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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Study protocol

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Abstract

Background: 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 is common in East Asian women. 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.

Discussion: 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, future large-scale RCT, and the development of general clinical guidelines for CHHF in the Korean medical field.

Trial registration: CRIS, KCT0004306. Registered on October 14, 2019. https://cris.nih.go.kr/cris/search/search_result_st01.jsp?seq=14865

Background

Cold hypersensitivity in the hands and feet (CHHF) is defined as having a heightened cold sensation in the hands and feet in a relatively low-temperature area or sensation of coldness in an environment not considered cold by unaffected people [1]. According to a Korean study on twin genetics, the ratio of female to male 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 one's daily activities. The presumed causes of CHHF are peripheral neuropathy, autonomic nervous dysfunction, anemia, diabetes mellitus, and median neuritis [4]. However, there are few studies onthe pathophysiology of CHHF [2]. Furthermore, established treatment methods for CHHF are not available. The current treatment methods often include behavior modification [5]. Therefore, there is a need to establish an effective treatment method for CHHF.

Electroacupuncture (EA), a modern way of administering acupuncture, refers to the application of a pulsed electrical current to acupuncture needles for stimulating acupoints [6]. EA is known to have effects on neuropathic pain [7], persistent pain [8], analgesia [9], etc. Additionally, EA has been used to treat cold hypersensitivity. EA treatment for cold hypersensitivity has been reported in an experimental study [10] and a case report [11], showing relieving effects.

Although EA and acupuncture have been widely used for the treatment of CHHF, randomized clinical trial (RCT) has not yet been conducted for evaluating the efficacy and safety of EA or acupuncture for the treatment of CHHF. This open-label, randomized, parallel design, multicenter clinical trial aims to determine the effects of EA in CHHF patients. We hope this study will provide basic evidence for the treatment of CHHF with EA, future large-scale RCT, and the development of general clinical guidelines for CHHF in the Korean medical field.

Methods

Objectives

The study aims to objectively evaluate the efficacy and safety of EA treatment on Korean women patients with CHHF.

Study design and setting

This study will be a randomized, multicenter, and parallel design clinical trial. It will be 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 will be enrolled in this study from three hospitals. The EA treatment group, acupuncture treatment group, and untreated control group will have 24 participants each. All participants will be fully informed before they sign a written informed consent form. Principal investigator (PI) or researchers will obtain the written informed consent. The eligible participants will be assigned a subject identification code and will be randomly assigned to three groups. In the case of EA and acupuncture treatment groups, EA or acupuncture treatment will be performed a total of 10 times at intervals of twice a week for five weeks. Follow-up visits will be performed four weeks after the end of treatment. In the case of the untreated control group, three visits will be made: visit 1, visit 10 (when treatment will be terminated), and visit 11 (four weeks after treatment). Participants will not be allowed to take other medicines that could affect CHHF symptoms during the trial. The protocol design is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist (see Additional File 1). The flow chart of the study is presented in Fig. 1.

Randomization

Participants who have signed the informed consent form and who meet the inclusion criteria will be randomly assigned to the EA treatment group, acupuncture treatment group, and untreated control group

in 1:1:1 ratio on visit 1. An independent statistician from the Kyunghee University Korean Medicine Clinical Trial Center (K-CTC) or an independent researcher will conduct randomization. Generation of random assignment numbers will be performed using a web-based randomization system-blockrand package (version 1.3 or later versions; Intermountain Healthcare, Greg Snow, USA) and will be stratified by the institution. The sealed envelope method will be used for randomization concealment.

Blinding

This study will be an open-label, unblinded study for all group assignments. However, the evaluator who evaluates the participant's symptoms will be blinded separately from the operator, thereby minimizing the bias that may occur during the evaluation.

Participants

Inclusion criteria

The inclusion criteria are presented in Table 1.

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.

Exclusion criteria

The exclusion criteria are described in Table 2.

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 trialsor 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.

Withdrawals

All participants have the right to discontinue their participation from the clinical trial whenever they request. The detailed withdrawal criteria of this trial are described in Table 3. In case report forms (CRF), reasons for withdrawal will be documented, and data will be analyzed using the intention-to-treat (ITT) method.

Table 3
Withdrawal criteria of theclinical 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 tothe 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.

Procedure

Recruitment

Eligible participants who passed the screening will be recruited from three Korean medicine university hospitals. Sangji University Korean Medical Hospital will recruit 18 patients, Semyung University Korean Medical Hospital at Chungju will recruit 24 patients, and Dongguk University Korean Medical Hospital at Ilsan will recruit 30 patients. Participants will be recruited through public outdoor advertising.

Study schedule

The clinical trial schedule is presented in Table 4.

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		●		●	●

	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)
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).

Abbreviations: *AE*, Adverse event; *ALT*, Alanine aminotransferase; *AST*, Aspartate aminotransferase; *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.

Interventions

The acupuncture treatment group will receive acupuncture treatment on acupoints (LI4-TE5 and LR3-SP6) using a 0.25 × 30 mm sterile needle (Dongbangmedical, Boryeong, Korea) with a subcutaneous depth of 10–25 mm for 15 minutes. The treatment will be performed ten times, twice a week for five weeks. The EA treatment group will receive EA treatments on acupoints (both LI4-TE5 and LR3-SP6, LI4 connects to

TE5 and LR3 to SP6) using intra-muscle stimulator, CELLMAC PLUS, STN-330 (Stratek, Anyang, Korea) with a subcutaneous depth of 10–25 mm. The treatment will be performed ten times, twice a week for five weeks. One EA treatment lasts for 15 minutes with a frequency of 2 Hz. The untreated control group will not receive EA or acupuncture treatment. They will visit to check for any change in symptoms at visits 1, 10, and 11, three times in total.

Outcomes

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

Primary outcome measures

CHHF VAS score

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

Secondary outcome measures

Body temperature (BT) of hands and feet

Participants will be asked to avoid consuming alcohol, caffeine, smoking, taking hot showers, and exercising hard 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, 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) will be 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. It will be measured at every visit in the acupuncture treatment and EA treatment groups.

WHOQOL-BREF

The WHOQOL-BREF, a questionnaire estimating quality of life, is composed of 26 items. It 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] will be used for evaluating the quality of life of CHHF patients at visits 1, 10, and 11.

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

It consists of five categories: capacity for locomotion, self-management, daily life, pain/discomfort, and anxiety/depression. It will be checked at visits 1, 10, and 11.

Questionnaire of pattern identification

Pattern identification will be checked at screening visit to correlate the symptoms and change of VAS score in patients with CHHF with pattern identification index.

Questionnaire of cold hypersensitivity

Cold hypersensitivity will be checked at visits 1, 10, and 11 for examining subjective or objective symptoms of the patient's coldness.

Safety assessment

To assess safety, vital sign and general physical state will be examined at every visit. Hematological examination (WBC, RBC, Hb, platelet), blood chemistry test (BUN, Cr, AST, ALT, r-GTP, glucose), thyroid function test (free T4, TSH), urine test, and pregnancy test (urine hCG) will be performed at screening visit in all three groups. Hematological examination (WBC, RBC, Hb, platelet) and blood chemistry test (BUN, Cr, AST, ALT, r-GTP) will be performed at visit 10 in two treatment groups. Adverse event (AE) monitoring will be conducted from visit 2 to visit 11.

Compliance calculation

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

AE reporting

AEs are instances of undesired or unintended symptoms or illness 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 intervention should be recorded on the CRF in detail with items such as type, time of occurrence, extent, treatment, medication, course, acausal relationship with intervention, etc. The PI should report immediately to the investigational review board (IRB) if SAEs occur during the trial to decide whether to continue or discontinue the study. Medical expenses for physical damage incurred in the study will be paied by the insurance company subscribed for this study unless it is a serious negligence due to the intention or carelessness of the subject.

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 ten weeks after randomization (within ± 3 days) in the acupuncture treatment group.

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

Δ3: Average change in CHHF VAS score ten weeks after randomization (within ± 3 days) in no treatment control group.

Since there were no reference studies using acupuncture or EA for CHHF, we intended to calculate the number of participants based on the VAS score of the CHHF clinical trial using the oxygen chamber [13]. Therefore, this study was designed to enroll 72 patients, 24 patients in each group, considering the dropout rate of 25%.

Statistical analyses

The basic analysis method will be the degree of change between the results of the basic test performed before and after the clinical trial. For the evaluation of the efficacy of this study, both ITT, a method of including all randomized participants in the analysis, regardless of dropout or protocol violation, and per-protocol analysis (PP), a method of excluding participants with missing data or non-compliance from the analysis, will be performed. Missing data of the efficacy evaluation variables will be adjusted using the last-observation-carried-forward (LOCF) method. For safety evaluation variables, missing values will be considered as missing. The statistical significance level will be set at $P < 0.05$ using a two-sided test. For conducting statistical analyses, SPSS for windows version 25.0 (IBM Inc., Chicago, IL, USA) will be used.

General characteristics

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

Efficacy

In the case of CHHF VAS, the primary outcome variable, repeated measures ANOVA and paired t-test will be conducted to test whether there is a difference in the VAS score between the groups after intervention. A comparison of the degree of improvement in the VAS score within each group will be performed using a paired t-test. For secondary outcome variables to evaluate BT, repeated measures ANOVA will be

performed for between-group analysis and paired t-test for within-group analysis. The results of WHOQOL-BREF will be assessed using ANOVA and post-hoc analysis for between-group analysis and paired t-test for within-group analysis. To evaluate the result of the questionnaire of pattern identification, ANOVA and post-hoc tests will be performed, and for the analysis of the questionnaire of cold hypersensitivity, Cronbach's alpha and item-total correlation analyses will be performed.

Safety

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

Data management and monitoring

CRF files will be stored in a secured place for protecting confidentiality. Information regarding the participant's identification and privacy will be removed from all study documents. Once the trial is finished, a double independent data entry will be performed for improving the quality of data. After completing the data entry, an independent statistician will analyze the database under the confirmation of the PI. Site investigators can access directly the final datasets from their own sites.

The K-CTC will monitor institutions performing the clinical trial according to the standard operating procedure (SOP) while the trial is in progress. Monitoring will be started after the first participant finishes the entire course of the study. Double data entry and range checks for data values will be conducted to promote the data quality. Auditing is not scheduled for this study.

Discussion

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 is common in East Asian women [2, 14]. The exact cause of CHHF is not yet known, but it is assumed to be because of vasoconstriction of 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 treatment of disease. However, 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, including Danggui-SayukGa-Osuyu-Saenggang-tang [21], Ojeok-san [22], Sipjeondaebotang [23], Ucha-Shinki-Hwan [24], Onkyeong-tang [25], Korean Red Ginseng [26], for the treatment of CHHF. Studies of acupuncture or EA treatment for coldness have also been conducted. In an experimental study, low frequency EA has a marked relieving effect on oxaliplatin-induced cold hypersensitivity in rats [10]. In one pilot study, hand acupuncture therapy increased the temperature of the peripheral parts of the body [27].

In a case report with a patient with systemic lupus erythematosus, coldness in fingers and toes had eased, and the temperature recovery rate was alleviated after EA treatment [11]. Additionally, there have been many case reports on CHHF; however, most of them have used herbal medicine and acupuncture treatment together asthe treatment method, and RCTs for evaluating the effectiveness and safety of acupuncture or EA treatmentfor CHHF have not been conducted so far. Therefore, this study aims to assess the efficacy and safety of EA treatment on 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(□) 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 located on the posterior aspect of the forearm, midpoint of the interosseous space between the radius and the ulna, 2 B-cun(□) proximal to the dorsal wrist crease[28]. 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 of the extremitiescan suggest a problem with the spleen [29–30]. All acupuncture points used in our study are effective for activating 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 has been known. CHHF can accompany several chronic symptoms and diseases of gynecology [29, 31].

Acupuncture has been widely used in clinical practice in the East and is increasingly being used by practitioners and patients in the West [32–33]. 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 [34–36]. It is believed that EA has two distinct advantages: (i) the therapy can be performed consistently, and (ii) electrical stimulation can be applied, and therefore, the traditional acupuncture can be combined with modern neuromodulation theory [37]. Hence, we decided to compare and evaluate the efficacy and safety of both acupuncture and EA treatments simultaneously.

Our study has some strengths. First, ours is the first RCT to assess the efficacy and safety of EA for the treatment of CHHF. There have been many RCTs to evaluate the effectiveness and safety of herbal medicines for the treatment of CHHF, but there have been no studies on 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 of 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 where the study will be conducted are Wonju, Chungju, and Ilsan oriental hospitals located adjacent in the distance. Secondly, owing to the nature of the acupuncture treatment, there may be subtle differences in

acupuncture stimulation intensity depending on the operator. Additionally, this test will be divided into three groups: EA treatment group, acupuncture treatment group, and untreated control group, and sham acupuncture will not be performed. Hence, it is difficult to rule out the possibility of improvement in the primary outcome variable, CHHF VAS, owing to psychological factors.

Despite these limitations, our 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, future large-scale RCTs, and the development of general clinical guidelines for CHHF in the Korean medical field.

Trial Status

The recruitment of participants is ongoing from December 2, 2019, and it will be completed in March 2021. The current active protocol version is 2.4 (November22, 2019).

Abbreviations

Adverse event (AE)

Alanine aminotransferase (ALT)

Analysis of variance (ANOVA)

Aspartate aminotransferase (AST)

Body temperature (BT)

Blood urea nitrogen (BUN)

Cold hypersensitivity in the hands and feet (CHHF)

Creatinine (Cr)

Case report form (CRF)

Diastolic blood pressure (DBP)

Electroacupuncture (EA)

Electrocardiogram (ECG)

Gamma-glutamyl transpeptidase (r-GTP)

Hemoglobin (Hb)

Human chorionic gonadotropin (hCG)

Institutional Review Board (IRB)

Intention-to-treat (ITT)

Korea Food and Drug Administration (KFDA)

Last-observation-carried-forward (LOCF)

Principal investigator (PI)

Per-protocol (PP)

Red blood cell (RBC)

Randomized clinical trial (RCT)

Serious adverse event (SAE)

Systolic blood pressure (SBP)

Standard operating procedure (SOP)

Thyroid-stimulating hormone (TSH)

Visual Analogue Scale (VAS)

White blood cell (WBC)

World Health Organization Quality of Life Scale Abbreviated Version (WHOQOL-BREF)

Declarations

Trial Status

The recruitment of participants is ongoing from December 2, 2019, and it will be completed in March 2021. The current active protocol version is 2.4 (November22, 2019).

Ethics approval and consent to participate

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). This trial will be performed according to the Helsinki Declaration and the Good Clinical Practice Guidelines of the Korea Food and Drug Administration (KFDA). The current protocol version is 2.4. Before starting the trial procedures, written informed consent will be obtained from all participants. We will protect the participant's confidentiality using coded identification numbers when dealing with the data. The results of

this trial will be disseminated through scientific journals or presentations at scientific conferences. So far, public access to any clinical trial data is not planned.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

KYL, SHS, and ISH wrote the first manuscript for the clinical trial. DIK, HYG, DNL, and JSY contributed to the funding and the design of this study. DIK and DNL calculated the sample size and decided on the methods for statistical analyses. HYG, DNL, KYL, SHS, and JSY participated in the design of the study. ISH, SHS, HYG, JSY, and KYL coordinated obtaining the data and critically revised the manuscript. All authors read and approved the manuscript.

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Figures

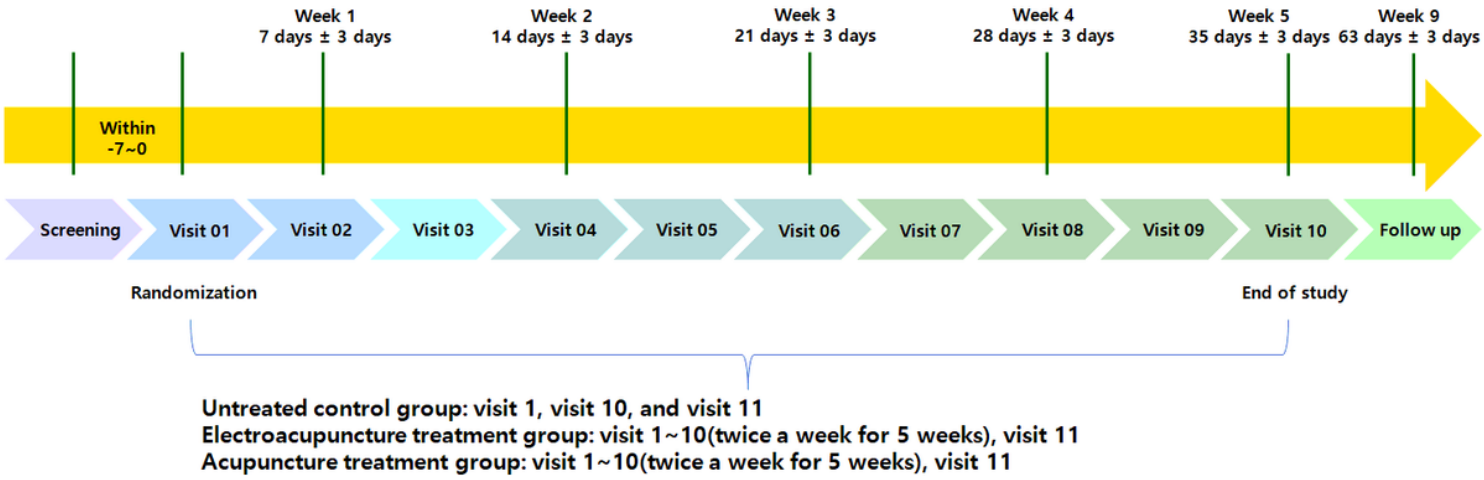

Figure 1

Flow chart of the study.

Supplementary Files

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