PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial
AUTHORS	Chen, Shan; Wang, Siyou; Xuan, Li; Lu, Hanti; Hu, Zhikai; Zhang, Chao; Zhang, Huifang

VERSION 1 – REVIEW

REVIEWER	Renly Lim Universiti Sains Malaysia, Malaysia
REVIEW RETURNED	25-Feb-2018

GENERAL COMMENTS	Introduction The introduction is well-written, providing important information introducing the importance of the research question and study proposed. I would be interested to know why the authors think that it is best to compare electroacupuncture at 'four sacral points' and the conventional electroacupuncture, given that the efficacy of conventional electroacupuncture for urinary incontinence is still debatable. We know that up to 30-40% of patients undergoing treatments with high intensity/close monitoring experience significant placebo effect. In this study, the authors will compare two treatments which both requires high treatment frequency, and so patients in both groups have high likelihood of treatment success attributed to placebo effect. Can the authors comment on this. Methods 1) Sample size: 'With reference to a similar study .....', please include reference to the study. The authors quoted the efficacy rates of 70% and 45% - is this a study which also compares 'four sacral points' versus 'conventional'? Suggest giving more details - currently it is unclear how the authors came up with the sample size. 2) How will the authors exclude patients with existing UI? 3) One of the exclusion criteria was 'SUI or mixed UI', how about UUI, lower urinary tract symptoms, overflow incontinence etc...are these excluded? 4) How do you define poor participant compliance? 5) The authors chose incontinence episode diary and the 24-hour pad test as the primary outcome measures; however, the CONSORT guideline does not recommend use of more than one primary outcome measure because it will incur problems with result interpretation. Suggest that the authors consider using one primary outcome measure only.

	6) The statistical analysis is vague. Authors need to delineate how each outcome measure (primary and secondary) will be analysed. Will the authors perform an intention-to-treat or per protocol analysis? How will the authors handle missing data? What happens if there is imbalance in baseline characteristics and outcome measures - the student t-test, Wilcoxon etc do not account for these. 7) Will the authors perform any subgroup analyses based on types of post-stroke incontinence? General comment The manuscript still lack some details needed for clinical trial reporting. Please refer to the CONSORT guideline.

REVIEWER	Ran Pang Guang An Men Hospital, China Academy of Chinese Medical Sciences, Beijing, China.
REVIEW RETURNED	08-Apr-2018

GENERAL COMMENTS	Thank you for designing this meaningful study. I have some questions and comments. 1. Because the sample size is calculated based on the result from a similar study, the related reference should be listed. 2. It would be great to add some details for inclusion and exclusion criteria, which may be helpful for readers to understand the protocol. For example, how can you define the patients who is refractory to antimuscarinics? It should be clarified whether the patients with pre-stroke UI will be excluded. 3. According to the exclusion criteria, patients with refractory urinary tract infection will be excluded. I am wondering if patients with acute urinary tract infection will also be excluded. 4. Similar to the description in treatment group, the details about the connection of electro-acupuncture device for selected acupoints in control group should be presented. 5. Based on the protocol, both the incontinence episodes and result from 24-h pad test will be used as primary outcomes. Since more than one primary outcome will be analyzed, the family-wise error rate would be increased significantly. To reduce the type I error, some statistical strategies should be taken into consideration, such as Bonferoni, or Schaffer method. 6. What kind of test will be used to identify whether the data meet normal distribution should be described. 7. By the way, some typos need to be corrected. For example, LI15(Jiangyu) should be LI15(Jianyu).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment 1: The introduction is well-written, providing important information introducing the importance of the research question and study proposed. I would be interested to know why the authors think that it is best to compare electroacupuncture at 'four sacral points' and the conventional electroacupuncture, given that the efficacy of conventional electroacupuncture for urinary incontinence is still debatable. We know that up to 30-40% of patients undergoing treatments with high intensity/close monitoring experience significant placebo effect. In this study, the authors will compare two treatments which both requires high treatment frequency, and so patients in both groups

have high likelihood of treatment success attributed to placebo effect. Can the authors comment on this.

Response 1: It is known that the placebo effect is a pervasive phenomenon and can be produced by any active medical intervention (medication or treatment or other procedure) during clinical practice. This is in acupuncture treatment. In spite of the placebo effect of the two treatments in our study, we will able to compare the therapeutic effect of electroacupuncture at “four sacral points” and the conventional electroacupuncture.

Change in the paper: No change in the paper.

Comment 2: Sample size: “With reference to a similar study .....”, please include reference to the study. The authors quoted the efficacy rates of 70% and 45% - is this a study which also compares“four sacral points”versus “conventional”? Suggest giving more details - currently it is unclear how the authors came up with the sample size.

Response 2: The related reference should be listed. The similar study was from our previous research comparing 'four sacral points' (also known as electrical pudendal nerve stimulation therapy, EPNS) versus transvaginal electrical stimulation (TES). We used PASS 11 software to calculate the sample size based on the efficacy rate (70.1%:45%). The result indicated the need for 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).

Change in the paper: The related reference has been listed.

Comment 3: How will the authors exclude patients with existing UI?

Response 3: We agree that patients with existing UI should be excluded, which can be identified by taking patients’ medical history.

Change in the paper: Existing UI has been added to the exclusion criteria.

Comment 4: One of the exclusion criteria was “SUI or mixed UI”, how about UUI, lower urinary tract symptoms, overflow incontinence etc...are these excluded?

Response 4: UUI is defined as “involuntary loss of urine associated with urgency.” The typical symptoms of UI after stroke include the involuntary leakage of urine accompanied or immediately preceded by urgency. Therefore, most post-stroke UI is UUI. Other neurological conditions attributed to UUI like Parkinson’s disease, multiple sclerosis, spinal injury, or Alzheimer’s disease will be excluded in our study. In addition, non-neurogenic conditions like urinary tumor or calculus also contribute to UUI. Most other patients with UUI have no known neurologic deficit, which is termed idiopathic UUI. Idiopathic UUI does not meet the inclusion criteria so it will not be included during our study. Lower urinary tract symptoms (LUTS) refers to a group of clinical symptoms involving the bladder, urinary sphincter, urethra, and in men, the prostate. It also affects women. LUTS can be related to a large number of causes including benign prostatic hyperplasia, overactive bladder, urinary tract infection, chronic prostatitis, nocturnal polyuria, detrusor hypocontractility, neurogenic bladder dysfunction, and so on. LUTS can present storage symptoms with or without urge incontinence. LUTS without urge incontinence does not meet the inclusion criteria so these patients will not be included in our study. Overflow incontinence is characterized by the involuntary release of urine from an overfull urinary bladder, often in the absence of any urge to urinate. Overflow incontinence following an acute stroke has been reported in a number of studies due to detrusor hyporeflexia. Our study aims to observe the most common type of post-stroke UI, so overflow incontinence will be excluded.

Change in the paper: Overflow incontinence has been added to the exclusion criteria.

Comment 5: How do you define poor participant compliance?

Response 5: Poor participant compliance is defined as patients who do not adhere to treatment for personal reasons.

Change in the paper: A detailed description has been added after the related sentence.

Comment 6: The authors chose incontinence episode diary and the 24-hour pad test as the primary outcome measures; however, the CONSORT guideline does not recommend use of more than one primary outcome measure because it will incur problems with result interpretation. Suggest that the authors consider using one primary outcome measure only.

Response 6: We agree, and have changed the manuscript to include only one primary outcome measure, in accordance with the CONSORT guideline.

Change in the paper: The 24-hour pad test has been removed from the paper.
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Comment 7: The statistical analysis is vague. Authors need to delineate how each outcome measure (primary and secondary) will be analysed. Will the authors perform an intention-to-treat or per protocol analysis? How will the authors handle missing data? What happens if there is imbalance in baseline characteristics and outcome measures - the student t-test, Wilcoxon etc do not account for these.

Response 7: We will provide a more detailed statistical analysis of each outcome measure. We will perform an intention-to-treat analysis. We will use LOCF (last observation carried forward) analysis to handle the missing data, which means that we will input outcome data of the patients who were lost to follow-up in our analysis. If there is imbalance in the baseline characteristics and outcome measures, we will use ANCOVA (analysis of covariance). ANCOVA can evaluate if the means of a dependent variable (DV) are equal across levels of a categorical independent variable (IV), often called a treatment, while statistically controlling for the effects of other continuous variables that are not of primary interest, known as covariates (CV). ANCOVA can adjust the DV by the group means of CV(s).
Change in the paper: Detailed information was added to the sections of data management and statistical analysis

Comment 8: Will the authors perform any subgroup analyses based on types of post-stroke incontinence?

Response 8: The application of subgroup analysis is to control the heterogeneity in patients like age, gender, course, degree of disease, and so on. According to our previous study, post-stroke incontinence is a very frequent problem in male and female patients. Direct stroke-induced damage to the neuromicturition pathways is considered the most common cause for it, leading to uninhibited detrusor overactivity and urge incontinence. We will study the most common type of post-stroke incontinence and so will not include a subgroup analysis in the planned study.

Change in the paper: No change in paper.

Reviewer: 2
Comment 1: Because the sample size is calculated based on the result from a similar study, the related reference should be listed.

Response 1: We agree that the related reference should be listed.

Change in the paper: The related reference has been listed.

Comment 2: It would be great to add some details for inclusion and exclusion criteria, which may be helpful for readers to understand the protocol. For example, how can you define the patients who is refractory to antimuscarinics? It should be clarified whether the patients with pre-stroke UI will be excluded.

Response 2: We agree that it will be better for readers to understand the protocol with the addition of more detailed information about the inclusion and exclusion criteria. We define a patient refractory to antimuscarinics as one who has taken an antimuscarinic agent with no UI improvement. Existing UI before stroke will also be excluded.

Change in the paper: Detailed information has been added to the inclusion and exclusion criteria.

Comment 3: According to the exclusion criteria, patients with refractory urinary tract infection will be excluded. I am wondering if patients with acute urinary tract infection will also be excluded.

Response 3: Patients with acute urinary tract infection will also be excluded.

Change in the paper: This information has been added to the exclusion criteria.

Comment 4: Similar to the description in treatment group, the details about the connection of electro-acupuncture device for selected acupoints in control group should be presented.

Response 4: We agree that it is better to provide a similar description about the connection of the electro-acupuncture device for selected acupoints in the control group.

Change in the paper: Detailed information has been added to the related paragraph.

Comment 5: Based on the protocol, both the incontinence episodes and result from 24-h pad test will be used as primary outcomes. Since more than one primary outcome will be analyzed, the family-wise error rate would be increased significantly. To reduce the type I error, some statistical strategies should be taken into consideration, such as Bonferoni, or Schaffer method.

Response 5: We referred to the CONSORT guideline and found that it recommends using only one primary outcome measure otherwise it is possible to incur problems with the interpretation of results. We modified the protocol so that incontinence episodes is the primary outcome.

Change in the paper: 24-hour pad test has been removed from the paper.

Comment 6: What kind of test will be used to identify whether the data meet normal distribution should be described.

Response 6: A normality test will be used to identify whether the data meet normal distribution.

Change in the paper: A description of this has been added to the section on statistical analysis.
Comment 7: By the way, some typos need to be corrected. For example, LI15(Jiangyu) should be LI15(Jianyu).

Response 7: Yes, there are some typos. LI15(Jiangyu) should be LI15(Jianyu).

Change in the paper: LI15(Jiangyu) has been corrected as LI15(Jianyu).

VERSION 2 – REVIEW

REVIEWER	Renly Lim University of South Australia
REVIEW RETURNED	07-Jun-2018

GENERAL COMMENTS	Suggest that the authors seek advice from statistician with experience analyzing clinical trial data.

REVIEWER	Ran Pang Guang An Men Hospital, China Academy of Chinese Medical Sciences, Beijing, China
REVIEW RETURNED	15-Jun-2018

GENERAL COMMENTS	The revised manuscript is satisfactory. Congratulations.