Effect of herb-partitioned moxibustion on pain and quality of life in women with endometriosis: a protocol for a randomized clinical trial

Hu Hantong, Chen Lifang, Jin Xiaofei, Li Ru, Fang Jianqiao

Hu Hantong, Department of Acupuncture and Moxibustion, the Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, China; Zhejiang Chinese Medical University, Hangzhou 310053, China

Chen Lifang, Department of Acupuncture and Moxibustion, the Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, China

Jin Xiaofei, Li Ru, Zhejiang Chinese Medical University, Hangzhou 310053, China

Fang Jianqiao, Zhejiang Chinese Medical University, Hangzhou 310053, China

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Correspondence to: Prof. Fang Jianqiao, Department of Neurobiology and Acupuncture Research, the Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, Hangzhou 310053, China. fangjianqiao7532@163.com and Chen Lifang, Department of Acupuncture and Moxibustion, the Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, China. clfang@163.com

Telephone: +86-18667103032

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Abstract

OBJECTIVE: To investigate the effect of herb-partitioned moxibustion (HPM) on pain and quality of life in women with endometriosis.

METHODS: Thirty-six patients will be randomly assigned to a treatment group or a wait-list control group. The treatment group will receive 12 sessions of HPM in the lower abdomen and lumbosacral region for 3 months. Wait-list participants will not receive any specific treatments until the trial is completed.

RESULTS: The primary outcome measure is pain intensity assessed by a Visual Analogue Scale at baseline, months 1, 2, and 3 in the treatment period, and months 4, 5, and 6 in the follow-up period. Secondary outcome measures include quality of life assessed by the Short Form 36 Health Survey, change in CA125, change in cyst diameter (assessed by ultrasound examination), and rescue medication dosage.

CONCLUSION: This study will provide evidence to confirm if HPM may be used as a therapeutic option for treating endometriosis.

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Keywords: Moxibustion; Endometriosis; Pain; Randomized controlled trial; Protocol

INTRODUCTION

Endometriosis (EM) is a common, recurrent gynecological disease characterized by chronic pelvic pain and subfertility. Other common symptoms include deep dyspareunia, cyclical bowel or bladder symptoms, abnormal menstrual bleeding, chronic fatigue, and low back pain. EM generally affects women of reproductive age.
age, with an estimated point prevalence of 10%-15% worldwide. EM may also be associated with substantially reduced quality of life.

The pathogenic mechanism of EM remains unclear. Several pathogenic theories have been proposed (e.g., retrograde menstruation, coelomic metaplasia, and Müllerian remnants). Risk factors potentially involved in the development of EM have also been investigated, including genetics, immune factors, inflammatory factors, eutopic endometrium specificity, and environmental toxins. Currently, the main treatment options for EM are pharmacological and surgical interventions. However, these therapies remain unsatisfactory and have low adherence, which is limited by side effects of medication, high cost, and the recurrent rate for surgical ablation of the lesions. Therefore, a key challenge is seeking other effective treatments for EM. Patients with EM present with significant pain as their most common symptom. Traditional Chinese Medicine (TCM) is widely adopted in pain management, and may be an option for EM treatment. The three major TCM modalities are acupuncture, Chinese herbal medicine, and moxibustion, which has been used to treat a variety of diseases including EM. Some experimental studies have reported moxibustion showed beneficial effects for EM in rats. Herb-partitioned moxibustion (HPM) is a modified moxibustion therapy that combines the advantages of heat stimulation, herbal stimulation, and acupoint stimulation. Previous clinical studies suggested HPM may alleviate EM symptoms. However, these findings should be interpreted with caution because of the lack of robust study designs and the assessment methodology in existing clinical studies. The potential curative effect of HPM in ameliorating EM symptoms requires further robust evaluation. Therefore, there is a need for a well-designed randomized controlled trial (RCT) to validate the clinical efficacy and safety of HPM in treating EM.

METHODS

Study design

This single-center trial will adopt a randomized, wait-list controlled, and assessor-blinded design, meaning all participants will benefit from the intervention that is staggered over time. Eligible participants will be randomly assigned to the moxibustion group or the
wait-list group using a 1:1 allocation ratio. The total duration of the trial will be 6 months, and include 3 months of intervention and 3 months of follow-up. An outline of the patient flow is presented in Figure 1, and the trial schedule is shown in Table 1.

Participants and recruitment
Participants will be recruited from the acupuncture or gynecology departments of the Third Affiliated Hospital of Zhejiang Chinese Medical University. Participants’ eligibility will be assessed by physicians and acupuncturists using the criteria described below.

Inclusion criteria
Participants will be included if they meet the following criteria.
(a) Women with ovarian EM or ovarian EM cyst diagnosed by gynecologists. The diagnostic criteria is based on the ESHRE guideline for management of women with EM published in 2014.21 (b) Women aged 18-50 years. (c) Women with a history of EM for more than 6 months that had dysmenorrheal, pelvic pain, or other common symptoms associated with EM for more than 6 months, and an EM cyst with a 2-6 cm diameter evaluated by ultrasound examination (including recurring EM cyst after operation). (d) Women with a regular menstrual cycle and no pregnancy plan during the trial. (e) Women that are not currently receiving other therapies (e.g., hormonal treatment or analgesics medication) to treat EM. (f) Women that agree to participate in this trial and sign the informed consent form.

Exclusion criteria
Women will be excluded if they: (a) Get pregnant or are preparing to be pregnant, are in the lactation period, or in the perimenopausal/postmenopausal period. (b) Have received herbal medicine or acupuncture in the past 3 months. (c) Have cicatricial diathesis, or shallow sensory disorder, skin that tends to be allergic to herbal medicine, or who cannot tolerate the smell of smoke released by burning moxa. (d) Are unable to receive moxibustion because of other primary diseases or mental disorders. (e) Are participating in other clinical trials.

Randomization and allocation concealment
Randomization will be performed by an independent statistician using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The generated list of random numbers will be concealed using sequentially numbered, opaque, sealed envelopes. Participants’ screening sequence numbers will be printed on the outside of the envelope, and the group name will be printed inside. The envelopes will be held by a designated screener, and will not be opened until new participants are enrolled. When an eligible participant is included, the researchers will inform the screener to open the envelope to obtain the group information. Once an envelope is opened, it will not be used again. Participants will then be informed to which group they are assigned.

Blinding
Because of the characteristics of moxibustion, neither
participants nor moxibustion manipulators will be blinded. However, the treatment, assessment, and statistical analysis will be performed independently. Outcome assessment will be conducted by assessors blinded to the treatment allocation. Participants will also be asked not to mention any details of their treatment or group allocation to the assessor. The statistical analyses will be performed by statisticians blinded to the treatment allocation.

**Intervention**

Rescue medication: in cases of acute pain or other discomfort, rescue medication (e.g., analgesic drugs) will be permitted to relieve discomfort in both groups throughout the study period. However, the details of rescue medication will be documented in pain diaries kept by participants. These details will include the medication name, administration time, and dosage.

Treatment group: participants in the treatment group will receive one session of HPM in the pelvic and sacral region each week. One session of treatment will last for about 1 h. The treatment course will last for 3 months, consisting of 12 treatment sessions. Follow-ups will be performed for another 3 months.

(a) Prescription of herbal mixture for HPM: the herbs will be mixed in specific proportions. The herbal prescription (Table 2) consists of seven kinds of Chinese herbs, including Fuzi (Radix Aconiti Lateralis Preparata), Rougui (Cortex Cinnamomi Cassiae), Lujiaoshuang (Cornu Cervi Degelatinatum), Puhuang (Pollen Tiphae), Wulingzhi (Rhizoma Sparganii), Sanleng (Rhizoma Sparganii), and Ezhu (Rhizoma Curcumae Phaeocaulis). The herbs will be shattered into herbal pulverata by a pulverizer, and then mixed using a ratio of 6:1:1:1:1:1:1, and saved in a sealed container for later use. If a participant happens to receive treatment during their menstrual period, four adjoining Chinese herbal medicines will be added using a 1:1:1:1 ratio: Chuanxiong (Rhzoma Chuanxiong), Xixin (Herba Asari Mandshurica), Yanhusuo (Rhizoma Corydalis Yanhusuo), and Chuanliai (Fructus Toosendan).

(b) Moxibustion: based on TCM theory and previous clinical trials, specific regions will be chosen for HPM. In the lower abdomen region, HPM will be applied in the middle of the lower abdomen in the shape of an inverted “T” as shown in Figure 2A. The longitudinal band is from Shenque (CV 8) to Qugu (CV 2). The herbal mixture will be placed on this line in a width of about 10 cm. The lateral band starts from Guanyuan (CV 4) and Qugu (CV 2) and extends laterally to the lateral abdomen, to look like a rectangle with a width of about 20 cm. This area covers important acupoints such as Zigong (EX-CA 1), Shuidao (ST 28), and Guilai (ST 29). In the lumbosacral region, HPM will be manipulated in the posterior median line [from Mingmen (GV 4) to Yaoshu (GV 2)]. The herbal mixture will be placed on this line in a width of about 10 cm, as shown in Figure 2B.

(c) Moxibustion treatment procedure: first, participants will be asked to lie on the treatment couch in a comfortable supine position to receive HPM in the lower abdomen. Next, they will adopt a prone position to receive HPM in the lumbosacral region. They will be asked to adjust clothing to fully expose the aforesaid sites. The room will be temperature controlled at 25-30 °C. The skin will be sterilized and the moxibustion sites covered with a layer of gauze. The herbal powder will be mixed thoroughly with 20% alcohol liquid and made into herbal paste. Next, the herbal mixture will be applied to the selected regions in a strip (2 cm in height), and the moxa (pure wormwood fiber in material; produced by the Dongfang mugwort floss factory, Suzhou, China) will be placed on the central line of the herbal strip mixture and ignited. Two units of moxa will be applied for each region (lower abdomen and lumbosacral regions). Once the first unit of moxa is burnt out, it will be removed and a second unit of moxa will be placed on the herbal mixture. During the manipulation, the heat of moxibustion will be regulated according to participants’ tolerance. The technique requires the participant to experience a sensation of heat but no painful burning sensation. It is recommended that the skin becomes a little red, but the skin should not be scalded. This allows the moxa-effect enhanced by the active components of the herbal mixture to penetrate the skin, acupoints, and meridians. If par-

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**Table 2 Prescription for the Chinese herb ingredients**

<table>
<thead>
<tr>
<th>Chinese name</th>
<th>Pharmaceutical name</th>
<th>Ratio</th>
<th>Effect according to TCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuzi</td>
<td>Radix Aconiti Lateralis Preparata</td>
<td>6</td>
<td>Tonifying fire and helping Yang; dispelling cold to relieve pain</td>
</tr>
<tr>
<td>Rougui</td>
<td>Cortex Cinnamomi Cassiae</td>
<td>1</td>
<td>Tonifying fire and helping Yang; dispelling cold to relieve pain</td>
</tr>
<tr>
<td>Lujiaoshuang</td>
<td>Cornu Cervi Degelatinatum</td>
<td>1</td>
<td>Warming kidney and enhancing Yang; hemostasis with astringents</td>
</tr>
<tr>
<td>Puhuang</td>
<td>Pollen Tiphae</td>
<td>1</td>
<td>Promoting blood circulation and removing blood stasis</td>
</tr>
<tr>
<td>Wulingzhi</td>
<td>Faeces Tropopteri</td>
<td>1</td>
<td>Promoting blood circulation and removing blood stasis</td>
</tr>
<tr>
<td>Sanleng</td>
<td>Rhizoma Sparganii</td>
<td>1</td>
<td>Promoting blood circulation and removing blood stasis</td>
</tr>
<tr>
<td>Ezhu</td>
<td>Rhizoma Curcumae Phaeocaulis</td>
<td>1</td>
<td>Promoting blood circulation and removing blood stasis</td>
</tr>
</tbody>
</table>
Participants feel pain or a burning sensation, the moxa cones will be removed immediately and reset after several minutes. The moxibustion manipulator will be required to observe participants carefully and will remove the burning ash quickly to avoid injury during the procedure.

Control group
The control arm will be a waiting-list group. Participants in the control group will not receive any specific treatments until the completion of the trial.

Outcome measures
Primary outcome: the primary outcome will be pain intensity, including dysmenorrheal and intermenstrual pain. Pain intensity will be assessed on a 10-point Visual Analogue Scale (VAS). On the VAS scale, a 10-cm horizontal line from no pain on the far left to the worst possible pain on the far right is scored by determining the distance from the far left to the edge of the mark made by the patient. This distance represents the pain intensity.

Baseline VAS will be assessed based on the dysmenorrheal and intermenstrual pain experienced in the previous menstrual cycle. Throughout the intervention period, participants will be asked to keep pain diaries in which they will record their pain intensity according to the VAS. The primary outcome will be assessed at baseline, throughout the first, second, and third menstrual cycles during treatment (months 1, 2, and 3), and throughout the 3-month follow-up period (months 4, 5, and 6). Table 1 presents the study design schedule.

Secondary outcomes
(a) Health-related quality of life assessed by the Short Form 36 Health Survey (SF-36).
(b) Change in the content of CA 125 in serum.
(c) EM cyst diameter assessed by ultrasound examination.
(d) Dosage and administration time of rescue medication used during the study period.

The secondary outcomes will be assessed at baseline, the third menstrual cycle during treatment (month 3), and the third menstrual cycle (month 6) in the follow-up period.

Safety and adverse events (AEs): AEs that occur during the trial will be recorded and assessed by the investigators at the end of each treatment session and at subsequent visits. AEs related to moxibustion may include skin allergies, skin burns, hematoma, pallor, sweating or dizziness, fainting during the moxibustion treatment, and unbearable burning pain or skin pigmentation after treatment. AEs related to medication may include drug allergies and gastrointestinal discomfort. The investigators will record the date of AEs occurrence, duration, degree, and rescue measures.

If serious AEs occur, the investigators will immediately report to the principal investigator and ethics committee, who will make a decision as to whether or not the participant needs to be withdrawn from the study.

Criteria for discontinuity of intervention
(a) Participants who are unable to complete the treatment for personal reasons and request withdrawal from the study.
(b) Participants that suffer serious AEs during the trial and cannot continue to participate in this study based on the participant’s request or decision by the principal
investigator. 
(c) Participants whose condition becomes worse and requires other treatment.

Quality control
All practitioners involved in this study will be trained uniformly before the start of the trial. The training program will cover participant screening and recruitment, moxibustion manipulation method, outcome measures, and data processing. HPM will be performed by licensed acupuncturists who have passed the national qualification exam for Chinese TCM doctors, and practiced acupuncture and moxibustion for more than 5 years. In addition, any dropout and withdrawal from the trial during the intervention and follow-up periods will be recorded in detail. Moreover, clinical supervisors will monitor the study regularly to ensure the quality of the trial.

Data management
Data collection will be performed in accordance with the pre-approved protocols. All assessors will be trained uniformly to record outcomes and complete the case report forms. One independent supervisor will regularly audit the trial to verify the consistency of the raw and recorded data. The Data Safety Monitoring Board will be from the Clinical Evaluation Center of Zhejiang Provincial Hospital of Traditional Chinese Medicine (TCM), and comprise individuals who are independent of the investigational site and who have expertise in multiple disciplines, including gynecology, acupuncture, and biostatistics. This Board will review the performance and safety of the trial monthly, and provide recommendations to the sponsor regarding stopping/continuing enrollment in the study, including conducting planned formal interim analyses. The costs of treatment and all outcome measurements will be provided at no cost for participants.

Sample size estimation
Participants will be distributed into two groups using a 1:1 ratio. The required sample size was determined based on the results from relevant literature studies.13,14 We assume that the pain intensity assessed using the VAS scores in the treatment group will be approximately 3.4 lower than the control arm. A two-sided 5% significance level and 80% power will be considered. On the basis of the calculation, approximately seven participants in each group are required for a sufficient sample size. With an estimated dropout rate of 20%, each group requires nine initial participants. However, given the adequate funding and sources of participants, the sample size will be doubled to 36, meaning we will include 18 women in each group.

Statistical analysis
Statistical analyses will be performed using SPSS version 17.0 for Windows (SPSS Inc. Released 2008, SPSS Statistics for Windows, Version 17.0., Chicago, IL, USA) by a third statistician who will not otherwise participate in this trial. Numeric data with normal distribution will be expressed as mean ± standard deviations, and data with skewed distributions as median and 95% confidence intervals. Categorical data will be shown as counts and percentages. Repeated measures analysis of variance will be used to assess changes in continuous variables before and after the intervention. Paired samples t-test will be used to compare changes within the groups, and independent samples t-test will be used for between-group comparisons. Within-group/between-group comparisons for data with skewed distributions will be performed using non-parametric tests. Between-group differences in baseline dichotomous variables (e.g., age) will be tested using χ² tests. A P-value < 0.05 will be considered statistically significant.

Ethical approval and study registration
Ethics approval (approval document No. ZSLL-KY-2016-04, December 1, 2016) was obtained from the Ethics Committee of The Third Affiliated Hospital of Zhejiang Chinese Medical University. The purpose, nature, and potential risks of the research will be fully explained to participants. All participants will complete an informed consent form before participating in this study. All participants’ personal and disease information will be kept confidential.

The study protocol has been registered in the Chinese Clinical Trial Registry, with the identification code ChiCTR-INR-17010326.

DISCUSSION
Currently, conventional treatments for EM are associated with unsatisfactory efficacy, high rates of side effects, and low adherence, and also entail significant cost to patients and society.15-21 Therefore, seeking an optional effective therapy is urgently required. Previous studies suggested moxibustion may have an effect on pain intensity and quality of life in women with EM.22-23 However, this is a complementary and alternative medicine approach, and the introduction of such approaches into mainstream treatments is often limited by lack of robust evidence. Therefore, we designed this RCT using a rigorous methodology. To our knowledge, this will be the first RCT investigating the effect and safety of HPM for treating EM with a wait-list design. The design of this study has several strengths. First, the highlight of this study is that it will adopt a modified HPM method as the intervention. TCM theory suggests EM is etiologically caused by blood stasis and influenced by liver stagnation, Qi stagnation, kidney deficiency, and cold condensate. HPM combines the advantage of heat stimulation, herbal stimulation, and...
acupoint stimulation, and is considered suitable for gynecological diseases such as EM. However, conventional HPM is often only performed at specific acupoints or a small region of the body surface. We chose a much wider area in the lower abdomen and lumbosacral regions in which key meridians are distributed to receive moxibustion, rather than focusing on specific acupoints. With a wider moxibustion region and more moxa on the herbal mixture, this modified HPM method is expected to have stronger firepower and higher temperature than conventional HPM, and may therefore have better efficacy. During the HPM process, the moxa is burned to warm up an herb-partition to stimulate meridians, accelerating the penetration of the herbs into the human body.

In terms of the selection of the moxibustion region, TCM closely associates EM with six meridians: Governor vessel (GV), Conception vessel (CV), Stomach meridian (ST), Bladder meridian (BL), Kidney meridian (KI), and Liver meridian (LR). The GV and CV meridians could coordinate other meridians and balance Yin and Yang. ST and BL are Yang meridians with rich Qi and blood, so they could dispel cold by warming the meridians. KI and LR are closely related to gynecological diseases and may modulate deficiency and excess in the kidney or liver to achieve clinical effects. The herbal paste used during moxibustion includes seven kinds of Chinese herbs, which may activate blood circulation, remove blood stasis, and reduce pain. Therefore, we choose the lower abdomen and the lumbosacral regions as the moxibustion sites, in which the aforesaid six meridians are distributed. From the perspective of TCM, the integrative moxibustion we used in this study is likely to be effective for EM. Moreover, modern experimental studies have also been conducted to explore the biological mechanism of how moxibustion could impact on EM. These investigations revealed that HPM can inhibit p38 MAPK signaling pathways and IL-4 expression, induce the differentiation of Th cells into Th1 cells, and restore the dynamic balance of Th cells. It has also been suggested that lowering the level of plasma 6-keto-PGF1a may be a mechanism by which HPM treats EM. Second, we will make efforts to blind outcome assessors in this trial to minimize detection bias, which could be regarded as the result of the interaction between observers’ predispositions and the subjectivity of the outcomes. Previous reports have found that the use of non-blinded assessors is common, especially in non-pharmacological (e.g., acupuncture and moxibustion) trials. Non-blinded assessors of subjective measurement scale outcomes in RCTs tend to generate substantially biased effect sizes. Third, we carefully considered efficacy indicators when we designed this trial. The selection of appropriate outcomes and outcome measures in clinical trials is critical. Considering that Chinese participants are likely to expect acupuncture and moxibustion to be effective, the placebo effect may exert a more significant influence on the results than if the study was performed with Western participants. To reduce this population bias, we will use multiple outcome measurements, including subjective (VAS and SF-36) and objective outcomes (serum CA125 level and EM cyst diameter assessed by ultrasound examination). The placebo effect may significantly affect subjective outcomes but will not significantly influence objective measurements. The primary outcome measure we will adopt in this study is pain intensity assessed by a VAS, which is the most common scale for the quantification of endometriosis-related pain and skin graft donor site-related pain. It is also the best adapted pain scales for pain measurement in EM. Secondary outcomes will include the SF-36, because the existence of EM-associated symptoms has an adverse impact on physical, mental, and social wellbeing and therefore a negative effect on health-related quality of life. This variable is often assessed using the SF-36. A previous study showed that the SF-36 is a valid and responsive measure for EM and its treatment.

Several limitations of this trial have to be addressed. First, we will not set a placebo control group, which will make it difficult to confirm whether the results are due to the efficacy of moxibustion or its placebo effect. Second, given limitations inherent in the characteristics of moxibustion and Chinese patients’ common knowledge of this therapy, it is impractical to achieve blinding of participants and therapists in our study. Once the participants are aware to which group they are assigned, there may be non-compliance and a high drop-out rate in the control group. Therefore, all participants will be provided with some financial compensation to improve compliance. Third, it would be helpful if the present study could have a longer follow-up period to explore whether HPM has a long-term therapeutic effect.

In conclusion, this protocol describes a randomized, assessor blinded, and wait-list controlled trial that aims to investigate the effect of HPM on pain and quality of life among women with EM. It is believed that this trial will provide evidence in this field and establish a solid foundation for future, large-scale, multicenter clinical trials. Moreover, it will be of great significance for clinical practice to identify an integrative modality of moxibustion for treating EM.

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