Author’s response to reviews

Title: Effect and safety of acupuncture for Hwa-byung, an anger syndrome: a study protocol of a randomized controlled pilot trial

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Responses to reviewers’ comments

We would like to thank the editor and the reviewers of Trials for taking the time to review our article. We have made corrections and clarifications to the manuscript after reading the reviewers’ comments carefully. The changes are summarised below:

Reviewer #1: The protocol is an innovative and potential effective TCM interventions for people with Hwa-byung (an anger syndrome), which may be new to most researchers in psychiatry. The protocol has been written satisfactory and included most of the important information clearly for a pilot clinical trial proposal. However, there are several points to be clarified or addressed before further consideration of publication:
Comment 1.

a) Throughout the protocol, the aspects of assessment or evaluation of feasibility and acceptability are not clear, thus needing restructuring or clarification. There are inconsistencies in the aim/objectives such as "to determine the study feasibility of acupuncture treatment..." in the abstract, "clinical outcomes will be used to investigate the acceptability and tolerability of the acupuncture” in Clinical outcome section, "The acceptability of the treatment will also be evaluated according to basic information about the effect and safety" in the discussion".

b) in addition, some terms have been used inconsistently, such as "harms" in the abstract and "safety" in the protocol content; "acceptability", "tolerability", "integrity of study protocol" in relation to feasibility, so on.

Response 1:

a) Thank you very much for your comments. We have modified the use of the term according to the reviewer’s advice. We have included a consistent description of the trial purpose (p 11, line 12; p16, lines 14-20).

b) We have unified the two terms (harm and safety) into safety (p 1, lines 11, 19; p 2, line 2). Acceptability and tolerability have been integrated into acceptability, and detailed evaluation methods have been added. ‘Integrity’ has been used to describe the completeness of the study and to ascertain whether the trial design will be able to proceed without modification in the future full-sized study (p 10, lines 22-24; p11, lines 1-9; p16, line 18).

Comment 2. One personal query is about the open access and international acceptability of the trail registration site - CRIS.

Response 2: CRIS is an open site for pre-registering clinical trials in South Korea. It has been established at the Korea Centres for Disease Control and Prevention (KCDC) with support from the Ministry of Health and Welfare (MOHW). The CRIS joined the WHO International Clinical Trials Registry Platform (ICTRP) as the 11th member of the Primary Registry (https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp).

Comment 3.

a) In the background, 2nd paragraph, you mentioned the HB is often treated as a "novel anger disorder" and it is not clear whether it is classified in DSM-V or other psychiatric disorder diagnosis system or not. Please clarify.
b) And you also mentioned in the 3rd paragraph that there are "limited quantity and quality of studies investigating the effects of pharmacological and psychosocial intervention for HB. Please describe the important and latest research evidence on this issue and any conclusion or recommendations from the available recent research.

c) For the effect of acupuncture in HB in the 4th paragraph, you mentioned that studies reported significant improvements in the main symptoms of HB, which study(ies) are you referring to? And if that is the case, why you have to pilot test about this intervention for HB again?

d) You also need to specify what the clinical guideline for HB in 2013 is referred to and is that an evidence-based or standard one used by researchers or clinicians?

Response 3:

a) In accordance with your comment, we have clarified the diagnostic system containing HB and have described the research on the development of the diagnostic tool (p 3, lines 3-10).

b) The limitations of previous studies have been described in more detail (p 3, lines 19-23; p 4, lines 1-6).

c) In accordance with your comment, we have included the details of the effects and limitations of these studies (p 4, lines 8-18).

d) We have described the current status, significance and limitations of the guidelines (p 4, lines 18-22). Thank you for the constructive advice.

Comment 4. The study design can be restructured or reworded as it is not clear: "this study is a randomized, controlled, parallel clinical trial."

Response 4: We have modified the description for clarity (p 1, lines 10-11; p 5, lines 1-2; p 6, line 4).

Comment 5.

a) For settings, describe or clarify what is the "academic hospital setting" referred to? Are they inpatients?

b) For the approach and recruitment of patients, it is unclear to just mentioned "when they are found eligible for the study, they will be randomly assigned..." in the setting section. How and where to approach and assess them?
Response 5:

a) We apologise for the misinterpretation of the setting due to our unclear description. We have clarified that the study will be conducted in the outpatient department of a hospital and will include people who are recruited through advertising (p 6, line 9).

b) We have added detailed descriptions of the recruitment, explanation and consent of the subject and the final registration procedure (p 6, lines 9-13).

Comment 6. For recruitment, a total of 26 participants will be used. Please give rationale for 26 participants (13 for each group). In addition, not sure how to ensure enough subjects responded to the advertisements. Please clarify.

Response 6: We have removed the description from the “recruitment” paragraph, have moved it to the “sample size” paragraph, and have added a description and references about the calculation (p 6 line 22; p 7 lines 14-20).

Comment 7. For randomization, there should be possible reasons for that "if randomization cannot be performed, the number and reason for the lack of randomization will be recorded in a screening log..."; and, what are the expected number of this non-randomisation encountered?

Response 7: We intended to say that the participants will be dropped by using the statement “randomization cannot be performed”. We apologise for this misunderstanding, and have modified the text for clarity (p 7, lines 8-10).

Comment 8. For sample size calculation you mentioned about no previous similar studies on this topic. Therefore, the sample size will be decided according to the minimum number needed to achieve feasibility and on the number of people available to be recruited from the clinical trial site. This is fully unclear to me. You should know and estimate the total patient population in the setting, the minimum number of sample expected. Otherwise, I can't understand how can you estimate the total number of participants is 26 (in the recruitment section).

Response 8: We fully agree with your opinion that the sample size should be determined through valid reasoning and be calculated explicitly. The “setting” and “sample size” paragraphs were not unclearly described, which caused the readers to misunderstand the content. We have now modified the unclear description and have added details and references to the sample size calculation. We thank the reviewers for helping us improve this part (p 7, lines 14-20).
Comment 9. some unclear issues in the sample inclusion and exclusion:

a) why they should be aged 20 or above? Any reasons behind?

b) what are the main criteria of HBDIS?

c) what are the serious psychiatric or neurologic disorders meant? How to consider its severity as "serious"?

d) why not including those with the use of medication related to HB and its if often they are not medically treated when being diagnosed? Could it be difficult to find some HB patients without medication use?

e) what is meant by "a seriously unstable medical condition"? Any example?

f) if they are recruited from hospital setting, why "residents of collective dwelling facilities" will be found?

g) it is a vague and invalid exclusion criterion: "lack of eligibility for the trial for other reason as determined by the principal investigator."

Response 9. The details of the inclusion/exclusion criteria have been added to the Discussion, according to the reviewer’s suggestion. Thank you.

a) The reasoning has been described in the Discussion (p 17, lines 3-4).

b) The diagnostic criteria according to HBDIS has been briefly added to the inclusion criteria section (p 8, lines 12-17).

c) We apologise for not disclosing this clearly in advance. Details have been provided in the exclusion criteria section (p 8, lines 22-23).

d) The rationale has been described in the Discussion (p 17, lines 4-10).

e) We apologise for not specifying this in advance. Examples of this have been provided (p 9, lines 2-3).

f) This is also a problem caused by our unclear description of “setting”. We hope it has become clear that we are not targeting the inpatient population by the modification of the “setting” paragraph. We also have added the reason for their exclusion to the Discussion (p 17, lines 10-12).

g) We have clarified the other reasons according to the reviewer’s advice (p 9, lines 8-9).

Comment 10. For the acupuncture procedure, sham control and acupoints, you need to specify the standard or guidelines used and its reference.

Response 10: The references for the selection of the acupuncture points have been described in the Discussion (p 17, lines 13-17). The location of the acupuncture points has been added to the STRICTA checklist (p 9, lines 18-19). The rationale and references of the sham control have been described in the Discussion (p 17, lines 20-24).
Comment 11. In section 8.3, you mentioned "medications that participants have been taking before the start of this study will be maintained unless the medications affect the assessment of the results." It is vague what kinds of medications referring to and would this be contradicted with the above mentioned exclusion criterion on those with the use of medication related to HB?

Response 11: We have clarified this point according to the reviewer’s comment (p 10, lines 16-18).

Comment 12. For trial feasibility, it is not clear about its aspects of assessment. How is it related to integrity of study protocol and acceptability? The integrity of protocol will be assessed with a binding index but it is not clearly described. How is the validity of this index?

Response 12: We have clearly described how to assess the feasibility in terms of integrity and acceptability separately. We thank the reviewer for pointing out this error (p 10, lines 22-24; p 11, lines 1-9).

Comment 13. The primary outcome and one secondary outcome are in the form of VAS scale. There is not any reliability and validity results described.

Response 13: We are in full agreement with the comment that reliable and valid outcome measurements represent critical points in clinical trials. Unfortunately, a definite scale optimised for HB has not yet been developed, but studies are currently underway. Therefore, we investigated the effect on the main items of the HB diagnosis SCID, which are symptoms essential for the diagnosis of HB, and used VAS, which is widely used for subjective symptom evaluations, as a measurement tool. We have described the assessment method in more detail (p11, lines 14-17). Based on the results of this study, our results can be used as a meaningful reference material in the selection of evaluation tools in the future studies.

Comment 14. For data collection, it is not clear about the experience of KMD and what was the training provided?

Response 14: We have clarified this section (p 9, line 20; p13, lines 1-3).

Comment 15. For statistical analysis, the statistical tests for or approaches to outcome analysis at multiple time-points are limited. The compliance and completion of the intervention should be defined. The effect size should specify which time point(s) are referred to?
Response 15. We appreciate the help in improving this section. We have specified the time point when the effect size will be obtained (p 13, lines 13-14) and have described why participants might be dropped, e.g., for poor compliance (p 12, lines 15-22).

Comment 16. For safety as one important objective, more detail of reporting procedure and forms used for adverse effects should be given.

Response 16. More detailed information has been added to this section (p 14, lines 19-23).

Comment 17. For discussion (and methods), there should have been clear, structured description and discussion of all aspects of feasibility and acceptability to be assessed or evaluated. The sentence "The acceptability of the treatment will also be evaluated according to the basic information about the effect and safety." On p. 10 is unclear.

Response 17. The acceptability has been more clearly described (p 10, lines 22-24; p 11, lines 1-3).

Reviewer #2: Thank you for submitting your work to Trials. The paper reports a study protocol for a pilot RCT of acupuncture for Hwa-byung (HB).

The paper is generally well written and structured, with good use of English language. The topic is interesting, albeit it rather limited in relevance to only Korean settings (given that HB is a Korean-bound cultural syndrome).

I have some comments and suggestions, which the authors can consider to improve the clarity of the manuscript.

Comment 1: It would be useful (for the acupuncture uninitiated readers) to provide a summary of the hypothetical therapeutic mechanisms of acupuncture therapy (either in the introduction/background or the discussion).

Response 1: The hypothetical therapeutic mechanisms have been described in the Discussion (p 18, lines 10-14).
Comment 2: It is clear that HB is a Korean culturally bound syndrome, but as the journal has an international readership it would be useful to briefly mention the relevance of the proposed study beyond Korea. For example, is HB ever reported in other Asian settings? Or is there anything in the protocol which would be helpful/transferrable for researcher/clinicians in other international settings?

Response 2: We fully agree with the reviewer that what it means to readers is important. The significance of this study to international readers has been noted in the Discussion (p 18, lines 15-22).

Comment 3: The mention of the various acupuncture points (i.e. GV20) in the summary may not be necessary, as this information will not mean much for many readers. Similarly, it would be useful to mention where these are located in the methods section (currently the location of non-acupuncture points are detailed, but not the real points).

Response 3: We have deleted the names of acupuncture points in the abstract. The location of real acupuncture has been added to the STRICTA checklist, and it has been referred to in the Methods section (p 1, lines 10-19; p 9, lines 18-19).

Comment 4: The background mentions that previous studies report the effectiveness of acupuncture for HB. If previous studies were effective, why conduct the proposed study? The rationale for conducting the study should be clearer/stronger (this is briefly mentioned in the discussion, but would probably be better placed in the background section).

Response 4: A more detailed and accurate description has been added, and the related content in the discussion has been moved to the background according to the reviewer (p 4, lines 8-24).

Comment 5: The final paragraph of the introduction uses the past tense, whereas future tense is used elsewhere. Please correct this for consistency.

Response 5: We have corrected the verb tense. Thank you for the help (p 4, lines 1-4).

Comment 6: Study design - blinding should be mentioned here.

Response 6: A description of the blinding has been added according to the reviewer’s suggestion (p 1, lines 10-11; p 5, line 1; p 6, line 4).
Comment 7: Setting of study: (line three) currently states: "randomly assigned into two groups" should read: "randomly assigned into ONE OF two groups"

Response 7: We have corrected this phrase. Thank you for the help (p 6, line 14).

Comment 8: Sample size:

More justification should be provided for such a small sample size. Also, the data analysis mentions using means and standard deviations - but with such a small sample size this may not be appropriate?

Response 8: We completely agree that there should be reasonable justifications for estimating the sample size and that the sample size should be calculated to maintain the significance of the study results. We appreciate the reviewer’s constructive comment. We have added a related description to the manuscript (p 7, lines 14-20).

cmment 9: Serotonin levels:

The rationale for measuring serotonin levels should be provided (i.e. how do these relate to HB?). In addition, details about the process of serotonin sample collection and analysis should be given.

Response 9: The rationale for measuring serotonin levels has been added to the Discussion (p 18, lines 10-14). The process of serotonin sample collection and analysis has been described in the Methods section (p 12, lines 5-7).

Comment 10: Exclusion criteria:

Examples of "serious psychiatric disorders" and "neurological disorders" could be provided to add to clarity. Please also mention how these will be determined (i.e. diagnosed by whom and using which diagnostic criteria?).

Response 10: We have specified examples according to the reviewer’s suggestion (p 8, lines 22-23).

Comment 11: Similarly, "lack of eligibility…. For other reasons as determined..." - it would be useful to know what might these reasons be, otherwise the PI could exclude people that are not felt to respond to treatment, hence biasing results.
Response 11: We have listed the details (p 9, lines 8-9).

Comment 12: Allowed or prohibited concomitant treatment:

Psychotropic medications are mentioned as these might affect the results, but what about medications for gastrointestinal disorders or treatment for palpitations (as these are also symptoms of HB)? What will the researchers do if participants report use of prohibited treatments during the trial/at follow-up?

Response 12: We appreciate the detailed comments and questions. We have described this in more detail to clarify the content of our study (p 10, lines 16-18).

Comment 13: Outcome measures:

The validity/psychometric properties of the Korean versions of assessments should be provided.

Response 13: We have added references as the reviewer suggested (ref 35-37).

We hope the revised manuscript will better meet the requirements of your journal. We again thank the editor and the reviewers of Trials for the constructive review of our paper.