Author’s response to reviews

Title: Warm Needling Acupuncture and Medicinal Cake-separated Moxibustion for Hyperlipidemia: Study Protocol for a Randomized Controlled Trial

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Responses to Reviewers

Reviewer #1: The responses for the questions are satisfactory, besides, some of concerns for the study design, please clarify
1. What is the rationale to combine Moxibustion and Acupuncture with TLC? Where the effects comes from, TLC, moxibustion or acupuncture? Please provide more explanation.

This has been explained in the “4. Discussion” section:

“The TLC will be included prior to both interventions of acupuncture and moxibustion and statin, which enables this study to reflect the actual practice in clinical settings to the most extent. According to the guideline of hyperlipidemia treatment (1), TLC is recommended as the first step before any other treatment. By adhering to the commonly-adopted clinical guideline during study procedure, on the one hand, we can take good care of the “non-maleficence” and “justice” principles in study ethics, because the opportunity of receiving appropriate medication will not be compromised for patients attending this study; on the other hand, this can enhance the generalizability of this study due to following the clinical operations in real life.”

Meanwhile, the objective of this study is to compare the efficacy of acupuncture and moxibustion vs. simvastatin. As long as the two groups have both undergone TLC, we could ensure these two groups are comparative at the baseline; in this case, we could achieve our study objective by comparison at the end of the study. TLC itself will not make a difference in this comparison, so there is no need for us to distinguish its effect from acupuncture and moxibustion OR simvastatin.

2. Why combine Moxibustion and acupuncture together? Any preliminary data?

This has been discussed in the section of “1.1 Background and rationale”:

“Acupuncture and moxibustion has been widely applied to hyperlipidemia treatment in clinical practice of China. Thus, an increasing number of studies have explored whether acupuncture and moxibustion could serve as an alternative treatment for subjects with hyperlipidemia. As shown in a meta-analysis, acupuncture solely, compared to statins, has demonstrated a more significant effect on decreasing TG and increasing HDL-C, but no superiority in lowering the LDL-C and TC (2). Meanwhile, moxibustion, which is often administered with acupuncture in Traditional Chinese Medicine (TCM) practice, also plays an essential role in lipid-lowering by warming meridians and facilitating lipid conversion in the TCM theory. The recent studies have further revealed the biological pathway in lipid-lowering of moxibustion (3-5). This modality, especially the warm needling acupuncture (acupuncture with moxa stick), can enhance microcirculation, adjust the lipid metabolism, and thus lower the blood viscosity (3-5).

Medicinal cake-separated moxibustion, an important kind of moxibustion, applies the acupoints, moxibustion, and traditional Chinese herb in an integrative way. It has gained increasing popularity in the practice of hyperlipidemia treatment and thus been further assessed on its potential impact. Some findings have shown, from a perspective of gene transcription and protein expression, that the medicinal cake-separated moxibustion could prevent the formation of atheromatous plaque by adjusting Toll-Like Receptor (TLR) signaling pathway as well as peroxisome proliferator-activated receptors (PPARs), in order to delay atherosclerosis (AS) formation and stabilize atheromatous plaque (6, 7). Chang XR et al. indicated that both the
medicinal cake-separated moxibustion and direct moxibustion have a certain protective action on endothelial cells of the aorta in the rabbit of hyperlipidemia (6). Yue ZH et al. found that herb-partition moxibustion delays the formation of atherosclerosis through the inhibition of TLR4 expression (7). This has provided a new strategy for the research on AS pathogenesis and prevention. In addition, based on clinical observation and systematic review of TCM literature, the selection of meridians and acupoints potentially having effect on hyperlipidemia treatment, has been studied and identified, which includes ten meridians (five Yin and five Yang meridians), and five acupoints (Stomach (ST), Spleen (SP), Ren (RN), Bladder (BL) and Pericardian (PC)) (8). Based on these findings, several clinical studies on assessing medicinal cake-separated moxibustion have been undertaken, testing different acupoint prescriptions, medicinal cake ingredients, treatment duration, etc., in attempt to identify an effective and standardized regimen (3, 9-13). Most of these studies have shown possible therapeutic effects of the medicinal cake-separated moxibustion on hyperlipidemia, superior to the placebo or non-inferior to statins.

In general, acupuncture and moxibustion is shown to be possibly effective in treating hyperlipidemia separately, with lower cost and fewer serious adverse events (14, 15). However, due to the lack of robust study design and assessment methodology in existing clinical studies, the findings should be interpreted with caution. According to previous attempts on identifying an optimal regimen of acupuncture and moxibustion for treating hyperlipidemia, the warm needling acupuncture along with medicinal cake-separated moxibustion seems to be a modality that successfully combine the advantages of both acupuncture and moxibustion. This is worth further exploring to warrant its therapeutic effects (9, 12, 13). So far, very few studies on this combined intervention are available. Hence, there is a need for a well-designed randomized control trial to validate the efficacy and safety of warm needling acupuncture along with medicinal cake-separated moxibustion, by comparing it with statins.”

3. How can make sure those participants be blinded in the allocation?

This study is an open-label RCT; no blinding is designed for patients. More details have been discussed in section of “2.12 Blinding”.

“Due to the nature of the acupuncture and moxibustion interventions, neither participants nor care providers can be blinded to allocation and treatment stages, but are strongly inculcated not to disclose the allocation status of the participant at the follow up assessments. The outcome assessment will be conducted by outcome assessors blind to the treatment allocation. In the stage of data analyses, an employee outside the research team will feed data into the computer in separate datasheets so that the data analysts can analyze data without having access to information about the allocation.

To maintain the overall quality and legitimacy of the clinical trial, code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient. Investigators, including the outcome assessors and data analysts blind to treatment allocation, are encouraged to discuss with the Medical Advisor physicians if he/she believes that unblinding is necessary. The Investigator is encouraged to maintain the blind as far as possible. The actual allocation must NOT be disclosed to the patient
and/or other study personnel. There should not be any written or verbal disclosure of the code in any of the corresponding patient documents. The Investigator must report all code breaks (with reason) as they occur on the corresponding case report form page. Unblinding should not necessarily be a reason for study drug discontinuation.”

Reviewer #3: 1. The intervention is too complicated. To add a schematic diagram will help the readers to understand it better.

The Figure 1 – Treatment regimen and flowchart for intervention of warm needling acupuncture and medicinal cake-separated moxibustion has been included to the paper.

2. To present the details of the intervention in a table based on STRICTA will help increasing the readers’ understanding.

The section of “2.5.2 Acupuncture and moxibustion vs. Simvastatin – Acupuncture and moxibustion” was presented according to the STRICTA, which has covered all the key elements in the STRICTA checklist. In order to ensure the clarity of the contents, we have presented the “needling/moxibustion details” in table; it may be clearer to demonstrate the rest of the contents in text.

The Table 5 – the needling/moxibustion details for warm needling acupuncture and medicinal cake-separated moxibustion has been included to the paper.

3. The therapeutic regimen is too complex. The warm needling acupuncture is actually a combination of acupuncture + moxibustion. In addition, two types of medicinal cake-separated moxibustion is applied at acupoints on back area and abdomen area. And the medicinal cake-separated moxibustion is composed of a cake made from various herbs and a moxa cone maybe composed of mugwort. In fact, any one among those methods has not yet been clearly revealed. It is questionable why you had to choose such a complicated regimen. I worry that it will be very difficult to interpret the results from this study using such a complicated regimen.

The rationale of using the warm needling acupuncture and medicinal cake-separated moxibustion for hyperlipidemia treatment has been discussed in the section of “1.1 Background and rationale”; please refer to our discussions there.

The intervention details of the acupuncture and moxibustion have been re-organized in the paper which are presented along with a table and a flowchart (please refer to section of “2.5.2 Acupuncture and moxibustion vs. Simvastatin – Acupuncture and moxibustion”). They were provided in a standardized format (according to the STRICTA guideline), which ensures that this intervention is duplicable and generalizable. Meanwhile, the treatment regimen used in the intervention of our study was developed based on the clinical practice. There are no acupoints assigned in the back and abdomen areas at the same time. The reason why two groups of acupoints alternate week by week is to try to avoid potential fatigue and non-response of acupoints due to constant stimulation. Therefore, the intervention of acupuncture and moxibustion in our study will not be too complex to be applied in real life practice.
The warm needling acupuncture and medicinal cake-separated moxibustion are considered as an entity in the intervention – producing integrated therapeutic effect. In Traditional Chinese Medicine (TCM) practice, acupuncture is often administered with moxibustion for a better therapeutic effect. In our study, we do not aim to distinguish the effect of warm needling acupuncture from the one of medicinal cake-separated moxibustion. Our objective is to examine the efficacy of this combined intervention by comparing the outcomes of acupuncture & moxibustion vs. Simvastatin. Therefore, there should not be a problem in interpreting the results.

We have included the ingredients of moxa-stick and moxa-cone in the paper, which contain mugwort.

4. Consideration should be given to the economic feasibility of the treatment intervention and simvastatin.

In terms of economic evaluation, prior to this study, 85 patients from the First Affiliated Hospital of Hunan University of Traditional Chinese Medicine have been observed for their cost on hyperlipidemia treatment. They were prescribed with Simvastatin and their relevant average cost was 3,000 RMB per person per year. But if they had used medicinal cake-separated moxibustion instead, the estimated cost would have been 1,000 RMB per person per year – based on the market price of medicinal cake, acupuncture and moxibustion. Meanwhile, compared to the acupuncture and moxibustion, the statin therapy is always associated with low treatment compliance and high rate of side effects, which may introduce more economic burden and lower quality of life. Therefore, although this is only a rough estimation of the cost, it may still imply the acupuncture and moxibustion as a favorable alternative in economic evaluation. However, in our current study, we hope to first focus on efficacy assessment; after the presence of efficacy of acupuncture and moxibustion is proved, the economic evaluation will be the next step.

5. This study is actually a comparative study of warm needling acupuncture + cake-separated moxibustion versus simvastatin. You can use abbreviations 'like acupuncture and moxibustion' in the text or running head, but the title of the manuscript should clearly state what the target intervention for this study.

This has been adjusted. The new title is “Warm Needling Acupuncture and Medicinal Cake-separated Moxibustion for Hyperlipidemia: Study Protocol for a Randomized Controlled Trial”.

6. The resolution of figure 1 is too low to understand for readers.

This has been adjusted.

References


