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CLINICAL STUDY

Study on improving blood flow with korean red ginseng substances using digital infrared thermal imaging and doppler sonography: randomized, double blind, placebo-controlled clinical trial with parallel design

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Abstract

OBJECTIVE: To examine the efficacy of Korean red ginseng for improving blood flow in healthy people.

METHODS: Participants were randomized and treated with 1500 mg of Korean red ginseng extract or placebo for 8 weeks. The effect of Korean red ginseng was evaluated by digital infrared thermal images, and Doppler sonography, and blood test.

RESULTS: Forty subjects completed the protocol. Imbalance in local thermal distribution was significantly decreased in the Korean red ginseng group confirmed by digital infrared thermal images. Doppler sonography showed no significant change in maximum and average rates of blood circulation in single or complex areas. Blood analyses for coagulation and lipid metabolism factors revealed no significant changes. No abnormal reactions to the Korean red ginseng were observed.

CONCLUSION: Digital infrared thermal imaging showed that the temperature deviation in the whole body decreased safely in the Korean red ginseng group, which mitigated the body-temperature imbalance. This result suggests that the Korean red ginseng improves blood circulation in the human body.

Key words: Radix et rhizome ginseng rubra; Blood circulation; Body temperature; Ultrasonography, doppler; Infrared thermal imaging; Double-blind method

INTRODUCTION

Korean red ginseng (the steamed root of Panax ginseng) is a well-known traditional medicinal remedy used in Asian countries as well as in the United States and Europe.[1,2] Korean red ginseng is prepared by steaming or otherwise heating the root with skins intact and subsequently drying. In the course of the steaming process, ginseng starch is gelatinized, causing an increase in saponin content. Traditionally, Korean red ginseng has been used to restore and enhance normal well-being and is often referred to as an adaptogenic.[3] Active constituents found in most

ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. Recent studies have reported that the major active ingredients such as ginsenosides have antioxidant, antiinflammatory,[4,5] antiapoptosis,[6] anticancer,[7,8] antiallergic,[9,10] and hematopoietic effects.[11,12] A major compound of Korean red ginseng, ginsenoside-Rb1, has been reported to improve blood circulation by functioning as a calcium antagonist.[13]

The Korean population is predicted to be an "aging" society by 2018 and a "super-aging" society by 2026.[14] As the population age, the incidence of vascular disease increases. Because vascular diseases can present serious health problems, early diagnosis and prevention are becoming more important.[15,16] Although, recent studies have investigated the efficacy of Korean red ginseng on blood circulation, most studies have been observational and of low quality.[17,18]

The aim of this study was to elucidate the effect of Korean red ginseng on blood circulation including blood coagulation time, blood-flow velocity, and local thermal distribution in a randomized, double-blind clinical trial.

MATERIALS AND METHODS

Trial design

This study was designed as a randomized, double-blind, placebo-controlled, parallel group trial. This study was approved by the Institutional Review Board of Cheonan Oriental Hospital of Daejeon University and conducted in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.[19]

Participants

Participants were recruited by outdoor and homepage advertising sponsored by Cheonan Oriental Hospital. Subjects were required to be in satisfactory health and free from any significant disease. Volunteers (aged 30-50 years) were eligible for participation. Excluded from this study were subjects with cholesterol levels over 240 mg/dl; those with diabetes mellitus, hypertension, or with blood coagulation problems; those with a history of taking blood circulation agents or antioxidative agents within 3 weeks; and those who were currently pregnant or were planning to become pregnant in the near future. All the procedures associated with this study were conducted at the clinical trial center at Cheonan Oriental Hospital of Daejeon University.

Sample size

Based on a previous study,[18] the difference in activated partial thromboplastin time (aPPT) was estimated to be 5 min with a standard deviation (*SD*) of 5. Sample size was calculated by the sample-size parameters for 80% statistical power at a 5% significance level. The predicted drop-out rate was 20% , and the calculated sample size was 20 subjects per group.

Intervention

Participants received one ginseng capsule (500 mg) manufactured by Korea Tobacco and Ginseng (KTNG, Daejeon, Republic of Korea) or one placebo three times per day for 8 weeks. In terms of composition, Korean red ginseng main root comprises 70% of ginseng capsules and Korean red ginseng lateral root comprise 30% . The placebo material was carefully prepared to match the appearance, volume, weight, color, flavor, and taste of ginseng and consisted of a capsule containing starch (95.25%), artificial Korean red ginseng flavor (4%), natural coloring agent (0.15%), and caramel color (0.6%).

Randomization

To conceal the identity of the group to which subjects were assigned, participants were randomized centrally. Assignment to one of the two parallel treatment groups (20 in each) was performed by a statistician using a randomization program. The two groups were randomized by blocks of four.

Trial protocol

Subjects were scheduled to visit the clinical trial center three times. On the first visit, participants consent and medical history were collected. On the second visit (1 week later), laboratory tests, digital infrared thermal imaging (DITI), and Doppler sonography were performed, and sufficient study drugs for 8 weeks were given. On the third visit (8 weeks later), the tests performed during the second visit were repeated. Compliance and adverse events were monitored three times between the second and third visits by telephone.

Outcome measurment

Efficacy was assessed by laboratory tests related to blood coagulation (prothrombin time; PT and activated partial thromboplastin time; aPTT), lipid profiles (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) and DITI, as well as by Doppler sonography. Safety was assessed by laboratory blood tests [blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine], urine tests [specific gravity (SG), glucose, nitrite, bilirubin, blood, red blood cells (RBC), white blood cells (WBC), and ketones], and adverse-effect monitoring.

DITI and Doppler sonography

Before and after administration of Korean red ginseng, temperatures of the whole body (face, trunk, and both upper and lower limbs) were measured with the DITI System, IRIS-XP (Medicore, Korea) in a temperature-

controlled dark room maintained at around 19℃-21℃ . A 10-mm circle of local temperatures was measured in both zygomata, forehead, center of the sternum, abdomen, torso, both palms, shin, and dorsa of both feet. Subjects sat quietly in front of the machine for 15 min before the DITI was taken. They were directed to refrain from smoking within 2 h of the DITI, and not to drink alcohol, bathe, undergo physical therapy or heliotherapy, or receive an electromyogram within a day before the DITI.

Doppler sonographic examinations were performed with a Vasodop VD 1000 (ELCAT, Germany) using 4-, 2- and 8-MHz probes in a multidirectional ultrasound probe-holder construction. The opthalmic artery was identified through the orbital window, with the flow direction normally toward the probe, about 50 mm from the skull surface. The vertebral artery was insonated between 70-80 mm with the probe through the suboccipital window. The internal carotid artery was isonated through the submandibular window. The radial artery was identified 1 cm from the wrist joint, and the dorsal artery of foot was isonated around the extensor hallucis.[20,21]

Adverse events monitoring

All subjects were monitored for adverse events (including adverse drug reactions and onset of illnesses) during the study. All adverse events were forwarded in a blind fashion to the primary investigator to be rated as mild, moderate, or severe. The physician graded the severity of adverse events as mild (present, but did not interfere with the ability to carry out duties or require medical intervention), moderate (some interference with daily duties and required no or minimal medical therapy), and severe (daily duties could not be completed and required medical intervention or hospitalization). The relationship between the study drug and adverse events were recorded as certain, probable/likely, possible, unlikely, unrelated, and unassessable/unclassifiable. Monitoring adverse events was performed during the study period by telephone call and physical examination.

Statistical methods

Statistical analyses were performed using a modified intent-to-treat (ITT) analysis as outlined in the original study protocol. Data were compared by independent *t*-tests. Differences at the level of $P<0.05$ were regarded as statistically significant. Data processing and analyses were performed with SPSS for Windows, version 12 (SPSS Inc., Japan).

RESULTS

Participant flow

We identified 42 volunteers from August 20, 2010 to October 20, 2010. Forty-two subjects were screened, and two declined to participate after receiving the study information. After excluding the two subjects, we randomly assigned 40 volunteers who met our inclusion criteria to the Korean red ginseng (n=20) and placebo (n=20) groups (Figure 1) Compliance was verified at over 80% for 30 participants and at 70%-80% for the remaining participants. No adverse events were recorded throughout the study period.

Demographic characteristics

Baseline demographic characteristics of the study subjects are presented in Table 1. The parameters before treatment were not significantly different between the two groups.

Blood coagulation and lipid profiles

We found no statistically significant differences

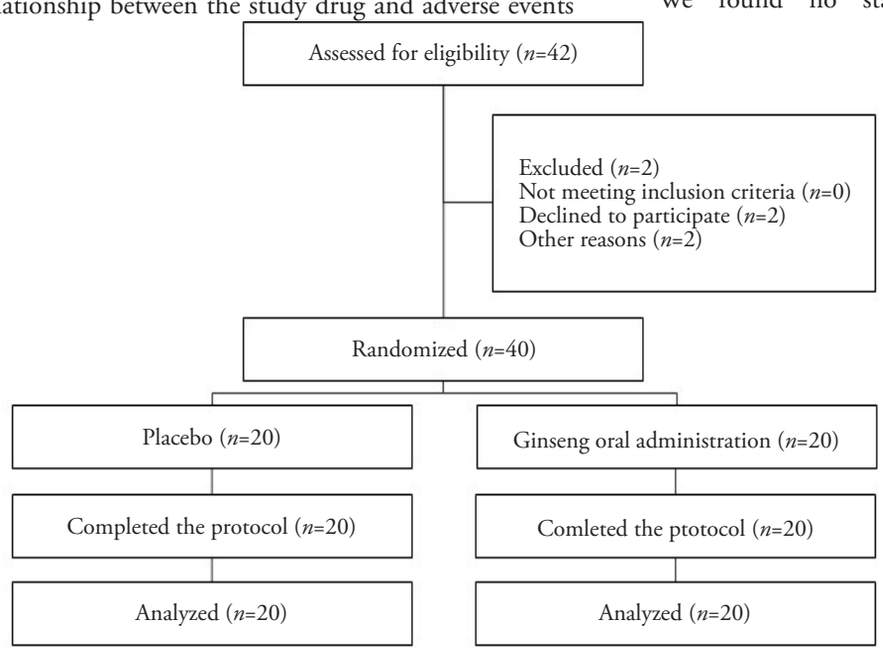

Figure 1 Flow diagram of selection

Table 1 Demographic characteristics of the subjects ($\bar{x}$ ±s)

Group	*n*	Male (*n*)	Female (*n*)	Age (year)	Height (cm)	Weight (kg)
Korean red Ginseng	20	9	11	38±6	163±8	64±11
Placebo	20	8 (46%)	12 (54%)	42±5	161±8	62±10

between the two groups with respect to pre-and post-study laboratory tests for blood coagulation and lipid profiles. Although the aPTT and PT values were prolonged in the Korean red ginseng group, this difference did not reach statistical significance (data not shown).

DITI

The body temperatures of the groups did not differ before the study (all $P>0.05$) (Table 2). The temperature of the abdomen increased significantly in the Korean red ginseng group (35.1℃ ± 0.6℃) compared with that in the placebo group (34.6℃ ± 1.0℃) ($P=0.044<0.05$). Local temperatures of the zygomata, forehead, palms, dorsa of the feet, and center of the sternum did not differ between the two groups (Table 3). A comparison of forehead and abdomen temperatures [Δ(temperature of forehead − temperature of abdomen)] revealed a significant difference in the Korean red ginseng (-0.61℃ ± 0.51℃) and placebo (0.03℃ ± 0.67℃) groups ($P=0.002<0.05$). The whole body and forehead temperatures [Δ(temperature of whole body − temperature of forehead)] were significantly higher in the Korean red ginseng group (-0.21℃ ± 0.49℃ than in the placebo group (0.57℃ ± 0.56℃) ($P=0.041<0.05$). Administration of Korean red ginseng vs placebo was not associated with a statistically significant difference in the temperature differences observed between abdomen and palms, dorsa of the feet, and limbs [Δ(temperature of abdomen − temperature of palms, dorsa of feet, and limbs)] (all $P>0.05$). Similarly, we found no statistically significant differences between the groups with respect to differences between whole body temperature and temperatures of palms, dorsa of the feet, and limbs [Δ (temperature of whole body − temperature of palms, dorsa of feet, and limbs)] (all $P>0.05$) (Tables 4).

Doppler sonography

Values representing the peak systolic flow and mean flow velocity in the Korean red ginseng group were higher than those in the placebo group, although these differences did not reach statistical significance (all $P>0.05$) (Table 5, 6). Comparisons of differences in the mean flow velocities of the whole blood vessel (WBV) and basilar artery, vertebral artery, dorsal artery of the foot, and popliteal artery did not reflect any significant differences (all $P>0.05$) (Table 7).

Table 2 Body part temperatures before administration in the two groups (℃, $\bar{x}$ ±s)

Body part	Korean red Ginseng	Placebo	*P* value
Right zygoma	34.9±1.0	34.9±0.7	0.965
Left zygoma	34.8±1.0	34.8±0.8	0.859
Right palm	35.3±0.8	34.9±1.3	0.277
Left palm	35.1±0.8	34.7±1.4	0.243
Right shin	34.8±0.5	34.7±0.5	0.396
Left shin	34.8±0.5	34.7±0.5	0.309
Center of sternum	35.7±0.6	35.8±0.5	0.642
Abdomen	35.0±0.9	35.0±0.8	0.860
Torso	35.3±0.5	35.4±0.6	0.617
Right dorsum of foot	33.0±1.6	33.0±1.4	0.948
Left dorsum of foot	33.0±1.4	32.9±1.3	0.820
Forehead	36.4±0.4	36.3±0.3	0.648

Table 3 Body part temperatures after administration in the two groups (℃, $\bar{x}$ ±s)

Body part	Korean red Ginseng	Placebo	*P* value
Right zygoma	34.1±0.8	34.1±1.2	0.891
Left zygoma	34.0±0.9	34.0±1.4	0.903
Right palm	34.0±1.6	33.2±1.9	0.212
Left palm	34.1±1.7	33.2±1.8	0.105
Right shin	34.4±0.5	34.2±0.4	0.222
Left shin	34.3±0.5	34.1±0.6	0.198
Center of sternum	35.9±0.5	35.6±0.7	0.139
Abdomen	35.1±0.6	34.6±1.0	0.044[a]
Torso	35.3±0.4	35.0±0.7	0.103
Right dorsum of foot	31.1±1.5	30.9±1.7	0.646
Left dorsum of foot	31.2±1.2	30.8±1.6	0.319
Forehead	35.9±0.6	35.9±0.5	0.677

Note: [a]$P<0.05$ by independent *t*-test.

Safety assessment

Laboratory tests of AST, ALT, BUN, and creatinine did not show any hepatotoxicity or nephrotoxicity. Urinalyses of SG, glucose, ketone, nitrite, bilirubin, blood, RBC, and WBC did not reveal any abnormal results. No adverse events were observed throughout the study period.

Table 4 Temperature differences of specific parts before and after administration in the two groups (℃, $\bar{x}$ ±s)

Temperature difference	Korean red Ginseng	Placebo	*P* value
Abdomen − Palm[a]	1.3±1.5	1.2±1.5	0.813
Abdomen − Dorsum of foot[b]	1.9±1.6	1.7±1.7	0.657
Abdomen − Limb[c]	1.6±1.6	1.4±1.4	0.670
Whole body − Palm[d]	0.5±1.5	0.6±1.0	0.627
Whole body − Dorsum of foot[e]	1.1±1.6	1.1±1.3	0.910
Whole body − Limb[f]	0.8±1.6	0.9±0.8	0.662

Notes: [a]Temperature difference between abdomen and palm temperatures after administration − difference before administration. [b]Temperature difference between abdomen and dorsum of foot temperatures after administration − difference before administration. [c]Temperature difference between abdomen and limb temperatures after administration − difference before administration. [d]Difference between whole body and palm temperatures after administration − difference before administration. [e]Temperature difference between whole body and dorsum of foot temperatures after administration − difference before administration. [f]Temperature difference between whole body and limb temperatures after administration − difference before administration.

Table 5 Peak systolic flow velocity after administration in the two groups (cm/s, $\bar{x}$ ±s)

Blood artery	Korean red Ginseng	Placebo	*P* value
BA	59±20	65±15	0.351
Right VA	51±19	50±14	0.925
Left VA	50±14	43±12	0.072
Right QA	86±17	80±18	0.332
Left OA	75±14	76±22	0.805
Right ICA	54±12	52±10	0.658
Left ICA	59±18	54±11	0.308
Right RA	44±21	40±17	0.556
Left RA	38±17	36±14	0.602
Right DA	28±19	26±16	0.634
Left DA	25±17	25±17	0.935
Right PA	23±08	21±05	0.381
Left PA	23±07	21±05	0.399

Notes: BA: basilar artery; VA: vetebral artery; OA: ophthalmic artery; ICA: internal carotid artery; RA: radial artery; DA: dorsal artery of foot; PA: popliteal artery.

DISCUSSION

The purpose of our study was to investigate the efficacy and safety of Korean red ginseng for improving blood flow using DITI and Doppler ultrasonography. Previous studies focused only on the relationship between Korean red ginseng and anti-coagulation.[16,17] Thus, we measured the flow velocities of the arteries as well as the body-temperature distribution after Korean red ginseng administration using DITI and Doppler ultrasonography.

The clinical utility of transcranial Doppler (TCD) ultrasonography in cerebrovascular disease has been extended recently. Although a number of studies have defined normal reference values of TCD measurements, these studies have several limitations, including their use of a relatively small number of subjects and a lack of data regarding some cerebral vessels and/or parameters.[22] Recently, many studies examining the effects of acupuncture and herbs on brain blood flow have used Doppler ultrasonography.[23]

Thermal imaging is a non-contact, non-invasive diagnostic method for studying human bodily

Table 6 Mean flow velocity after administration in the two groups (cm/s, $\bar{x}$ ±s)

Blood artery	Korean red Ginseng	Placebo	*P* value
BA	38±12	42±10	0.269
Right VA	32±11	33±09	0.874
Left VA	33±08	29±08	0.094
Right siphon	56±11	53±14	0.426
Left siphon	48±10	50±14	0.589
Right ICA	34±11	32±06	0.371
Left ICA	36±12	34±09	0.443
Right RA	20±09	20±10	0.986
Left RA	18±07	16±06	0.414
Right DA	15±10	12±07	0.368
Left DA	13±08	14±08	0.702
Right PA	13±04	12±03	0.163
Left PA	12±04	11±03	0.292

Notes: BA: basilar artery; VA: vetebral artery; OA: ophthalmic artery; ICA: internal carotid artery; RA: radial artery; DA: dorsal artery of foot; PA: popliteal artery.

Table 7 Differences in the mean flow velocity of blood vessels after administration in the two groups (cm/s, $\bar{x}$ ±s)

	Korean red Ginseng	Placebo	*P* value
WBV − BA	-10±11	-14±07	0.111
WBV − VA	-04±08	-03±04	0.581
WBV − DA	16±04	16±05	0.714
WBV − PA	15±07	15±06	0.963
WBV − RA	10±07	10±07	0.989

Notes: WBV: whole blood vessel; BA: basilar artery; VA: vasilar artery; DA: dorsal artery of foot; PA: popliteal artery; RA: radial artery.

temperatures.[24] Thermography can be applied as a diagnostic tool in many clinical applications, including oncology, allergic diseases, angiology, plastic surgery, and rheumatology.[25-27] Moreover, the body-temperature distribution in peripheral circulatory disturbances can be measured using DITI.[28]

We found that administration of Korean red ginseng did not affect PT or aPTT. Our results do not support a previous study that reported the efficacy of Korean red ginseng for prolonging aPTT.[18] Further clinical trials are needed to investigate the effect of Korean red ginseng on blood coagulation in blood-circulatory-disturbed subjects.

No significant changes were found in Doppler ultrasonography, possibly because we used healthy subjects. In the DITI study, we found that Korean red ginseng treatment increased only local temperatures of the abdomen. It has been suggested that taking Korean red ginseng remedies can cause fever or headache because of the thermal-stimulating effect of Korean red ginseng on the face or forehead. However, we conclude that no scientific linkage between Korean red ginseng treatment and headache or flushing of the face exists.

Korean red ginseng administration significantly reduced the temperature difference between the forehead and abdomen and between the whole body and forehead. Therefore, Korean red ginseng treatment improved the unbalanced thermal distribution. Laboratory blood tests, urinalyses, and adverse-events monitoring demonstrated the safety of Korean red ginseng.

We showed that Korean red ginseng did not influence blood coagulation or blood flow velocity but improved body temperature distribution. This result links the preventative effect of Korean red ginseng with improvement in the homeostasis of healthy people. Further studies are needed to research the effect of Korean red ginseng on blood-circulatory disturbances in disease settings.

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