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Title page:

Article title:

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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Running title: acupuncture for stress-predominant mixed urinary incontinence

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Abstract

Introduction: There is a lack of evidence targeted at stress-predominant mixed urinary incontinence (MUI) at present. Acupuncture might help to relieve the incontinence symptoms. We plan to conduct a multi-center, three-armed, randomized controlled to investigate the efficacy of electroacupuncture (EA) on women with stress-predominant MUI.

Methods and analysis: The trials will be conducted in 5 recruitment centers in China. 232 eligible participants will be randomly assigned to EA, sham electroacupuncture (SE) or Waiting List (WL) group, at 2:1:1 ratio, to receive 8-week EA/SA with 24-week follow-up, or 20-week watchful waiting. The primary outcome is defined as the proportion of participants with at least 50% reduction in incontinence episode frequency (IEF) from baseline at week 8. Secondary outcomes will mainly be measured at weeks 4, 8, 12, 20 and 32 by 3-day voiding diary, International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and 1-hour pad test. All outcomes will be analyzed in intention to treat population (defined as participants randomized) with a two-sided *P* value of less than .05 considered significant.

Ethics and dissemination: The protocol was approved for by Guang'anmen Hospital Institution of Review Board (2019-241-KY). Detailed information of the trial will be informed to the participants and written informed content will be obtained from every participant before randomization. Results of the trial will be expected to be published on a peer-reviewed journal.

Key words: Acupuncture; Mixed urinary incontinence; Female;

Trial registration: Clinicaltrials.gov identifier: NCT04299932

Strengths and limitations of this study

- The first randomized controlled trial to investigate the efficacy of acupuncture on stress-predominant mixed urinary incontinence.
- Sham control and no intervention control are designed to eliminate the influence

of placebo effects and disease's nature course on efficacy of acupuncture;

- Minimal electroacupuncture serve as a sham intervention to blind participants in electroacupuncture and sham electroacupuncture groups.
- One limitation is that participants in waiting list group and acupuncturists cannot be blinded.

INTRODUCTION

Mixed urinary incontinence (MUI) is a condition where incontinence occurs with both physical exertion and urgency.[1] Compared with pure urinary incontinence (UI), MUI tends to present with more severe symptoms and put greater burden on the health of individual and economy of society.[2] An estimate of 21%-33% females in the world[3] and 9.4% females in China[4] are troubled with MUI, while the report and treatment rates are under one second[5].

Stress-predominant MUI mainly constitutes of stress component, featuring leakage on increased abdominal pressure, such as exertion, sneeze or cough. Though leakage with urgency also exists, stress incontinence episode frequency (IEF) outnumbers 50% of total IEF.[6]

Current European Association of Urology (EAU) guideline on incontinence recommends to initiate treatment targeted at predominant component of MUI.[7 8] However, as to whether the interventions for stress urinary incontinence (SUI) can be effectively generalized to stress-predominant MUI, there is still no powerful evidence to support it.[6] Systematic reviews indicated that pelvic floor muscle training (PFMT） can alleviate the symptoms of SUI patients, but the effects of it may decrease to some degree in the treatment of MUI.[9] For moderate to severe SUI, surgery might be more useful than PFMT[10], and long-term follow-up revealed that about half patients conducting PFMT will turn to surgery for help at last[11]. When it refers to surgery for MUI, other therapies might need to be combined with to conquer the urgency component.[12] In addition, the existence of urgency symptoms might aggravate after surgery[13], and even reduce the success rate of operation[14]. Considering all those reasons, it is necessary to seek for interventions specific to stress-predominant MUI.

Results of previous studies indicated that acupuncture might help to relieve the incontinence symptoms.[15 16] It is proven effective in reducing leakage amount of pure SUI patients[15] and reducing IEF of MUI patients.[16] Future analysis into the results of the two trials showed that EA can relieve the symptoms of stress-related urinary

incontinence.[17] Considering the fact that the two trials weren't focused on stress-predominant MUI patients specifically, we plan to conduct this multi-center, three-armed, randomized controlled to evaluate the efficacy of EA, compared with sham electroacupuncture (SA) and waiting list (WL) on participants with stress-predominant MUI.

METHODS AND ANALYSIS

Hypotheses

Our primary hypothesis is that, the effects of EA is superior to SA in improving proportion of stress-predominant MUI participants with at least 50% reduction of stress IEF from baseline at week 8. Our secondary hypothesis is that the effects of EA is superior to WL in improving the proportion mentioned above at week 8.

Study design

This is a three-armed, randomized, SA and WL-controlled trial conducted in five recruitment centers, that is Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated hospital of Beijing university of Chinese Medicine and Jiangxi Provincial Hospital of traditional Chinese Medicine. Participants will be enrolled from both hospitals and communities.

The study durations are 33 weeks for participants in EA and SA group with one-week baseline assessment, 8-week treatment and 24-week follow-up, while 21 weeks for participants in WL group, with one-week baseline assessment and 20-week follow-up (Figure 1. Flow Chart). Participations in EA and SA groups, outcome assessors, data managers and statisticians will be blinded to the group allocations, while acupuncturists and participants in WL group will not be blinded for obvious reasons.

Inclusion criteria

1) Diagnosis of MUI by the coexistence of SUI and UUI symptoms in accordance

with EAU guideline[8];

2) Female participants aged between 18 and 80;

3) Stress index > urge index in accordance with Medical, epidemiologic, and social aspects of Aging(MESA) questionnaire[18];

4) SUI episodes outnumber 50% total IEF documented in 3-day voiding diary;

5) Less than 12 micturition episodes in average 24 hours documented in 3-day voiding diary;

6) Positive cough stress test;

7) Urine leakage > 1 g in 1-hour pad test[19];

8) Voluntary participation in the trial and signed written informed content.

Participants meeting all these eight criteria might be able to be recruited in the trial.

Exclusion criteria

1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic bladder;

2) Uncontrolled symptomatic urinary tack infection;

3) Tumor in urinary system and pelvic organ;

4) Pelvic organ prolapse ⩾ degree Ⅱ;

5) Residual urine volume ⩾ 100ml;

6) History of treatments targeted at UI, such as acupuncture and PFMT;

7) History of surgery targeted at UI or in pelvic floor, including hysterectomy;

8) Uncontrolled diabetes or severe high blood pressure;

9) Nervous system diseases that may hamper the function of urinary system, such as Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury, cauda equina nerve injury, or multiple system atrophy;

10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or with obvious cognitive dysfunction

11) Installed cardiac pacemaker;

12) Inconvenient or unable to walk, run, go up and down stairs;

13) Allergy to metal, severely fear of acupuncture needles or unbearable to EA;

14) Pregnant at present, plan to conceive in future one year, at lactation period or within 12 months after childbirth.

Participants with either situation mentioned above will not be enrolled in the trial.

Randomization and allocation concealment

The randomization allocation sequence will be produced by a third independent party (Linkermed Technology Co., Ltd. [Beijing, China]). Eligible participants will be randomly assigned into EA group, SA group or WL group at 2:1:1 ratio, with varied blocks and using recruitment sites as stratification factor. The randomization number and group allocation will be acquired by acupuncturists in each recruitment site by logging in the Central Randomization System and typing in basic information of eligible participants.

Interventions

Participants in EA group will receive stimulation at bilateral BL33 (Zhongliao), BL35 (Huiyang) and SP6 (Sanyinjiao). BL 33 is located in the third posterior sacral foramen; BL 35, 0.5 cun (≈10mm) lateral to the extremity of the coccyx; and SP6 posterior to the medial border of the tibia, 3 cun superior to the prominence of the medial malleolus.[20] Bilateral BL33 will be inserted by acupuncture needles (Huatuo, Suzhou Medical Appliance) of 0.30×75mm size at the angle of 45°, inward and downward, till the depth of 60-70mm. Bilateral BL35 will be inserted by needles of 0.30×75mm size, slightly outward and upward, till the depth of 60-70mm. Bilateral SP6 will be inserted by needles of 0.30×40mm till the depth of 25-30mm. All the needles will be lifted, thrusted and twisted evenly for three times, right after insettion, to induce the sensation of *deqi*. Electronic acupuncture apparatus (Yingdi KWD 808 I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device Co., Ltd) will be connected to the three pairs of needles transversally, with continuous wave of 20Hz, electric current of 2mA-6.5mA for BL33 and BL35, and 1mA-3.5mA for SP6. The EA stimulation will last 30mins for each session, 3

sessions a week (ideally every other day) for a succession of 8 weeks.

Participants in SA group will receive minimal stimulation at bilateral sham BL33 (Zhongliao), BL35 (Huiyang) and SP6 (Sanyinjiao). Sham BL33 is in the area of 1 cun (≈20mm) horizontally outside BL33; sham BL35, 1 cun (≈20mm) horizontally outside BL35; Sham SP6, in the middle of SP6 and tendons. The three pairs of acupoints will be inserted by acupuncture needles of 0.30×40mm size to a depth of 2-3mm till the needles can stand still. No manipulations will be conducted, and the sensation of *deqi* will not be induced. Electronic acupuncture apparatus will be connected to the three pairs of needles transversally, with continuous wave of 20Hz and minimal electric current (ideally at a degree which participant can just percept). In about 30 seconds, the electric current will be turned off, leaving the indicator light and ticking sound on. The treatment sessions are similar to those in EA group.

Participants will be told ahead of time that they may receive either traditional EA treatment, or modern EA treatment; they might not feel the electrical stimulation during the process out of body adaption. To evaluate the success of blindness, within 5 minutes after the last treatment at week 8, participants in both EA and SA groups will be asked to answer the question do you think you have received traditional EA, and choose the answer between the options of Yes or No.

Participants in WL group will not receive active treatments. After the trial, they will receive 24-session EA treatment as mentioned above as compensation.

Participants in the three groups will receive handbook of healthcare education and advice on lifestyle modification, such as the conditions of exercise, fluid intake, weight, smoking, constipation, urinary tract infection, lifting, and respiratory symptoms, etc. The lifestyles changed accordingly will be documented in case report form. During the process, participants are not allowed to take other specialized medication and treatments for UI. Any medications that might influence the function of lower urinary tract function should be documented in case report form.

Outcomes

Primary outcome

In this trial, the primary outcome is defined as the proportion of participants with at least 50% reduction in IEF from baseline, measured by 3-day voiding diary at weeks 8. Three-diary voiding diary is a reliable and validated tool for urinary incontinence in both clinic and research, without placing great burden on participants.[21] In 3-day voiding diary, IEF of different types, micturition and nocturia episodes, fluid intake, and pad consumptions will all be documented. Participants are required to fill in the diary in baseline assessment period (week 0), weeks 4, weeks 8, weeks 20 and weeks 32 (participants in EA and SA group only).

Secondary outcomes

Secondary outcomes will be measured by 3-day voiding diary, International Consultation on Incontinence Questionnaire-short form (ICIQ-SF), 1-hour pad test and patient global impression of improvement (PGI-I). (Figure 2. Study schedule)

ICIQ-SF questionnaire is a validated questionnaire to assess the severity of incontinence symptoms and influence on QoL in the past four weeks. The questionnaire includes items of IEF, urinary leakage amount and general influence on life to be scored. Total number of the score ranges from 1 to 21, with higher scores representing greater severity and 2.52 as minimal clinically important differences[22]. Participants will complete the Chinese-version questionnaire[23] at baseline assessment period (week 0), weeks 4, weeks 8, weeks 20 and weeks 32 (participants in EA and SA group only).

One-hour pad test is the only tool standardized with a set protocol to measure the urinary leakage[19]. Participants will be instructed to drink 500 ml solid-free water, and perform a series of activities including standing and sitting, coughing, running, picking up a coin and putting hands under water. The leakage amount in one hour will be measured via pad.[24] Participants will conduct 1-hour pad test in baseline assessment period (week 0) and weeks 8.

PGI-I is a global index, with only one item, used to rate the participants' subject

perception on symptom improvement. In weeks 8 and 20, participants in the three groups will describe their impression from very much better to very much worse.[25] Improvement was considered to be clinically significant if the participant's response is "much better" or "very much better".

To better evaluate the efficacy and safety of acupuncture, participants expectations towards outcome and beliefs on acupuncture will also be assessed. Adverse events and severe adverse events will be documented in case report form throughout the trial. Acupuncturists in each site will decide whether the events are related to the treatments or not.

Quality control and data management

To ensure the quality of the study, personnel in recruitment sites will be trained by the principal investigator (ZS Liu) on the details of the protocol and manipulating methods. Acupuncture in both EA and SA groups are required to be conducted by licensed acupuncturists with at least two-year clinical experience. In each site, at least two acupuncturists are needed for rotation, while the treatment of each participant should be restricted to one specific doctor.

Measures will be taken to improve the compliance. The same participants should be taken charged by the same outcome assessor/acupuncturist throughout the trial, including instruction on the documentation of voiding diary, explanation on the contents of handbook if necessary, and informing the assessment time by phone or we-chat.

The data will be recorded in paper CRF first, and typed into EDC system within one week, so that the information can be traced back, monitored by CRA and system in time, and supplemented without delay, if missing or inaccuracy. In follow-up period, missing data in voiding diary can be asked by phone rather than in person. The database will be protected by a password and only the principal investigator will have access to the final dataset. Data are available upon reasonable request to the principal investigator, excluding the private information of patients.

Sample size

A sample size of 232 participants will provide the trial with 80% power to detect a between-group difference of about 23% of participants with at least 50% reduction from baseline in the stress IEF measured by 3-day voiding diary with a two-sided significance level of 0.05 and 10% dropouts, assuming that a reduction rate of 25% for the IEF in the SA group on the basis of previous study[15 16].

Statistical analysis

For primary hypothesis, we will compare the proportion of participants with at least 50% reduction in mean 24-hour stress IEF at week 8 among the three groups. The primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to compare the rate of participants with at least 50% reduction in stress IEF at week 8 between the EA group and the WL group. If this analysis is significant, the hierarchical testing will be used the EA group versus the SA group.

For other categorical variables, comparisons between treatment groups will be assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other continuous variables. Chi-square or Fisher's exact tests will be used to compare the frequency of AEs between groups.

All outcomes will be analyzed in intention to treat (ITT) population (defined as participants randomized). Analysis will be performed using SAS version 9.4 (SAS Institute Inc) with a two-sided P value of less than .05 considered significant.

Patient and public involvement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and dissemination

The protocol was approved for by Guang'anmen Hospital Institution of Review

Board (2019-241-KY), and registered on Clinicaltrials.gov (NCT04299932). The revisions of the protocol will be reported on the website. The trial will be conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice. Detailed information of the trial will be informed to the participants and written informed content will be obtained from every participant before randomization. Participants in WL group will receive 24-session EA treatment for compensation. Results of the trial will be expected to be published on a peer-reviewed journal.

DISCUSSION

MUI is a condition frustrating almost a third women globally, while about half of them feel embarrassed to speak it out[3 5]. In clinic, a reduction of at least 50% IEF is regarded as successful treatment.[26] Since the specific and non-specific effects of acupuncture towards stress-predominant MUI are still unclear, we make effort to explore the efficacy of EA under clinical meaningful outcome with SA and WL as controls. The acupoint regimen and administration protocol in this trial are based on the results of previous studies[15 16] and specialist consensus.

Apart from specific physiological effect, participants' expectation of a positive outcome and belief in acupuncture may have a physiological effect on the brain, adding non-specific clinical response to acupuncture.[27] For this reason, we design participants' expectations towards outcome and beliefs on acupuncture to assess the efficacy.

Given the fact that a large proportion of participants in China have received acupuncture treatment in their experience, to better blind the participants in SA group, acupuncture needles will be inserted minimally into skin at none-acupoint areas. The minimal insertion also makes participants to be more sensitive to the electrical current and percept the stimulation as soon as possible. The electrical current may further improve the blindness even if it is connected to needles for only about 30 seconds.

Limitation also exists in that the participants in WL group and acupuncturists

cannot be blinded, which might induce performance and detection bias into the trial. To decrease influence towards the results, the outcome assessment will be undertaken by an independent research assistant who know nothing about the allocation.

Ethical Approval and Consent to participate: The study has received approval from the Guang'anmen Hospital Institution of Review Board (2019-241-KY). Written informed content will be obtained from every participant.

Consent for publication: Not applicable.

Authors' contributions: Zhishun Liu conceived the study, initiated the design, and revised the manuscript; Yan Liu is responsible for statistical analysis plan and drafted the manuscript; Yuanjie Sun participated the design and drafted the manuscript; Huan Chen participated the design and revised the manuscript; Yan Yan helped to draft the manuscript. All authors have read and approved the final manuscript.

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Competing interests: The author declare that they have no competing interests.

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Reference:

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn* 2010;29(1):4-20.
2. Minassian VA, Devore E, Hagan K, et al. Severity of urinary incontinence and effect on quality of life in women by incontinence type. *Obstet Gynecol* 2013;121(5):1083-90.
3. Dooley Y, Lowenstein L, Kenton K, et al. Mixed incontinence is more bothersome than pure incontinence subtypes. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19(10):1359-62.
4. Zhu L, Li L, Lang J, et al. Epidemiology of mixed urinary incontinence in China. *Int J Gynaecol Obstet* 2010;109(1):55-8.
5. Thom DH, van den Eeden SK, Ragins AI, et al. Differences in Prevalence of Urinary Incontinence by Race/Ethnicity. *Journal of Urology* 2006;175(1):259-64.
6. Myers DL. Female mixed urinary incontinence: a clinical review. *JAMA* 2014;311(19):2007-14.
7. Frick AC, Huang AJ, Van den Eeden SK, et al. Mixed urinary incontinence: greater impact on quality of life. *J Urol* 2009;182(2):596-600.
8. Burkhard FC, Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence in adults. https://uroweb.org/guideline/ urinary-incontinence. Accessed November 4, 2017.
9. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev* 2018;10:CD005654.
10. Labrie J, Berghmans BL, Fischer K, et al. Surgery versus physiotherapy for stress urinary incontinence. *New Engl J Med* 2013;369(12):1124-33.
11. Bo K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. *Obstet Gynecol* 2005;105(5 Pt 1):999-1005.
12. Aoki Y, Brown HW, Brubaker L, et al. Urinary incontinence in women. *Nat Rev Dis Primers* 2017;3:17042.
13. Lee JK, Dwyer PL, Rosamilia A, et al. Persistence of urgency and urge urinary incontinence in women with mixed urinary symptoms after midurethral slings: a multivariate analysis. *BJOG* 2011;118(7):798-805.
14. Richter HE, Litman HJ, Lukacz ES, et al. Demographic and clinical predictors of treatment failure one year after midurethral sling surgery. *Obstet Gynecol* 2011;117(4):913-21.
15. 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(24):2493-501.
16. Liu B, Liu Y, Qin Z, et al. Electroacupuncture Versus Pelvic Floor Muscle Training Plus Solifenacin for Women With Mixed Urinary Incontinence: A

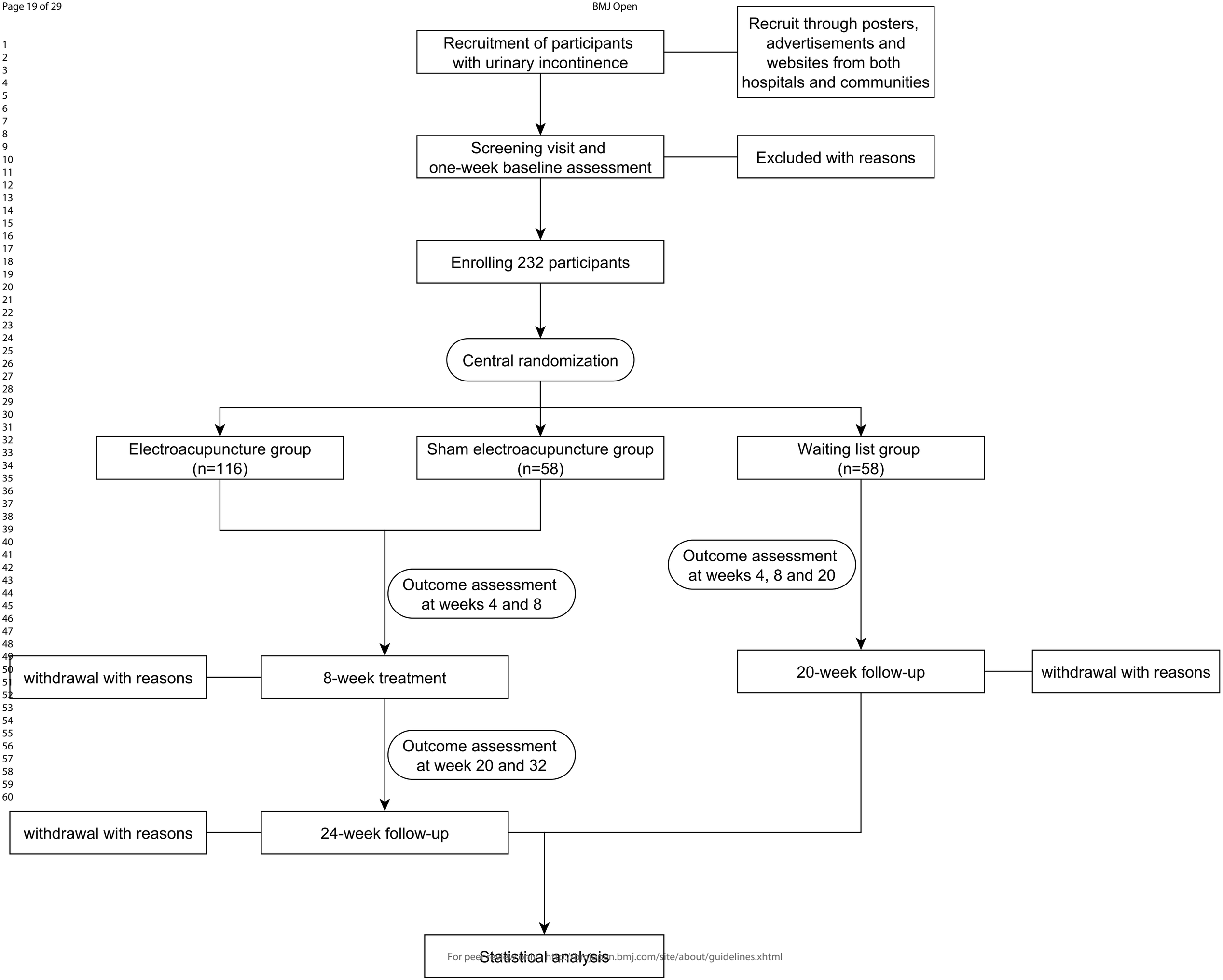
Randomized Noninferiority Trial. *Mayo Clin Proc* 2019;94(1):54-65.
17. Wang W, Liu Y, Su T, et al. Comparing the effect of electroacupuncture treatment on obese and non-obese women with stress urinary incontinence or stress-predominant mixed urinary incontinence: A secondary analysis of two randomised controlled trials. *Int J Clin Pract* 2019:e13435.
18. Herzog AR, Diokno AC, Brown MB, et al. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. *J Gerontol* 1990;45(2):M67-74.
19. Krhut J, Zachoval R, Smith PP, et al. Pad weight testing in the evaluation of urinary incontinence. *Neurourol Urodyn* 2014;33(5):507-10.
20. WHO Regional Office for the Western Pacific.WHO Standard Acupuncture Point Locations in the Western Pacific Region. Geneva: World Health Organization Pr; 2008.
21. Bright E, Cotterill N, Drake M, et al. Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. *Eur Urol* 2014;66(2):294-300.
22. Avery K, Donovan J, Peters TJ, et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* 2004;23(4):322-30.
23. Huang L, Zhang SW, Wu SL, et al. The Chinese version of ICIQ: a useful tool in clinical practice and research on urinary incontinence. *Neurourol Urodyn* 2008;27(6):522-4.
24. Abrams P, Blaivas JG, Stanton SL, et al. Standardisation of terminology of lower urinary tract function. *Neurourology and Urodynamics* 1988;7(5):403-27.
25. Viktrup L, Hayes RP, Wang P, et al. Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *BMC Urol* 2012;12:30.
26. Yalcin I, Peng G, Viktrup L, et al. Reductions in stress urinary incontinence episodes: what is clinically important for women? *Neurourol Urodyn* 2010;29(3):344-7.
27. Pariente J, White P, Frackowiak RS, et al. Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. *Neuroimage* 2005;25(4):1161-7.

Figure legends

Figure 1. Flow chart

Figure 2. Study schedule

* Only for participants in electroacupuncture and sham electroacupuncture groups



TIMEPOINT		Week -1	Week 0	Week 4	Week 8	Week 20	Week 32*
ENROLMENT	Eligibility screen	×					
	Informed consent	×					
	Allocation		×				
INTERVENTIONS	Electroacupuncture			×	×		
	Sham electroacupuncture			×	×		
	Waiting list			×	×	×	
ASSESSMENTS	Demography information	×					
	3-day voiding diary	×		×	×	×	×
	1-hour pad test	×			×		
	International Consultation on Incontinence Questionnaire short form	×		×	×	×	×
	Patient global impression of improvement			×		×	
	Adverse events	×	×	×	×	×	×
	Blindness assessment*				×		
	Expectation assessment*	×					
	Belief assessment*	×		×			

Testimonials of sponsor

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We provide the cover page and signature and seal pages of project assignment paper as testimonials.

Attachment 1: Cover page of project assignment paper

Attachment 2: Signature and seal pages of project assignment paper

课题编号：2017YFC1703602 密　级：公开

国家重点研发计划
课题任务书

课题名称：电针治疗神经源性尿潴留、膀胱过度活动症的疗效评价

所属项目：针灸优势病种疗效评价国际合作研究

所属专项：中医药现代化研究

项目牵头承担单位：中国中医科学院中医临床基础医学研究所

课题承担单位：中国中医科学院广安门医院

课题负责人：刘志顺

执行期限：2018 年 03 月 至 2021 年 12 月

中华人民共和国科学技术部制

2018 年 01 月 26 日

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任务书签署

甲乙双方根据《国务院关于改进加强中央财政科研项目和资金管理的若干意见》（国发[2014]11号）、《国务院印发关于深化中央财政科技计划（专项、基金）管理改革方案的通知》（国发[2014]64号）、《科技部 财政部关于印发<国家重点研发计划管理暂行办法>的通知》（国科发资[2017]152号）、《财政部 科技部关于印发<国家重点研发计划资金管理办法>的通知》（财科教[2016]113号）、《科技部财政部关于印发<中央财政科技计划（专项、基金等）监督工作暂行规定>的通知》（国科发政[2015]471号）等有关文件规定，以及有关法律、政策和管理要求，依据项目立项通知，签署本任务书。

项目牵头承担单位（甲方）：

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（公章）

2018年3月1日

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2018年3月5日

Table 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11-12,14

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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Title page

Article title:

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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Running title: acupuncture for stress-predominant mixed urinary incontinence

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Abstract

Introduction: Evidence targeted at stress-predominant mixed urinary incontinence is still lack at present, and acupuncture might help to relieve the symptoms. We plan to conduct this multi-center, three-armed, randomized controlled trial to investigate the efficacy and safety of electroacupuncture on women with stress-predominant mixed urinary incontinence.

Methods and analysis: The trial will be conducted in 5 hospitals in China. 232 eligible women will be randomly assigned to electroacupuncture, sham electroacupuncture or waiting list group, at 2:1:1 ratio, to receive 24-session acupuncture or sham acupuncture treatment over 8 weeks and 24-week follow-up, or 20-week watchful waiting. The primary outcome is the proportion of participants with at least 50% reduction in mean 24-hour stress incontinence episode frequencies from baseline to week 8. The outcome will be analyzed in intention to treat population (defined as participants randomized) with a two-sided *P* value of less than .05 considered significant.

Ethics and dissemination: The protocol was approved by Guang'anmen Hospital Institution of Review Board (2019-241-KY). Detailed information of the trial will be informed to the participants and written informed content will be obtained from every participant before randomization. Results of the trial will be expected to be published on a peer-reviewed journal.

Key words: Acupuncture; Mixed urinary incontinence; Female; Stress urinary incontinence

Trial registration: Clinicaltrials.gov identifier: NCT04299932

Strengths and limitations of this study

- The first randomized controlled trial to investigate the efficacy and safety of acupuncture on stress-predominant mixed urinary incontinence.
- Sham control and waiting-list control are designed to eliminate the influence of placebo effects and disease's natural course on the efficacy of acupuncture;
- Minimal electroacupuncture serves as a sham intervention to blind participants in the electroacupuncture and sham electroacupuncture groups.
- One limitation is that acupuncturists and participants in the waiting list group cannot be blinded.

INTRODUCTION

Mixed urinary incontinence (MUI) is a complaint of involuntary loss of urinary associated with both physical exertion and urgency.[1] Compared with pure urinary incontinence (UI), MUI presents with more severe symptoms and puts greater burden on the health of individuals and economy of the society.[2] An estimate of 21%-33% females in the world[3] and 9.4% females in China[4] are troubled with MUI, while less than fifty percent of such population report it to doctors and receive treatment[5].

Stress-predominant MUI constitutes mainly of stress component. It features leakage on increased abdominal pressure, which can be induced by exertion, sneeze, cough, etc. Despite the existence of leakage with urgency, stress incontinence episode frequency (IEF) outnumbers 50% of total IEF.[6]

Current European Association of Urology (EAU) guideline on incontinence recommends to initiate treatment targeted at predominant component of MUI.[7] However, no strong evidence supported that the interventions for stress urinary incontinence (SUI) is as effective when treating stress-predominant MUI.[6] The effects of pelvic floor muscle training (PFMT), first-line therapy for pure SUI, decrease among MUI patients.[8] About half of patients practicing PFMT will seek help from surgery eventually in long-term follow-up[9], and surgery might be more useful than PFMT for moderate to severe symptoms[10]. When surgery is considered for MUI, other therapies might need to be combined with to control the urgency component.[11] In addition, the existence of urgency symptoms might be aggravated after surgery[12], and even reduce the success rate of stress incontinence operation[13]. Therefore, it is necessary to seek for interventions specific to stress-predominant MUI.

Results of previous studies indicates that acupuncture may help to relieve the incontinence symptoms.[14 15] It is proven effective in reducing leakage amount of pure SUI[14] and total IEF of MUI.[15] Further analysis of the two trials suggests EA might relieve the symptoms of stress-related UI.[16] Since the two trials didn't focus on stress-predominant MUI specifically, this multi-center, three-armed, randomized controlled

is designed to evaluate the efficacy and safety of EA in participants with stress-predominant MUI.

Hypotheses

Our primary hypothesis is that the effects of EA is superior to sham electroacupuncture (SA) and waiting list (WL) in improving proportion of stress-predominant MUI participants with at least 50% reduction of mean 24-hour stress IEF from baseline to week 8.

METHODS AND ANALYSIS

Study design

This is a three-armed, randomized, SA and WL-controlled trial conducted in five recruitment sites, which are Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated hospital of Beijing university of Chinese Medicine and Jiangxi Provincial Hospital of traditional Chinese Medicine.

The study durations are 33 weeks for participants in the EA and SA groups with one-week baseline assessment, 8-week treatment and 24-week follow-up; while 21 weeks for participants in the WL group, with one-week baseline assessment and 20-week watchful waiting (Figure 1. Flow Chart). The study will start recruitment on October 9, 2020, and is anticipated to finish the treatment and follow-up on September 30, 2023. Participations in the EA and SA groups, outcome assessors, data managers and statisticians will be blind to the group allocation, while acupuncturists and participants in the WL group will not be blind for obvious reasons.

Patient and public involvement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Inclusion criteria

1) Diagnosis of MUI by the coexistence of SUI and UUI symptoms in accordance

with EAU guideline[7];

2) Female participants aged between 35 and 75;

3) Stress index > urge index in accordance with Medical, epidemiologic, and social aspects of Aging(MESA) questionnaire[17];

4) Symptoms of MUI for at least three months, and SUI episodes outnumber 50% total IEF documented in 3-day voiding diary;

5) Less than 12 micturition episodes in average 24 hours documented in 3-day voiding diary;

6) Positive cough stress test;

7) Urine leakage > 1 g in 1-hour pad test[18];

8) Voluntary participation in the trial and signed written informed content.

Participants meeting all these eight criteria might be able to be recruited in the trial.

Exclusion criteria

1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic bladder;

2) Uncontrolled symptomatic urinary tack infection;

3) Tumor in urinary system and pelvic organ;

4) Pelvic organ prolapse ≥ degree Ⅱ;

5) Residual urine volume ≥ 100ml;

6) History of treatments targeted at UI, such as acupuncture, PFMT and medications in the previous one month;

7) History of surgery targeted at UI or in pelvic floor, including hysterectomy;

8) Uncontrolled diabetes or severe high blood pressure;

9) Nervous system diseases that may hamper the function of urinary system, such as Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury, cauda equina nerve injury, or multiple system atrophy;

10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or with obvious cognitive dysfunction

11) Installed cardiac pacemaker;

12) Inconvenient or unable to walk, run, go up and down stairs;

13) Allergy to metal, severely fear of acupuncture needles or unbearable to EA;

14) Pregnant at present, plan to conceive in future one year, at lactation period or within 12 months after childbirth.

Participants with either situation mentioned above will not be enrolled in the trial.

Randomization and allocation concealment

The randomization allocation sequence will be produced by a third independent party (Linkermed Technology Co., Ltd. [Beijing, China]). Eligible participants will be randomly assigned into the EA, SA or WL group at 2:1:1 ratio, stratified by recruitment sites and using varied blocks. The randomization number and group allocation will be acquired by acupuncturists in each recruitment site by logging in the Central Randomization System and typing in basic information of eligible participants.

Interventions

The acupoint regimen and administration protocol are both based on the results of previous studies and specialist consensus[14 15]. Participants in the EA group will receive stimulation at bilateral BL33 (Zhongliao), BL35 (Huiyang) and SP6 (Sanyinjiao). BL 33 is located in the third posterior sacral foramen; BL35, 0.5 cun (≈ 10mm) lateral to the extremity of the coccyx; and SP6 posterior to the medial border of the tibia, 3 cun superior to the prominence of the medial malleolus.[19] Bilateral BL33 will be inserted by acupuncture needles (Huatuo, Suzhou Medical Appliance) of 0.30×75mm size at the angle of 45° , inward and downward, till the depth of 60-70mm. Bilateral BL35 will be inserted by needles of 0.30×75mm size, slightly outward and upward, till the depth of 60-70mm. Bilateral SP6 will be inserted by needles of 0.30×40mm till the depth of 25-30mm. All the needles will be lifted, thrusted and twisted evenly for three times, right after insertion, to induce the sensation of *deqi*. Electronic acupuncture apparatus (Yingdi KWD 808 I electro pulse

acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device Co., Ltd) will be connected to the three pairs of needles transversally, with continuous wave of 20Hz, electric current of 2mA-6.5mA for BL33 and BL35, and 1mA-3.5mA for SP6. The EA stimulation will last 30mins for each session, 3 sessions a week (ideally every other day) for a succession of 8 weeks.

Participants in the SA group will receive superficial insertion at bilateral sham BL33 (Zhongliao), sham BL35 (Huiyang) and sham SP6 (Sanyinjiao). Sham BL33 is in the area 1 cun (≈20mm) horizontally outside of BL33; sham BL35, 1 cun (≈ 20mm) horizontally outside of BL35; Sham SP6, in the middle of SP6 and tendons. The three pairs of acupoints will be inserted by acupuncture needles of 0.30×40mm size to a depth of 2-3mm till the needles can stand still. No manipulations will be conducted, and the sensation of *deqi* will not be induced. Electronic acupuncture apparatus will be connected to the three pairs of needles transversally, with continuous wave of 20Hz and minimal electric current (ideally at a degree which participant can just percept). In about 30 seconds, the electric current will be turned down, leaving the indicator light and ticking sound on. The treatment sessions are similar to those in the EA group.

Participants in the EA and SA groups will be blind to the group allocations. Acupuncturists and research assistants will be instructed not to tell the group allocation to participants. Addition, to avoid the occurrence of inadvertent unblinding, the contacts between participants and project staff during treatment will be reduced as much as possible, and the manipulation of acupuncture, connecting to electronic apparatus and withdrawal of needles will be separately undertaken by acupuncturists and another research assistant. Participants will be treated separately with curtain drawing and their companions waiting outside the clinic, if any. Before manipulation, participants will be told that during the treatment they may feel the electrical stimulation fade down gradually, even to the degree that they cannot percept. That is because the body has built up a tolerance to the electrical stimulation during the

treatment process. Within 5 minutes after either treatment at week 8, participants will be told that they may have received EA treatment with deep insertion, or SA treatment with shallow insertion, and asked to answer the question do you think you have received EA treatment, and choose the answer between the options of Yes and No.

Participants in the WL group will not receive active treatments. After the trial, they will receive 24-session EA treatment mentioned above as compensation.

Participants in all the three groups will receive handbook of healthcare education and lifestyle modification advice, concerning exercise, fluid intake, weight loss, smoking and respiratory symptoms, constipation, heavy lifting and urinary tract infection. During the process of the trial, participants are not allowed to take other specialized medication and treatments for UI, such as PFMT or antimuscarinic agents; details should be recorded in CRF if used. Any medications that might influence the function of lower urinary tract function should also be documented in CRF.

Outcomes

Primary outcome

The primary outcome is the proportion of participants with at least 50% reduction in mean 24-hour stress IEF from baseline to week 8, measured by 3-day voiding diary. At least 50% reduction in IEF is regarded as successful treatment in clinic,[20] and 3-day voiding diary is a reliable and validated tool for UI in both clinic and research, without much burden placed on participants.[21] In 3-day voiding diary, IEF of different types, micturition and nocturia episodes, fluid intake, and pad consumptions will be documented.

Secondary outcomes

Secondary outcomes will be measured by 3-day voiding diary, International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and Overactive Bladder Questionnaire short form (OAB-q SF) at weeks 4, 8, 20 and 32; 1-hour pad test at week 8; and Patient Global Impression of Improvement (PGI-I) at weeks 8 and

20 (Figure 2. Study schedule). The specific secondary outcome measures and time frame are displayed in Table 1. Secondary outcome measures.

ICIQ-SF is a validated tool to assess the frequency, severity and influence on QoL of UI in the past 4 weeks[22 23]. The total score of the questionnaire ranges from 1 to 21, with higher score indicating greater severity.

OAB-q SF is used to assess the OAB symptom bother and the health-related quality of life (HRQL) in the past 4 weeks[24 25]. The domains include coping, concern, sleep and emotional interactions. The scores are transformed to a 0- to 100-point scale, with higher scores indicating severe symptoms and better HRQL.

One-hour pad test is the only tool standardized with a set protocol to measure the urinary leakage[18]. Participants will be instructed to drink 500 ml solid-free water, and perform a series of activities including standing and sitting, coughing, running, picking up a coin and putting hands under water. The leakage amount in one hour will be measured via pad.[26]

PGI-I is a global index, with only one item, used to rate the participants' subject perception on symptom improvement. Participants will describe their impression from very much better to very much worse.[27] Improvement was considered to be clinically significant if the participant's response is "Much better" or "Very much better".

To assess participants' expectations of improvement in UI, at baseline, participants will be asked how do they expect the UI to be in two months. They will choose the answer form the options of "Much better", "Better", "Don't know", "Same", and "Worse".

To assess participants' belief that acupuncture might help, both at baseline and week 4, participants in the EA and SA groups will be asked how do they think their incontinence problem may be helped by acupuncture. They will choose the answer from the options of "Very ineffective", "Fairly ineffective", "Can't decide", "Effective", and "Very effective".

Safety assessment

Adverse events (AEs), associated with the intervention or not, will be monitored and documented by participants and research assistants in Adverse Event Record Form and CRF throughout the trial. Whether the events are related to the treatments will be decided by acupuncturists and related specialists in each site within 24 hours of occurrence. Acupuncture related AEs are defined as following: broken needle, needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or abscess at the needling site, and other discomfort induced by acupuncture, such as pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia that lasts for one hour or longer after treatment.

Quality control

To ensure consistency of the study, personnel in recruitment sites will receive exactly the same training from the principal investigator (ZS Liu) concerning the protocol, manipulating methods of acupuncture and blinding of participants, etc.

At least two acupuncturists (with no less than two-year clinical experience) are needed for rotation in each site, while the 24-session treatment of each participant should be completed by one specific acupuncturist. Additionally, the same participants should be taken charge of by the same research assistant/outcome assessor throughout the trial. They will instruct participants to complete voiding diary, explain the contents of handbook if necessary, and remind the participants of their schedule by phone or we-chat.

To promote the adherence on lifestyle modification, the research assistants will remind the participants to adjust their lifestyle per the suggestions and record the changes of condition and lifestyle on Lifestyle Record Form every week. On each outcome assessment visit, the forms will be collected and examined by outcome assessors, and recorded in CRF in time.

All the data collected will be documented in paper CRF first, and typed into EDC system within one week. This rule is set to ensure the date be traced back, monitored by the system automatically and CRA, and supplemented without delay, if missing or

inaccuracy. In follow-up period, missing data in voiding diary can be asked by phone rather than in person. The database will be protected by a password and only the principal investigator will have access to the final dataset. Data are available upon reasonable request to the principal investigator, excluding the private information of patients.

Sample size

Based on our previous study[14 15], we assume that 25% participants in the SA group will have at least 50% reduction of mean stress IEF from baseline to week 8. To detect a difference of 23% between the EA and SA group, a sample size of 232 participants will need to provide the trial with 80% power with a two-sided significance level of 0.05 and 10% dropouts.

Statistical analysis

For primary hypothesis, we will compare the proportion of participants with at least 50% reduction in mean 24-hour stress IEF at week 8 among the three groups. The primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to compare the rate of participants with at least 50% reduction in stress IEF at week 8 between the EA group and the WL group. If this analysis is significant, the hierarchical testing will be used the EA group versus the SA group.

For other categorical variables, comparisons between treatment groups will be assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other continuous variables. Chi-square or Fisher's exact tests will be used to compare the frequency of AEs between groups.

All outcomes will be analyzed in intention to treat (ITT) population (defined as participants randomized). Analysis will be performed using SAS version 9.4 (SAS Institute Inc) with a two-sided *P* value of less than .05 considered significant.

Ethics and dissemination

The protocol was approved by Guang'anmen Hospital Institution of Review Board (2019-241-KY). It is registered on Clinicaltrials.gov (NCT04299932), and any revision of the protocol will be reported on the website. The trial will be conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice. Detailed information of the trial will be informed to the participants and written informed content will be obtained from every participant before randomization. Participants in WL group will receive 24-session EA treatment for compensation. Results of the trial will be expected to be published on a peer-reviewed journal.

DISCUSSION

MUI is a condition frustrating almost thirty percent of women globally, while about half of them feel embarrassed to report[3 5]. The physiology underlying MUI remains unclear. Intrinsic urethral sphincter deficiency caused by weak pelvic floor muscles have been proposed as the main pathophysiology of SUI[28] and detrusor overactivity is one of the main reasons leading to UUI[11]. Via acupuncture point BL33 and BL35, electroacupuncture may stimulate the S3 nerve and both motor and afferent fibers of the pudendal nerve, which can not only strengthen the pelvic muscles and raise the patient's awareness of these muscles, but also decrease the sensation of urgency and inhibit parasympathetic activity and involuntary detrusor contractions[29].

Since plenty of patients in China have received acupuncture before, the form of superficial insertion at non-acupoint area with minimal and transient electric current is applied as sham control to eliminate placebo effects. The superficial insertion enables participants to promptly percept the stimulation and electric current, which may further enhance the blinding even if it lasts only about 30 seconds. It is argued that minimal acupuncture may evoke physiologic effects[30], especially for pain and depression[31 32]. However, the pathology of MUI is mainly sphincter insufficiency and detrusor overactivity. Studies indicates the rheobase of the normal bladder was 1-

5mA[33]. The transient and minimal current output may not produce effects on the function of bladder. In the WL group, participants only receive healthcare education and lifestyle modification. The WL-control is applied to eliminate the influence of disease's natural cause.

Limitation also exists in the design of this trial. Participants in WL group and acupuncturists cannot be blinded, which might induce performance and detection bias into the trial. However, large bias is unlikely to be induced to the results since the primary outcome of stress IEF is subjective; and to decrease influence towards the results, the outcome assessment will be undertaken by an independent research assistant who know nothing about the allocation.

Ethical Approval and Consent to participate: The study has received approval from the Guang'anmen Hospital Institution of Review Board (2019-241-KY). Written informed content will be obtained from every participant.

Consent for publication: Not applicable.

Authors' contributions: Zhishun Liu conceived the study, initiated the design, and revised the manuscript; Yan Liu is responsible for statistical analysis plan and drafted the manuscript; Yuanjie Sun participated the design and drafted the manuscript; Huan Chen participated the design and revised the manuscript; Yan Yan helped to draft the manuscript. All authors have read and approved the final manuscript.

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Competing interests: The author declare that they have no competing interests.

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Reference:

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1):4-20. doi: 10.1002/nau.20798 [published Online First: 2009/11/27]
2. Minassian VA, Devore E, Hagan K, et al. Severity of urinary incontinence and effect on quality of life in women by incontinence type. Obstet Gynecol 2013;121(5):1083-90. doi: 10.1097/AOG.0b013e31828ca761 [published Online First: 2013/05/03]
3. Dooley Y, Lowenstein L, Kenton K, et al. Mixed incontinence is more bothersome than pure incontinence subtypes. Int Urogynecol J Pelvic Floor Dysfunct 2008;19(10):1359-62. doi: 10.1007/s00192-008-0637-4 [published Online First: 2008/05/21]
4. Zhu L, Li L, Lang J, et al. Epidemiology of mixed urinary incontinence in China. Int J Gynaecol Obstet 2010;109(1):55-8. doi: 10.1016/j.ijgo.2009.10.017 [published Online First: 2009/12/22]
5. Thom DH, van den Eeden SK, Ragins AI, et al. Differences in Prevalence of Urinary Incontinence by Race/Ethnicity. Journal of Urology 2006;175(1):259-64. doi: 10.1016/s0022-5347(05)00039-x
6. Myers DL. Female mixed urinary incontinence: a clinical review. JAMA 2014;311(19):2007-14. doi: 10.1001/jama.2014.4299 [published Online First: 2014/05/23]
7. Burkhard FC, Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence in adults. https://uroweb.org/guideline/ urinary-incontinence. Accessed November 4, 2017.
8. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2018;10:CD005654. doi: 10.1002/14651858.CD005654.pub4 [published Online First: 2018/10/06]
9. Bo K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005;105(5 Pt 1):999-1005. doi: 10.1097/01.AOG.0000157207.95680.6d [published Online First: 2005/05/03]
10. Labrie J, Berghmans BL, Fischer K, et al. Surgery versus physiotherapy for stress urinary incontinence. New Engl J Med 2013;369(12):1124-33. doi: 10.1056/NEJMoa1210627 [published Online First: 2013/09/21]
11. Aoki Y, Brown HW, Brubaker L, et al. Urinary incontinence in women. Nat Rev Dis Primers 2017;3:17042. doi: 10.1038/nrdp.2017.42 [published Online First: 2017/07/07]
12. Lee JK, Dwyer PL, Rosamilia A, et al. Persistence of urgency and urge urinary incontinence in women with mixed urinary symptoms after midurethral slings: a multivariate analysis. BJOG 2011;118(7):798-805. doi: 10.1111/j.1471-

0528.2011.02915.x [published Online First: 2011/03/12]
13. Richter HE, Litman HJ, Lukacz ES, et al. Demographic and clinical predictors of treatment failure one year after midurethral sling surgery. Obstet Gynecol 2011;117(4):913-21. doi: 10.1097/AOG.0b013e31820f3892 [published Online First: 2011/03/23]
14. 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(24):2493-501. doi: 10.1001/jama.2017.7220 [published Online First: 2017/06/28]
15. Liu B, Liu Y, Qin Z, et al. Electroacupuncture Versus Pelvic Floor Muscle Training Plus Solifenacin for Women With Mixed Urinary Incontinence: A Randomized Noninferiority Trial. Mayo Clin Proc 2019;94(1):54-65. doi: 10.1016/j.mayocp.2018.07.021 [published Online First: 2019/01/07]
16. Wang W, Liu Y, Su T, et al. Comparing the effect of electroacupuncture treatment on obese and non-obese women with stress urinary incontinence or stress-predominant mixed urinary incontinence: A secondary analysis of two randomised controlled trials. Int J Clin Pract 2019:e13435. doi: 10.1111/ijcp.13435 [published Online First: 2019/10/18]
17. Herzog AR, Diokno AC, Brown MB, et al. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol 1990;45(2):M67-74. doi: 10.1093/geronj/45.2.m67 [published Online First: 1990/03/01]
18. Krhut J, Zachoval R, Smith PP, et al. Pad weight testing in the evaluation of urinary incontinence. Neurourol Urodyn 2014;33(5):507-10. doi: 10.1002/nau.22436 [published Online First: 2013/06/26]
19. WHO Regional Office for the Western Pacific.WHO Standard Acupuncture Point Locations in the Western Pacific Region. Geneva: World Health Organization Pr; 2008.
20. Yalcin I, Peng G, Viktrup L, et al. Reductions in stress urinary incontinence episodes: what is clinically important for women? Neurourol Urodyn 2010;29(3):344-7. doi: 10.1002/nau.20744 [published Online First: 2009/05/29]
21. Bright E, Cotterill N, Drake M, et al. Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. Eur Urol 2014;66(2):294-300. doi: 10.1016/j.eururo.2014.02.057 [published Online First: 2014/03/22]
22. Huang L, Zhang SW, Wu SL, et al. The Chinese version of ICIQ: a useful tool in clinical practice and research on urinary incontinence. Neurourol Urodyn 2008;27(6):522-4. doi: 10.1002/nau.20546 [published Online First: 2008/03/21]
23. Avery K, Donovan J, Peters TJ, et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23(4):322-30. doi: 10.1002/nau.20041 [published Online First: 2004/07/01]
24. McKown S, Abraham L, Coyne K, et al. Linguistic validation of the N-QOL (ICIQ), OAB-q (ICIQ), PPBC, OAB-S and ICIQ-MLUTSsex questionnaires in 16

languages. Int J Clin Pract 2010;64(12):1643-52. doi: 10.1111/j.1742-1241.2010.02489.x [published Online First: 2010/08/21]
25. Coyne KS, Thompson CL, Lai JS, et al. An overactive bladder symptom and health-related quality of life short-form: validation of the OAB-q SF. Neurourol Urodyn 2015;34(3):255-63. doi: 10.1002/nau.22559 [published Online First: 2015/03/19]
26. Abrams P, Blaivas JG, Stanton SL, et al. Standardisation of terminology of lower urinary tract function. Neurourology and Urodynamics 1988;7(5):403-27. doi: 10.1002/nau.1930070502
27. Viktrup L, Hayes RP, Wang P, et al. Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. BMC Urol 2012;12:30. doi: 10.1186/1471-2490-12-30 [published Online First: 2012/11/09]
28. Yoshimura N, Miyazato M. Neurophysiology and therapeutic receptor targets for stress urinary incontinence. International Journal of Urology 2012;19(6):524-37. doi: 10.1111/j.1442-2042.2012.02976.x
29. Berghmans B, Hendriks E, Bernards A, et al. Electrical stimulation with non-implanted electrodes for urinary incontinence in men. Cochrane Database Syst Rev 2013(6):CD001202. doi: 10.1002/14651858.CD001202.pub5 [published Online First: 2013/06/07]
30. Lund I, Naslund J, Lundeberg T. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: a physiologist's perspective. Chin Med 2009;4:1. doi: 10.1186/1749-8546-4-1 [published Online First: 2009/02/03]
31. Smith CA, Armour M, Lee MS, et al. Acupuncture for depression. Cochrane Database Syst Rev 2018;3:CD004046. doi: 10.1002/14651858.CD004046.pub4 [published Online First: 2018/03/05]
32. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;172(19):1444-53. doi: 10.1001/archinternmed.2012.3654 [published Online First: 2012/09/12]
33. Katona F. Stages of vegatative afferentation in reorganization of bladder control during intravesical electrotherapy. Urol Int 1975;30(3):192-203. doi: 10.1159/000279979 [published Online First: 1975/01/01]

Figure legends

Figure 1. Flow chart

Figure 2. Study schedule

* Only for participants in the electroacupuncture and sham electroacupuncture groups

ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

Table

Table 1. Secondary outcome measures

No	Outcome measure	Time Frame
1	Proportion of participants with at least 50% reduction of urinary leakage amount from baseline.	week 8
2	Change of urinary leakage amount from baseline	week 8
3	Proportion of participants with at least 50% reduction of mean 24-hour stress IEF from baseline.	weeks 4, 20 and 32
4	Change of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
5	Change of mean 24-hour stress IEF from baseline	weeks 4, 8, 20 and 32
6	Proportion of participants with at least 50% reduction of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
7	Change of total and sub-score of International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) from baseline	weeks 4, 8, 20 and 32
8	Change of total and sub-score of Overactive Bladder Questionnaire short form (OAB-q SF) from baseline	weeks 4, 8, 20 and 32
9	Change of mean 24-hour pad consumption from baseline	weeks 4, 8, 20 and 32
10	Proportion of participants with adequate improvement assessed by Patient global impression improvement (PGI-I)	weeks 8 and 20
11	Change of mean 24-hour urgency episodes from baseline	weeks 4, 8, 20 and 32
12	Change of mean 24-hour micturition episodes from baseline	weeks 4, 8, 20 and 32
13	Participants' expectations of improvement to urinary incontinence	Baseline
14	Participants' belief that acupuncture might help	Baseline and week 4
15	Blinding assessment	Week 8

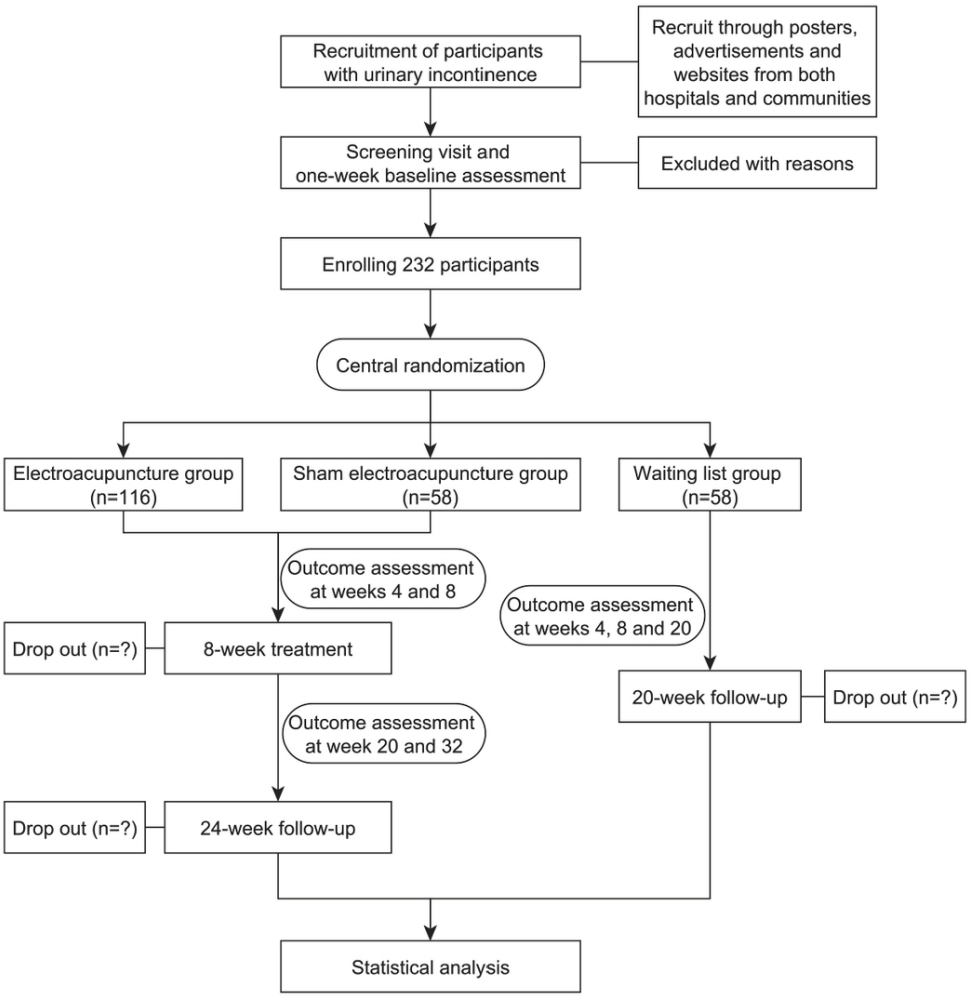

Figure 1. Flow chart

91x93mm (300 x 300 DPI)

TIMEPOINT (W, week)	W -1	W 0	W 4	W 8	W 20	W 32*
ENROLMENT						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Demography characteristics	×					
Medical history	×					
Urine routine	×					
Residual urine volume	×					
Urine pregnancy test	×					
INTERVENTIONS						
Electroacupuncture			×	×		
Sham electroacupuncture			×	×		
Waiting list			×	×	×	
ASSESSMENTS						
3-day voiding diary	×		×	×	×	×
1-hour pad test	×			×		
ICIQ-SF		×	×	×	×	×
OAB-q SF		×	×	×	×	×
PGI-I				×	×	
Adverse events	×	×	×	×	×	×
Expectation assessment		×				
Belief assessment*		×	×			
Blindness assessment*				×		

Figure 2. Study schedule
* Only for participants in the electroacupuncture and sham electroacupuncture groups
ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

91x94mm (300 x 300 DPI)

Table 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5-12
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11, Table 1

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13,15

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11-12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11-12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9,13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11-12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Content inform
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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Secondary Subject Heading:	Urology, Complementary medicine
Keywords:	Urinary incontinences < UROLOGY, Bladder disorders < UROLOGY, COMPLEMENTARY MEDICINE

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Title page

Article title:

Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial

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Running title: acupuncture for stress-predominant mixed urinary incontinence

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Abstract

Introduction: Evidence specific for stress-predominant mixed urinary incontinence is still lack at present, and acupuncture may relieve the symptoms. We plan to conduct this multi-center, three-armed, randomized controlled trial to investigate the efficacy and safety of electroacupuncture among women with stress-predominant mixed urinary incontinence.

Methods and analysis: The trial will be conducted at 5 hospitals in China. 232 eligible women will be randomly assigned (2:1:1) to the electroacupuncture, sham electroacupuncture or waiting list group to receive either 24-session acupuncture/sham acupuncture treatment over 8 weeks and 24-week follow-up, or 20-week watchful waiting. The primary outcome is the proportion of participants with at least 50% reduction in mean 24-hour stress incontinence episode frequencies from baseline to week 8. The outcome will be analyzed in intention to treat population (defined as participants randomized) with a two-sided *P* value of less than .05 considered significant.

Ethics and dissemination: The protocol has been approved by Guang'anmen Hospital Institutional Review Board (2019-241-KY). Detailed information of the trial will be informed to the participants and written informed consent will be obtained from every participant. Results of the trial are expected to be published in a peer-reviewed journal.

Key words: Acupuncture; Mixed urinary incontinence; Female; Stress urinary incontinence

Trial registration: Clinicaltrials.gov identifier: NCT04299932

Strengths and limitations of this study

- The first randomized controlled trial to investigate the efficacy and safety of acupuncture on stress-predominant mixed urinary incontinence.
- Sham control and waiting-list control are designed to eliminate the influence of placebo effects and the disease's natural course on the results.
- Minimal electroacupuncture serves as a sham control to blind participants in the electroacupuncture and sham electroacupuncture groups.
- One limitation is that acupuncturists and participants in the waiting list group cannot be blinded.

INTRODUCTION

Mixed urinary incontinence (MUI) is a complaint of involuntary loss of urine associated with both physical exertion and urgency.[1]It presents with more severe symptoms in comparison with pure urinary incontinence (UI), and thus puts greater burden on health of individuals and economy of the society.[2] Approximately 21%-33% of females in the world[3] and 9.4% of females in China[4] are troubled with MUI, while less than 50% of such population reports it to doctors and receives treatment[5].

Stress-predominant MUI constitutes mainly of stress component. It features leakage on increased abdominal pressure, which can be induced by exertion, sneeze, cough etc. Despite the existence of leakage with urgency, stress incontinence episode frequencies (IEFs) outnumber 50% of total IEFs.[6]

Current European Association of Urology (EAU) guideline on incontinence recommends to initiate treatment for predominant component of MUI.[7] However, no strong evidence supports that the interventions for stress urinary incontinence (SUI) is as effective when used to treat stress-predominant MUI.[6] The effects of pelvic floor muscle training (PFMT), first-line therapy for pure SUI, decrease among MUI patients.[8] About half of patients practicing PFMT will seek help from surgery eventually in long-term follow-up[9], and surgery might be more useful than PFMT for moderate to severe symptoms[10]. When surgery is considered for MUI, other therapies might need to be combined with to control the urgency component.[11] In addition, the existence of urgency symptoms might be aggravated after surgery[12], and even reduce the success rate of stress incontinence operation[13]. Therefore, it is necessary to seek for interventions specific for stress-predominant MUI.

Previous studies indicates acupuncture may relieve the incontinence symptoms.[14 15] It is proven effective in reducing leakage amount of pure SUI[14] and total IEFs of MUI.[15] Further analysis of the two trials suggests EA might relieve the symptoms of stress-related UI.[16] Since the two trials didn't focus on stress-predominant MUI specifically, this multi-center, three-armed, randomized controlled is designed to

evaluate the efficacy and safety of EA among participants with stress-predominant MUI.

Hypotheses

Our primary hypothesis is that the effects of EA is superior to sham electroacupuncture (SA) and waiting list (WL) in improving proportion of stress-predominant MUI participants with at least 50% reduction of mean 24-hour stress IEFs from baseline to week 8.

METHODS AND ANALYSIS

Study design

This is a three-armed, randomized, SA and WL-controlled trial conducted at five recruitment sites, which are Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Hengyang Hospital Affiliated to Hunan University of Chinese Medicine; Yantai Hospital of Traditional Chinese Medicine; The third affiliated hospital of Beijing university of Chinese Medicine; and Jiangxi Provincial Hospital of traditional Chinese Medicine.

The study duration is 33 weeks for participants in the EA and SA groups, with one-week baseline assessment, 8-week treatment and 24-week follow-up; while 21 weeks for participants in the WL group, with one-week baseline assessment and 20-week watchful waiting (Figure 1. Flow Chart). The study will start recruitment on October 9, 2020, and is anticipated to finish the treatment and follow-up on September 30, 2023. Participations in the EA and SA groups, outcome assessors, data managers and statisticians will be blinded to the group allocation, while acupuncturists and participants in the WL group will not be blinded for obvious reasons.

Patient and public involvement

Patients or the public are not involved in the design, conduct, report or dissemination of our research.

Inclusion criteria

1) Diagnosis of MUI by the coexistence of SUI and UUI symptoms in accordance

with EAU guideline[7];

2) Female participants aged between 35 and 75;

3) Stress index > urge index in accordance with Medical, epidemiologic, and social aspects of Aging(MESA) questionnaire[17];

4) Symptom of MUI for at least three months, and SUI episodes outnumber 50% total IEFs documented in 3-day voiding diary;

5) Less than 12 micturition episodes in average 24 hours documented in 3-day voiding diary;

6) Positive cough stress test;

7) Urine leakage > 1 g in 1-hour pad test[18];

8) Voluntary participation in the trial and signed written informed consent.

Participants meeting all these eight inclusion criteria might be able to be enrolled.

Exclusion criteria

1) Urgency-predominant MUI, pure SUI, pure UUI, overflow UI and neurogenic bladder;

2) Uncontrolled symptomatic urinary tack infection;

3) Tumor in urinary system and pelvic organ;

4) Pelvic organ prolapse ≥ degree Ⅱ;

5) Residual urine volume ≥ 100ml;

6) History of treatments specific for UI, such as acupuncture, PFMT and medications in the previous one month;

7) History of surgery specific UI or in pelvic floor, including hysterectomy;

8) Uncontrolled diabetes or severe high blood pressure;

9) Nervous system diseases that may hamper the function of urinary system, such as Multiple sclerosis, Alzheimer's disease, Parkinson's disease, spinal cord injury, cauda equina nerve injury, or multiple system atrophy;

10) Severe heart, lung, brain, liver, kidney, mental illness, coagulation dysfunction or obvious cognitive dysfunction;

11) Installed cardiac pacemaker;

12) Inconvenient or unable to walk, run, go up and down stairs;

13) Allergy to metal, dreadfully fear of acupuncture needles or unbearable to EA;

14) Pregnant at present, plan to conceive in future one year, at lactation period or within 12 months after childbirth.

Participants with either situation mentioned above will not be enrolled in the trial.

Randomization and allocation concealment

The random sequence will be produced by a third independent party (Linkermed Technology Co., Ltd. [Beijing, China]). Eligible participants will be randomly assigned into the EA, SA or WL group at 2:1:1 ratio, stratified by recruitment sites and using variable blocks. The random number and group allocation will be acquired by acupuncturists in each recruitment site by logging in the Central Randomization System and typing in basic information of eligible participants.

Interventions

The acupuncture point regimen and administration protocol are both based on the results of previous studies and specialist consensus[14 15]. Participants in the EA group will receive stimulation at bilateral BL33 (Zhongliao), BL35 (Huiyang) and SP6 (Sanyinjiao). BL 33 is located in the third posterior sacral foramen; BL35, 0.5 proportional bone (skeletal) cun (B-cun) (≈10mm) lateral to the extremity of the coccyx; and SP6, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus.[19] Bilateral BL33 will be inserted by acupuncture needles (Huatuo, Suzhou Medical Appliance) of 0.30×75mm size at an angle of 45°, inward and downward, till the depth of 60-70mm. Bilateral BL35 will be inserted by needles of 0.30×75mm size, slightly outward and upward, till the depth of 60-70mm. Bilateral SP6 will be inserted by needles of 0.30×40mm till the depth of 25-30mm. All the needles will be lifted, thrusted and twisted evenly for three times, right after insertion, to induce the sensation of *deqi*. Electronic acupuncture apparatus (Yingdi KWD 808 I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi

Electronic Medical Device Co., Ltd) will be connected to the three pairs of needles transversally, with a continuous wave of 20Hz, electric current of 2mA-6.5mA for BL33 and BL35, and 1mA-3.5mA for SP6. The EA stimulation will last 30mins for each session, 3 sessions a week (ideally every other day) for a succession of 8 weeks.

Participants in the SA group will receive superficial insertion at bilateral sham BL33 (Zhongliao), sham BL35 (Huiyang) and sham SP6 (Sanyinjiao). Sham BL33 is in the area 1 B-cun (≈20mm) horizontally outside of BL33; sham BL35, 1 B-cun (≈ 20mm) horizontally outside of BL35; Sham SP6, in the middle of SP6 and tendons. Acupuncture needles of 0.30×40mm size will be inserted at a depth of 2-3mm till the needles can stand still. No manipulation will be conducted, and the sensation of *deqi* will not be induced. Electronic acupuncture apparatus (Yingdi KWD 808 I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device Co., Ltd) will be connected to the three pairs of needles transversally, with a continuous wave of 20Hz and minimal electric current (ideally at a degree which participant can just percept). In about 30 seconds, the electric current will be turned down, leaving the indicator light and ticking sound on. The treatment sessions are similar to those in the EA group.

Participants in the EA and SA groups will be blinded to the group allocation. Acupuncturists and research assistants will be instructed not to tell the group allocation to participants. Additionally, to avoid inadvertent unblinding, contact between participants and project staff will be reduced as much as possible during treatment. The manipulation of acupuncture, connecting to electronic apparatus and withdrawal of needles will be separately undertaken by acupuncturists and another research assistant. Participants will be treated separately with curtain drawn and their companions waiting outside the clinic, if any. Before manipulation, participants will be told they may feel the electrical stimulation fade down gradually, even to the degree that they cannot percept, and that is because the body has built up a tolerance to the electrical stimulation during the treatment process. Within 5 minutes after either

treatment session at week 8, participants will be told they may have received EA treatment with deep insertion, or SA treatment with shallow insertion. Then, the participants will be asked to answer the question do you think you have received EA treatment, and choose answer between the options of Yes or No.

Participants in the WL group will not receive active treatment. After the trial, they will receive 24-session EA treatment mentioned above as compensation.

Participants in all the three groups will receive handbook of advice on healthcare education and lifestyle modification, concerning exercise, fluid intake, weight loss, smoking and respiratory symptoms, constipation, heavy lifting and urinary tract infection. During the process of the trial, participants are not allowed to take other specialized medication or therapies for UI, such as PFMT or antimuscarinic agents; details should be recorded in case report form (CRF), if used. Any medications that might influence the function of lower urinary tract should also be documented in CRF.

Outcomes

Primary outcome

The primary outcome is the proportion of participants with at least 50% reduction in mean 24-hour stress IEFs from baseline to week 8, measured by 3-day voiding diary. Reduction of at least 50% in IEF is regarded as successful treatment in clinic,[20] and 3-day voiding diary is a reliable and validated tool for UI in both clinic and research, without much burden placed on participants.[21] In 3-day voiding diary, IEF of different types, micturition and nocturia episodes, fluid intake, and pad consumptions will be documented.

Secondary outcomes

Secondary outcomes will be measured by 3-day voiding diary, International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) and Overactive Bladder Questionnaire short form (OAB-q SF) at weeks 4, 8, 20 and 32; 1-hour pad test at week 8; and Patient Global Impression of Improvement (PGI-I) at weeks 8 and

20 (Figure 2. Study schedule). The specific secondary outcome measures and time frame are displayed in Table 1 Secondary outcome measures.

ICIQ-SF is a validated tool to assess the frequency and severity of UI, and its influence on QoL in the past 4 weeks[22 23]. The total score of the questionnaire ranges from 1 to 21, with higher score indicating greater severity of symptoms.

OAB-q SF is used to assess the OAB symptom bother and the health-related quality of life (HRQOL) in the past 4 weeks[24 25]. The domains include coping, concern, sleep and emotional interactions. The scores are transformed to 0- to 100-point scales, with higher scores on the symptom bother scale indicating severe symptoms and higher scores on the HRQOL indicating a better HRQOL.

One-hour pad test is the only tool standardized with a set protocol to measure the urinary leakage[18].Participants will be instructed to drink 500 ml sodium-free water, and perform a series of activities including standing and sitting, coughing, running, picking up a coin and putting hands under water. The leakage amount in one hour will be measured via pad.[26]

PGI-I is a global index, with only one item, used to rate the participants' subjective perception on symptom improvement. Participants will describe their impression from very much better to very much worse.[27] Improvement was considered to be clinically significant if the participant's response is "Much better" or "Very much better".

To assess participants' expectations of improvement in UI, at baseline, participants will be asked how do they expect the UI to be in two months. They will choose the answer form the options of "Much better", "Better", "Don't know", "Same", and "Worse".

To assess participants' belief that acupuncture might help, both at baseline and week 4, participants in the EA and SA groups will answer how do they think their incontinence problem may be helped by acupuncture. They will choose the answer from the options of "Very ineffective", "Fairly ineffective", "Can't decide", "Effective", and "Very effective".

Safety assessment

Adverse events (AEs), associated with the intervention or not, will be monitored and documented by participants and research assistants in Adverse Event Record Form and CRF throughout the trial. Whether the events are related to the treatments will be decided by acupuncturists and related specialists in each site within 24 hours of occurrence. Acupuncture related AEs are defined as following: broken needle, needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or abscess at the needling site, and other discomfort induced by acupuncture, such as pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia that lasts for one hour or longer after treatment.

Quality control

To ensure consistency of the study, personnel in recruitment sites will receive extensive training from the principal investigator (ZS Liu) concerning the protocol, manipulating methods of acupuncture and blinding of participants, etc.

At least two certified acupuncturists (with no less than two-year clinical experience) are needed for rotation in each site, while the 24-session treatment of each participant should be completed by one specific acupuncturist. Additionally, the same participants should be taken charge of by the same research assistant/outcome assessor throughout the trial. They will instruct participants to complete voiding diary, explain the contents of handbook if necessary, and remind the participants of their schedule by phone or we-chat.

To promote the adherence on lifestyle modification, the research assistants will remind the participants to adjust their lifestyle per the suggestions and record the changes of condition and lifestyle on Lifestyle Record Form every week. On each outcome assessment visit, the forms will be collected and examined by outcome assessors, and recorded in CRF in time.

All the data collected will be documented in paper CRF first, and typed into EDC system within one week by clinical research coordinator. This rule is set to ensure the

date be traced back, monitored by the system automatically and clinical research associate, and supplemented without delay, if missing or inaccuracy. In follow-up period, missing data in voiding diary can be asked by phone rather than in person. The database will be protected by a password and only the principal investigator will have access to the final dataset. Data are available upon reasonable request to the principal investigator, excluding the private information of patients.

Sample size

Based on our previous study[14 15], we assume that 25% participants in the SA group will have at least 50% reduction of mean stress IEF from baseline to week 8. To detect a difference of 23% between the EA and SA group, a sample size of 232 participants will need to provide the trial with 80% power with a two-sided significance level of 0.05 and 10% dropouts.

Statistical analysis

For the primary hypothesis, we will compare the proportion of participants with at least 50% reduction in mean 24-hour stress IEF at week 8 among the three groups. The primary outcome analysis will use the Cochran-Mantel-Haenszel (CMH) test to compare the rate of participants with at least 50% reduction in stress IEF at week 8 between the EA group and the WL group. If this analysis is significant, the hierarchical testing will be used the EA group versus the SA group.

For other categorical variables, comparisons between treatment groups will be assessed using the Fisher exact test or Chi-squared test as appropriate. We will use the *t* test or Wilcoxon rank-sum test to analyze change of urinary leakage amount from baseline, change of mean 24-hour IEF from baseline, change of total and sub-score of ICIQ-SF from baseline, change of 24-h urgency episodes from baseline, and other continuous variables. Chi-square or Fisher's exact tests will be used to compare the frequency of AEs between groups.

All the outcomes will be analyzed in intention to treat (ITT) population (defined as participants randomized). Analysis will be performed using SAS version 9.4 (SAS

Institute Inc) with a two-sided *P* value of less than .05 considered significant.

Ethics and dissemination

The protocol has been approved by Guang'anmen Hospital Institutional Review Board (2019-241-KY). It is registered on Clinicaltrials.gov (NCT04299932), and any revision of the protocol will be reported on the website. The trial will be conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice E6 Guidance for Good Clinical Practice. Detailed information of the trial will be informed to the participants and written informed consent will be obtained from every participant. Participants in the WL group will receive 24-session EA treatment for compensation. Results of the trial are expected to be published on a peer-reviewed journal.

DISCUSSION

MUI is a condition frustrating almost thirty percent of women globally, while about half of them feel embarrassed to report[3 5]. The physiology underlying MUI remains unclear. UUI is closely associated with physiological perturbations to bladder function, such as detrusor overactivity, poor detrusor compliance and bladder hypersensitivity[11], while urethral hypermobility resulting from weak pelvic floor or poorly supported urethral sphincter, or intrinsic urethral sphincter deficiency have been proposed as the main pathophysiology of SUI[28]. Electroacupuncture may relieve the symptoms of MUI by modulate the function of related nerves. Acupuncture points of BL 33, BL35 and SP6 are located in the lumbosacral region and posterior tibial region, in the distribution area of sacral plexus and pudendal nerves. Either by direct stimulation or indirect stimulation via sacral roots or plexus, the pudendal afferent can be activated to induce a strong inhibition of the detrusor hyperreflexia and cause detrusor relaxation [29]. Additionally, stimulation of pudendal nerves can contract the pelvic floor muscle and simulate PFMT[30], which can improve urethral function and relieve SUI symptoms[31].

Since plenty of Chinese have received acupuncture before, superficial insertion at

non-acupuncture point area with minimal and transient electric current is applied as sham control to eliminate placebo effects. The superficial insertion enables participants to percept the stimulation and electric current promptly, and the transient electric current can enhance the blinding even if it lasts only about 30 seconds. It is argued that minimal acupuncture may evoke physiologic effects[32], especially for pain and depression[33 34]. However, the pathology of MUI is mainly sphincter insufficiency and detrusor overactivity. Studies indicates the rheobase of the normal bladder was 1-5mA[35]. The transient and minimal current output may not produce effects on the function of bladder. In the WL group, participants only receive healthcare education and lifestyle modification. The WL-control is applied to eliminate the influence of disease's natural cause.

Limitation also exists in the design of this trial. Participants in the WL group and acupuncturists cannot be blinded, which might induce performance and detection bias. However, large bias is unlikely to be attached to the results since the primary outcome of stress IEF is objective. In addition, the outcome assessors will be blinded to group allocation.

Ethical Approval and Consent to participate: The study has received approval from the Guang'anmen Hospital Institutional Review Board (2019-241-KY). Written informed consent will be obtained from every participant.

Consent for publication: Not applicable.

Authors' contributions: Zhishun Liu conceived the study, initiated the design, and revised the manuscript; Yan Liu was responsible for statistical analysis plan and drafted the manuscript; Yuanjie Sun participated the design and drafted the manuscript; Huan Chen participated the design and revised the manuscript; Yan Yan helped to draft the manuscript. All authors have read and approved the final manuscript.

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Competing interests: The author declare that they have no competing interests.

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Reference:

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1):4-20. doi: 10.1002/nau.20798 [published Online First: 2009/11/27]

2. Minassian VA, Devore E, Hagan K, et al. Severity of urinary incontinence and effect on quality of life in women by incontinence type. Obstet Gynecol 2013;121(5):1083-90. doi: 10.1097/AOG.0b013e31828ca761 [published Online First: 2013/05/03]

3. Dooley Y, Lowenstein L, Kenton K, et al. Mixed incontinence is more bothersome than pure incontinence subtypes. Int Urogynecol J Pelvic Floor Dysfunct 2008;19(10):1359-62. doi: 10.1007/s00192-008-0637-4 [published Online First: 2008/05/21]

4. Zhu L, Li L, Lang J, et al. Epidemiology of mixed urinary incontinence in China. Int J Gynaecol Obstet 2010;109(1):55-8. doi: 10.1016/j.ijgo.2009.10.017 [published Online First: 2009/12/22]

5. Thom DH, van den Eeden SK, Ragins AI, et al. Differences in Prevalence of Urinary Incontinence by Race/Ethnicity. Journal of Urology 2006;175(1):259-64. doi: 10.1016/s0022-5347(05)00039-x

6. Myers DL. Female mixed urinary incontinence: a clinical review. JAMA 2014;311(19):2007-14. doi: 10.1001/jama.2014.4299 [published Online First: 2014/05/23]

7. Burkhard FC, Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence in adults. https://uroweb.org/guideline/ urinary-incontinence. Accessed November 4, 2017.

8. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2018;10:CD005654. doi:

10.1002/14651858.CD005654.pub4 [published Online First: 2018/10/06]
9. Bo K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005;105(5 Pt 1):999-1005. doi: 10.1097/01.AOG.0000157207.95680.6d [published Online First: 2005/05/03]
10. Labrie J, Berghmans BL, Fischer K, et al. Surgery versus physiotherapy for stress urinary incontinence. New Engl J Med 2013;369(12):1124-33. doi: 10.1056/NEJMoa1210627 [published Online First: 2013/09/21]
11. Aoki Y, Brown HW, Brubaker L, et al. Urinary incontinence in women. Nat Rev Dis Primers 2017;3:17042. doi: 10.1038/nrdp.2017.42 [published Online First: 2017/07/07]
12. Lee JK, Dwyer PL, Rosamilia A, et al. Persistence of urgency and urge urinary incontinence in women with mixed urinary symptoms after midurethral slings: a multivariate analysis. BJOG 2011;118(7):798-805. doi: 10.1111/j.1471-0528.2011.02915.x [published Online First: 2011/03/12]
13. Richter HE, Litman HJ, Lukacz ES, et al. Demographic and clinical predictors of treatment failure one year after midurethral sling surgery. Obstet Gynecol 2011;117(4):913-21. doi: 10.1097/AOG.0b013e31820f3892 [published Online First: 2011/03/23]
14. 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(24):2493-501. doi: 10.1001/jama.2017.7220 [published Online First: 2017/06/28]
15. Liu B, Liu Y, Qin Z, et al. Electroacupuncture Versus Pelvic Floor Muscle Training Plus Solifenacin for Women With Mixed Urinary Incontinence: A Randomized Noninferiority Trial. Mayo Clin Proc 2019;94(1):54-65. doi: 10.1016/j.mayocp.2018.07.021 [published Online First: 2019/01/07]
16. Wang W, Liu Y, Su T, et al. Comparing the effect of electroacupuncture treatment on obese and non-obese women with stress urinary incontinence or stress-

predominant mixed urinary incontinence: A secondary analysis of two randomised controlled trials. Int J Clin Pract 2019:e13435. doi: 10.1111/ijcp.13435 [published Online First: 2019/10/18]

17. Herzog AR, Diokno AC, Brown MB, et al. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol 1990;45(2):M67-74. doi: 10.1093/geronj/45.2.m67 [published Online First: 1990/03/01]

18. Krhut J, Zachoval R, Smith PP, et al. Pad weight testing in the evaluation of urinary incontinence. Neurourol Urodyn 2014;33(5):507-10. doi: 10.1002/nau.22436 [published Online First: 2013/06/26]

19. WHO Regional Office for the Western Pacific.WHO Standard Acupuncture Point Locations in the Western Pacific Region. Geneva: World Health Organization Pr; 2008.

20. Yalcin I, Peng G, Viktrup L, et al. Reductions in stress urinary incontinence episodes: what is clinically important for women? Neurourol Urodyn 2010;29(3):344-7. doi: 10.1002/nau.20744 [published Online First: 2009/05/29]

21. Bright E, Cotterill N, Drake M, et al. Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. Eur Urol 2014;66(2):294-300. doi: 10.1016/j.eururo.2014.02.057 [published Online First: 2014/03/22]

22. Huang L, Zhang SW, Wu SL, et al. The Chinese version of ICIQ: a useful tool in clinical practice and research on urinary incontinence. Neurourol Urodyn 2008;27(6):522-4. doi: 10.1002/nau.20546 [published Online First: 2008/03/21]

23. Avery K, Donovan J, Peters TJ, et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23(4):322-30. doi: 10.1002/nau.20041 [published Online First: 2004/07/01]

24. McKown S, Abraham L, Coyne K, et al. Linguistic validation of the N-QOL (ICIQ), OAB-q (ICIQ), PPBC, OAB-S and ICIQ-MLUTSsex questionnaires in 16 languages. Int J Clin Pract 2010;64(12):1643-52. doi: 10.1111/j.1742-

1241.2010.02489.x [published Online First: 2010/08/21]

25. Coyne KS, Thompson CL, Lai JS, et al. An overactive bladder symptom and health-related quality of life short-form: validation of the OAB-q SF. Neurourol Urodyn 2015;34(3):255-63. doi: 10.1002/nau.22559 [published Online First: 2015/03/19]

26. Abrams P, Blaivas JG, Stanton SL, et al. Standardisation of terminology of lower urinary tract function. Neurourology and Urodynamics 1988;7(5):403-27. doi: 10.1002/nau.1930070502

27. Viktrup L, Hayes RP, Wang P, et al. Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. BMC Urol 2012;12:30. doi: 10.1186/1471-2490-12-30 [published Online First: 2012/11/09]

28. Yoshimura N, Miyazato M. Neurophysiology and therapeutic receptor targets for stress urinary incontinence. International Journal of Urology 2012;19(6):524-37. doi: 10.1111/j.1442-2042.2012.02976.x

29. Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. BJU Int 2006;98 Suppl 1:43-8; discussion 49. doi: 10.1111/j.1464-410X.2006.06316.x [published Online First: 2006/08/17]

30. Wang S, Zhang S. Simultaneous perineal ultrasound and vaginal pressure measurement prove the action of electrical pudendal nerve stimulation in treating female stress incontinence. BJU Int 2012;110(9):1338-43. doi: 10.1111/j.1464-410X.2012.11029.x [published Online First: 2012/03/16]

31. Deng K, Balog BM, Lin DL, et al. Daily bilateral pudendal nerve electrical stimulation improves recovery from stress urinary incontinence. Interface Focus 2019;9(4):20190020. doi: 10.1098/rsfs.2019.0020 [published Online First: 2019/07/03]

32. Lund I, Naslund J, Lundeberg T. Minimal acupuncture is not a valid placebo

control in randomised controlled trials of acupuncture: a physiologist's perspective. Chin Med 2009;4:1. doi: 10.1186/1749-8546-4-1 [published Online First: 2009/02/03]

33. Smith CA, Armour M, Lee MS, et al. Acupuncture for depression. Cochrane Database Syst Rev 2018;3:CD004046. doi: 10.1002/14651858.CD004046.pub4 [published Online First: 2018/03/05]

34. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;172(19):1444-53. doi: 10.1001/archinternmed.2012.3654 [published Online First: 2012/09/12]

35. Katona F. Stages of vegatative afferentation in reorganization of bladder control during intravesical electrotherapy. Urol Int 1975;30(3):192-203. doi: 10.1159/000279979 [published Online First: 1975/01/01]

Figure legends

Figure 1. Flow chart

Figure 2. Study schedule

* Only for participants in electroacupuncture and sham electroacupuncture groups

ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

Table

Table 1. Secondary outcome measures

No	Outcome measure	Time Frame
1	Proportion of participants with at least 50% reduction of urinary leakage amount from baseline.	week 8
2	Change of urinary leakage amount from baseline	week 8
3	Proportion of participants with at least 50% reduction of mean 24-hour stress IEF from baseline.	weeks 4, 20 and 32
4	Change of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
5	Change of mean 24-hour stress IEF from baseline	weeks 4, 8, 20 and 32
6	Proportion of participants with at least 50% reduction of mean 24-hour IEF from baseline	weeks 4, 8, 20 and 32
7	Change of total and sub-score of International Consultation on Incontinence Questionnaire-short form (ICIQ-SF) from baseline	weeks 4, 8, 20 and 32
8	Change of total and sub-score of Overactive Bladder Questionnaire short form (OAB-q SF) from baseline	weeks 4, 8, 20 and 32
9	Change of mean 24-hour pad consumption from baseline	weeks 4, 8, 20 and 32
10	Proportion of participants with adequate improvement assessed by Patient global impression improvement (PGI-I)	weeks 8 and 20
11	Change of mean 24-hour urgency episodes from baseline	weeks 4, 8, 20 and 32
12	Change of mean 24-hour micturition episodes from baseline	weeks 4, 8, 20 and 32
13	Participants' expectations of improvement to urinary incontinence	Baseline
14	Participants' belief that acupuncture might help	Baseline and week 4

15	Blinding assessment	Week 8

Figure 1. Flow chart

91x93mm (350 x 350 DPI)

TIMEPOINT (W, week)	W -1	W 0	W 4	W 8	W 20	W 32*
ENROLMENT						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
Demography characteristics	×					
Medical history	×					
Urine routine	×					
Residual urine volume	×					
Urine pregnancy test	×					
INTERVENTIONS						
Electroacupuncture			×	×		
Sham electroacupuncture			×	×		
Waiting list			×	×	×	
ASSESSMENTS						
3-day voiding diary	×		×	×	×	×
1-hour pad test	×			×		
ICIQ-SF		×	×	×	×	×
OAB-q SF		×	×	×	×	×
PGI-I				×	×	
Adverse events	×	×	×	×	×	×
Expectation assessment		×				
Belief assessment*		×	×			
Blindness assessment*				×		

Figure 2. Study schedule
* Only for participants in the electroacupuncture and sham electroacupuncture groups
ICIQ-SF, International Consultation on Incontinence Questionnaire short form; OAB-q SF, Overactive Bladder Questionnaire short form; PGI-I, Patient Global Impression of Improvement.

91x94mm (350 x 350 DPI)

Table 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5-12
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11, Table 1

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13,15

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11-12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11-12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9,13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11-12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Content inform
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.