Author's response to reviews

Title: Acupuncture for Sequelae of Bell's Palsy: A Randomized Controlled Trial Protocol

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Author's response to reviews: see over
Dear reviewers

Re: MS: 5204063894524380 - Acupuncture for Sequelae of Bell's Palsy: A Randomized Controlled Trial Protocol

We appreciate the more comments for improving our protocol “Acupuncture for Sequelae of Bell's Palsy: A Randomized Controlled Trial Protocol”

We revised several important points according to the reviewer’s recommendation.

According to the comments my colleagues and I made the further correction.

The responses are in following pages.

Yours faithfully,

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Reviewer’s report 1

In general, this protocol needs much more detail before it should be published. The pages were not numbered. This reviewer numbered them from 1 to 18.

COMMENT 1. P(age) 1, Author emails. There are 2 people with short forms [CJY] and [LSH]. They need to be clarified by making each unique.
→Revised) We have now clarified by making each unique as follows.

“KHJ: jamykwon@gmail.com
KJI: hann8400@hanmail.net
KSK: kskacu@hanmail.net
Choi, Jun-Yong: orientdoct@gmail.com
KYJ: hotyjlover@hanmail.net
Lee, Seung-Hoon: aimforyou@hanmail.net
Lee, Sanghoon: docere@hanmail.net
NDW: hanisanam@hanmail.net
Chung, Jie-Yoon: jyspica@gmail.com
KYS: ackys@hanmail.com
LJD: ljdacu@khmc.or.kr
CDY: choi4532@unitel.co.kr
”

COMMENT 2. P 2, p(paragraph) 2, l(ine) 2. Drop [ed] from [waitlisted] to read [waitlist]. Also, P 5, p 4, l 5; P 7, p 1, l 2; P 10, p 4, l 2.
→Revised) We have now dropped [ed] from [waitlisted] at P2, p2, l2; P5, p 4, l 5; P 7, p 1, l 2; P 10, p 4, l 2.

→Revised) We have now inserted [8 week] after [this]

“….. Participants in the waitlist group will not receive any acupuncture treatments during this 8 week period,…”

COMMENT 4. P 2, last line. Insert the date of registration as well as the date the first patient has been randomized.
→Revised) We have inserted the date of registration as well as the date the first patient has been randomized.

“Current Controlled-Trials ISRCTN43104115; registration date: 06 July 2010; the date of the first patient randomization: 04 August 2010

COMMENT 5. P 3, p 2, l 1. Since [incidence] is time related, there needs to be time listed or the term needs to be changed to [prevalence]. Also, P 9, p 2, l 2.
→Revised) We have inserted time at P 3, p 2, l 1 and changed the word “incidence” into “prevalence” at P 3, p 2, l 1.; P 10, p 2, l 2.

“The incidence of Bell’s palsy is approximately 30/100,000 people per year.”

“All adverse events reported during the study will be included in the clinical report, and the prevalence of adverse events will then be calculated.”

We have now replaced [recent] by [2009].

“According to a 2009 study, the effect of steroids on acute Bell’s…”


We have now replaced [recent] by [2007].

“In a 2007 systematic review, the effect…”

COMMENT 8. P 4, p 1, last line. Without a credible literature search, this claim is not justified. This may be the authors’ opinions, however, they have not justified it here.

We have now deleted the sentence “To date, this has not been investigated.”

COMMENT 9. P 5, p 1, l 1. Delete [protocol].

We have now deleted [protocol].

COMMENT 10. P 5, outcome measures. Each of the outcome measures should be described, that they are validated in Korean unless the patients all speak English well, and how they are interpreted with relevant measurement properties. The references appear to be all in English.

We have now supplemented some description in the secondary outcome section as follows at the end of P5 in the revised manuscript.

“Unfortunately, there has been no validation study of Korean version of each of the primary and secondary outcomes. In our study, two professional translators made each outcome measurement questionnaire in Korean, which has been used in our clinical facial palsy center for evaluating sequelae of facial palsy. So we decided that these questionnaires are readable and suitable to our study.”


We have now deleted [and at].

COMMENT 12. P 6, p 3, l 3. Provide references to these conditions such as [Ramsay-Hunt Syndrome].

We have now supplemented reference to [Ramsay-Hunt Syndrome].


COMMENT 13. P 7, p 1, l 9. What is the city in Korea for the needles?

We have added the city name.

“(Dongbang Acupuncture Inc, Boryeong, Korea)”
COMMENT 14. P 8, p 4. When will the control group be asked?

Revised) We have deleted the sentence “Participants in the control group will be asked which group they would prefer if they had the choice,” and are not asking patients in control group because this question is inappropriate.


Revised) We have now replaced the word [separated] with [independent] at P 8, p 5.; P 11, p 1, l 4.

“Because the knowledge of the group assignment could modify outcome assessment, we will ensure that the independent assessor is blinded.”

“To eliminate observation bias, the independent assessor will be blinded prior to the analysis of the data.

COMMENT 16. P 8, p 6, l 2. This is not the definition of intention to treat. All patients randomized need to be analysed; not subject to a measurable outcome.

Revised) We have now deleted the phrase “with at least one measurable outcome report following acupuncture treatment” and revised as follows.

“Analysis will be performed for an intention-to-treat population consisting of all randomized participants regardless of their actual treatment received.”

COMMENT 17. P 8, p 6, l 3. Using last observation carried forward is a poor imputation method. One should use a multiple imputation technique and justify the choice of the method, by providing a reference to one of the standard texts for imputation.

Revised) We have now changed imputation method as you recommended providing a reference.

“Any missing data will be replaced with ones using a multiple imputation technique”


COMMENT 18. P 9, sample size. The sample size is not adequately explained. First of all why choose a 2:1 allocation ratio? The 8 things used to justify a sample size should be argued as to why they were chosen. The Minimum Clinically Important Difference between the groups for the primary outcome measure needs to be included in the sample size, as well as for the other measures. The full size of such a trial and feasibility at the location of the study needs to be added as well.

Revised) Since we cannot find any MCID-related research regarding our primary outcome (FDI-social), we calculated sample size from a similar designed study. We have now re-written our manuscript on sample size as follows and will recruit 8 more participants after re-submit and acceptance of our revised protocol.

“Sample size was calculated from the result of a mime therapy trial conducted on patients with sequelae of Bell’s palsy of which design was randomized paralleled waitlist controlled trial [17]. We assumed that the effect size of our invasive acupuncture therapy will be at least
equal to this non-invasive mime therapy. Also we decided the allocation ratio to be 2:1 with the consideration that lesser patients should be allocated to the waitlist group.

In the mime trial, the mean difference of follow-up FDI-social score between groups was 14.5 and pooled standard deviation was 14.5 within each group [17]. The alpha value and power were 0.05 and 0.8 respectively. From these values we calculated sample size for independent two sample t-test (one-tailed) that is 25 for acupuncture group and 13 for waitlist group with consideration of 20% drop-out. And this assumed mean difference of FDI-social score between groups is considered to be sufficiently important in an expert discussion consisting of clinicians who work in Bell’s palsy clinics for more than 10 years.”

COMMENT 19. P 10, p 3, l 1. The sample size of 30 has not been justified; nor has its feasibility been shown.

→ Revised) We have now changed our sample size calculation section as follows.

“Sample size was calculated from the result of a mime therapy trial conducted on patients with sequelae of Bell’s palsy of which design was randomized paralleled waitlist controlled trial [17]. We assumed that the effect size of our invasive acupuncture therapy will be at least equal to this non-invasive mime therapy. Also we decided the allocation ratio to be 2:1 with the consideration that lesser patients should be allocated to the waitlist group.

In the mime trial, the mean difference of follow-up FDI-social score between groups was 14.5 and pooled standard deviation was 14.5 within each group [17]. The alpha value and power were 0.05 and 0.8 respectively. From these values we calculated sample size for independent two sample t-test (one-tailed) that is 25 for acupuncture group and 13 for waitlist group with consideration of 20% drop-out. And this assumed mean difference of FDI-social score between groups is considered to be sufficiently important in an expert discussion consisting of clinicians who work in Bell’s palsy clinics for more than 10 years.”

COMMENT 20. P 10, p 4, l 2. It does not make sense to publish the block size choice, because other investigators making inclusion/exclusion patient choices will be able to anticipate the subsequent allocations. This should be concealed from them until time of paper publication, not in the published protocol.

→ Revised) We have now changed our manuscript as follows

“A balanced block randomization will be used to assign 25 participants to the acupuncture group and 13 to the waitlist group; the exact block size will be concealed from any personnel who will be in direct contact with patients.”

COMMENT 21. P 11, p 1. Subjects need to be told there is a possibility they will be allocated to the control and how long they will be in the study.

→ Revised) We have now changed our manuscript as follows

“All subjects will be informed that there is a possibility they will be allocated to the waitlist control group and in that case, they should wait 8 weeks before receiving acupuncture treatments during 8 weeks.”
COMMENT 22. While the references were not checked for accuracy, the following errors were noted.

- Revised) We have now revised references as you pointed out.

COMMENT 23. P 13, R 3. There is no volume number.

- Revised) We have now added the volume number of R3.


COMMENT 24. P 13, R 9. Does not have a publication date.

- Revised) We have now revised R 9 as follows.


COMMENT 25. P 18, the [N] should be lower case as [n], and the diamond should be a circle for randomization.

- Revised) We have now changed [N] into [n] and have changed the diamond into circle for randomization.
Reviewer’s report 2

COMMENT 1. Background: Is this an efficacy or effectiveness study? Under Background information, the following statement suggests that this is an efficacy study, “our aim is to evaluate the safety and efficacy of acupuncture on the sequelae of Bell’s palsy…” However, under Objective, it suggests that this is an effectiveness study, which is debatable given the small size of the study (The primary objective of this study protocol is to investigate the effectiveness of acupuncture use in patients with sequelae of Bell’s palsy.)

→ Revised) This study is an efficacy study and we have now changed Objective as follows.
“The primary objective of this study is to investigate the efficacy and safety of acupuncture in patients with sequelae of Bell’s palsy.”

COMMENT 2. Primary Outcome
The reasons for choosing the Facial Disability Index need to be apparent. Is this tool reliable and valid? The information are important for the readers to know.

→ Revised) We have now changed our description for primary outcome as follows
“The change in the Facial Disability Index (FDI) social [14] score after completing eight weeks of acupuncture treatment will be compared to the score prior to treatment. This scoring system consists of two domains; physical score and social score, and has been investigated for the reliability and validity [14].”

COMMENT 3. Secondary Outcome
Again, what are the reasons for using the “House-Brackmann Grade, lip mobility, and stiffness scales”? Is there information on reliability and validity?.

→ Revised) We have now changed our description for secondary outcome as follows
“Secondary outcome measures will include FDI-social score from baseline to week five, FDI-physical score, House-Brackmann (H-B) Grade [15], lip mobility (lip-length and snout indices) [16], and stiffness scales [17]. The H-B grade has been tested for its reliability [18] and lip-length and snout indices showed a high correlation with H-B Grade [19]. Stiffness scale is a simple five-point scale for facial stiffness (1 = no stiffness, 5 = very stiff)”

COMMENT 3. Exclusion criteria
There are many exclusion criteria listed. What are the reasons for the exclusion criteria?

→ Revised) The first paragraph of Exclusion criteria section describes general serious conditions that can apparently affect patients’ participation to the trials. From the second paragraph we have now supplemented reasons for exclusion as follows

“Eligible participants will be excluded if they have complicated pathophysioligic conditions of secondary facial palsy from infection, multiple neuritis, tumors invading the temporal bone, brain contusion or stroke. Patients with Ramsay-Hunt Syndrome [21] will also be excluded from the study, as well as those with bilateral or recurrent facial palsy. To avoid confounding effects that can influence patients’ outcome measures, the oral administration of steroids or antiviral drugs (acyclovir, valaciclovir, famciclovir, or ganciclovir), a surgical history for
facial palsy, such as facial nerve decompression, reconstruction of the facial nerve or muscle, and history of acupuncture, moxibustion, vesiculation and massage therapy within three months will also result in exclusion from the study. With regard to safety and compliance issues, patients with other neurological illnesses, neuropsychiatric diseases, present or planned pregnancy, current lactation, or scars on the treatment area will also be excluded.”

COMMENT 4. Acupuncture Intervention
How did the researchers come up with this list of points? What are the rationales for their selections?

⇒ Revised) We have now added the rationales for acupuncture point selection as follows.
“These selected acupuncture points were based on acupuncture specialist forums and the textbook of acupuncture in Korea [23].”

COMMENT 5. Statistical Analysis
A description of the variable is required. Is it a discrete or continuous variable?
⇒ Revised) We have now added variable characteristics of outcome measures as follows.
“Of the primary and secondary outcome measurements, variables of FDI, H-B grade and stiffness scale are discrete ordinal variables whereas lip mobility is recorded as continuous variables.”

The statistical test planned should be specified ahead of time. Are they planning to use the two-sample t-test or the rank sum test, which one?
⇒ Revised) We have now changed analysis section as follows.
“For primary and secondary outcome measurements, the mean differences from the baseline values to the end of treatment will be compared between the two groups using the two-sample t-test if data distribute normally. In case of non-normally distributed data, Wilcoxon rank-sum test will be performed. If baseline values of outcome measurements are significantly different between groups, analysis of co-variance (ANCOVA) will be performed using any imbalanced variables as covariates and assigned group as fixed factor.”

Also, the alpha value is set at 0.05. What is the reason for not making the correction for multiple analyses (primary and secondary outcomes)? ANOVA or regression analysis may be more appropriate.
⇒ Revised) As predetermined sample size calculation was based on t-test, we decided to analyze our result using independent t-test.

Intention-to-treat may have different meaning to different researchers. What do they mean by intention-to-treat?
⇒ Revised) We have now revised our manuscript as follows.
“Analysis will be performed for an intention-to-treat population consisting of all randomized participants regardless of their actual treatment received. Any missing data will be replaced with ones by a multiple imputation technique [25].”

There was no mention of confounding factors. How do the investigators control for the effects of over-the-counter medications. Are they going to measure that or simply not allow their patients to take them?
Revised) We have now added a paragraph including OTC medications at the end of Exclusion criteria section as follows.

“Over-the-counter (OTC) drugs for common colds, dyspepsia, headaches, etc. will be allowed. However OTC drugs of unknown components or indicated for Bell’s palsy related symptoms will not be allowed. All patients will be instructed to disclose all medication use prior to enrollment. Records on the drugs taken by each patient will be obtained at every visit, and patients will be requested to inform us of any change to their medication or supplement regimen. Additional acupuncture treatments, herbal medicines, or medical interventions elsewhere will not be allowed throughout the study.”

They mentioned that they would measure expectations. How do they determine whether expectations have an effect or not?

Revised) We have now revised “outcome measures” section as follows

“The expectations of the participants will be recorded using the credibility and expectancy questionnaire [24] to determine whether expectations affected outcomes.”

COMMENT 6. Sample Size
Since no sample size calculation was done, how do they know that 30 participants “will be sufficient”? What is the rationale for the 2:1 design? Please explain.

Revised) We have now changed our sample size section as follows

“Sample size was calculated from the result of a mime therapy trial conducted on patients with sequelae of Bell’s palsy of which design was randomized paralleled waitlist controlled trial [17]. We assumed that the effect size of our invasive acupuncture therapy will be at least equal to this non-invasive mime therapy. Also we decided the allocation ratio to be 2:1 with the consideration that lesser patients should be allocated to the waitlist group.

In the mime trial, the mean difference of follow-up FDI-social score between groups was 14.5 and pooled standard deviation was 14.5 within each group [17]. The alpha value and power were 0.05 and 0.8 respectively. From these values we calculated sample size for independent two sample t-test (one-tailed) that is 25 for acupuncture group and 13 for waitlist group with consideration of 20% drop-out. And this assumed mean difference of FDI-social score between groups is considered to be sufficiently important in an expert discussion consisting of clinicians who work in Bell’s palsy clinics for more than 10 years.”

COMMENT 7. Randomization and allocation
Allocation concealment is so important. Under this section, a very detailed description of the process of allocation concealment will strengthen the study design.

Revised) We have now revised the “Randomization and allocation” section as follows

“…………A sealed envelope containing allocation sequence number for each patient will be opened right after each patient meets eligibility criteria and informed consent is made. If any error or disclosure with regard to randomization occurs, a new randomization sequence will be generated starting from the problematic serial number and applied to the patients from then on.”
Ultimately, 38 participants will be enrolled in the study.

A balanced block randomization will be used to assign 25 participants to the acupuncture group and 13 to the waitlist group; the exact block size will be concealed from any personnel who will be in direct contact with patients. Following the baseline assessment, eligible participants will be assigned to one of two groups: a group receiving acupuncture or a control waitlist group. All subjects will be informed that there is a possibility they will be allocated to the waitlist control group and in that case, they should wait 8 weeks before receiving acupuncture treatments during 8 weeks. To eliminate observation bias, the separate assessor will be blinded prior to the analysis of the data.