Author's response to reviews

Title: The effectiveness of moxibustion for the treatment of functional constipation: a randomized, sham-controlled, patient blinded, pilot clinical trial

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Version: 4 Date: 10 October 2011

Author's response to reviews: see over
Answer for reviewers

Thanks for your helps and suggestions. The point to point responses to the comments of the reviewer(s) are listed below. We checked the changed sentence in red color.

Reviewers' comments:
Reviewer #1:

The paper describes a small, but well performed randomized controlled trial (RCT) comparing treatment with moxibustion and placebo for constipation. I have no major objections, but several minor objections/proposals that should be addressed/commented upon by the authors.

1. Abstract. Most readers don’t know what moxibustion is. Could it be explained in a few words? The same applies to qi deficiency and qi excess. The abstract is difficult to understand for readers from my part of the world without knowledge of these words which, however, are explained in the paper. If you are short of words, leave out some of the within group results (see below).
   -> We have added the brief explanation of moxibustion and qi deficiency/excess in abstract. (page 2, background and results)

2. The primary outcome of an RCT is the comparison between the two randomized groups. Please give these results first, followed by the results of the analyses within each of the groups (or leave out the statistical analyses of the results within groups). This applies to the abstract and the paper.
   -> We have changed the order of results in the abstract and the paper.

3. The results of the comparisons between the groups (the primary outcome) are not reported in the abstract which only says that p > 0.05. Please give the results (the differences between the groups) with 95% confidence intervals (CI). In general for the whole paper, give the main results with 95% CI.
   -> We reported 95% CI in abstract and results as recommended.

4. Page 7 – the Constipation Assessment Scale (CAS). If I understand correctly, there are eight items scored from 0 to 3. Does it mean that CAS has a score from 0 to 24? Please explain.
   -> We have added the detailed explanation in page 7.
   "It is rated three point at each item, from 0 (no problem) to 2 (severe problem). The CAS has 8 items, so total CAS score has ranged from 0 to 16. “

5. Page 8 – statistics. The sample size calculation is missing. What is the power of this small trial to show a clinically significant effect? Please report the sample size calculation made before starting the trial. The small trial makes a type II error rather likely, should you discuss the possibility in the “Discussion” section?
   -> We have added the explanation of sample size calculation in page 9. And we also add the shortcoming of this study, caused by small sample size, in the ‘Discussion’ section. (page 9 and 13)

6. Page 10, the end of the first paragraph: “….. there was a difference between the groups in terms of weight (Table 1)”. According to table 1, there was also a
difference in the BSS score.

-> We have modified the text and table as recommended. (page 10)

At baseline, p-value of weight was 0.0549, and p-value of BSS was 0.0555. So, nothing was significant between 2 groups at baseline.

7. Page 10 – primary outcome. See p2 above. Please rearrange with the primary outcome first and give the results with 95%CI.

-> We have rearranged that, as you said, and added 95% CI. (page 10-11)

8. The conclusion – last sentence: “….. are needed to verify the effect…” The sentence shows that the authors believe that there is an effect. I would prefer: 
“More rigorous studies with larger sample size are needed to verify if there is an effect of moxibustion...”

-> Thank you for your comment. We have modified this sentence, as recommended. (page 14)

9. Table 1 and 2: It is written at the bottom (footnote) “ * p<0.05, by…..”. What does the “ * ” mean? Table 3: When the p-value in the table is 0.03, it is not necessary to explain in the footnote that p<0.05.

-> We have changed as recommended in Table 1,2, and 3.

10. Figures 3 and 4: the titles are: “Changes in defecation.....”. Is it correct that the figures show the changes, or do they show “Frequency of defecation....”? I think that it is impossible to show changes at baseline, and that the figure shows the frequency of defecation (number per week) at different points of time.

-> We have changed the title of Figure 3, 4, as “Defecation frequency in ...”

11. Figures 3 and 4: What are the points, I guess that it is the mean. What are the error bars, is it SD, SEM or confidence interval of the mean? Please make it clear on the figures.

-> We modified the figure 3 and 4. These figures show the mean change of defecation frequency, without SD or SEM.

12. Figures 3 and 4: There are no significant differences between real and sham moxibustion (fig3) and qi excess and qi deficiency (fig4), except for qi excess and qi deficiency at week 4 (p=0.03). I think both significant and not significant differences should be shown clearly on the figures.

-> We have added ‘*’ on the significant result in Figure 4 and attached p-value.
Reviewer #2

The study titled “The effectiveness of moxibustion for the treatment of functional constipation: a randomized, sham-controlled, patient blinded, clinical trial” is an interesting one. Concerns about the manuscript involve the trial design and results interpretation. The major concerns are as follows:

1. How the randomization was conducted?
   -> We added this in page 6.
   As briefly explained, the subjects admitted to the trial, were randomized into either the moxibustion group or control group. Participants were randomized before the first treatment by computer generated randomization table. A block size of 4 was used.

2. How about the severity of the constipation based on BSS scale?
   -> BSS is an important tool to assess the form of defecation, and it has been used several previous studies. It classifies the form of defecation from Type 1 to Type 7, but there is no criterion to separate them into mild or severe. BSS score of participants of this study is described in Table 1, 2.

3. How about the successful rate of blinding?
   -> Sorry, we did not try to check the successful rate of participants’ blinding. However, it might be considered to be blinded, based on previous study. (page 7) We have added this point in discussion session. (page 13)

4. What is the base for sample size calculation?
   -> We have added sample size calculation and explanation about it in page 9.
   As there was no previous study comparing moxibustion with sham moxibustion, this was a pilot study for further randomized controlled study. Therefore, we included minimum sample size for evaluating the effect of moxibustion for future study.

5. What is the base to decide the treatment course?
   -> We have added this in page 6 with detailed explanation.
   Treatment course including acupuncture points, frequency of moxibustion, number of session, was determined by consensus of 4 Oriental medical doctors. Each doctor has practical experience of more than 5 years. Acupuncture points of moxibustion treatment were also based on literatures. (page 6)

6. The reporting style do not match CONSORT standards very well.
   -> We modified several parts according to CONSORT standards, and described this in Appendix 1. We tried to describe all items of CONSORT standards, except several items which are not applicable.

7. The shortcoming of the study should be added.
   -> We have added shortcoming of this study in ‘Discussion’ section and discussed about it. (page 13)

8. Based on the sample size and the nature of this study, it is only a pilot one.
   -> There was no previous study using sham moxibustion as control group. So, it was designed a pilot study for future rigorous randomized clinical trial. We modified the title and context as a pilot trial.

Thank you for all valuable comments.
**Appendix 1.**

### CONSORT 2010 checklist of information to include when reporting a randomised trial*

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(for specific guidance see CONSORT for abstracts)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>3</td>
</tr>
<tr>
<td>objectives</td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td>4</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial design</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>NA</td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>5</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>NA</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Randomisation:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sequence generation</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>6</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions</td>
<td>5</td>
</tr>
<tr>
<td>Implementation 10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
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<tr>
<td>Blinding 11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
<td></td>
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<tr>
<td>Blinding 11b</td>
<td>If relevant, description of the similarity of interventions</td>
<td></td>
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<tr>
<td>Statistical methods 12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
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<tr>
<td>Statistical methods 12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
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</tbody>
</table>

**Results**

- **Participant flow (a diagram is strongly recommended)**
  - 13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
  - 13b For each group, losses and exclusions after randomisation, together with reasons

- **Recruitment**
  - 14a Dates defining the periods of recruitment and follow-up
  - 14b Why the trial ended or was stopped

- **Baseline data**
  - 15 A table showing baseline demographic and clinical characteristics for each group

- **Numbers analysed**
  - 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

- **Outcomes and estimation**
  - 17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
  - 17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

- **Ancillary analyses**
  - 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

- **Harms**
  - 19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

**Discussion**

- **Limitations**
  - 20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

- **Generalisability**
  - 21 Generalisability (external validity, applicability) of the trial findings

- **Interpretation**
  - 22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

**Other information**

- **Registration**
  - 23 Registration number and name of trial registry

- **Protocol**
  - 24 Where the full trial protocol can be accessed, if available

- **Funding**
  - 25 Sources of funding and other support (such as supply of drugs), role of funders