Author's response to reviews

Title: Interaction and Efficacy of Keigai-rengyo-to extract and acupuncture in male patients with acne vulgaris: A study protocol for a randomized controlled pilot trial

Authors:

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Author's response to reviews: see over
Dear Editors-in-Chief,

Enclosed please find a revised manuscript entitled “Interaction and Efficacy of Keigai-rengyo-to extract and acupuncture in male patients with acne vulgaris: A study protocol for a randomized controlled pilot trial” (MS: 1657729038508789) by Kyu Seok Kim and Yoon-Bum Kim along with 1 table and 1 figure, which we wish to resubmit to the “Trials” for publication.

In accordance with reviewer's comments and recommendations, we revised our paper (we highlighted all changes with colored text in the revised manuscript,) and in this cover letter, we would describe in detail how each of the reviewer concerns were addressed in this manuscript as follows.

Reviewer 1:

Major comments

1. The introduction and objectives are written as for a fully powered trial: “Considering these methodological flaws, we will conduct a trial to assess the interaction effect and efficacy of Keigai-rengyo-to extract (KRTE) and acupuncture”. The entire statistics section is then written in terms of tests to determine differences between groups. But then right at the end, the authors reveal that it is a feasibility study with only 11 patients per group. If the trial truly is only a feasibility study, then i) this has to be made more explicit in the background and objectives; ii) the statistics section has to be rewritten changing from efficacy objectives to feasibility objectives. For example, in place of tests to address “did acupuncture reduce acne?”, the statistics section should look at things such as accrual rate, proportion of drop-outs, blinding, compliance with questionnaire completion and so on.

✓ → This study is a pilot study for the interaction effect and efficacy of KRTE and acupuncture, and for the feasibility of a large clinical trial.

✓ → So we added and revised the following contents to ‘Background in Abstract’ part.

➢ “…Therefore, considering these methodological flaws, this study was designed to assess the interaction and efficacy of an available herbal medicine, Keigai-rengyo-to extract (KRTE), and acupuncture for treatment of acne using the 2x2 factorial design and the feasibility of a large clinical trial”

✓ → We added and revised the following contents to ‘Background’ part.

➢ “…Considering these methodological flaws, we will conduct a trial to assess the interaction effect and efficacy of Keigai-rengyo-to extract (KRTE) and acupuncture using the 2x2 factorial design and the feasibility of a large clinical trial.”

✓ → We added and revised the following contents to ‘Objective in Method / Design’ part.

➢ “The aim of this study is to investigate the efficacy and interaction of KRTE in male patients with acne vulgaris and evaluate the feasibility of a large clinical trial.”

✓ → We have already defined ‘proportion of drop-out and compliance with KTRE’ in ‘Compliance’ part. So we added and revised the following contents to ‘Baseline data and Outcome data in Statistical methods’ part.
2. The randomization section is vague. The authors need to be absolutely explicit as to methods for preventing researchers guessing allocation before a patient is unambiguously registered on study or changing allocation after registration. A password protected database, or fax registration to a central statistical office would be examples.

This study is an assessor single blinding trial. So we added and revised the following contents to ‘Randomization and blinding’ part.

2×2 factorial design. Randomization scheme is a following figure. If there is an interaction between KRTE and acupuncture, only the interaction will be shown. If not, the main effect of KRTE and acupuncture will be reanalyzed and presented. We discussed the statistical methods of this trial with a statistician. He said that when controlling for baseline and other covariates, a two-way ANCOVA (two independent variables=acupuncture and KRTE; dependent variables=primary and secondary outcomes) and a repeated measured ANCOVA (comparing between baseline and the end of the trial) will be enough to evaluate the outcomes. If you think that statistical methods are not enough to assess the outcomes, please inform us.

<table>
<thead>
<tr>
<th>Acupuncture</th>
<th>Keigai-rengyo-to extract (KRTE)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>KA</td>
<td>AO</td>
<td>N=22</td>
</tr>
<tr>
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<tr>
<td>N=22</td>
<td>N=22</td>
<td>N=44</td>
<td></td>
</tr>
</tbody>
</table>

3. This is a complex four-arm trial and the statistical methods must be presented more clearly. It is not enough to say that an ANCOVA will be conducted controlling for baseline and other covariates. The predictor variables have to be made absolutely explicit. My guess is that the model is follow-up score=b1. Baseline score + b2. Acupuncture + b3. Herb + b4. Acupuncture + herb.

This study will analyze using 2x2 factorial design. Randomization scheme is a following figure. If there is an interaction between KRTE and acupuncture, only the interaction will be shown. If not, the main effect of KRTE and acupuncture will be reanalyzed and presented. We discussed the statistical methods of this trial with a statistician. He said that when controlling for baseline and other covariates, a two-way ANCOVA (two independent variables=acupuncture and KRTE; dependent variables=primary and secondary outcomes) and a repeated measured ANCOVA (comparing between baseline and the end of the trial) will be enough to evaluate the outcomes. If you think that statistical methods are not enough to assess the outcomes, please inform us.

4. Percentage change is highly inefficient. In place, raw baseline and follow-up scores should be entered
in the statistical model.

✓ → I agree with your concerns. But, the mean percentage change of inflammatory and non-inflammatory lesions from baseline to end of trial is one of the most common outcomes in the clinical study of acne. You can find lots of clinical trial of acne using the mean percentage change of inflammatory and non-inflammatory lesions registered in website ‘www.clinicaltrials.gov’. And we will also analyze raw baseline and follow-up scores. We have already explained these contents in ‘Baseline data and Outcome data’ part as follows: “…A repeated measured ANCOVA test will be performed for evaluation of any significant difference in count of inflammatory and non-inflammatory lesions, Skindex-29 score, and VAS score between baseline and the end of the trial.”.

Minor comments

1. Some of the inclusion criteria are vague. For example, it states that patients will be excluded for having bloods outside the normal range but then does not state specifically what bloods will be assessed, merely giving examples. Inclusion and exclusion criteria have to be 100% explicit, so that two different researchers applying the criteria to 100 patients, would select exactly the same patients to be eligible.

✓ → We added and revised the following contents to ‘exclusion criteria in Participants and Eligibility’ part to explain the normal range of blood test.

➢ ‘The author will exclude patients outside the normal range on blood tests, including aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (Bun), creatinine, hemoglobin, and platelet (normal range: 13 ≤ hemoglobin ≤ 17 g/dl, 150000 ≤ platelet ≤ 350000/mm³, aspartate transaminase (AST) < 40 IU/L, alanine transaminase (ALT) < 40 IU/L, 8 ≤ blood urea nitrogen (BUN) 23 mg/dl and 0.6 ≤ Creatinine ≤ 1.2 mg/dl),”

2. Mean percentage change of inflammatory lesion counts from baseline to the end of the trial is given as both a primary and secondary outcome measure.

✓ → We revised from inflammatory lesion counts to non-inflammatory lesion counts in ‘Secondary outcomes’ part as follows.

➢ “Secondary outcomes will be shown by the mean percentage change of non-inflammatory lesion counts from baseline to the end of the trial,…”

3. Statistics section: “A two-way analysis of variance (ANOVA) test will be performed for comparison of baseline values”. Testing of baseline values is irrational and the null hypothesis is known to be true.

✓ → We deleted this sentence in ‘Baseline data and Outcome data’ part.

In addition to reviewers’ comments and recommendations, we revised partly to make our point clear.
KSK participated in the study design, including statistical design, and drafted the manuscript. YBK was the general supervisor for this research and participated in both the study design and critical revision of the manuscript. All authors read and approved the final manuscript. This paper has not been published elsewhere in any form of any language.

Correspondence and phone calls about the paper should be directed to us at the following address and phone number:

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Thank you for your kind considerations in advance and I am looking forward to hearing a positive reply from you soon.

Sincerely yours,

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