Author's response to reviews

Title: The Efficacy and Safety Study of Electro-acupuncture for Severe Chronic Functional Constipation: Study protocol for a Multicenter randomized controlled trial

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Author's response to reviews: see over
Answers to the comments

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The Efficacy and Safety Study of Electro-acupuncture for Severe Chronic Functional Constipation - a Multicenter, Randomized Controlled Trial
Zhishun Liu, Jia Liu, Ye Zhao, Yuying Cai, Liyun He, Huanfang Xu, Xiaohua Zhou, Shiyan Yan, Lixing Lao and Baoyan Liu

1. Reviewer’s report comments—Reviewer: Michael Camilleri
1.1 Will the study design adequately test the hypothesis?
In general, the study design would adequately test the hypothesis although there are enhancements to the study that would enhance the quality of the result and make the study more consistent with recent high quality RCTs in chronic functional constipation. It is relevant to note that the sample size proposed is appropriate for the primary endpoint and effect size to be demonstrated, if one accepts the proposed endpoint. Therefore, it is acknowledged that the current design would adequately test the proposed hypothesis. However, the endpoint does not reflect current state-of-the-art.

The areas of enhancement of the clinical trial are listed below:
A. Given that it is estimated that ~25% of patients with chronic constipation patients evaluated in gastroenterology practice have evidence of pelvic floor dyssynergia or rectal evacuation disorder (Gut 61:1132-1139, 2012), the exclusion criteria should detail how much patients will be either excluded or equally distributed in the two treatment arms. Symptoms criteria for chronic functional constipation are insufficient to exclude evacuation disorder e.g. they permit up to 25% of days with sense of incomplete evacuation in the Rome criteria of functional constipation.

Answer: We will not consider pelvic floor dyssynergia or rectal evacuation disorder as exclusion criteria in this trial, but we designed strict central randomization to ensure the patients could be equally distributed in the two treatment arms.

B. Duration of the trial: the recent literature and FDA guidance suggests that trial should be of 12 weeks’ duration.

Answer: Our previous study of 4 weeks electro-acupuncture (EA) treatment showed that EA has post-treatment effect. According to the result of this pilot study and the consultation responses of experienced acupuncturist, we designed the duration of the trial as 8 weeks of treatment and 12 weeks of follow-up.

C. Primary Endpoint: The current recommendation is to use a composite endpoint of at least 3CSBMs per week plus at least 1 CSBM per week over baseline (2 week observation with diary, not just recall); this composite result has to be recorded in at least 9 of 12 weeks including at least 3 of the last 4 weeks (9-12) of the 12 week trial. The current primary endpoint would be an appropriate secondary endpoint.

Answer: According to the duration designing, we designed that the primary outcome of the study is the increased value of weekly average CSBM during 8
weeks treatment, compared with baseline. Observation with diary will be conducted from 2 weeks before the randomization (Screening period) to the end of the follow-up period, which including 22 weeks in all.

D. Power: The sample size will have to be adjusted according to the revised primary endpoint.

Answer: The sample size is based on the primary outcome of the study is the increased value of weekly average CSBM during 8 weeks treatment, compared with baseline.

E. Missing data imputation by the “multiple imputation method” needs to be more clearly spelled out and any correction for alpha based on the number of data imputed will be relevant.

Answer: Inverse probability weighting method will be used for Multiple Imputation to deal with the Missing-Data.

1.2 Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The protocol provides sufficient detail to allow replication. Additional details of the follow up period after the 8 week RCT period are needed e.g. how will treatment be standardized, what about concomitant medications. If this is not “controlled” the data at 12, 16 and 20 weeks cannot be used to appraise longer term efficacy after cessation of the active treatment period.

Answer: During the 2 weeks of screening period and the 12 weeks of follow-up period, the patients are asked to try to take no treatment after 8 weeks of acupuncture treatment. An emergency treatment is designed if participants do not have a bowel movement for three or more consecutive days during the trial. They were permitted to take 110ml of Glycerol Enema (Glycerol Enema, H11022362110, Beijing Maidihai Medical Co., Ltd, Beijing China, 110ml/bottle) as rescue medication, which is provide by the investigators. Every use of Glycerol Enema should be recorded in the diary. And any other concomitant medications should also be recorded in the diary.

1.3 Is the planned statistical analysis appropriate?

The proposal of the statistical analysis of the main efficacy outcome is to use a one-side because the study is designed to demonstrate superiority. This is unacceptable for most RCTS and it is certainly conceivable that the active treatment arm may show worse outcomes than the sham arm. Therefore 2 sided tests should be applied to the primary endpoint, as authors propose for the secondary endpoints.

Answer: All statistical analysis is two-side test. This has been revised in the protocol.

1.4 Is the writing acceptable?

English language editing is required e.g. portion of participants should be proportion. Reference 3 and 15 are identical.

Answer: Some writing mistakes have been corrected. Portion of participants has been corrected to proportion. Reference 15 was cancelled.
"Could the authors specify the names of the ethics committees please? In addition, I would recommend asking the authors if it might be possible for a native-English speaking colleague to check the paper for clarity of language prior to resubmission."

**Answer:** Guang An Men Hospital is the investigator hospital and the trial is conducted in 15 hospitals. The protocol was submitted to the Ethical committee of Guang An Men Hospital firstly and passed the ethical review. Then the protocol was submitted to the ethical committees of 15 hospitals where the trial taking place and all of the ethical committees approved the protocol.

The names of the ethics committees are:

1. Guang An Men Hospital of China Academy of Chinese Medical Sciences (South Branch)
2. West China Hospital of Sichuan University
3. Guangdong Hospital of TCM
4. Heilongjiang Institute of TCM
5. Beijing Hospital of TCM
6. Huguosi TCM Hospital of Beijing University of TCM
7. 1st Affiliated Hospital of Tianjin University of TCM
8. Dongzhimen Hospital of Beijing University of TCM
9. 3rd Affiliated Hospital of Zhejiang University of TCM
10. 301 Hospital
11. Wuhan Hospital of Integrated TCM and Western Medicine
12. Yueyang Hospital of Shanghai University of TCM
13. Nanjing University of TCM
14. Jiangsu Hospital of TCM
15. Anhui Hospital of TCM.

We submitted all the original files of these ethical committees in file named “Ethical Approvals”.

We revised the English writing and all the changes are highlighted with ‘tracked changes’ in the manuscript.

3. **Editorial requests:**

3.1 Please ensure the title conforms to journal style for study protocol articles. The title should follow the format: ___________: study protocol for a randomized controlled trial?

**Answer:** The title has been revised as:

*The Efficacy and Safety Study of Electro-acupuncture for Severe Chronic Functional Constipation: Study protocol for a Multicenter randomized controlled trial*

3.2 Please upload the figures as separate files via the online submission system. They should not be included within the main manuscript document.

**Answer:** The figures and pictures have been uploaded as separated files.

3.3 Please include the names of all the ethical approval bodies that granted approval for your study to take place.
Answer: All the names of all the ethical approval bodies that granted approval for your study to take place have been included in the protocol item “Ethical considerations”