Author's response to reviews

Title: Impact of electroacupuncture on quality of life for patients with Relapsing-Remitting Multiple Sclerosis under treatment with immunomodulators: A randomized study

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Version: 4 Date: 14 August 2012

Author's response to reviews: see over
Dear Dr. Rowles:

I am hereby re-submitting our manuscript *Impact of electroacupuncture on quality of life for patients with Relapsing-Remitting Multiple Sclerosis under treatment with immunomodulators: A randomized study*. We have corrected the TRN number (the correct form is RBR-58yq52) and incorporated the suggestions of the two reviewers, as discussed below.

**Referee 1:**

**Reviewer:** Byung-Cheul Shin

**Major comments**

1. please follow the revised STRICTA guideline for acupuncture trials [1].


The article was very helpful in deciding how much detail to give about the methodology, and the relevant information has been added to the text.

2. In abstract

- There is no research aim.

The research aim has been included at the end of the “Background” section of the abstract.

- Abstract needs to be updated with consistency.

We did not understand what the reviewer meant by his comment that the abstract should be “updated with consistency”, but if he would explain better the kind of change he has in mind, we would be glad to make the relevant modifications.

3. Please present the inclusion / exclusion criteria in methods

As originally written, the inclusion criteria involved distance from the hospital and exclusion was based on previous experience with acupuncture (Fig 1).
4. Please explain the conventional treatment (immunomodulators) of multiple sclerosis of included patients in ‘intervention’ in Methods in page 5. What are they? Is there any changes?

A brief explanation of the use of immunomodulators in the conventional treatment has been included in the sub-item “Intervention”.

5. Please supply the simple explanation of the Expanded Disability Status Scale (EDSS) in page 6 in methods. Which range? What is the meaning of this scale?

A brief explanation of the Expanded Disability Status Scale has been included, including its role in the evaluation of neurological impairment and an explanation of the scale values.

6. Was the blinding of patients successful?

The issue of blinding was addressed in the sub-item on randomization and blinding. This was guaranteed by treatment of the patients at different times to avoid contact with each other and the agreement of the patients to avoid discussion of their treatment.

7. In statistical analysis,

- please supply the information of sample size estimation. Did you estimate the sample size?

No sample size was estimated, because all of the patients living close enough to the hospital to enable participation in the weekly acupuncture sessions were included. This was 18.6% of the total number of patients under treatment at the hospital.

- Which software was used for statistical analysis?

- The statistical analysis was conducted using SAS for Windows, version 9.2, as now specified in the text.

- Please change SD to interquartile range in page 18, Table 1 because the statistics are non-parametric data as median rather than parametric analysis.

- The original Table 1 erroneously reported the mean as being the median, which clearly led to the confusion of the reviewer, because the data are indeed parametric.

8. I think, FAMS total in figure 4 might be better to become figure 3 and all subscale of FAMS including thinking/fatigue of figure 3 might be good to be figure 4.

We have presented the composite total of the FAMS as Figure 3. Figure 4 was reorganized according to the suggestions of Reviewer 2.

9. How about reporting the adverse events? Generally, the reporting of safety is common secondary outcome of clinical trials in many trials.
No adverse effects of acupuncture treatment were encountered, as explicitly stated in the text.

**Minor comments.**

1. Please check abbreviations. Please define it at its first appearance, if defined, please use the defined one.

   E.g.)
   Quality of life, in page 4, Background -> QOL
   True electroacupuncture, in page 9, 10, 11 -> TEA
   Quality of life, in 10 -> QOL

   The abbreviations have been checked. The authors prefer not to use the abbreviation when a the generic concept is involved. Therefore, on page 6, “quality of life” has intentionally been maintained. The other generic references have been reported in a slightly modified form to avoid identity with the abbreviation, thus referring to the quality of the life of patients and electroacupuncture, without the adjective “true”, since true electroacupuncture is still electroacupuncture.

2. placebo SEA (in page 7) -> SEA

   The modification was made.

3. Please check the references. The description methods are not accordance with each other. Please check “the guideline for authors.”

   The references have been checked.
Referee 2:
Reviewer: Insoo Jang

1. Intervention (p.6)

It is needed to explain more about the electrical characters, the most important factors of the intervention of EA trial: whether in alternating current (AC) or in direct current (DC), current (mA), voltage (mV), and the name and the manufacturer of the device. There are only Frequency (Hz), duration and the session in this paper.

The information about the electrical characteristics requested has been included.

2. Lack of rationale (p.6)

There is the lack of rationale for the selection of acupoints, but only mentioned as "focusing on the immune system"

The discussion of the selection of acupoints has been modified.

3. Statistical Analysis

The authors used repeated measured ANOVA test, but there was no result of test for Gaussian distribution (normal distribution). If you did that, You should use the analysis of non-numeric data like Kruskal-Wallis test, than ANOVA.

In the original Table 1, the “mean” was misnamed “median”. This has been corrected. As explained to Reviewer 1, the data are numeric/parametric, which means there was no need to use the Kruskal-Wallis test.

4. Results

Too many data are included in Figure 4.

We agree with the reviewer that there is an excess of data in Figure 4. We have alleviated the problem by separating the information. The information about the mobility subscale of the FAMS has been included with the results of the EDSS, which also assesses mobility, in Figure 2. We have also eliminated the graph depicting the thinking/fatigue subscale, since the results were not significant. The composite total FAMS is now presented in a separate figure (Figure 3), as requested by Reviewer 1. The results of the other four subscales of the FAMS have been presented as two separate figures (Figures 4 and 5).

There are no baseline comparison of all data, but some seems to have a difference between EA group and Sham group, inspite of the standard deviations.
It was not clear exactly what the reviewer wanted. The baseline comparisons showed the two groups to be initially equivalent in relation to all of the parameters investigated. The initial p-values were not included in the figures, although this information has been included in the text to make the equivalence clear.

In addition, it is needed to check the delta value of the data, than the actual value.

The use of the delta value is normally associated with studies involving only two points in time. In the present study, however, three times were included in the analysis: initial, after three months, and after six months. The progress with treatment was thus more visible, since after three months some of the subscales revealed that intergroup differences had already emerged, whereas only after six was this clear for the rest of the subscales.

Proofreading in detail points.

---------------p.3 Methods 3rd line

experimental and placebo group ==> electroacupuncture and placebo group

The term “experimental” used on p. 3 has been removed

p.6

Yintang --> Ex-HN 3 or Ex-HN 3 (Yintang)


If there are any further questions, please let us know and we will be glad to address them.

Sincerely,

Juan G. Quispe-Cabanillas