Author's response to reviews

Title: Effect of acupuncture on patients with insomnia: A study protocol for a randomized controlled trial

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Author's response to reviews: see over
Dear Professor Wing-Fai Yeung

We highly appreciate your precious review about our manuscript entitled "Effect of Acupuncture on Patients with Insomnia: A Study Protocol for A Randomized Controlled Trial" by Kyung-Hun Han et al. And it is honor to us having review from a famous scholar like you. We read your systematic review interestingly. We totally agreed to all your comments and we appreciate once again.

We revised our manuscript according to you major and minor revisions. And we answered to all your comments and questions like below and resubmitted a revised version of the manuscript. The red colored letters are the part that we added and changed in manuscript. And the manuscript has been edited again English grammar by a professional native editor.

Sincerely yours,

Sun-Yong Chung, KyungHun HAN

Reviewer's report: I thank the Editor for giving me a chance to review the manuscript for Trials. The manuscript written by Hua et al. is a protocol of a randomized controlled trial of acupuncture treatment for insomnia. The study aims to compare acupuncture and sham acupuncture (needling at 1-cm away from true acupoint) in improving subjective insomnia symptoms. The study will add knowledge to the current evidence regarding acupuncture treatment for insomnia. However, some parts of the protocol are unclear. I hope my suggestions would further improve the study.

Major Compulsory Revisions

Introduction
1. The authors cited recent systematic reviews of acupuncture for the treatment of insomnia. However, there are 2-3 RCTs published recently but not included in the reviews. It would be helpful if the authors briefly described the recent RCTs, especially for the RCTs which compared acupuncture with sham/ placebo acupuncture.
We reviewed three recent studies (as below) and added to the manuscript:

Several other studies investigate the effect on acupuncture as a treatment for insomnia by comparing different acupuncture therapies, the effects of using and not using moxa, and comparison with placebo sleeping pills [9-11]. One of these studies show that auricular acupuncture therapy is more effective on insomnia than two other therapies, and another suggests that acupuncture therapy with moxa is more effective than without [9,10].


2. Any justification for including EEG and heart rate variability as outcomes?

Method

We added on the manuscript as below some evidence studies.

Regarding the pathophysiology of insomnia, several studies show that beta electroencephalogram (EEG) activities increase while alpha EEG activities decrease in patients with insomnia [14]. Other studies observed decreasing beta EEG activities in patients with insomnia after cognitive behavior therapy or treatment [15]. Some Event Related Potentials (ERPs) studies report of increasing N1 amplitude and decreasing N350 amplitude in insomnia patients compared to controls; these ERPs components are related to hyperarousal and inhibition or regulation of arousal [16, 17]. Additionally, a recent study shows that HF (high frequency) in heart rate variability (HRV) is more dominant than LF (low frequency) in patients with insomnia [18]. However, according to one review, there are no consistent results of HRV in studies of effect in acupuncture treatment, although HRV is a useful tool for observing how acupuncture treatment affects the autonomic nervous system related to sleep cycles [19].

3. The writing of hypothesis is strange. The authors may consider rephrasing it.

First, the authors mentioned acupuncture will be compared to a “placebo control”, but the authors later used the term “sham”. Second, the sentence “insomnia symptoms will be measured with ISI” should not be placed here.

You are totally right. It’s wrong to say ‘placebo’ because that is absolutely a acupuncture stimulation even though the spot where we use as sham is not a spot on the body suitable for acupuncture. Then we deleted all words “placebo”, and “placebo control” and used only “Sham”.

“insomnia symptoms will be measured with ISI” was not appropriate, so we deleted the sentence too.
4. Objectives, the points will look better if they begin with “to examine…”, or “to compare” etc.

We changed as your suggestion. Thanks

5. Sleep log is used for only 2-day which is obviously too short. Sleep log is usually used for at least 1 week. Some standard assessments for insomnia are not used e.g. objective actigraphy/ polysomnography. The authors may need to discuss these limitations. It would be helpful for the author to look at this paper: Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006 Sep;29(9):1155-73.

Our description was unclear. We added the following to our manuscript. Practically all patients complete a sleep log every day for 2 weeks. We just asked to complete sleep log for screening and excising before the trial. They shall also be instructed to complete a sleep log for 2 days prior to their second visit to the center for the baseline evaluation and the first treatment, in order to see whether they had insomnia recently and could properly keep their sleep logs. On the day of the second visit, an expert will check whether patients have completed their sleep logs correctly and re-conduct them on their sleep log writing methods if necessary. The patients will complete their sleep logs during 2 weeks from the second visit. We totally agree with you to use both tools that highly recommended assessing for insomnia. But we have certain limitations due to constraints of time, expense and space in the hospital considering the present trial is still in level of pilot study. We discussed about this limitation in the end of discussion citing some reference too. Furthermore, there are limitations associated with the lack of polysomnographic data due to constraints of time, expense, and space in the hospital, as the present trial is still a pilot study. The actigraphy and polysomnography are objective tools for assessing insomnia and highly recommended as well, but many other studies have used them as secondary outcomes while still others did not use actigraphy and/or polysomnography as outcomes at all [31-33, 10, 11]. However, polysomnography will be assessed in our planned future expanded trials.

Recent trials only used PSQI as primary outcome not assessing ATG and PSG

A trial used only actigraph as secondary outcome
6. The description of intervention is somehow unclear and is not detail enough to allow other researchers to replicate the treatment protocol. It is stated that “acupuncture treatment (or sham acupuncture treatment if in the control group) followed by intradermal acupuncture (IDA)” does it mean that each subject will receive 2 types of acupuncture treatments? In addition, “acupuncture injection” is used. Does it mean acupuncture needle insertion?

Yes our description seems to be unclear as you commented. We described again concretely like below.

We used both types of acupuncture treatments (needle and IDA) to both groups. The clinician administers needle acupuncture treatment first and then clinician puts IDA too on same acupoints after needle acupuncture treatment. The sham acupuncture treatment group is treated same way as well. Then both groups are instructed to stimulate IDA before sleeping.

In the experimental group, patients will receive needle acupuncture treatment on 5 specified acupoints (PC6, SP6, HT7, KI6, and BL62) for 20 minutes. After 20 minutes, the needles will be removed and intradermal acupuncture (IDA) placed at the same points. The smaller IDA shall be kept attached on the skin for 48–72 hours and all patients will be instructed to stimulate themselves before sleep.

In the control group, all interventions shall be the same as those of the experimental group except the location of the acupoints, substituting them with 5 sham acupoints. The sham acupoints shall be about 1.0 cm from the real acupoints in the experimental group and are spots that do not belong to standard acupoints on the body and are not suitable for actual acupuncture based on anatomical and other conditions. IDA will be placed at 5 sham acupoints in the control group as well with the same instructions as that of the experimental group.

We changed from “acupuncture injection” to “insertion”.

7. It seems that sleep log has not been mentioned in the secondary outcome.

Sorry we missed this, we added as secondary outcome.

The sleep log is a diary to be kept by the patients themselves of their sleeping and waking times as well as additional sleep-related information. It is a useful tool in diagnosing insomnia and monitoring whether treatment is working. Sleep logs include 16 points of information such as sleep-onset latency, waking after sleep onset, time in bed, total sleep time,
8. Randomization is not described properly. I am puzzled how and why “randomization will be done seven to nine times among four or six patients who passed the screening test.” Instead, the authors should describe how the random sequence would be generated and the allocation concealment would be ensured.

Randomization will be done by Microsoft Excel. An expert generates block size (4 or 6) sequence randomly. We decide to use two different block sizes (4 or 6) for preventing clinician’s prediction. We used this way of randomization for the case that we recruit only 30 in the end, then we will have other problem of balancing between groups because all left 8 numbers unallocated can be all “experimental” or “control”. We want to have the sample size on a ratio 1:1 between experimental and control group.

We revised the description of randomization more concretely like below

An expert will randomly generate a block size (4 or 6) sequence using Microsoft Excel. After that, with the allocation ratio of the experimental and control group within each block kept 1:1, the expert will randomly generate the numbers 0 (control group) or 1 (experimental group) through Microsoft Excel. This expert will not contact any of the patients during the experiment. Once the expert generates the random numbers, the expert will seal each number in an opaque envelope. The expert lets the clinician know each random number as the clinician calls a patient by telephone. Two other experts (neuropsychologists)—who measure the self-reported tests, the psychological (cognitive) tests, the EEG and HRV—will be blinded. Only the clinician who treats acupuncture therapy knows what treatment the patient has been administered, but he is prohibited from accessing any measurements for outcomes. Double-blinding is almost impossible due to the specifications of the acupuncture treatment. Thus, in this trial, only the neuropsychologist (assessor), the statistical expert, and patients will be blinded.

9. Statistical method, I highly suggest the authors consulting a statistician in writing the part on statistical analysis. It is incorrect to use ANOVA comparison between 2 groups. Moreover, the primary endpoint has not been defined.

Yes we consulted a statistician. We seem to have neglected to describe several points and are incorrect, too. ISI and PSQI are ours primary outcomes and we compare difference pre-, post-level of treatment between 2 groups. And we used repeated-measures ANOVA due to it makes us to observe main effect, correlation, session and group effect at once. We had such recommendation from a statistician.

Independent t-tests between the two groups and a repeated-measures analysis of variance (ANOVA) will be used to determine and compare the effect of acupuncture. The factors were...
treatment (three levels: pre-, post-acupuncture and 1-week follow-up) and groups (two levels: treatment and sham) and their interaction. The significance level was set at P<0.05 and post-hoc analyses were performed where appropriate.

10. Monitoring, please specify the person/organization who will be responsible for monitoring.

Our trial will be monitored by a professional clinical research associate. We added below context on the manuscript.

A qualified clinical trial expert will monitor this study. This trial in particular will be monitored by Gajin Han, OMD, PhD, a professor at the College of Korean Medicine, Kyung Hee University. Han is a professional clinical research associate, having completed a formal training program organized by the Korea National Enterprise for Clinical Trials. Monitoring will commence after the first participant completes the entire period of this study.

Minor Essential Revisions
1 Assessment, trial was wrongly spelled as trail.

We checked out all again. Thanks

2. DSM, fifth ed should be written as DSM-5, not DSM-IV. Moreover, the reference [10] wrongly cited DSM-IV.

This is our big mistake. We changed to DSM-IV. In Korea DSM-IV is used more commonly yet because many scholars are thinking DSM-5 is not well established yet for applying in clinical use.