Author's response to reviews

Title: Banha-sasim-tang as an herbal formula for the treatment of functional dyspepsia: A randomized, double-blind, placebo-controlled, two-center trial

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

We thank the reviewer for kindly providing us with comments on our paper. According to the reviewer’s suggestions, we made substantial changes to the manuscript and provided explanations where required. Below, we have listed our revisions and addressed your concerns in detail.
(Red characters in cover letter and main manuscript indicate modified or newly included sections.)

1. The diagnostic criteria for functional dyspepsia (FD) are not clear. In order to make this trial valuable, the authors should consider using the Rome III criteria. The patients may need to be further classified to the FD subtypes.

=> The reviewer kindly pointed out the application of the Rome III criteria as the diagnostic criteria for functional dyspepsia. We already applied the Rome III criteria for FD and classified FD into 2 subtypes: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), according to a previous study (Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada J, Stanghellini V: Functional gastroduodenal disorders. Gastroenterology 2006, 130:1466-1479). To further clarify the diagnostic criteria of FD, we have provided the following detailed explanation in the “Inclusion criteria” section of the main manuscript.

Page 6-7 (Inclusion criteria):
Patients 19–75 years old who complain of dyspepsia for the previous 3 months, and who have an onset of symptoms at least 6 months prior, meet the definition of the Rome III criteria for FD [21]. ~

~ Patients who are diagnosed with FD can be categorized as having either 1) meal-induced dyspeptic symptoms (postprandial distress syndrome; PDS) or 2) epigastric pain syndrome (EPS) and, in this trial, all FD patients will be classified into one of the abovementioned subtypes (PDS and EPS) [21]. ~

2. Helicobacter pylori status is not assessed in this trial. Based on Rome III: “Noninvasive testing of H pylori infection, followed by eradication (‘test and treat’) is indicated for the patient with no alarm features.” Thus we recommend H pylori assessment as part of this study.

=> We have included the following text regarding the assessment of H. pylori status in the “inclusion criteria” section of the main manuscript.

Page 7(Inclusion criteria):
On the other hand, the *Helicobacter pylori* status of the patients and history of *H. pylori* eradication therapy will be assessed before enrolment by noninvasive tests (urea breath test) or the rapid urease test.

3. Medications that can result in dyspepsia such as aspirin and nonsteroidal anti-inflammatories (NSAIDs) need to be excluded to diagnose FD.

=> We have included ingestion of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) as a part of the “exclusion criteria” section of the main manuscript; the following revision was made:

*Page 7(Exclusion criteria):*
~ ingestion of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), and women who are pregnant or lactating. ~

4. Endoscopy should be considered as part of the protocol.

=> In this trial, endoscopic evaluation of dyspepsia will be included as one of main techniques that can determine whether dyspeptic symptoms arise from structural diseases of the stomach or not. We have included the following text in the revised manuscript to convey this.

*Page 7(Inclusion criteria):*
~ Then, all the participants will undergo endogastroduodenoscopy (EGD) before enrolment and be examined by gastroenterologists to determine whether the EGD observations are related to the present dyspeptic symptoms. ~

5. The term “gastric dynamic agent” in the inclusion criteria is not clear.

=> According to the reviewer’s suggestion, we deleted the term “gastric dynamic agent” and included more specific and detailed terms; the revised text is shown below.

*Page 8(Exclusion criteria):*
~ At the screening phase, patients who are using any antibiotic, proton-pump inhibitor, bismuth salt, prokinetic agents such as itopride, herbal formulas, or who are participating in any other clinical trial, will be excluded from this study. ~

6. I am not sure about the value of EGG in this study. Inconsistent correlations have been
shown between symptoms and abnormalities of gastric function as assessed by gastric barostat or electrogastrography.

=> We agree with the reviewer’s opinion on the value of EGG in this study. Therefore, we changed the purpose of the application of EGG in this trial. EGG will now be used to confirm the relationship between cutaneous EGG recordings and dyspeptic symptoms in the Korean population, thus assessing the possibility of the application of EGG in Korean FD patients. To this effect, we have included the following text in the revised manuscript.

Page 2-3 (Abstract):
~ The current study is designed to evaluate the efficacy and safety of Banha-sasim-tang for FD patients and to examine whether there will be a significant correlation between cutaneous electrogastrography recordings and dyspeptic symptoms in FD patients, and between changes in gastric myoelectrical activity and improvement in dyspeptic symptoms during Banha-sasim-tang administration. ~

~ Furthermore, based on the assessment of the relationship between cutaneous electrogastrography recordings and dyspeptic symptoms in this trial, the possibility of clinical applications of cutaneous electrogastrography in the treatment of FD will be elucidated.

Page 4-5 (Background):
~ However, the relationship between dyspeptic symptoms and cutaneous EGG recordings remains a controversial topic in FD. ~

~ We will also examine the relationship between the frequency or power variables in cutaneous EGG and dyspeptic symptoms of FD patients in this trial and determine whether the changes in GMA recorded by cutaneous EGG before and after the oral administration of BST can reflect the clinical efficacy of BST in the treatment of FD.

Page 5 (Objectives):
(2) To examine the relationship between dyspeptic symptoms and cutaneous EGG recordings and a possible biological evidence of BST’s efficacy via cutaneous EGG recordings.

Page 5 (Hypothesis):
(2) In patients with FD or FD subtypes according to the Rome III criteria, there will be a significant correlation between the degree of dyspeptic symptoms and cutaneous EGG recordings and 6 weeks of
oral administration of BST can improve the abnormal frequency and power parameters on cutaneous EGG.

Pages 14–15 (Discussion):
~ Because many researchers have suggested that cutaneous EGG could be a relatively easy technique that can be used to assess GMA in clinical settings, and EGG recordings showed a significant correlation with dyspeptic symptoms in FD patients, and changes in cutaneous EGG parameters in FD patients could reflect changes in their gastric motility and their dyspeptic symptoms [29, 30], it is postulated that a significant correlation can be found between dyspeptic symptoms of FD patients and cutaneous EGG recordings in this trial, and the improvement in dyspeptic symptoms after the oral administration of BST may be assessed by measuring the changes in cutaneous EGG parameters. Correlations in these parameters can evaluate the possibility of clinical applications of cutaneous EGG in the treatment of FD, and a detailed guide, based on biological evidences, for treatment with BST in FD patients.

7. It is not clear how the duration of treatment (6 weeks) was determined. Could 4 weeks of treatment be enough?

=> Many randomized controlled trials (RCTs) use natural products or herbal formulas in FD researches. In the RCTs cited below, various treatment periods were suggested.

1) 2 weeks’ treatment RCT

2) 4 weeks’ treatment RCTs

3) 5 weeks’ treatment RCT

**4) 6 weeks’ treatment RCT**

**5) 8 weeks’ treatment RCTs**

**6) 12 weeks’ treatment RCT**

On the basis of the variable treatment periods in the above RCTs, it can be concluded that no fixed treatment period for FD has been established. However, to streamline protocol design, it is important to establish the shortest treatment period for the verification of the effect of BST.

A single-arm clinical trial* aimed at assessing the efficacy of BST in FD patients has showed an improvement in FD symptoms after 4 weeks’ treatment. Therefore, 4 weeks’ treatment period, also recommended by the reviewer, might be relevant. However, there is an important difference between the previous study* and this one, i.e., the use of an experimental herbal formula in this study.

Although the same herbal formula (BST) was used in 2 of the abovementioned clinical studies, an ethanol-extract of the BST granule (*Hange-shashin-to* granule, Tsumura Co., Japan) was administered in the previous study*, whereas a water-extract of the BST granule mixed with starch and lactose will be administered in this trial (as mentioned in main manuscript). Thus, compared to previous study, in this trial, BST might contain a relatively low percentage of the active components. In addition, the IRB would not permit the dosage of BST (3 g TID) to be changed, because this clinical trial is a sort of post-marketing survey and this dosage is the recommended dosage approved by the Korean Food and Drug Administration. Thus, the treatment period in this trial must be longer than that in the previous study*, and therefore, we chose a 6 weeks’ treatment period instead of a 4-week period.

8. **Are the patients treated for FD during the 2-month period of follow-up? This needs to be specifically stated.**

=> In this protocol, conventional treatments for FD will be permitted during the 2-month follow-up period. This was also discussed during the IRB review in the view of participants' rights. According to the reviewer’s suggestion, we added the following detailed explanation regarding treatments for FD during the follow-up period.

**Page 6 (Design):**
~ During the 2-month follow-up period, conventional treatments for dyspepsia will be permitted if the dyspeptic symptoms are exacerbated or recur. Any treatment received by the patient during the follow-up period will be reported by them or documented in their diary (Figure 1).

If you have any questions pertaining to our revised manuscript, please let me know.

We hope that you will find our revised manuscript suitable for publication in *Trials*.

Thank you.

With kind regards,

Yours faithfully,

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