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Original Article
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Study Protocol for Multi-Center, Open-Label, Randomized Controlled Trial for Assessing the Efficacy and Safety of Electroacupuncture for Cold Hypersensitivity in Hands and Feet

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Objectives: Cold hypersensitivity in the hands and feet (CHHF) is defined as the symptom of a sensation of coldness in the extremities under conditions that are not considered cold by an unaffected person. CHHF can affect the quality of life by placing restrictions on one's daily activities. Although electroacupuncture (EA) and acupuncture have been widely used for treating CHHF, randomized clinical trial (RCT) has not yet been conducted for evaluating the safety and efficacy of EA or acupuncture for the treatment of CHHF. This study aims to evaluate the effects of EA in CHHF patients.
Methods: This study is a randomized, multicenter, and parallel design clinical trial. Overall, 72 participants will be randomly assigned to the EA treatment group, acupuncture treatment group, and untreated control group in 1:1:1 ratio via a web-based randomization system. The EA treatment group and acupuncture treatment group will receive EA or acupuncture treatment by visiting ten times at intervals of twice a week for five weeks. Follow-up visits will be made four weeks after the end of treatment. For the untreated control group, three visits will be made. The primary outcome measures will be the CHHF visual analogue scale score. Secondary outcome measures will be the body temperature of hands and feet, total scores of the Korean version of the World Health Organization Quality of Life Scale abbreviated version, the results of the questionnaire of health-related quality of life, questionnaire of demonstration, and questionnaire of cold hypersensitivity.
Conclusion: This study will be the first clinical trial to evaluate the efficacy and safety of EA for the treatment of CHHF. We expect this study to provide basic evidence for the treatment of CHHF with EA and future large-scale RCTs.

Keywords: acupuncture, cold hypersensitivity, electroacupuncture, randomized clinical trial

INTRODUCTION

Cold hypersensitivity in hands and feet (CHHF) is defined as a heightened cold sensation in these extremities at a relatively low temperature or a sensation of coldness in an environment not considered cold by unaffected people [1]. According to a Korean genetic study on twins, the ratio of females to males exhibiting CHHF is 3:2 [2]. The prevalence of CHHF in Korean, Japanese, and Chinese women is 25%, 54.3%, and 20%, respectively [3].

CHHF can affect the quality of life by restricting daily activities. The presumed causes of CHHF are peripheral neuropathy, autonomic nervous dysfunction, anemia, diabetes mellitus, and

median neuritis [4]. However, few studies have examined the pathophysiology of CHHF [2]. Furthermore, established treatment methods for CHHF are currently unavailable, with present treatment methods often including behavior modification [5]. Therefore, an effective treatment method for CHHF needs to be developed.

Electroacupuncture (EA) is a modern way of administering acupuncture, which involves applying a pulsed electrical current to acupuncture needles to stimulate acupoints [6]. EA is known to have effects on neuropathic pain [7], persistent pain [8], analgesia [9], and other conditions. Additionally, EA has been used to treat cold hypersensitivity. An experimental study [10] and a case report [11] have shown that EA treatment for cold hypersensitivity can promote relieving effects.

Although EA and acupuncture have been widely used to treat CHHF, randomized clinical trials (RCTs) have not yet been conducted to evaluate their efficacy and safety. This open-label, randomized, parallel-design, multicenter clinical trial aims to determine the effects of EA in CHHF patients. This study aimed to provide basic evidence for the treatment of CHHF with EA and future large-scale RCTs.

MATERIALS AND METHODS

1. Objectives

This study aimed to objectively evaluate the efficacy and safety of EA treatment in Korean women patients with CHHF.

2. Study design and setting

This study is a randomized, multicenter, parallel-design clinical trial performed at three Korean Medical Hospitals: Sangji University Korean Medical Hospital, Semyung University Korean Medical Hospital at Chungju, and Dongguk University Korean Medical Hospital at Ilsan.

A total of 72 participants from three hospitals were enrolled in this study. The EA treatment group, acupuncture treatment group, and untreated control group contained 24 participants each. All participants were fully informed before signing the written informed consent form. The principal investigator (PI) or researchers obtained written informed consent. The eligible participants were assigned a subject identification code and randomly assigned to three groups. In the case of EA and acupuncture treatment groups, EA or acupuncture treatment was performed 10 times at intervals of twice a week for five weeks. Follow-up visits were performed four weeks after the treatment ended. Three visits were made for the untreated control group: visits 1, 10 (when treatment was terminated), and 11 (four weeks after treatment). During the trial, participants were prohibited from administering other medicines that could affect CHHF symptoms. The study flow chart is presented in Fig. 1.

3. Randomization

Participants who signed the informed consent form and met the inclusion criteria were randomly assigned to the EA treatment group, acupuncture treatment group, and untreated control group in a 1:1:1 ratio on visit 1. An independent statistician from the Kyunghee University Korean Medicine Clinical Trial

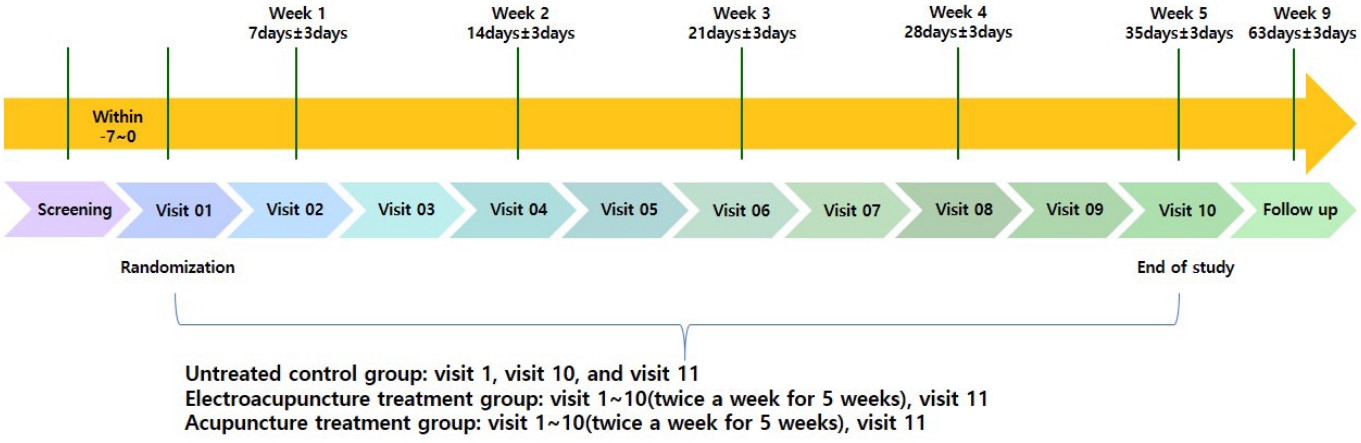

Figure 1. Flow chart of the study.

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Center (K-CTC) or an independent researcher conducted the randomization. Random assignment numbers were generated using a web-based randomization system blockrand package (version 1.3 or later; Intermountain Healthcare, Greg Snow, USA) and stratified according to the institution. The sealed envelope method was used for randomization concealment.

4. Blinding

This study was an open-label, unblinded study for all group assignments. However, the evaluator who evaluated the participant's symptoms was blinded separately from the operator, minimizing the evaluation bias.

5. Participants

1) Inclusion criteria

The inclusion criteria are presented in Table 1.

2) Exclusion criteria

The exclusion criteria are described in Table 2.

3) Withdrawals

All participants had the right to discontinue their participation in the clinical trial upon request. The detailed withdrawal criteria are described in Table 3. The reasons for withdrawal were documented in the case report forms (CRFs), and the data

Table 1. Inclusion criteria of the clinical trial

Inclusion criteria
1. Women aged 19-59 years with CHHF.
2. Participants must have at least one or more of the following symptoms below. 2.1. Participants have the symptoms of cold hands and feet in normal temperature, which is not cold for most individuals. 2.2. Participants have the symptoms of severe cold hands and feet in colder than normal temperature exposure. 2.3. Even when the participant returns to a warmer environment, the symptoms of cold hands and feet does not completely disappear.
3. During screening visits, the participant's visual analogue scale (VAS) score of cold hypersensitivity on hands or feet is four or more.
4. When the participant's both upper arms are exposed to room temperature (24℃ ± 2℃) for 10 minutes, the thermal deviation between the foot (acupuncture point, LR3) and the thigh (acupuncture point, ST32) may be higher than 2℃ or the thermal deviation between the hand (acupuncture point, PC8) and the forearm (acupuncture point, LU4) may be higher than 0.3℃.
5. Ability to comply with all study-related procedures, medications, and evaluations.
6. Ability to provide informed consent.

Table 2. Exclusion criteria of the clinical trial

Exclusion criteria
1. Patients who were administered calcium antagonists or beta-blockers for CHHF treatment.
2. Patients with one or more finger gangrene or ulceration.
3. Patients diagnosed with hypothyroidism or under thyroid medications.
4. Patients diagnosed with an autoimmune disease.
5. Patients diagnosed with Carpal Tunnel Syndrome or Tarsal Tunnel Syndrome or having a positive Tinel's sign and Phalen's tests.
6. Patients diagnosed with cervical disc herniation or lumbar intervertebral disc herniation.
7. Patients diagnosed with diabetes.
8. Patients taking drugs that may affect CHHF (e.g., anticoagulants).
9. Moderate level of liver dysfunction (each of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels > 100 IU/L) or kidney dysfunction (creatinine [Cr] levels > 2 mg/dL) in the patient.
10. Patients who do not cooperate with treatment and follow-ups because of behavioral disorder, depression, anxiety neurosis, schizophrenia, or serious mental illness.
11. Adult non-pregnant women with hemoglobin (Hb) level of < 7 g/dL, white blood cell (WBC) count of > 11,000/mm^3, and random plasma glucose level of < 50 mg/dL or > 250 mg/dL.
12. Patients whose systolic blood pressure (SBP) is ≥ 180 mmHg or diastolic blood pressure (DBP) is > 100 mmHg based on the average value of at least two measurements.
13. Patients with pulmonary tuberculosis lesion or pneumothorax other than inactive tuberculosis on chest X-ray.
14. Patients with suspected arrhythmia that showed up on electrocardiogram (ECG) or those diagnosed with heart disease, such as ischemic heart disease.
15. Patients who abuse alcohol or drugs.
16. Women patients who are pregnant (positive urine human chorionic gonadotropin [hCG]) or lactating or having the chances of pregnancy.
17. Patients diagnosed with malignant tumors.
18. Patients participating in other clinical trials or within two months of completion of the study.
19. Patients refusing to participate in this trial or do not provide written informed consent.
20. Patients who are unable to understand or speak Korean.
21. Patients who are judged to be unfit for the clinical study by the researchers.

Table 3. Withdrawal criteria of the clinical trial

Withdrawal criteria
1. Participants whose treatment compliance is < 70%.
2. Participants who get pregnant during the clinical trial period.
3. When surgery or hospitalization is necessary owing to accidents or other diseases.
4. Participants' withdrawal of consent.
5. Participants who received prohibited medicines or treatments (e.g., anticoagulants, psychotropic drugs, and other medications that may affect CHHF symptoms).
6. Participants who require standard treatment owing to the aggravation of CHHF symptoms.
7. Occurrence of serious adverse events (SAEs).
8. Occurrence of other inevitable reasons: difficult to maintain the trial process or PI's decision to discontinue the trial owing to some factors that may have an effect on the study results.

were analyzed using the intention-to-treat (ITT) method.

6. Procedure

1) Recruitment

Eligible participants who passed the screening were recruited from three Korean Medical University Hospitals. Sangji University Korean Medical Hospital recruited 18 patients, Semyung University Korean Medical Hospital at Chungju enlisted 24 patients, and Dongguk University Korean Medical Hospital at Ilsan enrolled 30 patients. Participants were recruited through public outdoor advertising.

2) Study schedule

The clinical trial schedule is presented in Table 4.

7. Interventions

The acupuncture treatment group received acupuncture treatment on acupoints (LI4–TE5 and LR3–SP6) using a 0.25 × 30 mm sterile needle (Dongbang Medical, Boryeong, Korea) with a subcutaneous depth of 10-25 mm for 15 minutes. The treatment was performed ten times, twice a week for five weeks. The EA treatment group received EA treatments on acupoints (both LI4–TE5 and LR3–SP6; LI4 connects to TE5 and LR3 to SP6) using an intramuscular stimulator, CELLMAC PLUS, STN-330 (Stratek, Anyang, Korea) with a subcutaneous depth of 10-25 mm. The treatment was performed ten times, twice a week for five weeks. One EA treatment lasted for 15 minutes at a frequency of 2 Hz. The untreated control group did not receive EA or acupuncture treatment; instead, the control visited to check for any change in symptoms at visits 1, 10, and 11, three times in total.

8. Outcomes

The primary outcome measure in this clinical trial was the VAS of CHHF. Secondary outcome measures were the temperatures of hands and feet, a questionnaire of the Korean version of the World Health Organization Quality of Life Scale abbreviated version (WHOQOL-BREF), a questionnaire of health-related quality of life (EQ-5D), a questionnaire of demonstration, and a questionnaire of cold hypersensitivity.

1) Primary outcome measures

(1) CHHF VAS score

The VAS is a 10-point scale representing the severity of symptoms. Participants were asked to indicate the line corresponding to their coldness. The left end of the line (VAS 0) indicated no coldness, and the right end of the line (VAS 10) indicated the most severe coldness. The VAS score was then checked to assess the severity of CHHF symptoms at visits 0, 1, 10, and 11. The VAS score was also calculated at visits 4 and 8 in the acupuncture and EA treatment groups.

2) Secondary outcome measures

(1) Body temperature (BT) of hands and feet

Participants were asked to avoid consuming alcohol, caffeine, smoking, conducting hot showers, and extreme exercising for at least 2 hours before the measurement. After 10 minutes of sitting and resting with at least 10 cm of exposure above both elbows and the lower garment up to the knees in a room with 24℃ ± 1℃ and 40%-60% humidity, the BT of both palms (PC8), the center of the anterior upper arms (LU4), the center of the front thighs (ST32), and frontal part of the dorsum of feet (LR3) were measured within 10 minutes before and after treatment using a thermometer (Testo 835-T1, Lenzkirch, Germany) at visits 0, 1, 10, and 11 in the untreated control group. These recordings were measured in the acupuncture and EA treatment groups at every visit.

(2) WHOQOL-BREF

The WHOQOL-BREF, a questionnaire estimating the quality of life, comprises 26 items. Moreover, the WHOQOL-BREF

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Table 4. Study schedule of the clinical trial

	Screening	Treatment period			Follow-up
	Visit 0 (day−7 through−1)	Visit 1 (day 0)	Visit 2-9[1]	Visit 10 (day 35 ± 3)	Visit 11 (day 63 ± 7)
Informed consent	●				
Screening numbering	●				
Chest X-ray & ECG	●				
Eligibility criteria	●				
Randomization		●			
Untreated control group		■		■	■
Treatment compliance			○	○	○
Assessment of participant dropout			○	○	○
Vital signs	●	●	○	●	●
Body measurement[2]	●			●	●
Route and motive of study participation	●				
Collection of demographics, sociological[3], and gynecological information	●				
Medical history & medication	●	●	○	●	●
Questionnaire of constitution (KS-15)	●				
General physical examination	●	●	○	●	●
Thermometer measurement[4]	●	●	○	●	●
CHHF VAS	●	●	○[5]	●	●
Monitoring of AE			○	●	●
Questionnaire of Pattern Identification	●				
Questionnaire of Cold Hypersensitivity		●		●	●
WHOQOL-BREF		●		●	●
Questionnaire of health-related quality of life (EQ-5D)		●		●	●
Laboratory tests[6]	●			○	
Acupuncture or EA treatment		○	○	○	
Specifying next visit date		●	○	●	

●All three groups.
○Acupuncture and EA treatment groups only.
■Untreated control group visit date.
[1]Acupuncture and EA treatment groups should be treated twice a week and visit within 4 ± 3 days after treatment.
[2]Height and weight, but only weight, for visits 10 and 11.
[3]Age, occupation, digestion, exercise, smoking, drinking, sleep, etc.
[4]Thermometer measurements of ST32, LR3, PC8, and LU4 at every visit.
[5]Acupuncture and EA treatment groups additionally measure CHHF VAS at visits 4 and 8.
[6]Screening: Hematological examination (WBC, RBC, Hb, platelet), blood chemistry test (BUN, Cr, AST, ALT, r-GTP, glucose), thyroid function test (free T4, TSH), urine test, pregnancy test (urine hCG).
Visit 10: Hematological examination (WBC, RBC, Hb, platelet), blood chemistry test (BUN, Cr, AST, ALT, r-GTP).
AE, adverse event; ALT, alanineaminotransferase; AST, aspartateaminotransferase; BUN, blood urea nitrogen; CHHF, cold hypersensitivity in the hands and feet; Cr, creatinine; EA, electroacupuncture; ECG, electrocardiogram; r-GTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; hCG, human chorionic gonadotropin; RBC, red blood cell; free T4, free thyroxine; TSH, thyroid-stimulating hormone; VAS, visual analogue scale; WBC, white blood cell; WHOQOL-BREF, World Health Organization Quality of Life Scale abbreviated version.

contains five domains: psychological health, physical health, environmental health, general quality of life, and social relationships. The Korean version of the WHOQOL-BREF by Min et al. [12] was used to evaluate the quality of life of CHHF patients at visits 1, 10, and 11.

(3) Questionnaire of health-related quality of life (EQ-5D)

This questionnaire consists of five categories: capacity for locomotion, self-management, daily life, pain/discomfort, and anxiety/depression, and was assessed at visits 1, 10, and 11.

(4) Questionnaire of pattern identification

Pattern identification was checked at the screening visits to correlate the symptoms and changes in VAS scores in patients with CHHF with the pattern identification indexes.

(5) Questionnaire of cold hypersensitivity

Cold hypersensitivity was analyzed at visits 1, 10, and 11 to examine subjective or objective symptoms related to the patient's coldness.

9. Safety assessment

To assess safety, the vital signs and general physical states of each patient were examined at every visit. Hematological examinations (WBC, RBC, Hb, and platelet levels), blood chemistry tests (BUN, Cr, AST, ALT, r-GTP, and glucose), thyroid function tests (free T4, TSH), urine test, and a pregnancy test (urine hCG) were performed at each screening visit in all three groups. Hematological examinations (WBC, RBC, Hb, platelet) and blood chemistry tests (BUN, Cr, AST, ALT, r-GTP) were performed at visit 10 in the two treatment groups. Adverse event (AE) monitoring was conducted from visit 2 to visit 11.

10. Compliance calculation

Compliance was calculated from visit 2 to visit 11. Acupuncture treatment compliance was calculated as follows: Acupuncture treatment compliance (%) = (the number of acupuncture treatments participants received/10 times of acupuncture treatment) × 100.

11. AE reporting

AEs are undesired or unintended symptoms or illnesses occurring during the clinical trial and do not necessarily have a causal relationship with intervention. The PI should educate participants and the co-investigator about any AEs that may occur after acupuncture or EA interventions and should educate them to report all symptoms occurring after the intervention. The investigator should check the occurrence of abnormal cases through clinical laboratory test results and questionnaires. All symptoms after the intervention were recorded on the CRF in detail, including items such as type, time of occurrence, extent, treatment, medication, course, acausal relationship with intervention, etc. The PI immediately reported to the investigational review board (IRB) if SAEs occurred during the trial to decide whether to continue or discontinue the study. The insurance company agreed to pay medical expenses for physical damage incurred in the study unless it occurred through serious negligence due to the intention or carelessness of the subject.

12. Sample size calculation

This study was designed on the assumption that there would be a difference in results among the acupuncture treatment group, EA treatment group, and no treatment control group after interventions. The hypothesis based on the above assumptions is as follows:

H0: $\delta = \Delta1 = \Delta2 = \Delta3$

H1: $\delta = \Delta1 \neq \Delta2$ or $\Delta1 \neq \Delta3$ or $\Delta2 \neq \Delta3$

Δ1: average change in CHHF VAS score 10 weeks after randomization (within ±3 days) in the acupuncture treatment group.

Δ2: average change in CHHF VAS score 10 weeks after randomization (within ±3 days) in the EA treatment group.

Δ3: average change in CHHF VAS score 10 weeks after randomization (within ±3 days) in the no-treatment control group.

We intended to calculate the number of participants based on the VAS score information of the previous CHHF clinical trial. In the referenced clinical trial results of Ha et al. [13], the mean VAS difference in the placebo group was –0.48, and the standard deviation was 1.03. The mean VAS difference in the experimental group was –1.52, and the standard deviation was 1.17. The expected difference in the acupuncture treatment group was estimated to be 1.04, and the standard deviation was estimated to be 1.102 using the pooled standard deviation formula. Therefore, this study was designed to enroll 72 patients (24 patients in each group), considering a dropout rate of 25%.

13. Statistical analyses

The basic analysis method was the degree of change between

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the basic test results performed before and after the clinical trial. To evaluate the efficacy of this study, both the ITT, a method that includes all randomized participants in the analysis, regardless of dropout or protocol violation, and per-protocol (PP) analysis, a method that excludes participants with missing data or non-compliance from the analysis, were performed. Missing data relating to the efficacy evaluation variables was adjusted using the last-observation-carried-forward (LOCF) method. Meanwhile, missing values were considered omitted for safety evaluation variables. A two-sided test established the statistical significance level at $p < 0.05$. SPSS for Windows version 25.0 (IBM Inc., Chicago, IL, USA) was used for the statistical analyses.

1) General characteristics

To test whether the distribution of the treatment and control groups was homogeneous, analysis of variance (ANOVA) or nonparametric methods were performed for continuous variables, and a chi-square test was performed for categorical variables.

2) Efficacy

For the CHHF VAS—the primary outcome variable—repeated measures ANOVA and paired t-test were conducted to evaluate whether any difference existed in the VAS score between the groups after intervention. A comparison of the degree of improvement in the VAS score within each group was performed using a paired t-test. For the secondary outcome variable, evaluating the BT, repeated measures ANOVA was conducted for the between-group analysis, and a paired t-test was performed for the within-group analysis. The WHOQOL-BREF results were assessed using ANOVA and post-hoc analysis for between-group analysis and paired t-test for within-group analysis. ANOVA and post-hoc tests were performed to evaluate the result of the questionnaire on pattern identification. Meanwhile, Cronbach's alpha and item-total correlation analyses were performed to analyze the cold hypersensitivity questionnaire.

3) Safety

Continuous data, such as hematology and blood biochemistry test results, vital signs, etc., were presented using descriptive statistics for each group and visit. Differences between each visit were analyzed using a paired t-test or nonparametric method. The 95% confidence intervals for the number of AEs and the proportion of participants who experienced one or more AEs were calculated within groups and compared between groups.

14. Data management and monitoring

The CRF files were stored in a secure place to protect confidentiality. Information regarding the participant's identification and privacy were removed from all study documents. Once the trial finished, a double independent data entry was performed to improve the data quality. After completing the data entry, an independent statistician analyzed the database under the supervision of the PI. Site investigators can directly access the final datasets from their sites.

The K-CTC monitored institutions performing the clinical trial according to the standard operating procedure (SOP) as the trial progressed. Monitoring began after the first participant completed the entire study. Double data entry and range checks for data values were conducted to promote data quality. However, auditing was not scheduled for this study.

DISCUSSION AND CONCLUSION

CHHF is defined as the symptom of a sensation of coldness in the extremities under conditions not considered cold by an unaffected person. CHHF is common in East Asian women [2, 14]. The exact cause of CHHF is unknown, but it is assumed to be because of vasoconstriction in the limbs owing to neurovascular disease, medical factors, or mental stress [2, 15, 16]. Most patients develop CHHF symptoms with no apparent cause. Western medicine tends to emphasize lifestyle management rather than the treatment of disease. However, the Korean medical system regards CHHF as an important clue to cold pattern identification and treats it with Korean herbal medicines, acupuncture, and moxibustion [17-20].

Several studies have been conducted to evaluate the efficacy and safety of Korean herbal medicines for the treatment of CHHF, including Danggui-SayukGa-Osuyu-Saenggang-tang [21], Ojeok-san [22], Sipjeondaebotang [23], Ucha-Shinki-Hwan [24], Onkyeong-tang [25], Korean Red Ginseng [26]. Studies that applied acupuncture or EA treatment for coldness have also been conducted. In an experimental study, low-frequency EA markedly relieved oxaliplatin-induced cold hypersensitivity in rats [10]. Additionally, in a pilot study, hand acupuncture therapy increased the temperature of the peripheral parts of the body [19]. In a case report on a patient with

systemic lupus erythematosus, coldness in fingers and toes was shown to ease, and the temperature recovery rate was alleviated after EA treatment [11]. Additionally, there have been many case reports on CHHF; however, most have used herbal medicine and acupuncture treatment together as the treatment method. Meanwhile, RCTs that evaluate the effectiveness and safety of acupuncture or EA treatment for CHHF have yet to be conducted. Therefore, this study aimed to assess the efficacy and safety of EA treatment in Korean women patients with CHHF.

Acupoint LR3 is located on the dorsum of the foot, between the first and second metatarsal bones, in the depression distal to the junction of the bases of the two bones, over the dorsalis pedis artery. SP6 is located on the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun (寸) superior to the prominence of the medial malleolus. LI4 is located on the dorsum of the hand and radial to the midpoint of the second metacarpal bone. TE5 is situated on the posterior aspect of the forearm, the midpoint of the interosseous space between the radius and the ulna, 2 B-cun (寸) proximal to the dorsal wrist crease [27]. LR3, SP6, and LI4 are effective for tonifying the spleen. The book Huangdi's Internal Classic introduced the concept of the "spleen and four extremities" and suggested that the function of the spleen is to control the four extremities, and dysfunction in the extremities can indicate a problem with the spleen [28, 29]. All acupuncture points used in our study effectively activate blood and qi. SP6 nourishes the uterus and is widely used for gynecological diseases. The relationship between CHHF and gynecological diseases such as infertility and menstrual pain is known. CHHF can accompany several gynecological diseases and associated chronic symptoms [28, 30].

Acupuncture has been widely used clinically in the East and is increasingly used by practitioners and patients in the West [31, 32]. EA is a modification of acupuncture treatment that stimulates acupoints with current instead of manual manipulations and appears to exhibit more consistent reproducibility in both clinical and research settings [33-35]. EA is believed to have two distinct advantages: (i) the therapy can be performed consistently, and (ii) electrical stimulation can be applied; therefore, traditional acupuncture can be combined with modern neuromodulation theory [36]. Hence, we decided to simultaneously compare and evaluate the efficacy and safety of both acupuncture and EA treatments.

Our study has some strengths. To our knowledge, this study is the first RCT to assess the efficacy and safety of EA for the treatment of CHHF. Many RCTs have evaluated the effectiveness and safety of herbal medicines for the treatment of CHHF; however, no studies have investigated the treatment of CHHF using EA or acupuncture. Second, the team members in our study had prior experience in RCTs related to CHHF, e.g., a pilot study on Danggui-SayukGa-Osuyu-Saenggang-tang [21], Ojeok-san [22], Sipjeondaebotang [23], Ucha-Shinki-Hwan [24], and Onkyeong-tang [25]; therefore, our study can be conducted more smoothly.

Our study has some limitations. Firstly, although this study is a multi-center clinical trial, it is difficult to discern how regional climate characteristics will affect our study results because the three institutions at which the studies were conducted are Wonju, Chungju, and Ilsan oriental hospitals located in different cities. Secondly, due to the acupuncture treatment, subtle differences in acupuncture stimulation intensity may exist depending on the operator. Additionally, this test will be divided into three groups: EA treatment group, acupuncture treatment group, and untreated control group, meaning sham acupuncture was not performed. Hence, it is difficult to exclude the possibility of improvement in the primary outcome variable, CHHF VAS, owing to psychological factors.

Despite these limitations, to our knowledge, this study will be the first clinical trial to evaluate the efficacy and safety of EA for treating CHHF. We expect this study to provide basic evidence for the treatment of CHHF with EA and future large-scale RCTs.

AUTHORS' CONTRIBUTIONS

Conceptualization: DNL, DIK, SHS, JSY; Methodology: DIK, DNL; Investigation: NYK, KYL; Project administration: DIK, DNL, JSY, SHS; Funding acquisition: DIK, DNL, JSY, SHS; Writing – Original draft: KYL, SHS, NYK; Review & Editing: KYL, DNL, NYK, DIK, JSY, SHS.

ETHICAL APPROVAL

This clinical trial has been approved by the IRBs of three hospitals (Sangji University Korean Medical Hospital: SJIRB-Human-19-003, Semyung University Korean Medical Hospital at Chungju: SMCJH 1904-05, and Dongguk University Korean Medical Hospital at Ilsan: DUIOH 2018-11-005-003). Written informed consent will be obtained from all participants before starting the trial procedures.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

Jun-Sang Yu has been an editorial board member of Journal of Pharmacopuncture since 2020 but has no role in the decision to publish this article. No other potential conflicts of interest relevant to this aricle were reported.

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