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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Author’s response to reviews:

Comments and concern from Reviewer 1

1, What is the rationale for the selection acupuncture and moxibustion to compare with positive drugs?
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 (1). 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 (2-4). This treatment, especially the warm needling acupuncture (acupuncture with moxa stick), can enhance microcirculation, adjust the lipid metabolism, and thus lower the blood viscosity (2-4).

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 (5, 6). 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 (5). Yue ZH et al. found that herb-partition moxibustion delays the formation of atherosclerosis through the inhibition of TLR4 expression (6). 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 effect on treating hyperlipidemia has ben 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)) (7). 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 (2, 8-12). 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, with lower cost and fewer serious adverse events (13, 14). 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 (8, 11, 12).

2. What is the rationale for treatment course determination? Any pilot study data?
In clinical practice, several studies with small sample sizes have assessed a variety of acupoint prescriptions, medicinal cake ingredients, treatment duration, etc. (8, 12). Among these studies, Li GH et al. applied warm needling acupuncture on acupoints such as Fenglong (ST40, bilateral), Zusanli (ST36, bilateral), etc., once a day for 35 days, over a period of 12 weeks, showing a significant decrease in LDL-C, non-inferior to statins (8). Li AJ et al. applied medicinal cake-separated moxibustion on two groups of acupoints, alternating over a period of 40 days with each group receiving 20 times of intervention (12). This study demonstrated a remarkable decrease in LDL-C and TC, superior to the effect of a placebo. With these two studies, so far we know that warm needling acupuncture and cake-separated moxibustion are both effective for hyperlipidemia, respectively. Together with our previous clinical experiences on treating hyperlipidemia, we selected the studies mentioned above as pilot studies of this trial in determining the procedure course of intervention.

3. Is it possible to provide more detailed information about the intervention of acupuncture and moxibustion?

The details of the intervention of acupuncture and moxibustion are described below.

- Needling/moxibustion details

  - Warm needling acupuncture:

    Acupoints: Fenglong (ST40, bilateral), Zusanli (ST36, bilateral), Sanyinjiao (SP6, bilateral)

    Depths of insertion: Fenglong (ST40) for 1.0 to 2.0cun, Zusanli (ST36) and Sanyinjiao (SP6) for 1.0 to 1.5cun (“cun” is a traditional Chinese unit of length. 1cun = 3.33 centimeters).

    Needle stimulation: manual manipulation.

    Responses elicited: de qi sensation.

    Needle retention time: 30min.

    Co-intervention: with small moxa stick with 1.5cm in length.

    Manipulation: needle punctured into the acupoints, and then the small moxa stick attached into the needle tail.

    Needle specifications: Sterile single-use acupuncture needles of 25-40 mm in length and 0.30mm in diameter.

    Manufacture: Suzhou Medical Supplies Co., Ltd., Suzhou, China.

  – Cake-separated moxibustion:
Acupoints: Juque (RN14), Tianshu (ST25, bilateral), Pishu (BL20, bilateral), Xinshu (BL15, bilateral), Ganshu (BL18, bilateral), Shenshu (BL23, bilateral).

Cake ingredients: Dan Shen (Radix Salviae Miltiorrhizae), Shan Zha (Fructus Crataegi), Yu Jin (Radix Curcumae), Da Huang (Radix et Rhizoma Rhei) and Ze Xie (Rhizoma Alismatis).

Cake specifications: cake ingredients in same quantities were collected, grounded into powder, mixed well with vinegar, and made into round-thin cakes of 1.5cm in diameter, 3mm in thickness and 3g in weight.

Moxibustion specifications: moxa-cone with 1cm in diameter.

Manipulation: the moxa-cone put on the cake.

Retention time: 3 cones with 30min.

Manufacture: moxa-cone and cake ingredients provided by Suzhou Medical Supplies Co., Ltd., Suzhou, China.

• Treatment regimen:

  – Group 1: Medicinal cake-separated moxibustion on Juque (RN14) and Tianshu (ST25, bilateral); along with warm needling acupuncture on Fenglong (ST40, bilateral), Zusanli (ST 36, bilateral), Sanyinjiao (SP6, bilateral)

  – Group 2: Only medicinal cake-separated moxibustion on Pishu (BL20, bilateral), Xinshu (BL15, bilateral), Ganshu (BL18, bilateral), Shenshu (BL23, bilateral)

  – Interventions on Group 1 and Group 2 will alternate by week over the administration period (i.e., Group 1 in week 1, 3, 5, etc., and Group 2 in week 2, 4, 6, etc.)

  – Warm needling acupuncture: 1) locate and sterilize the acupoints; 2) insert the needles and stimulate to elicit response; 3) attach a small moxa stick to the needle tail and light the moxa stick; and 4) retain needles with moxa sticks for 30 minutes

  – Medicinal cake-separated moxibustion: 1) locate the acupoints; 2) place the herbal cake on to the acupoints; 3) place the a moxa cone onto the herbal cake and lit the moxa cone; 4) renew the moxa cone once the last one is fully consumed, with a maximum of 3 moxa cones per acupoint; and 5) retain herbal cakes with moxa cones for 30 minutes

  – Number of treatment sessions: 6 weeks as a session, totally 2 sessions.

  – Frequency of treatment: five times each week for the first session, and three times each week for the second session.
4. How to assign the participant number to different sites? How to make sure the consistency among different sites?

Subjects will receive the intervention in the site he/she is recruited. We will not assign subjects recruited in one site to another site to receive intervention. Within each site, subjects will be stratified by risk groups (0-1 risk group, 2+ Risk Factor Group, and CHD or CHD risk equivalents group), as target lipid levels differ according to different risk groups. Subjects who have not reached the target lipid level after TLC, will be randomized to two arms at a ratio of 1:1 (acupuncture and moxibustion vs. Simvastatin). The randomization will be blocked (size=4) to ensure equal number of subjects’ allocation in each arm. A computer-generated, blocked randomization sequence will be used to randomize subjects in the study. Assignment to the 2 treatment arms will be generated by the principal biostatistician using R (version 3.1.1; R Foundation for Statistical Computing, Austria. ISBN 3-900051-07-0) before the start of the study. The sequence will be held in a secure location in the hospital by the principal biostatistician; the researchers will be blinded to the number of cases in each randomization block and individual subject allocation will be conducted remotely via telephone based on the randomization sequence. Once subject is eligible to receive the intervention, the principal biostatistician will be informed and let physicians know each subject’s allocation by phone.

Each site must follow this study protocol; otherwise, it will be closed. The steering committee will audit and review the intervention performed in each site, to ensure they are following this protocol.

5. Any standard procedure of intervention?

The standard procedure of intervention are specified as below.

- **Group 1:** Medicinal cake-separated moxibustion on Juque (RN14) and Tianshu (ST25, bilateral); along with warm needling acupuncture on Fenglong (ST40, bilateral), Zusanli (ST 36, bilateral), Sanyinjiao (SP6, bilateral)

- **Group 2:** Only medicinal cake-separated moxibustion on Pishu (BL20, bilateral), Xinshu (BL15, bilateral), Ganshu (BL18, bilateral), Shenshu (BL23, bilateral)

- Interventions on Group 1 and Group 2 will alternate by week over the administration period (i.e., Group 1 in week 1, 3, 5, etc., and Group 2 in week 2, 4, 6, etc.)

- Warm needling acupuncture: 1) locate and sterilize the acupoints; 2) insert the needles and stimulate to elicit response; 3) attach a small moxa stick to the needle tail and light the moxa stick; and 4) retain needles with moxa sticks for 30 minutes

- Medicinal cake-separated moxibustion: 1) locate the acupoints; 2) place the herbal cake on to the acupoints; 3) place the a moxa cone onto the herbal cake and lit the moxa cone; 4) renew the moxa cone once the last one is fully consumed, with a maximum of 3 moxa cones per acupoint; and 5) retain herbal cakes with moxa cones for 30 minutes
- Number of treatment sessions: 6 weeks as a session, and 2 sessions in total.

- Frequency of treatment: five times each week for the first session, and three times each week for the second session.

Comments and concerns from Reviewer 2

1. Abstract: Could you provide a brief background of the study?

The abstract background part has been updated as below:

Acupuncture and moxibustion has been widely applied to hyperlipidemia treatment in clinical practice in China, serving as an alternative treatment to statins. Warm needling acupuncture and medicinal cake-separated moxibustion have been separately reported with potential therapeutic effects on hyperlipidemia treatment in several studies but with limitations in study methodology. Combining these two modalities may provide a more advantageous strategy in treating hyperlipidemia. Therefore, a strict evaluation through well-designed Randomized Controlled Trials (RCT) is necessary to determine their efficacy and safety on hyperlipidemia.

2. Introduction: Could you add some references about the area of your study by other research groups?

We have added more references on this topic by other research groups in the introduction part. The introduction part has been re-written to enhance the rationale of this study and introduce the background more clearly.

References


