Author’s response to reviews

Title: Yukmijihwang-tang for the treatment of xerostomia in the elderly: study protocol for a randomized, double-blind, placebo-controlled, 2-center trial

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Author's response to reviews: see over
Dear Editor-in-chief in ‘Trials’:

We appreciate your considerate commentaries on our manuscript (The original manuscript ID number is 969761529762334). After careful reading commentaries from the reviewers, we have responded and revised our manuscript according to your reviewers’ suggestions. The contents we modified are detailed as follows:

Corrected parts (added or modified) in the revised manuscript were presented in red color.

- Commentaries of Referee 1 (Dr. Cindy Cooper)

The protocol is clear and provided in sufficient detail to allow reproduction. However, the safety monitoring is either insufficient or not well documented. Currently the safety monitoring is limited to blood tests at 8 weeks. There appears to be no adverse event or serious adverse event (SAE) monitoring or reporting until the end of the intervention period. Within the section labelled 'Safety' there is the following statement: "Throughout the present study, we will also check whether the 8-week administration of YMJ in xerostomia patients is safe by using these tests or CRF documentations." However, there is no detail of how this will be achieved. Authors should have procedures to identify SAEs and these need to be documented in the protocol.

1) We added following sentences mentioned about safety on page 16 (2nd paragraph in the Safety section) as follows:

‘In addition, at each visit, investigators will ask the subjects whether there are any adverse events (AEs) during the study period. If there is any AE, the investigator will provide the appropriate
treatment to the subject immediately and record AEs in the dedicated document of the CRF including its severity and causality with the experimental agent. These AEs occurred during the entire study will be reviewed and monitored by independent CRA.

In the case of serious adverse events (SAEs), the investigator will offer the corresponding treatment to the subject immediately and report to IRB within 24 h from the time of recognition. If necessary, blind will be broken by adequate procedure and the documented procedure will be kept in the investigator study file.’

2) As there are contents about adverse event (AE) and serious adverse event (SAE) in added paragraph, so we added two abbreviations (AE and SAE) on page 20 (in the List of Abbreviations section) as follows:

< Before correction >

List of Abbreviations
QoL: quality of life; YMJ: Yukmijihwang-tang; TKM: traditional Korean medicine; VAS: visual analogue scale; CRC: clinical research coordinator; CRO: contract research organization; DMSQ: dry mouth symptom questionnaire; USFR: unstimulated salivary flow rate; SSFR: stimulated salivary flow rate; Ig A: immunoglobulin A; CRF: case report form; CRA: clinical research associate; IRB: institutional review board.

< After correction >

List of Abbreviations
QoL: quality of life; YMJ: Yukmijihwang-tang; TKM: traditional Korean medicine; VAS: visual analogue scale; CRC: clinical research coordinator; CRO: contract research organization; DMSQ: dry mouth symptom questionnaire; USFR: unstimulated salivary flow rate; SSFR: stimulated salivary flow rate; Ig A: immunoglobulin A; CRF: case report form; CRA: clinical research associate; AE: adverse event; SAE: serious adverse event; IRB: institutional review board.
- Commentaries of Referee 2 (Dr. Andrew Vickers)

1. **Testing for baseline differences between groups in a randomized trial is irrationally testing a null hypothesis that is known to be true.**

   → We understood and agreed your reviewer’s opinion. Thus, as your reviewer pointed out, we removed the following sentence mentioned about testing for baseline differences between groups on page 17 in the **Statistical analysis** section:

   ‘Firstly, the baseline characteristics of the placebo and YMJ groups, such as age, sex, smoking, xerostomia medications, and the onset, type, and duration of xerostomia, will be compared by either the $\chi^2$-test or the independent $t$-test.’

2. **The difference between groups in outcome variables should be compared by ANCOVA (see Vickers and Altman BMJ 2001)**

   → According to your reviewer’s advice, we corrected statistical method that compares the difference between groups in outcome variables from independent $t$-test to ANCOVA on page 17 in the **Statistical analysis** section as follows:

   **< Before correction >**

   ‘Secondly, we will use the independent $t$-test to compare the changes in VAS scores (primary outcome) to evaluate the effects of YMJ and the placebo from the beginning (0 week) to the end (8 weeks) of the study period. Thirdly, the secondary outcomes (DMSQ scores, USFR, SSFR, volume of residual saliva, salivary Ig A, chromogranin A, cortisol, and “Yin-deficiency” score) will be analyzed in the same manner as the primary outcome.’

   **< After correction >**

   ‘Firstly, we will use the ANCOVA to compare the changes in VAS scores (primary outcome) to evaluate the effects of YMJ and the placebo from the beginning (0 week) to the end (8 weeks) of the study period. Secondly, the secondary outcomes (DMSQ scores, USFR, SSFR, volume of residual saliva, salivary Ig A, chromogranin A, cortisol, and “Yin-deficiency” score) will be analyzed in the
same manner as the primary outcome.’

3. Specify a single test for comparisons of adverse events, not Fisher’s OR Chi Squared

→ We are sorry to say that the sentence about comparison of adverse event was done wrong with drawing up. The original meaning we wanted to convey was that we will check and describe the frequency and characteristic of adverse event in YMJ and placebo group. So we revised the sentence on page 17 and 18 in the Statistical analysis section as follows:

< Before correction >
‘In addition, we will calculate adverse events and compare them using the $\chi^2$-test or Fisher’s exact test.’

< After correction >
‘In addition, we will check the AEs in YMJ and placebo group each and describe them using the descriptive statistics.’

4. The reporting of Pearson correlations for outcome variables is strange, what is being tested or estimated here?

→ We revised following sentences in the Statistical analysis section on page 17 as follows:

< Before correction >
‘Finally, correlations between changes in parameter findings will be analyzed by Pearson’s correlation coefficients or by Spearman’s Rho.’

< After correction >
‘Finally, correlation between subjective (VAS and DMSQ) and objective xerostomia-related variables (USFR, SSFR, and residual saliva) will be analyzed by Pearson’s correlation coefficients. Also, we will find out how xerostomia-related variables correlate with “Yin-deficiency” score or stress-related variables (salivary Ig A, chromogranin A, and cortisol) respectively using Pearson’s
correlation coefficients.’

5. Quality of written English: Needs some language corrections before being published

→ We ask for your understanding for unexpressive sentences. By the way, an authentic English editing company, ‘Editage by Cactus Communications (Inc.)’ corrected and proofread our manuscript in terms of grammar or style, so we attach the certificate (below captured picture file) of English editing by ‘Eitage by Cactus Communications (Inc.)’ for your information.
<Additional Items>

1. We revised the affiliation in the Title page and Author details (on page 21) section as follows:

< Before correction >

1Department of Clinical Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
2Department of Statistics, Sookmyung Women's University, Seoul, Republic of Korea

< After correction >

1Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea
2Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
3Department of Statistics, Sookmyung Women's University, Seoul, Republic of Korea
We hope your positive reply.

Thank you very much again.

Sincerely,

Jinsung Kim, K.M.D., Ph.D.
Professor