Journal of Ethnopharmacology 158 (2014) 25–32

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Research Paper

Efficacy and safety of Korean red ginseng for cold hypersensitivity in the hands and feet: A randomized, double-blind, placebo-controlled trial

Kyoung-Sun Park [a], Kang-In Park [a], Jin-Woo Kim [a], Young-Jin Yun [a], Se-Hwa Kim [a], Chang-Hoon Lee [a], Jae-Woo Park [b], Jin-Moo Lee [a,*]

[a] Department of Korean Medicine Obstetrics & Gynecology, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Republic of Korea

[b] Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Republic of Korea

ARTICLE INFO

Article history:
Received 9 May 2014
Received in revised form
19 August 2014
Accepted 16 September 2014
Available online 8 October 2014

Keywords:
Cold hypersensitivity in the hands and feet
Korean red ginseng
Infrared thermography
Cold stress test
Distal–dorsal difference

ABSTRACT

Ethnopharmacological relevance: In Korean medicine, the steamed root of *Panax ginseng* C.A. Meyer, known as Korean red ginseng (KRG), is used to invigorate the body, enhance *qi*, and improve blood flow. It is a potential treatment for cold hypersensitivity in the hands and feet (CHHF), a common complaint among Asians, especially women. However, few studies of its efficacy and safety for CHHF have been conducted.

Materials and methods: This randomized, double-blind, placebo-controlled trial included 80 female patients with CHHF at Kyung Hee University Hospital at Gangdong, Seoul, Korea. The participants took six capsules of 500-mg KRG powder or placebo twice daily for 8 weeks and were followed up for 4 weeks. The primary outcome measure was change in skin temperature of the hands. The secondary outcome measures included change in skin temperature of the feet, visual analog scale (VAS) scores of CHHF severity, recovered temperature (RT) of the hands after cold stress test, distal–dorsal difference (DDD) in temperature of the hands, power variables of heart rate variability (HRV), and 36-item Short-Form Health Survey (SF-36) scores.

Results: The KRG group had significantly higher skin temperature of the hands and feet, lower VAS scores, higher RT of the right 5th finger, and less parasympathetic activity than the placebo group at 8 weeks. No significant differences were noted in DDD of the hands and SF-36 scores. No serious adverse events were reported during the study.

Conclusions: Peripheral vasodilation by KRG may alleviate CHHF. Further controlled studies are required to elucidate the effects of KRG on the autonomic nervous system.

1. Introduction

Cold hypersensitivity in the hands and feet (CHHF) is a condition in which affected individuals feel excessively cold at low temperatures because of spastic peripheral vasoconstriction. It is significantly more prevalent among women than men in the Korean population (Hur et al., 2012). CHHF can disturb employers in cold climates, and lower the quality of life by interfering with daily activities. Various neurovascular, psychosocial, cultural, environmental, and medical factors might contribute to CHHF (Traynor and MacDermid, 2008). However, few studies have been performed to elucidate its etiology (Hur et al., 2012). Further, satisfactory treatments for this condition are not available; the current treatment approaches often involve behavioral modification (Craigen et al., 1999). Therefore, identification of an effective therapeutic modality for CHHF is essential.

Abbreviations: BMI, body mass index; BP, bodily pain; BP, blood pressure; CHHF, cold hypersensitivity in the hands and feet; CST, cold stress test; DDD, distal–dorsal difference; GH, general health perception; HF, high frequency; HF norm, high-frequency power normalized unit; HRV, heart rate variability; KRG, Korean red ginseng; LF, low-frequency; LF/HF ratio, low-frequency to high-frequency power ratio; LF norm, low-frequency power normalized unit; lnHF, logarithmic high-frequency power; lnLF, logarithmic low-frequency power; MH, mental health; NO, nitric oxide; PF, physical function; RE, role limitations owing to emotional problems; RP, role limitations owing to physical health problems; RT, recovered temperature; SF, social function; SF-36, the 36-item Short Form Health Survey; T_0, skin temperature immediately after cold stress; T_6, skin temperature 6 min after cold stress; VAS, visual analog scale; VT, energy and vitality

* Corresponding author. Tel.: +82 2 440 7129; fax: +82 2 440 7143.
E-mail addresses: lovepks82@naver.com (K.-S. Park), shinysmile714@gmail.com (K.-I. Park), shampoo1211@naver.com (J.-W. Kim), khclinic@empas.com (Y.-J. Yun), nimaru@hanmail.net (S.-H. Kim), lchgdsl@hanmail.net (C.-H. Lee), pjw2907@hanmail.net (J.-W. Park), hanbang9597@hanmail.net (J.-M. Lee).

http://dx.doi.org/10.1016/j.jep.2014.09.028
0378-8741/

Korean red ginseng (KRG) is the steamed root of *Panax ginseng* C.A. Meyer. It acquires additional physiological properties through chemical transformation of its active components, including ginsenosides, polysaccharides, peptides, and polyacetylenic alcohols (Park, 1996). Steamed ginseng, containing ginsenosides Rg3 and Rg5, has more potent endothelium-dependent vasodilator and radical-scavenging effects than raw ginseng (Kim et al., 2000). In Korean medicine, KRG is considered to have a warm quality: it is used as a tonic to invigorate the body, enhance *qi*, and improve blood flow (Kwan, 1999). However, its efficacy for treating CHHF has rarely been investigated. Only one clinical trial of subjective tolerance to cold stress has been conducted (Kaneko and Nakanishi, 2004).

This randomized, double-blind, placebo-controlled trial was aimed at evaluating the efficacy and safety of KRG comprehensively.

2. Materials and methods

2.1. Ethical approval

The study protocol adhered to the guidelines of the amended Declaration of Helsinki and was approved by the institutional review board and ethics committee of Kyung Hee University Hospital at Gangdong (approval number KHNMC-OH-IRB 2012-004). The trial is registered under identification number NCT01664156 (ClinicalTrials.gov). Written informed consent was obtained from all participants before enrollment, and patients were given adequate time to declare whether they wished to participate.

2.2. Patients

The inclusion criteria were as follows: (1) female patients aged 16–60 years; (2) complaint of CHHF; and (3) over 0.3 °C difference between the palm and the arm. We excluded patients who reported any of the following conditions: (1) skin ailments, radiculopathy, thrombophlebitis, and injuries affecting infrared imaging; (2) alcohol abuse or alcoholism; (3) history of cancer within the past 5 years; (4) severe cardiac, pulmonary, hepatic, or renal diseases; (5) severe depression or mental illness; (6) use of antihypertensive, antidiabetic, or thrombolytic agents; (7) pregnancy or breastfeeding; (8) allergy to KRG or ginseng; (9) ingestion of herbal medicines or nutritional supplements within a week before participation; and (10) participation in another clinical trial within the past 3 months.

Participants were recruited by sending text messages to patients with CHHF at Kyung Hee University Hospital at Gangdong. Advertisements were placed in the local newspaper and on the hospital homepage. In addition, posters, brochures, and banners were placed inside the hospital.

2.3. Randomization and blinding

Group allocation was performed by an independent statistician using a randomization program. The participants were randomly and equally assigned to the KRG or placebo group and were not stratified. The investigator was subsequently notified of the number assigned to each participant, and the participants were given a random number at their second visit. The allocation table of participants was kept by an independent statistician until the end of the study.

The participants, the investigator, and the clinical pharmacist were blinded to the treatment and only the independent statistician was aware of the randomization. Blinding was assessed at the end of the study.

2.4. Intervention

KRG was manufactured by Korea Ginseng Corporation (Seoul, Korea) from the root of 6-year-old *Panax ginseng* C.A. Meyer (Araliaceae) harvested in Korea. Fresh ginseng was steamed at 90–100 °C for 3 h and dried at 50–80 °C. Capsules containing KRG powder (KRG capsule; 500 mg/capsule) were prepared from hydroxypropyl methylcellulose, pectin, purified water, sucrose fatty acid ester, glycerin, calcium gluconate, and glacial acetic acid. The following ginsenosides were identified by high-performance liquid chromatography: Rb1, 5.61 mg/g; Rb2, 2.03 mg/g; Rc, 2.20 mg/g; Rd, 0.39 mg/g; Re, 1.88 mg/g; Rf, 0.89 mg/g; Rg1, 3.06 mg/g; Rg2(s), 0.15 mg/g; Rg3(r), 0.08 mg/g; Rg3(s), 0.17 mg/g; Rh1, 0.30 mg/g; and minor ginsenosides. Voucher specimens are kept at Korea Ginseng Corporation.

Each participant in the KRG group took six KRG capsules twice daily (1 h after breakfast and dinner), totaling 6 g of KRG per day, for 8 weeks. The dosage was determined on the basis of the total amount of Rb1 and Rg1 (6 mg/g), according to the Korean Food Standards Codex. Participants in the placebo group took placebo capsules similar in color, flavor, and smell to the KRG capsules for the same duration. The placebo was composed of cornstarch, natural color (Brown CG-11771; Jey's F.I., Inc., Seongnam, Korea), brown caramel color (Bolak Co., Seoul, Korea), and red ginseng flavor (C80509; French Korean Aromatics Co., Yongin, Korea). Every participant was asked to annotate a diary after taking the capsules to check compliance with the study protocol. Those with over 70% compliance were included in the per-protocol analysis.

The participants were prohibited from undergoing therapies that might affect symptoms of CHHF, including herbal therapy, acupuncture, moxibustion, cupping, and infrared treatment. They were also prohibited from taking antihypertensive, antidiabetic, or thrombolytic agents. However, medications that would not affect CHHF, such as those for common cold, stomachache, diarrhea, and menstrual pain, were allowed.

2.5. Outcomes measures

The primary outcome measure was change in skin temperature of the hands. The secondary outcome measures included change in skin temperature of the feet, visual analog scale (VAS) scores of CHHF severity, recovered temperature (RT) of the hands, distal–dorsal difference (DDD) of the hands, power variables of heart rate variability (HRV), and 36-item Short-Form Health Survey (SF-36) scores.

2.5.1. Infrared thermography

Skin temperature was measured by infrared thermography (IRCT 510; Dongseo Co., Seoul, Korea). The participants were asked to avoid hot showers, hot packs, smoking, exercise, acupuncture, and stimulants such as caffeine for 2 h before the examination. Each participant was acclimatized to room temperature (25 ± 1 °C) for 15 min and seated comfortably on a chair without physiological or psychological stress. The participant stood in the anatomical posture during thermal imaging of the limbs. Then, the average temperatures in 5-mm squares on the arm (LU4), palm (PC8), anterior thigh (ST32), and dorsum of the foot (LR3) were calculated (Fig. 1). Finally, thermal differences between the arm and the palm and between the anterior thigh and the dorsum of the foot were measured on both sides and the bilateral measurements were averaged as follows:

$\Delta T_{\text{right hand}}$ = skin temperature of the right arm − skin temperature of the right palm;

$\Delta T_{\text{left hand}}$ = skin temperature of the left arm − skin temperature of the left palm;