Author’s response to reviews

Title: Chinese herbal medicine TangBi Formula treatment of patients with type 2 diabetic distal symmetric polyneuropathy disease: Study protocol for a randomized controlled trial

Authors:

de jin (826901274@qq.com)
Wen-jing Huang (262055485@qq.com)
Xiang Meng (17888808656@163.com)
Fan Yang (1561662600@qq.com)
Yu-jiao Zheng (luoyuorz@163.com)
Qi Bao (153474877@qq.com)
Mei-zhen Zhang (1044388932@qq.com)
Ya-nan Yang (929810566@qq.com)
Qing Ni (niqing669@163.com)
Feng-Mei Lian (694397644@qq.com)
Xiao-Lin Tong (tongxiaolin66@sina.com)

Version: 1 Date: 22 Sep 2017

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Chinese herbal medicine Tang Bi Formula treatment of patients with type 2 Diabetic Distal Symmetric Polyneuropathy disease: Study protocol for a multi-center, double-blinded, placebo-controlled, randomized controlled clinical trial” (ID: TRLS-D-17-00517).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and...
have made correction, which we hope meet with approval. Revised portion are marked in red in
the paper. The main corrections in the paper and the responds to the reviewer’s comments are as
following:

Responds to the Editors’ comments:

1) Fully write all abbreviations the first time they appears in text. For example “NSAIDs”.
Response: Modified throughout the text according to the comment (Line 19, page 4). NSAIDs
(non-steroidal antiinflammatory drugs). Other parts are also modified.

2) Background. “The results showed CHM treatment was associated with a superiority in
effective (odds ratio [OR], 2.40; 95% confidence interval [CI]: 0.94 to 2.97; p<0.001)”. The 95%
interval of OR do contains 1. I do not understand why the authors stated that there is a
superiority. I wonder the 95% confidence interval contains 1 but the p value is <0.001
(supposing that the significate p value was < 0.05 in this study). Clarifications needed.
Response: Modified throughout the text according to the comment (Line 29, page 2).
This paragraph proved the effectiveness of CHM treatment by citing a Meta analysis’s outcome,
maybe there was less explanation.

(The results showed that compared with the control group, the CHM treatment group has
significant difference (p<0.01), and no serious adverse effects were reported.

A meta-analysis of 18 randomized clinical trials including 1575 cases of DSPN demonstrated a
beneficial effect of TCM on clinical symptoms, the results showed that compared with the
control group, the CHM treatment group has significant difference (p<0.01), and no serious
adverse effects were reported).

3) You will have to number the pages when you go submit the revised version, if you plan to do
so.
Response: Modified throughout the text according to the comment.

4) Background. “threedecadesinOutpatientDepartmentofGuangAnMen hospital of
theChinaAcademyofTraditionalChinese”. This sentence is unreadable please revise.
Response: “three decades in Outpatient Department of Guang An Men hospital of the China Academy of Traditional Chinese”

5) Figure should not be embedded in the main manuscript. Submit the figure as a separate file through the Editorial Manager System. Carefully read submission guidelines at https://trialsjournal.biomedcentral.com/submission-guidelines.

Response: Thanks for your suggestion. We have submitted Figure 1 and Table 2 as a separate file through the Editorial Manager System.


Response: Modified throughout the text according to the comment (Line 7, page 4)

EMG (electromyogram) nerve conduction velocity decreases, which we can diagnose the patients with EMG nerve conduction velocity decreasing if EMG indicates that any nerve of 16 nerves of Bilateral Motor nerves (Median nerve, Ulnar nerve, Sural nerve, Superficial peroneal nerve) and sensory nerves (Median nerve, Ulnar nerve, Peroneal nerve, Tibial nerve) was lower than normal

7) Describe intervention and “conventional treatment”. Give details to allow replication including how and will they will be administered, dosage, strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence, criteria for discontinuing or modifying allocated interventions for a given trial participant……

Response: Modified throughout the text according to the comment, ([line 34, page 4] to [Line 39, page 5]) in (Conditions and procedures for withdrawal of study subjects/Intervention measures/Data collection and monitoring.)

8) Fully describe all outcomes.

Response: Modified throughout the text according to the comment in page 6: Outcome measurements.

9) Describe who will be blinded after assignment to interventions.
Response: Modified throughout the text according to the comment (Line 18, page 5)

(All people involved in the trial (patients, investigators, project manager, data management team, clinical research associates, and statisticians) were masked as to the group assignments. The main investigator and other investigators performing outcome analyses were blinded to the group assignments of patients by use of the central randomization system in which the codes were kept by an independent allocator and revealed only after treatment and analyses were completed).

10) Describe data collection and management.

Response: Modified throughout the text according to the comment (Line 23, page 5)

(All data will be recorded by trained clinical investigators in a standardized case report form (CRF), and instantly recorded in the database via the ClinResearch Electronic Data Capture System (CEDCS) with the website at http://www.tcmcec.net/wcr. To ensure the accuracy and reliability of the data, the study monitor will verify and cross-check the CRFs against the investigator’s source document records and drug-dispensing log. Missing data or specific error in the data will be detected by programs, the results will be sent to the investigator for resolution. Except for the treatment code, any individual identification of the subjects will not be released until the database is closed. Written documentation of changes will be available via electronic logs and audit trails. Original CRF will be kept at the participating center for 5 years after completion of the study).

Responds to the reviewer’s comments:

Reviewer #1:

1. Response to comment: 1. This entire paper needs to be proof read and edited again to smooth out the English language. There are still a lot of typos and grammatical mistakes in the whole manuscript. And many sentences lost punctuations. Many sentences are too long to understand the meaning correctly. We suggest that the authors seek professional advice from a native English speaker.

Response: The English language of the revised manuscript has been carefully edited by an English reader, and corrections have been made in the revised manuscript.

2. Response to comment: 2. The detailed description of the treatment need to be added in your text.
(All patients in the group were treated with conventional treatment, which include oral Mecobalamin (500mg/tablet, three times a day), diet, exercise, and oral medicine to ensure access to steady levels of blood glucose, blood lipids, blood pressure according to American Diabetes Association guidelines. On this basis, subjects were randomly assigned to receive placebo (6g/bag, two times a day) or Tang bi Formul, a (6g/bag, two times a day) by the central randomization system.

3. If the patient has recently used other drugs, they'd better be eliminated.

Response: Modified throughout the text according to the comment (Line 22, page 4).

Exclusion criteria: Participate in other drug clinical or used other drugs within one month.

4. There were so many contents to describe the statistical analysis method.

Response: The statistical analysis method was completed according to the advice of our statistician. As a result, there may many contents to describe the statistical analysis method.

Reviewer #2:

Response to comment: 1. Minor: Language, spelling and punctuation needs thorough revision throughout the manuscript.

Response: The English language of the revised manuscript has been carefully edited by an English reader, and corrections have been made in the revised manuscript.

Response to comment: 2. Minor: In 'background', page 3 line 25 to line 34 seems to be repetitive and lacks an introducing sentence about 'type 2 diabetes' instead of just a general statement about 'deleterious complications of diabetes'.
Response: Modified throughout the text according to the comment. Deleted repeated sentences, and add introducing sentences about 'type 2 diabetes', in 'background',

(The latest figures from the International Diabetes Federation (IDF) indicate that as of 2015 more than 415 million people worldwide have diabetes and this number is expected to increase to 642 million by 2040. China has the largest numbers of people with diabetes (109.6 million) [1]. An epidemiological survey from China shows that Among adults in China, the estimated overall prevalence of diabetes was 10.9%[2])

Response to comment:

3. Minor: In the inclusion criteria, a statement regarding glycaemic control of the participants should be included.

3a. In addition, a more detailed statement of type 2 diabetes instead of only 'diabetes' should be included in the inclusion criteria.

Response: 3.Thanks for your advice. That's a very good question. We give careful consideration to this problem, we ensure that the blood glucose level is associated with DSPN, but under the circumstance of baseline balance, blood glucose level does not affect the evaluation of drug efficacy, therefore, we do not limit the patient's levels of blood glucose

3a. Modified throughout the text according to the comment. And we add statements of type 2 diabetes inclusion criteria in the Manuscript.

Response to comment : 4. Minor: Page 6 line 9 'EMG nerve conduction velocity decreases'. A definition of how a decrease in EMG nerve velocity is defined would contribute significantly to the manuscript.

Response: EMG(electromyogram)nerve conduction velocity decreases, which we can diagnose the patients with EMG nerve conduction velocity decreasing if EMG indicates that any nerve of 16 nerves of Bilateral Motor nerves(Median nerve、Ulnar nerve、Sural nerve、Superficial peroneal nerve) and sensory nerves(Median nerve、Ulnar nerve、Peroneal nerve、Tibial nerve) was lower than normal.
Response to comment: Details about the procedure/technique used to measure the secondary outcome 'nerve conduction velocity' is missing in the manuscript. and in combination with a sufficient sample size will lead to significant results. However, the submitted manuscript lacks details in background and methods section which demand revision. Furthermore, language

Response: Modified throughout the text according to the comment.

1. nerve conduction velocity is measured by EMG doctor. Procedure/technique is recorded in our SOP handbook.

The procedure: (Each center has a fixed and special EMG doctor to ensure the accuracy of EMG. Electromyography detection method: checked by Neurocare-C electromyography and evoked potential instrument and determine motor and sensory conduction velocity of bilateral median nerve, ulnar nerve, common personal nerve and tibial nerve. Keep the room quiet and the temperature remained at about 25 °C. Skin temperature shall be remained between 28°C and 30°C, hyperthermic treatment should be provided to whom with low body surface temperature. SCV sensory nerves conduction velocity) acquired by reverse method, which means proximal stimulus, remote reception. Sensory waveform is derived from the averaging deconvolution by machine automatically. SCV value = measured distance (between receiving point and the stimulus point) / incubation. MCV(Motor nerves conduction velocity) determination method is received in the corresponding distal muscles, and gives super-stimulation in the corresponding nerve branch to elicit 2 action potential, far-end and near-end, motor nerve conduction velocity value = distance between 2 points / incubation difference between 2 points points. Nerve conduction velocity normal value refers to "clinical electromyography" standard, median nerve and ulnar nerve MCV ≥ 45m/s and SCV normal values ≥ 47m/s individually. MCV normal value of peripheral nerve and tibial nerve separately were ≥ 42m/s and ≥ 40m/s. Values below all above indicates that NCV slowing down, that is NCV exception.)

1. About sample size

Modified throughout the text according to the comment (Lines 6 of page 6).

Sample size

According to the preliminary study of Tang bi prescription data, placebo group scale (MDNS scale) score difference is 3.45, while Tang bi prescription scale score was 4.14, and standard deviation $s = 1.33$. The sample size is estimated by hypothesis test formula of measurement data: $N = 2 \times [(Z_{\alpha} + Z_{\beta}) \times \delta / d] ^ 2$ (N is the sample size and $\sigma$ is the estimated standard deviation, d is two groups’ continuous variable mean difference; $Z_\alpha$ and $Z_\beta$ are the corresponding standard normal differences). Supposing: $\alpha = 0.05$, $\beta = 0.10$, according to one-sided check table, the
quantile $Z_\alpha = 1.64485$, $Z_\beta = 0.84162$, and put them into the formula. It is estimated that a sample size of 78 subjects per group will be required, considering 20% drop out and exit. This results in 188 in total. Intention-to-treat analysis will be applied to minimize bias due to drop-outs.