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

Authors:

Hui Yang (602474759@qq.com)
Hang Yang (15841123892@163.com)
Lixia Wang (wenwensl@yeah.net)
Honggang Shi (1666520879@qq.com)
Bojia Liu (715493908@qq.com)
Xue Lin (1987577265@qq.com)
Qingyong Chang (qychang0409@163.com)
Jiande Chen (jiandedzchen@gmail.com)
Zhijun Duan (cathydoctor@sina.com)

Version: 4 Date: 28 Jun 2020

Author’s response to reviews:

Dear editor,

It is a great honor for us to have the chance of publication in the journal. And many thanks to the very kind and responsible reviewers who give us many valuable comments and kind modification.

Review 2 Comments:

Thanks for your kind and careful reviewing and valuable comments which help us a lot.

1. Figure 3. Modulation of Plasma Bile Acid (BA) Metabolism. Each row is a bile acid. Each column represents a participant.
Figure 3 Modulation of Plasma Bile Acid Metabolism

(a) Comparison of plasma BAs in the PBC (pretreatment) group to the control group. After statistical analysis, TCDCA, TUDCA, UDCA, GCA, GDCA, GCDCA and TCA were significantly higher in the PBC patients (pretreatment) than the controls (P<0.05), and the color bars for the BAs in PBC group were browner indicating a higher level. (-4 ≤ log2 (x) < 4. It is obtained from the heat map website: https://www.metaboanalyst.ca/).

(b) Comparison of plasma BAs in the PBC group before (P1-10) and after TN combined with UDCA (P1.1-10.1) compared with the control group (C1-10). After TN combined with UDCA, bile acids had no significant change to pretreatment. The color bars look similar. Visually, this indicated no obvious changes in the metabolism of serum bile acids after TN combined with UDCA.

(c) Comparison of plasma BAs in the PBC group before (P1-10) and after sham-TN with UDCA (P1.1-10.1) with control group (C1-10). After Sham TN combined with UDCA, bile acids had no significant change to pretreatment. The color bars look similar. Visually, this indicated no obvious changes in the metabolism of serum bile acids after sham TN combined with UDCA.

2. Figure 4. Modulation of Fecal Bile Acid Metabolism. [Adjust this legend similar to figure 3].

Figure 4 Modulation of Fecal Bile Acid Metabolism

(a) Comparison of fecal BAs in the PBC (pretreatment P1-10) to the control group (C1-10).

(b) Comparison of fecal BAs in the PBC group before (P1-10) and after TN (P1.1-10.1) and the control group (C1-10). After TN combined with UDCA, bile acids had no significant change to pretreatment. The color bars look similar.

(c) Comparison of fecal BAs in the PBC group before (P1-10) and after sham-TN (P1.1-10.1) and the control group (C1-10). After Sham TN combined with UDCA, bile acids had no significant change to pretreatment. The color bars look similar.

After statistical analysis, there were no significant changes in fecal BAs. The color bars in three heatmap were also look similar. It indicated no obvious changes in the metabolism of fecal bile acids after TN combined with UDCA visually.
On the aspect of the heatmap, it just like a table, and we got them from the professional website (It is obtained from the heat map website: https://www.metaboanalyst.ca/). After uploading our data, a heatmap will be generated automatically like SPSS. More information can be obtained from the website. And all the data will receive data preprocessing, standardization, and normalization. The general method is clustering analysis. The 4 and -4, they are the results of the log2(x). BAs with significant change have been asterisked and showed in figure 3.

3. In the abstract, it still says that patients were randomly assigned to treatment. Please adjust to alternately assigned but blinded to participant.

It has been rewritten in the abstract.

“PBC patients were alternately but blindly assigned to group A (TN combined with UDCA) and group B (sham-TN combined with UDCA), and a crossover design was used.”

4. The editor asked that Reviewer 2 check the responses to Reviewer 1 comments. The authors successfully addressed most of the issues. Still outstanding is:

Rev 2 comment: The authors should include this discussion of sample size for the pilot study with references in the methods. Then, based on the pilot study data, add a discussion of what sample size would be needed in a trial, in the Discussion.

The small number calculation, the number less than 30 is defined as small number. The calculating formulas is https://www.surveysystem.com/sscalc.htm. So, we think there is no need to calculate the number, as it has been already a small number clinical trial like examples made in the link. And the crossover method was carried out.

It has been clarified at the end of the discussion.

“As this is a small number clinical trial (less than 30 samples), a crossover method was carried out to increase the number according to the features of PBC.”