Author's response to reviews

Title: Electro-acupuncture of different current intensity to treat functional constipation: a study protocol for a randomized controlled trial

Authors:

Cui Hong Zheng (635342693@qq.com)
Guang Ying Huang (gyhuang@tjh.tjmu.edu.cn)
Ming Min Zhang (mmzhang@tjh.tjmu.edu.cn)
Wei Wang (wwang_tjh@yahoo.com.cn)
Xiang Hong Jing (jxhtjb@263.net)
Bing Zhu (zhubing@mail.cintcm.ac.cn)

Version: 3 Date: 26 July 2013

Author's response to reviews: see over
Dear editors and reviewers,

I am very grateful for your elaborate suggestions. I have revised it thoroughly.

Now I will give the answer point by point.

**Reviewer: Jieyun Yin**

**Reviewer's report and my answer:**

1. Rationale of the method is not clear. It’s not clear why high or low current will be chosen and what the authors’ expectation is.

2. Method, Study Design: Although the major goal of this protocol is to explore the effects of electroacupuncture with different current intensity on symptoms of functional constipation. Not much effort was seen in testing different parameters. The author only stated “The stimulation parameters of electroacupuncture in the high current intensity group is an alternating wave of frequency 2/50 Hz, and the current is strong enough reaching the patient’s tolerance threshold value. The frequency is the same in the low current intensity group, while the current is relatively weak by can be clearly perceived by the participants”. This is not acceptable. The definition of high/low current intensity is not clear therefore this protocol is not reproducible.

   **Answer:** As suggested, this question is stated in the second paragraph of the “Discussion”: The rationale behind the study of electro-acupuncture intensity is that different parameters of stimulation may cause different therapeutic effects for the same disease; the same parameters of stimulation may also bring different effects for different diseases. That is, some dysfunction may need mild stimulation, while others may need
strong stimulation. In addition, different subjects, even different parts of one subject, can have different levels of sensitivity and acceptability. Therefore, the currents applied in the high and low intensity groups cannot be constant values, but instead, variable ranges. Based on the preliminary study, using an alternating wave of 2/50 Hz, the current reaching the patients’ tolerance threshold value ranged from 1.0-1.8 mA; while the current in low intensity group is relatively weak, a 0.2-0.7 mA current can be clearly perceived by the participants.

3. Outcome Measurements: The author stated “All outcomes will be assessed at baseline and 2, 4 and 8 weeks after randomization”. The measurement should be more frequently since electroacupuncture may have acute effect therefore the author may miss some positive results if only assessing measurement on those time points.

   **Answer:** This suggestion is very good. All of the outcomes are based on the patients’ constipation diaries. To avoid missing some effect of acupuncture, the first spontaneous defecation time (from the end of the first intervention to the first spontaneous defecation) will be measured. This has been added to the Outcome measures.

4. Sample Size: The sample size was based on a paper written by Dr. Camilleri. There are differences of symptoms report between American population and Asian population. It will be more acceptable the sample size is based on data from preliminary test.

   **Answer:** Yes, there are differences between American population and Asian population; it will be more acceptable if the sample size is based on data from preliminary
test. The paper written by Camilleri M (A placebo-controlled trial of prucalopride for severe chronic constipation) published by N Engl J Med may have higher credibility. Therefore, based on this study along with our preliminary test, the mean defecating frequency is 4.0 after acupuncture treatment, with a standard deviation of 3.

Reviewer: Zhaoxiang Bian

Reviewer’s report and my answer:

Major revision

1. Please follow up the SPIRIT format.
   
   **Answer:** As you suggested, we have revised the whole article according to the SPIRIT format.

2. Please follow ROME III suggestion to design the trial about functional constipation.
   
   **Answer:** As you suggested, we designed the trial about functional constipation according to the ROME III suggestion.

3. English writing should be polished by a native English speaker
   
   **Answer:** Two native speakers of English have reviewed and edited our manuscript for syntax and grammar.

Minor essential revision:

1. The trial will be conducted in three locations. How to make it consistent among different site, in terms of inclusion, exclusion, and assessment? Also how to conduct the randomization allocation?
The participants will be randomly assigned to three groups through complete randomization at a 1:1:1 ratio equally among the three centers: high current intensity group, low current intensity group, and mosapride citrate control group. Therefore, each group in each center will have 27 participants. The randomization sequence will be generated using R2.0 software. A designated researcher will prepare the assignments in opaque envelopes in sequence.

The acupuncturists will only know of the grouping scheme just prior to the treatment to ensure that the trial will be as blinded as possible. The researchers will not be permitted to predict a patient’s assignment or change it after the patients are randomized. Blinded evaluation (the curative effect will be evaluated by a third party who does not know the grouping) and blinded statistical analysis will be emphasized during the data collection and analysis stage.

To guarantee the quality of the study, all acupuncturists and researchers will be required to undergo special training, including theoretical and practical lessons. They must master all of the details of this trial before performing it. For instance, they will be trained on how to use the randomization method, fill in the case report form, manipulate the needles and electro-acupuncture apparatus, etc. After attending all of the training classes and passing the training test, the researchers will be qualified to perform this trial. During the trial, all adverse events, including broken needles, bleeding, hematoma, fainting, serious pain, local infection, are to be recorded during the treatment and the
follow-up period. Serious adverse events will be immediately reported to the principal investigator. All details will be recorded, and rescue procedures will be initiated at once.

To ensure the quality of this trial, clinical monitors designated by the principle investigator will check all of the details of the process at regular intervals. Moreover, the monitor will check the authenticity of the data from each research center.

2 What is the meaning of "the outcome at the fourth week is the most primary analysis"?

Answer: “the outcome at the fourth week is the most primary analysis” may be wrong; we therefore have deleted this sentence.

3. What is the rationale of acupoint selection? Why only two?

Answer: As for the rationale of acupoint selection, we screened acupoints through a systematic review of ancient books, acupuncture textbooks, and published articles. Meetings were held to further screen for a standardized acupuncture protocol and reach consensus among acupuncture experts in China. Based on the theory of acupuncture, Back-Shu and Front-Mu points (short for Shu-Mu points) are the classic combination for the treatment of internal organ disease, which are located in the abdomen or lower back of the body. Additionally, He-point (Quchi, LI11) and Lower He-point (Shangjuxu, S37) of large Intestine meridians are also positive points, which are respectively situated in the upper and lower limbs of the body. Nei Jing states: ‘He points are the best points to treat internal organ’s disease’. However, our preliminary results have indicated that the effect of Shu and Mu-points in rats mainly excite gastrointestinal motility, while the effect of acupuncture either in Quchi or Shangjuxu is characterized by inhibiting motility. Therefore,
the purpose of this study is to further validate the effect of acupuncture in He-points (Quchi and Shangjuxu) on functional constipation, as well as the relationship between the stimulation intensity and the resulting effect.

4. What is the rationale of intensity selection in the trial?

**Answer:** As suggested, this question is stated in the second paragraph of the “Discussion”: The rationale behind the study of electro-acupuncture intensity is that different parameters of stimulation may cause different therapeutic effects for the same disease; the same parameters of stimulation may also bring different effects for different diseases. That is, some dysfunction may need mild stimulation, while others may need strong stimulation. In addition, different subjects, even different parts of one subject, can have different levels of sensitivity and acceptability. Therefore, the currents applied in the high and low intensity groups cannot be constant values, but instead, variable ranges. Based on the preliminary study, using an alternating wave of 2/50 Hz, the current reaching the patients’ tolerance threshold value ranged from 1.0-1.8 mA; while the current in low intensity group is relatively weak, a 0.2-0.7 mA current can be clearly perceived by the participants.