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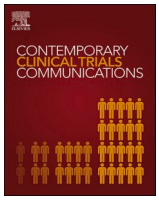

Electroacupuncture for hot flashes in early postmenopause: A study protocol for a randomized sham-controlled trial

Huixian Wang [a,1], Xintong Yu [b,1], Jing Hu [a], Jinjia Chen [a], Yuting Mei [a], Yunfei Chen [a,*]

[a] Department of Acupuncture and Moxibustion, Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[b] Acupuncture Anesthesia Clinical Research Institute, Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

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ABSTRACT

Introduction: Many early postmenopausal women experience hot flashes (HFs). Electroacupuncture (EA) is a safe and effective therapy for menopause-related symptoms. However, there are few rigorous clinical trials on this topic. This randomized controlled trial is designed to explore the feasibility and efficacy of EA in the treatment of early postmenopausal HF.

Methods: This study is a randomized, controlled trial involving 72 early postmenopausal patients. Patients will be randomized 1:1 to the EA or sham acupuncture (SA) group. The acupuncture points that will be used are Hegu (LI4), Fuliu (KI7), Taixi (KI3), Shenshu (BL23), Guanyuan (CV4), and Sanyinjiao (SP6). Participants in each group will receive 18 acupuncture sessions over 6 weeks (three times per week). The primary outcome is the hot-flash score at the end of the 6 week of intervention. Secondary outcome measures are the Pittsburgh Sleep Quality Index, Menopause-Specific Quality of Life, Menopause Rating Scale, Traditional Chinese Medicine Syndrome Score Scale, and estradiol, follicle-stimulating hormone, luteinizing hormone, and anti-Mullerian hormone levels. Safety will be assessed at every visit.

Conclusion: This prospective trial will evaluate the efficacy of EA in the treatment of HFs among early post-menopausal women. Our results will provide additional knowledge for clinicians in the treatment of HFs.

1. Introduction

Hot flashes (HFs) are a feeling of intense heat related to the expansion of skin blood vessels, usually lasting for 1–5 min [1]. The incidence and severity of HFs increase as women traverse menopause, with almost 85 % of women affected [2]. HFs are a common and characteristic marker of ovarian dysfunction in early postmenopausal women, leading to fatigue, a lack of concentration, and negative emotions such as social embarrassment, psychological distress, and anxiety. There is a strong correlation between HFs and sleep quality [3–5].

Early postmenopause is subdivided into three substages (+1a, +1b, and +1c). Stages +1a and +1b each last 1 year. Stage +1c is a period of stable high follicle-stimulating hormone levels and low estradiol values that is estimated to last 3–6 years [6]. Women undergoing menopause will experience HFs for approximately 7.4 years, most commonly within 4.5 years after their final menstrual period (FMP) [7]. A meta-analysis reported that, among 35,445 women, almost half had HFs 4 years after their FMP and 10 % reported symptoms 10 years after their FMP [8].

Although menopausal hormone therapy (MHT) is the most effective treatment for HFs [9], many women prefer to avoid MHT due to concerns about treatment risks, and prefer nonhormonal pharmacologic and nonpharmacologic treatments [10]. Therefore, alternative therapies with similar efficacy to MHT are crucial. Acupuncture has become a key component of the growing field of complementary and alternative therapy worldwide. It is accepted by physicians and patients extensively because of its satisfactory clinical efficacy, lack of drug resistance, and fewer side effects [11,12]. A good deal of scientific rigor has been dedicated to understanding the mechanism and evidence-based efficacy of acupuncture therapy. Evidence supports the use of acupuncture as a main or supplementary therapy to treat HFs [13].

Electroacupuncture (EA) has also been shown to assist with coping with the symptoms of early menopause, playing an important role in

* Corresponding author.
E-mail address: icyf1968@163.com (Y. Chen).
[1] Huixian Wang, Xintong Yu contributed equally to this work.

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Abbreviations

AE	adverse event
CRF	case report forms
EA	electroacupuncture
EOT	end of treatment
FMP	final menstrual period
HF	hot flashes
MENQOL	Menopause-Specific Quality of Life
MHT	menopausal hormone therapy
MRS	Menopause Rating Scale
PSQI	Pittsburgh Sleep Quality Index
SA	sham acupuncture
SE	sleep efficiency
SOL	sleep onset latency
SSC	sternal skin conductance
TCMSSS	Traditional Chinese Medicine Syndrome Score Scale
TIB	time in bed
TST	total sleep time
WASO	wake after sleep onset

daily rehabilitation and healthcare [14,15]. A recent meta-analysis also determined that EA consistently performed better than traditional acupuncture in reducing HFs in menopausal women over time (as compared to SA) and that EA was overall more efficacious than traditional acupuncture and significantly more efficacious than SA in reducing HFs at 8 weeks of intervention [16]. Many studies have confirmed the efficacy of acupuncture for HFs [17,18]. However, another recent network meta-analysis found that traditional acupuncture may be more effective than EA and SA in reducing HF frequency and severity, and SA may also be more effective than EA in reducing HF severity. The authors concluded that more high-quality randomized controlled trials are needed to better establish the effects of acupuncture on menopausal HFs [19]. The authors identified that most studies included in the review had an unclear or high risk of bias in allocation concealment and blinding and had small sample sizes [19]. Therefore, more studies should be conducted to better establish the efficacy of EA in alleviating HFs in women. Furthermore, the efficacy of EA in early postmenopausal women is not well understood.

We designed this study to investigate whether EA is effective in alleviating early postmenopausal HFs. Our primary objective was to evaluate the effectiveness of EA compared to sham acupuncture (SA) in early postmenopausal women with HFs. The secondary objective was to assess quality of life using Pittsburgh Sleep Quality Index (PSQI) and Menopause-Specific Quality of Life (MENQOL) directly, one month, and 3 months after the end of treatment (EOT). We hypothesized that EA would be superior to SA at alleviating the severity and frequency of early postmenopausal HFs.

2. Materials and methods

2.1. Study design

We designed the study as a randomized controlled trial. A total of 72 participants meeting the inclusion criteria will be recruited and randomly divided into two groups (EA group or SA group) in a 1:1 ratio. The trial will last 19 weeks, with a one-week baseline period, a 6-week treatment period, and 12 weeks of follow-up. Assessments will be conducted by an independent evaluator at four time points: before treatment, at the EOT, 4 weeks after treatment, and 12 weeks after treatment. The Shanghai University of Traditional Chinese Medicine will be responsible for data management and statistics. Measurements to be obtained during the trial are listed in Table 1. Fig. 1 shows the flow chart of the trial.

Table 1
Trial processes.

Time points	Study period				
	Recruitment	Baseline	Treatment	Follow-up	
	Week 1	Week 0	Week 6	Week 10	Week 18
Enrolment					
Eligibility screen	×				
Informed consent form	×				
Medical history	×				
Allocation		×			
Interventions					
Electroacupuncture	18 treatments				
Sham acupuncture	18 treatments				
Assessments					
Primary outcome					
Hot flashes		×	×	×	×
Secondary outcomes					
MENQOL		×	×	×	×
PSQI		×	×	×	×
MRS		×	×		
TCMSSS		×	×		
Serum sex hormone		×	×		
Others					
Adverse events			×	×	×
Patient compliance			×	×	×

PSQI, Pittsburgh Sleep Quality Index; MENQOL, Menopause-Specific Quality of Life; MRS, Menopause rating scale; TCMSSS, Traditional Chinese Medicine Syndrome Score Scale.

Ethical approval for this trial was obtained on March 6, 2023 by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine (Review number: 2023-047). The registration number in the Chinese Clinical Trial Registry (http://www.chictr.org.cn) is ChiCTR2300072002. This study protocol conforms to the guidelines of the recommendations for international trials (SPIRIT 2013) [20] and the Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines (SCRICTA) [21].

2.2. Recruitment

Patients will be recruited from the outpatient clinic in the Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine. We will recruit 72 eligible participants from the Department of Acupuncture and Moxibustion and the Department of Gynaecology. Our recruitment strategy includes delivering printed posters and posting online advertisements to briefly introduce our study and recruit patients who are willing to participate. We will also post an advertisement on the billboards of our outpatient clinic, with the advertisement shown outside to attract possible candidates.

Patients who sign up for this trial will initially be screened by phone and then asked to participate in a face-to-face interview to confirm that they meet our inclusion/exclusion criteria. All the investigators will be trained in patient selection and exclusion. Participants will be told that they will be assigned to one of two interventions and provided with information about the general content of the study procedures, its potential benefits, and its risks. Written informed consent will be obtained before study allocation.

2.3. Sample size

We calculated our sample size by comparing the hot-flash scores of two groups at their primary endpoint in a prior clinical study [22]. The mean scores ± standard deviations in the treatment and control groups were 4.80 ± 1.98 and 6.41 ± 1.46, respectively. To achieve a

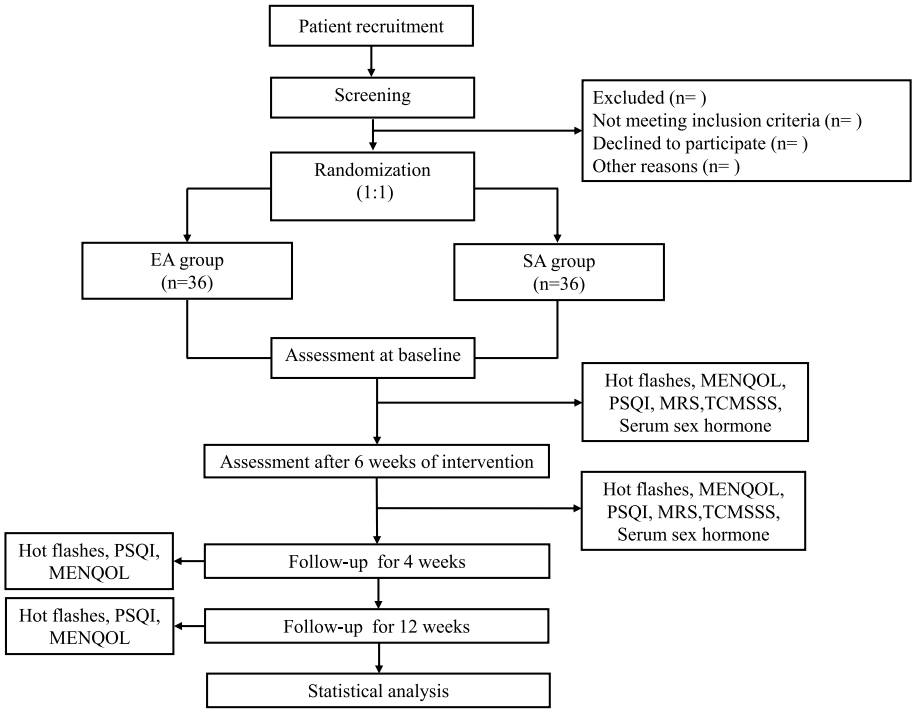

Fig. 1. Trial flow chart.

significance level of $\alpha = 0.05$ and a power (1-β) of 90 %, 64 participants are required to be recruited. Considering a possible dropout rate of 10 %, 72 individuals will be needed in total, 36 in each group.

2.4. Inclusion and exclusion criteria

Table 2 presents the study's inclusion and exclusion criteria.

2.5. Randomization

In this trial, SAS 9.4 (SAS Institute Inc., Cary, NC) will be used to generate a random sequence. The random allocation sequence will be implemented by one of the researchers not involved in recruiting and assessing the patients. Random allocation cards will be packed into opaque envelopes. Patients who meet the study eligibility criteria and provide consent can open the envelopes in the order of their visits. Participants will have the same probability of being allocated into either study group.

Table 2
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Female	Experiencing hot flashes that began or worsened after a breast cancer diagnosis or commencing treatment for breast cancer
Aged 40–60 years	Diagnosed with polycystic ovary syndrome, primary ovarian insufficiency, or premature ovarian failure
Meets criteria for early postmenopause according to the Stages of Reproductive Aging Workshop +10 (STRAW+10)	Undergone a hysterectomy or endometrial ablation
Hot-flash score recorded for 7 consecutive days with a total score of ≥6	Developed amenorrhea due to medical reasons
Diagnosed with kidney yin deficiency [23]	Used any medication or complementary therapy over the past 2 months to treat hot flashes or is taking hormonal medications
Voluntarily provides written informed consent	Experiencing hyperthyroidism, poorly controlled hypothyroidism, severe mental illness, or serious physical illness
	Underwent acupuncture within the 6 months preceding the study
	Pregnant or lactating

2.6. Blinding

Randomization and blinding will be coordinated by the manager of the research group. The participants as well as the statisticians assessing the outcome measures will be blinded to the allocation scheme. Investigators, responsible only for recruitment and evaluation, will also receive no information about the randomization and intervention process. Envelopes will be opened by the treating acupuncturists before the first session of the intervention. The acupuncturists cannot be blinded due to the nature of the intervention. Researchers will reveal participant group allocation after the completion of the statistical analysis.

2.7. Intervention

Participants will receive 30–45 min of EA or SA in a supine position, three times a week, for 6 weeks. The treatment will be performed by licensed acupuncturists with at least 5 years of clinical experience. All treatments will be performed at the outpatient clinic. Patients will wear appropriate eyewear during treatment. To monitor compliance, each treatment form and evaluation form will be filled out once the patient finishes the treatment. Each participant will be treated and assessed separately during the study.

2.7.1. EA group

The treatment provided to the EA group is based on a recognized acupuncture textbook [24] and will follow the standard approach used by the outpatient clinic of our study hospital, which was recently recognized as the best in the nation for integrated Traditional Chinese Medicine and Western Medicine. Specifically, size 0.25 × 40 mm disposable steel needles (Guizhou Andi Medical Instrument Co., Ltd.,

Guizhou, China) and the SDZ III EA apparatus (Hwato, Suzhou Medical Appliance Co., Ltd., Jiangsu, China) will be used. Patients will receive treatment at six acupuncture points: Hegu (LI4), Fuliu (KI7), Taixi (KI3), Shenshu (BL23), Guanyuan (CV4), and Sanyinjiao (SP6). These points were selected as per the WHO Standard Acupuncture Point Locations [25]. The locations of the acupoints are described in Table 3. After local skin disinfection with 75 % alcohol wipes, needles will be inserted perpendicularly into bilateral BL23 while the patients are in a sitting position. The acupuncturist will lift, thrust, and rotate the needles for 30 s to help the patients receive deqi sensation (a sensation of numbness, soreness, heaviness, or distention in response to acupuncture) [26]. Needles at BL23 will not be retained.

Patients will then be told to lie in a comfortable supine position. CV4 and bilateral LI4, KI7, KI3, and SP6 will be stimulated. The depth of needle insertion will be adjusted as per the standard permissible depth of insertion for each point. The electrodes from the EA device will be placed at LI4, KI7, and SP6 bilaterally. EA stimulation will be performed for 30 min with a continuous wave of 2 Hz. The current intensity will be adjusted according to the patient's sensitivity.

2.7.2. SA group

Participants in the SA group will receive no skin penetration [27]. Non-invasive acupuncture needles with blunt tips (40 mm in length and 0.25 mm in diameter) produced by Suzhou Hwato Medical Appliance Co. Ltd (Jiangsu, China) will be used to serve as a sham control. When the blunt needle tips touch the skin, the patients will feel a pricking sensation, but without the needle truly piercing the skin. After skin disinfection, patients will be placed in a sitting position. Sterile adhesive pads will be placed on the Shenshu points, and needles will be retained for 30 s without deqi sensation. After needle extraction, patients will lie down and sterile adhesive pads will be placed on the CV4 and bilateral LI4, KI7, KI3, and SP6. The same non-invasive acupuncture needles are used with the electric stimulator applied to LI4, KI7, and SP6 bilaterally. All the indicators of the electrostimulator will be set to "0." The needles will also be maintained for 30 min in each session.

2.8. Data management

We will use case report forms (CRFs) to collect data, and use Epidata software for data management. All clinical observation results will be recorded in the CRF. Withdrawal data and the reasons for withdrawal will be recorded. Information collected will be transcribed into the database, which was established based on planned observations. CRFs will be safely stored in a locked room for more than 5 years at Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine. Two investigators will be responsible for data entry and retention. Data access will be restricted to the study team. Only baseline characteristic data and study-related information will be collected. Participant confidential data will not be made available to the public.

Table 3
Acupoints and location.

Points	Location
Hegu (LI4)	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone
Fuliu (KI7)	On the posteromedial aspect of the leg, anterior to the calcaneal tendon, 2 B-cun superior to the prominence of the medial malleolus
Taixi (KI3)	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon
Shenshu (BL23)	In the lumbar region, at the same level as the inferior border of the spinous process of the second lumbar vertebra (L2), 1.5 B-cun lateral to the posterior median line
Guanyuan (CV4)	On the lower abdomen, 3 B-cun inferior to the center of the umbilicus, on the anterior median line
Sanyinjiao (SP6)	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus

1 B-cun is defined by dividing the height of the human body into 75 equal units, and then estimating the length and width of a certain part of the body according to such units. One unit is equal to one cun.

2.9. Outcome measures

The primary outcome is the hot-flash score at the end of the intervention. Validated hot-flash daily diaries will be used, which have become a recognized tool for clinical researchers to evaluate the severity of vasomotor symptoms [28]. Patients will record the hot-flash daily dairies for 7 consecutive days before and after treatment. This diary will include the number and degree of HF, represented as 1, 2, 3, or 4 for mild, moderate, severe, and very severe symptoms, respectively. We will calculate the HF score using the following equation: ([1 × number of mild HFs] + [2 × number of moderate HFs] + [3 × number of severe HFs] + [4 × number of very severe HFs]) ÷ number of days reported.

The secondary outcomes of the study include the following items: MENQOL; menopause rating scale (MRS); PSQI, Traditional Chinese Medicine Syndrome Score Scale (TCMSSS); and estradiol, follicle-stimulating hormone, luteinizing hormone, and anti-Mullerian hormone levels. The PSQI and MENQOL are measured at randomization and 6, 10, and 18 weeks thereafter. The other outcomes are measured before and 6 weeks after randomization.

The MENQOL will be used to assess symptoms relevant to menopause from 1 month prior. The questionnaire consists of 29 items in four dimensions as follows: physical, vasomotor, psychological, and sexual. Participants are asked to rate their menopausal symptoms with a score of 0–6, where a higher score indicates more severe symptoms. The total score of the scale is the sum of the scores for each item, which ranges from 0 to 174. The higher the score, the worse the patient's quality of life [29,30].

The MRS, which contains 11 items rated from 0 to 4, is a reliable method to measure the severity of menopause. This scale is used to describe psychological, somatic-vegetative, and urogenital symptoms. The total score is the sum of the scores for each item, and ranges from 0 to 44 (0, no symptoms; 44, severe symptoms) [31,32].

The PSQI scale is used to assess patient sleep quality over the last 30 days. The scale consists of nine questions, from which sleep onset latency (SOL), time in bed (TIB), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) are calculated. Responses to each question are scored from 0 (never in the past month or very good) to 3 (three or more times a week or very poor). The overall score ranges from 0 to 21. The combination of sleep quality and quantity can be utilized to assess sleep conditions [33,34].

The TCMSSS will be assessed at baseline and EOT according to the guidelines for clinical research on new Chinese medicines [35]. The two groups of patients will be evaluated for symptoms of HF and their quality of life. Scores for each item will range from 0 to 3, with higher scores indicating more severe symptoms.

2.10. Adverse events

All adverse events that occur after the participants receive EA or SA, whether they are related to the experimental method or not, will be recorded in the adverse event table. Adverse events include syncope, pain at the acupuncture point, bleeding, hematoma, vertigo, and infection. Abnormalities that are significantly unrelated to the current disease, if developed during the trial, will also be recorded. The time that the AE occurs and lasts, severity, and treatment thereof will be written down in detail. AEs will be managed by acupuncturists within 24 h. Prevention principles and methods will then be provided. Serious adverse events will be reported to the ethics committee of Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine.

2.11. Quality control

Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine will supervise the study. We will strive to standardize every stage of the trial, including the selection of acupuncture points, the EA procedure and the clinical expertise of the therapists. Before the trial, investigators will inspect the equipment and all staff will undergo strict training. The acupuncturists are fully informed of potential adverse events and will take appropriate action when they occur. Participants will wear blindfolds so they cannot see their manipulation. To avoid patient interaction, each patient will be treated in a separate room. In addition, patients participating in the study will receive free treatment sessions. EA safety protocols will be adhered to throughout the trial. Any changes to the study protocol will be provided to the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine. A qualified clinical trial expert will be invited to monitor the study, examine the collected data, and control for bias.

2.12. Statistical analysis

All clinical data will be recorded in a formatted case report form and statistically analyzed using SPSS 26.0 software (SPSS Inc, Chicago, IL) by statisticians who are not involved in the design and implementation of the trial. Descriptive analysis will be used to analyze the baseline characteristics between the two groups, and results will be written as mean ± standard deviation. T-tests or a one-way analysis of variance will be performed on data that conforms to homogeneity of variance according to the data type. Otherwise, the Mann–Whitney U-rank sum test will be performed. Comparisons between the two groups will be carried out via *t*-test or one-way analysis of variance according to the data type and methods. Repeated measures analysis of variance will be used to analyze the hot-flash score, MENQOL, and PSQI at different time points and interaction terms between the treatment groups versus time. Chi square analysis or Fisher's exact test will be used to compare adverse events between the two groups, and adverse events that occurred in this trial will be described in a list and analyzed. Missing research data will be imputed using multiple imputations. All statistical tests will use a two-sided test, with the significance level set at 0.05.

3. Discussion

The efficacy of EA in the treatment of HFs is now well established [36]. Cao et al. randomly divided patients with perimenopausal HF into EA and manual acupuncture groups using the acupoints Guanyuan (CV 4), Zigong (EX-CA 1), Tianshu (ST 25), and Sanyinjiao (SP 6) [37]. Both acupuncture and EA improved perimenopausal HF and serum sex hormone levels. These effects are similar to those of Xiao et al. who used Bu Shen Tiao Qi (supplementing the kidney and regulating gi) needling combined with EA to treat perimenopausal syndrome, which was compared with a control group that underwent shallow needling plus sham EA [38]. Their study suggested that EA could significantly improve HF and sweating [38]. Despite the positive effects of EA on HFs in that study, the efficacy in early postmenopausal women has not been confirmed.

For clinicians who are not familiar with traditional Chinese medicine, systemic manual acupuncture is a very difficult, even delicate technique to learn. EA is an enhancement of traditional acupuncture that uses electricity rather than manual manipulation to stimulate acupuncture points. It is believed that the electrical impulses can amplify the stimulation from needles at acupuncture points. EA may also be easier to standardize and have more stable, replicable results in both clinical and research settings [39]. Therefore, EA is an ideal technique for bringing acupuncture into the mainstream of healthcare. EA might serve as a reliable alternative therapeutic tool. First, considering differences in resistance between acupuncture points, the EA instrument can be designed to detect the resistance and potential of acupoints in the future, to provide more advanced and objective clinical data. Second, because the pulse frequency of the EA meter is fixed and the cycle is repeated, patients are prone to adapt to the stimulation frequency and intensity. Reinforcing and reducing methods in artificial acupuncture can be simulated through periodic changes in electrical stimulation. Third, traditional EA instruments do not allow for data storage, traceability, or treatment information analysis. If sensors can be intelligently integrated to monitor and store physiological parameters and the data uploaded onto the internet, more personalized treatment can be provided to patients.

Given the lack of standardized assays for key biomarkers, current menstrual cycle criteria are key, while biomarkers remain a supportive criterion. A highly sensitive, well characterized, and relatively stable biomarker is needed to discriminate between Stage +1 and + 2 menopause. The lack of standardized assays also limits the translation of research findings into cost-effective clinical tools [6]. Additional studies are needed to characterize hormonal changes from Stage +1 to +2 of menopause and to evaluate the effects of EA on other stages or symptoms of menopause.

In this study, reports of HF are recorded the next day in the diary. However, these records can be influenced by emotions, memory, and sleep quality [40]. Objective measures may be useful to precisely report HFs overnight. Such measures, including sternal skin conductance (SSC), can record increased skin conductance from the sternum, which is an objective marker of HFs [41,42]. SSC measures skin conductance induced by sweating or sympathetic activation. However, there is significant heterogeneity between studies, and SSC has been found to have considerable measurement error. It may be a less reliable indicator of hot-flash symptoms than self-reporting due to its accidental identification of other causes of sympathetic activation [43]. The overall accuracy and utility of SSC in the evaluation of HF remain controversial [44].

Our proposed study has many strengths. Our trial may clarify the optimal timing of acupuncture intervention for HF. Our EA protocol is based on an acupuncture textbook [24] and follows standard treatment approaches used by practitioners in our outpatient clinic, which is located in the Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine, a nationally recognized leader in integrated Traditional Chinese Medicine and Western Medicine. Patients will be treated by experienced, acupuncturists with at least 5 years of clinical experience. We will use validated measures that measure important outcomes related to HFs, including changes in the frequency and severity of HF, quality of life, and follicle-stimulating hormone, estradiol, and luteinizing hormone levels. We will also examine additional physical and mental health outcomes, including sleep quality, shown by some studies to be positively affected by acupuncture [45]. Our approaches to randomization and blinding introduce a low risk of bias [46], including minimizing risks of bias most commonly present in acupuncture trials of HFs (i.e., blinding of participants and personnel, blinding of outcome assessment). Lastly, our proposed sample size is greater than the majority of existing published randomized clinical trials investigating EA in treating symptoms of HFs [19].

There are some limitations to this trial. First, the study is unable to use a double-blind design, as the sensation of deqi obtained by acupuncturists is a core component [47]. Second, the measurements we will use are short-term outcomes, without long-term follow-ups beyond 12 months. Third, a high sensitivity and accurate objective measurement of HFs is not available. Fourth, we have not included a treatment control group that could evaluate the absolute effects of both interventions.

We expect that EA will have significant positive influence on HF and improve patient quality of life. To achieve the goals of this study, we will strictly implement randomization and data analysis to avoid systematic errors and minimize bias.

Declaration of generative AI in scientific writing

The authors declare that generative AI and AI-assisted technologies were not used in the writing process.

Author contributions

YC has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YC and XY conceived of the research plan. HW drafted the original protocol. JH formed the statistical analysis plan. HW and YC recruited the participants. YC, XY, HW, JH, JC and YM coordinated the study. All authors participated in, read and approved the final manuscript.

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The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; and the decision to submit the manuscript for publication.

Protocol version

Protocol version: 20230723; date: July 23, 2023.

Patient and public involvement

Patients and/or the public are not involved in the design, conduct, reporting or dissemination plans for this research.

Patient consent for publication

Not required.

Statement of human rights

The intervention conformed to ethical criteria.

Data sharing statement

The corresponding author can be contacted for data requests.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101234.

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