Author’s response to reviews

Title: Transcutaneous Neuromodulation improved inflammation and sympathovagal ratio in Patients with Primary Biliary Cholangitis and Inadequate Response to Ursodeoxycholic Acid : A Pilot Study

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Author’s response to reviews:

Dear Editor,

Thank you very much for the chance of revision and planning to publish this manuscript. It is a great honor for us to have the chance to share our research results and the potential TN treatment of PBC in this journal. We have tried our best to make the point-to-point reply and revised the manuscript carefully based on the reviewers’ valuable comments.

Editor Comments:

1. Please change the Introduction heading to Background.

Thank you, and we have changed it.
2. Please change the Materials and Methods heading to Methods.

Thank you, and we have changed it.

3. Please include the consent information in the Ethics approval and consent to participate section, and please specify if it is written or verbal.

Thank you for the comment. We have added the content. It is stated as follows:

The study protocol was approved by the hospital ethics committee (number PJ-KY-2017-113(X)) and registered in Chinese Clinical Trial Registry (number ChiCTR1800014633). All participants in the study signed the informed consent form and were free to quit the study at any time for any reasons.

4. We strongly encourage all authors to share their raw data, either by providing it in a supplementary file or depositing it in a public repository and providing the details on how to access it in this section. If you do not wish to share your data, please clearly state this in this section along with a justification.

The datasets of the current study are available and can be provided upon reasonable requests from the corresponding author-Zhijun Duan (cathydoctor@sina.com).

5. Please represent authors’ names using their initials, not their full name, in the Authors’ Contributions section. If there are any duplicated initials, please differentiate them to make it clear that the initials refer to separate authors.

Thank you. It is done as suggested.

Zhi Yu (Reviewer 1): Major comments:
1. In the "abstract" section: the method description in abstract is not complete. Authors should add more information about participant, randomization, especially for the statistics.

Thank you so much for the suggestion. And we have added the content as follows:

“Methods: According to inclusion and exclusion criteria, 10 healthy volunteers and 15 PBC patients were recruited to control group and TN group, respectively. The PBC patients were randomly assigned to group A (TN combined with UDCA) and group B (sham-TN combined with UDCA), and a crossover design was used. The TN treatment was performed via the posterior tibial nerve and Acupoint ST36 (Zusanli) 1 h twice/day for 2 weeks daily. T test and nonparametric test were used to analyze the data.

2. In the "Introduction" section: The part of TN is too wordy, please focus this part on the Biliary Cholangitis and refine it.

Thank you so much for the suggestion. We have refined the part TN treatment in the introduction.

3. In the "Materials and Methods" section:

The detail of randomization, allocation, and blinding should be clearly described in the manuscript(sequence generation, allocation concealment and implementation, etc). Please consult the sample size calculation. The sample size of the study is too small to draw the conclusions.

Base on some previous study related to the TN showed as follows, which indicates that the number was sufficient. As mentioned in the discussion, the small sample size is a shortcoming of our research. We eagerly hoped to increase the number of patients. We found some responsible indicators of PBC were alleviated significantly after treatment. So, we expect to share the effect and potential noninvasive therapy, even new mechanism for treating PBC. Due to the small number of samples in this experiment, crossover method was carried out to increase the number according to the features of PBC. Indeed, more validation experiments with increasing number of samples still need to be carried out.

On the aspect of randomization and blind method, we made the treatment plan for the first patient starting with TN treatment combined with UDCA, and the second patient starting with sham-TN treatment combined with UDCA which was alternate in sequence. None of the patients knew which kind of the treatment they received.

4. The dropped-out rate is too high to accept for the study.

Thanks for the comment. We would like to make an explanation about the rate. The total drop-out number was 4 in our study; one was afraid multiple blood drawing and another had to quit the study because of a business travel. Therefore, the actual number of drop-out that might be associated with the efficacy of the study was only 2.

Bridget Southwell (Reviewer 2):

Thank you very much for the edits and comments in the pdf. And we have read and adopted every edit in the revised manuscript. It is very valuable for our revision. Thank you very much for your edits.

1. Table 1 should only include the data of the 10 PBC patients and 10 HV who completed the study. Not those whose data is not included in analysis.

Thanks for the comment. In the table 1, we just included the data of 10 PBC patients and 10 HV. It can be seen in the column of 'male/female' and we have added the numbers of males and females.

2. In the table 2 show significant values with bold.

Thank you for the suggestion. It is done accordingly.

3. Include statement about comparison of effect of TN/UDCA to sham TN/UDCA on bile acids.(in the part of 3.3.1 Plasma Bile Acids)
Thank you so much for the suggestion. It is an awesome idea. And after carefully consideration and consulting a statistical expert again, finally we can view it in the way behind. Actually, the clinical trial was used crossover method. The data was compared among the three groups. We compared the bile acids before and after TN, as well as sham-TN, without significant changes. Indeed, the sham-TN is regarded as placebo.

4. Effect of sham TN/UDCA.(in the part of 3.3.2 Fecal Bile Acid)

Thanks for your suggestion. We have added the effect of sham-TN/UDCA. It was also no significant change on fecal bile acids by sham-TN/UDCA.

5. There are words missing in this sentence. It does not make sense.(in the part of Discussion)

Sorry for that. We have revised the sentence as follows: With the application of UDCA in the treatment of PBC patients, the prognostic efficacy of ALP and other biochemical markers, which are secondary indicators to replace the primary endpoints of death and liver transplantation, continues to be evaluated.

6. Add images of sham positions, label true TN and sham TN describe acupoints in the Figure 2.

Thank you for the comment. We have added a figure to show the sham-TN positions and a description of acupoints of TN and points of sham-TN.

7. Explain the plot for the reader not used to these plots. For example dark brown shows increase, light blue shows decrease? What do the bars on the left mean? What are the columns, rows are labelled on the right and are BA. Also view the plots in black and white to see what is lost.put the name of the group above the relevant columns.

We used the heat map to show the changes before and after TN, sham TN treatment, and control visually. There is no specific meaning of the bars on the left which is a kind of cluster. And the red, green, and blue bar on the right is responsible for three different groups. The bar with gradient color is responsible for the quantity of the results. Dark brown represents a higher quantity and light blue represents a lower quantity.
8. Do not show p values great than 0.05, this is confusing. Only show where the p value is $< 0.05$ and this draws attention to the significant ones. If you decide to show all p values, give the actual value. (in the Figure 5 and 6)

Thank you for the suggestion. We have deleted the label of $P > 0.05$ in the Figures 5 and 6.