, China, <sup>c</sup> Cleveland State University, Cleveland, OH.

\* Correspondence: Wei Wei, Wangjing Hospital of China Academy of Chinese Medical Sciences, Beijing, China (e-mail: sxxy@sina.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2018) 97:51(e13267)

Received: 17 October 2018 / Accepted: 23 October 2018

<http://dx.doi.org/10.1097/MD.0000000000013267>

## 1. Introduction

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder characterized by recurrent abdominal pain and/or bloating related to defecation without reliable biological markers.<sup>[1]</sup> The prevalence of IBS in Asia using Rome criteria was approximately 4.6% to 21.2% in adults, global prevalence of IBS was demonstrated in a meta-analysis of 11%.<sup>[2-4]</sup> IBS is associated with substantial burden, such as higher levels of anxiety, lost productivity at work, work absenteeism.<sup>[5]</sup> IBS-D is the common subtype, which accounts for 23.4% to 40% of all IBS patients.<sup>[4]</sup> IBS-D poses a substantial economic burden on the global healthcare system. Patients with IBS-D compared with the unaffected controls had significantly higher total all-cause health-care costs (\$9436 vs \$7169;  $P < .001$ ).<sup>[6]</sup> Although with a great progress of the drug therapy for IBS-D which have been proven to be effective in relieving symptoms and improving quality of life for patients with IBS-D, it is often hard to achieve the satisfactory curative effect. These drugs include antidepressants, antibiotics, probiotics, and serotonin receptor modulators.<sup>[7,8]</sup> The temporary

**Table 1****Search strategy.****Search**

#1 (((("Irritable Bowel Syndrome"[MeSH Terms]) OR Irritable Bowel Syndromes[Title/Abstract]) OR Syndromes, Irritable Bowel[Title/Abstract]) OR Syndrome, Irritable Bowel[Title/Abstract]) OR Colon, Irritable[Title/Abstract]) OR Irritable Colon[Title/Abstract]

#2 (((((((((((("Transcutaneous Electric Nerve Stimulation"[MeSH Terms]) OR Electric Stimulation, Transcutaneous[Title/Abstract]) OR Stimulation, Transcutaneous Electric[Title/Abstract]) OR Transcutaneous Electric Stimulation[Title/Abstract]) OR Percutaneous Electric Nerve Stimulation[Title/Abstract]) OR TENS[Title/Abstract]) OR Electrical Stimulation, Transcutaneous[Title/Abstract]) OR Transcutaneous Electrical Stimulation[Title/Abstract]) OR Transdermal Electrostimulation[Title/Abstract]) OR Electrostimulation, Transdermal[Title/Abstract]) OR Percutaneous Electrical Nerve Stimulation[Title/Abstract]) OR Transcutaneous Electrical Nerve Stimulation[Title/Abstract]) OR Transcutaneous Nerve Stimulation[Title/Abstract]) OR Nerve Stimulation, Transcutaneous[Title/Abstract]) OR Stimulation, Transcutaneous Nerve[Title/Abstract]) OR Percutaneous Neuromodulation Therapy[Title/Abstract]

#3 ((randomized controlled trial[Title/Abstract]) OR randomized controlled trial[MeSH Terms])

#1 and #2 and #3

and limited effect remains to be a difficult problem on account of the mechanisms by which symptoms that arise are poorly understood.<sup>[9]</sup> Owing to limited effect and the side effects of medications, patients with IBS-D often cannot get satisfying curative effect.<sup>[10]</sup> Therefore, an increasing number of patients tend to use complementary and alternative therapy.<sup>[11–13]</sup>

As an alternative therapy, transcutaneous electric nerve stimulation (TENS) has been increasingly studied in clinical practice, a Western treatment acts on the afferent nerve fibers to stimulate the nerves for therapeutic purposes.<sup>[14]</sup> TENS over acupoints (Acu-TENS) is a coordinated intervention merging TENS with acupuncture. Compared with traditional acupuncture and electro-acupuncture, it is not necessary to insert a needle into acupoints for stimulation. In recent years, it has been widely used in clinical practice.<sup>[15–17]</sup>

Considering there is a limited evidence concerning its efficacy for IBS-D, we performed this review that aims to systematically evaluate the efficacy of Acu-TENS for IBS-D and thus to provide a reliable evidence for clinical decision.

## 2. Methods and analysis

### 2.1. Inclusion criteria for study selection

All randomized controlled trials evaluating the effect of Acu-TENS comparing no interventions, placebo control, sham Acu-TENS on IBS-D will be included. Participants who are diagnosed with IBS-D according to the Rome II, III, or VI criteria will be included, regardless of their age, gender, and ethnicity. We will exclude those who had an acute exacerbation within 1 week before the study.

### 2.2. Outcome measures

Primary outcome measures will include average weekly stool frequency, visual analog scale (VAS), and the Bristol scale.<sup>[13]</sup> Secondary outcome measures will include SF-36, IBS-QOL, IBS-SSS, and rectal perception.<sup>[18–21]</sup> Rectal sensory thresholds will be evaluated by rectal balloon distension.

### 2.3. Literature search

Four English (PubMed, Embase, The Cochrane Library, Web of Science) and 4 Chinese electronic databases (Biomedical Literature Database, CNKI, VIP, and Wanfang Database) will be searched from their inception to November 26, 2018. There was no limit to the type of language. Reference lists of eligible studies will be reviewed to discover further eligible studies. We

have drawn up detailed search strategies for each electronic database to identify eligible studies totally. The search strategy is shown in Table 1.

### 2.4. Study selection

Two review authors (B-YH, Q-FS) will screen and extract independently titles and abstracts, then select potentially eligible studies. Finally, the full-text of literature will be reviewed carefully according to the inclusion and exclusion criteria. Disagreements and inconsistency will be resolved by a third review author (YC). The study flow diagram is shown in Fig. 1.

### 2.5. Data extraction

Two researchers will independently extract the data, the following content will be included: first author, the year of publishing, diagnosis criteria, study population, treatment protocol, outcome measurements, duration of treatment, duration of the follow-up period, and baseline characteristic. A third review author will resolve divergences through discussion.

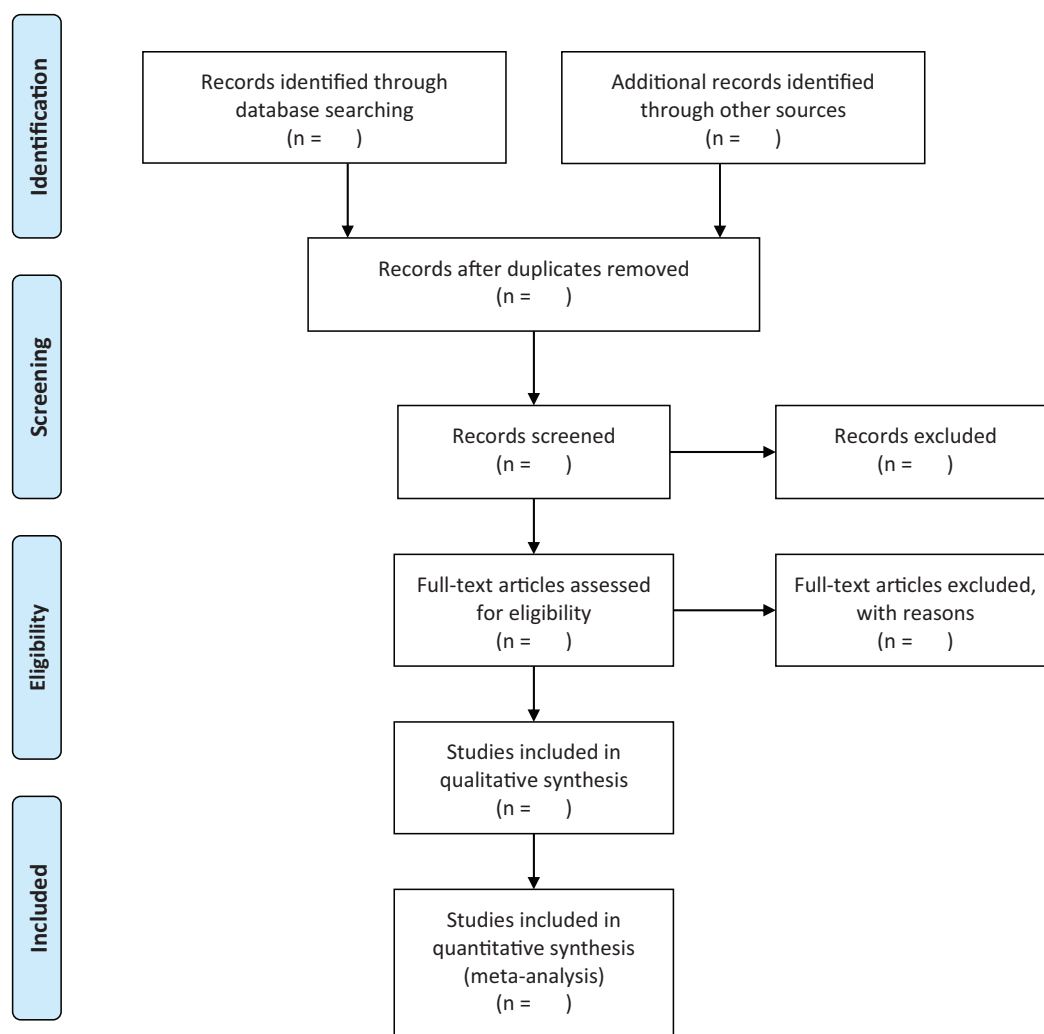
### 2.6. Risk of bias assessment

The Cochrane risk of bias tool will be used to evaluate methodologic quality, which is described in the Cochrane Handbook of Systematic Reviews of Interventions:

- Sequence generation (selection bias)
- Allocation sequence concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias) and other potential sources of bias

### 2.7. Statistical analysis

The data of all the eligible trials will be analyzed by RevMan5.3. Continuous data will be calculated by the mean differences and 95% confidence interval (95% CI), and dichotomous data will be calculated by the relative risks (RRs) and 95% CI. Heterogeneity will be assessed by the *I*-squared ( $I^2$ ) statistic. We will regard as substantial heterogeneity when  $I^2 > 50%$  or  $P < .05$ , and a random effect model will be chosen. Otherwise, a fixed effects model will be applied to calculate the pooled RR. We will conduct subgroup analysis and sensitivity analysis if necessary.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**Figure 1.** Study flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

### 2.8. Grading the quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation will be used to assess the quality of evidence for the outcomes.<sup>[22]</sup> The quality of outcome measures will be categorized into 4 levels: high, moderate, low, and very low quality.

### 3. Discussion

Owing to less high-level evidence-based medical research evaluating the efficacy of Acu-TENS on IBS-D, Acu-TENS has been gradually accepted and widely used in the treatment of IBS-D. To our knowledge, this is the first systematic review to investigate the efficacy of Acu-TENS for IBS-D. This review will provide evidence related to the efficacy of Acu-TENS in these evaluation aspects, stool frequency, VAS and the Bristol scale, SF-36, IBS-QOL, IBS-SSS, and rectal perception. It may be useful to medical workers considering the use of Acu-TENS in the treatment of IBS-D.

### Author contributions

Conceptualization: Bo-yu Han, Wei Wei  
 Data curation: Yu Cong, Song Guo  
 Formal analysis: Qian-Feng Shao, Xin-Yong Mao  
 Writing – original draft: Bo-yu Han  
 Writing – review & editing: Ru-Han Wei, Wei Wei  
**Data curation:** Yu Cong, Song Guo.  
**Formal analysis:** Qian-Feng Shao, Xin-Yong Mao.  
**Writing – original draft:** Bo-yu Han.  
**Writing – review & editing:** Ru-Han Wei, Wei Wei.

### References

- [1] Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology* 2016;150:1262–79.
- [2] Zhao Y, Zou D, Wang R, et al. Dyspepsia and irritable bowel syndrome in China: a population-based endoscopy study of prevalence and impact. *Aliment Pharmacol Ther* 2010;32:562–72.
- [3] Matsumoto S, Hashizume K, Wada N, et al. Relationship between overactive bladder and irritable bowel syndrome: a large-scale Internet

- survey in Japan using the overactive bladder symptom score and Rome III criteria. *BJU Int* 2013;111:647–52.
- [4] Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:712–21.
- [5] Pimentel M. Evidence-based management of irritable bowel syndrome with diarrhea. *Am J Manag Care* 2018;24(3 suppl):S35–46.
- [6] Buono JL, Mathur K, Averitt AJ, et al. Economic burden of irritable bowel syndrome with diarrhea: retrospective analysis of a U.S. commercially insured population. *J Manag Care Spec Pharm* 2017;23:453–60.
- [7] Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014;109:1350–66.
- [8] Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med* 2017;376:2566–78.
- [9] Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on management of irritable bowel syndrome. *Am J Gastroenterol* 2018;113(suppl 2):1–8.
- [10] Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104(suppl 1):S1–35.
- [11] Saito YA, Rey E, Almazar-Elder AE, et al. A randomized, double-blind, placebo-controlled trial of St John's wort for treating irritable bowel syndrome. *Am J Gastroenterol* 2010;105:170–7.
- [12] Kavuri V, Raghuram N, Malamud A, et al. Irritable bowel syndrome: yoga as remedial therapy. *Evid Based Complement Alternat Med* 2015;2015:398156.
- [13] Wang JK, Liu J. Neuromuscular electrical stimulation as an adjunctive therapy to drotaverine hydrochloride for treating patients with diarrhea-predominant irritable bowel syndrome: a retrospective study. *Medicine (Baltimore)* 2018;97:e11478.
- [14] Almeida T, Figueiredo F, Barbosa FV, et al. Effects of transcutaneous electrical nerve stimulation (TENS) on proinflammatory cytokines: protocol for systematic review. *Syst Rev* 2017;6:139.
- [15] Seifi M, Ebadifar A, Kabiri S, et al. Comparative effectiveness of low level laser therapy and transcutaneous electric nerve stimulation on temporomandibular joint disorders. *J Lasers Med Sci* 2017;8(suppl 1):S27–31.
- [16] Jin Y, Kong J. Transcutaneous vagus nerve stimulation: a promising method for treatment of autism spectrum disorders. *Front Neurosci* 2016;10:609.
- [17] Kwong PW, Ng GY, Chung RC, et al. Transcutaneous electrical nerve stimulation improves walking capacity and reduces spasticity in stroke survivors: a systematic review and meta-analysis. *Clin Rehabil* 2018;32:1203–19.
- [18] Zheng H, Li Y, Zhang W, et al. Electroacupuncture for patients with diarrhea-predominant irritable bowel syndrome or functional diarrhea: a randomized controlled trial. *Medicine (Baltimore)* 2016;95:e3884.
- [19] Hou X, Chen S, Zhang Y, et al. Quality of life in patients with Irritable Bowel Syndrome (IBS), assessed using the IBS-Quality of Life (IBS-QOL) measure after 4 and 8 weeks of treatment with mebeverine hydrochloride or pinaverium bromide: results of an international prospective observational cohort study in Poland, Egypt, Mexico and China. *Clin Drug Investig* 2014;34:783–93.
- [20] Gerson CD, Gerson MJ, Chang L, et al. A cross-cultural investigation of attachment style, catastrophizing, negative pain beliefs, and symptom severity in irritable bowel syndrome. *Neurogastroenterol Motil* 2015;27:490–500.
- [21] Xiao WB, Liu YL. Rectal hypersensitivity reduced by acupoint TENS in patients with diarrhea-predominant irritable bowel syndrome: a pilot study. *Dig Dis Sci* 2004;49:312–9.
- [22] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.