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원 저

Effects of *Insamsansa-eum (Renshenshanzha-yin)* on Hypercholesterolemia and Analysis of Its Effects according to the Pattern Identification

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Backgrounds : Hyperlipidemia is a major cause of cardiovascular disease (CVD). Lowering serum cholesterol levels could reduce the risk of CVD. *Insamsansa-eum (Renshenshanzha-yin, ISE)*, composed of Ginseng Radix and Crataegii Fructus, is a new medicine developed to treat hyperlipidemia and CVD.

Objectives : In this study, we intended to explore the clinical effects of ISE on patients with hypercholesterolemia, and moreover we also compared its effects according to the pattern identification.

Methods : Subjects were administered ISE with the dose of 600 mg three times a day for 4 weeks. Patterns of subjects were identified with diagnostic scoring system for Yin-Yang and the condition of Excess-Deficiency before treatment. Serum lipids were measured at baseline and after 4 weeks of medication.

Results : ISE lowered total cholesterol (TC), triglyceride (TG), total lipid (TL), phospholipid(PL) and low density lipoprotein cholesterol (LDL) significantly. Compared with the data of our previous study, it was less effective than Atorvastatin but showed equal lipids-lowering effect to Chunghyul-dan (Qingxue-dan, CHD). In Yang pattern group, ISE was less effective in lowering TG and LDL than it was in not-Yang-not-Yinpattern group. On safety assessment, there was no adverse effect, hepatic or renal toxicity.

Conclusions : We suggest that ISE is a safe and useful herbal medicine for hypercholesterolemia, and moreover it could be more useful when it is used for patients with not Yang pattern.

Key Words: *Insamsansa-eum (Renshenshanzha-yin, ISE)*, Hypercholesterolemia, Pattern identification

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Introduction

Hyperlipidemia, resulting from lipid metabolic changes, is a major cause of cardiovascular disturbance[1], such as atherosclerosis and coronary heart disease. Cardiovascular diseases (CVD) are the most common cause of mortality and morbidity worldwide[2]. Although several factors, such as cigarette smoking, high-fat diet, high blood pressure, physical inactivity, age and

heredity play a significant role in causing CVD, high blood cholesterol is mainly responsible for the onset of CVD [2-3]. Lowering serum cholesterol levels, by a drug or dietary interventions could reduce the risk of CVD. Therefore, it is worthwhile to develop new safe and effective cholesterol-lowering agents from natural products.

Many herbal medicinal products reported to have an anti-hyperlipidemic effect [4-11]. Insamsansa-eum (Renshenshanzha-yin, ISE)is a combinatorial drug consisting of Ginseng Radix and Crataegii Fructus. Many reports from clinical and experimental studies suggested that ginseng and Hawthorn (Crataegus) fruitsmay have an antihyperlipidemic effect[12-16] and ISE showed significant antioxidant and lipid-lowering effects in our previous experimental study (Y. S. Kim et al., unpublished observations, 2004).

Therefore, in the present study we intended to explore the clinical effects of ISE, a new medicine developed to treat hyperlipidemia, on humans with hypercholesterolemia, and moreover we also compared its effects according to the pattern identification.

Subjects and Methods

Subject selection

Subjects were recruited from the patients visiting cardiovascular center, Kyung Hee University Kangnam Korean Hospital between November 2003 and December 2004.

Inclusion criteria was that serum total cholesterol was more than 240 mg/dL.

Table 1. Composition of *Insamsansa-eum*

Constitute herbs	Scientific name	Mass (g/capsule)
Ginseng Radix	*Panax ginseng* C. A. MEYER	1
Crataegii Fructus	*Crataegus pinnatifida* BGE.	3
Total		4

Table 2. Diagnostic scoring system for *Yin-Yang*

A: *Yang* indicating signs		B: *Yin* indicating signs	
Feeling of heat inside, desire for thin clothes, sweating in the region of the neck and head	+20	Feeling of cold, desire for warm clothes	-20
Desire for cold water, cold liquids	+10	Desire for heating, hot bath, etc	-20
Red face, inflamed sclera	+10	Pale face	-5
BT 36.7°C and above	+10	BT 36.2°C and below	-10
Red tip of the tongue	+10	Cold of the neck, back and lumbosacral region	-10
Pulsus frequens	+5	Subj. a. obj. coldness of limbs	-5
Pulsus superficialis	+5	Pulsus profundus et inequalis	-5
Distress of the chest and resistance tender on pressure of the right subcostal region	+5	Impaired hearing, articulation of words not clear	-5
Diarrhea accompanied by burning sensation of the anus	+10	Diarrhea without burning sensation of the anus	-5
Burning sensation during micturition, strong stream	+10	Only faint smell of the feces	-5
Strong smell of fecesB: Yin indicating signs	+5	Pollakisuria, weak stream	-10

A total score of more than +35 points indicates a condition of *Yang*.
A total score of more than -35 points indicates a condition of *Yin*.

Table 3. Diagnostic scoring system for the condition of *Excess or Deficiency*

Shining eyes, strong voice	+5	Dull eyes, weak voice, fatigue, Ki-deficiency	-5
Pulse of excess-type	+20	Pulse of deficiency-type	-10
Marked increased abdominal tension	+10	Marked reduction of abdominal tension	-10
Physiological skin color	+5	Pathological skin color	-5
Eczema, induration, pain	+10	Sweating easily without physical exertion	-5
Severe pain(chest, abdomen)	+20	Night sweat	-10
Painful tension of muscles	+10	Sound of fluctuating liquid in the stomach	-20
Offensive smell of feces, constipation	+10	No constipation, only faint smell of feces	-10
Subcutaneous edema of the abdominal skin with impressions of examiner's fingers quickly extinguished	+10	Subcutaneous edema of the abdominal skin with impressions of examiner's fingers slowly extinguished	-10
Steerhorn stomach	+10	Ptosis of organs/stomach	-20

Mild symptoms are scored with half the corresponding points. A total score of more than +30 points indicates a condition of *Excess*, a total score of -30 points is typical for a condition of *Deficiency*. A total score less than +30 or -30 describes the status of KI between *Excess and Deficiency*.

Exclusion criteria included[1] diabetes mellitus,[2] hepatic or renal diseases[3], cardio or cerebral vascular diseases within 3 months[4], patients who had taken anti-hyperlipidemic agents, or steroids within 6 months, and[5] alcoholic abusers.

Informed consents were obtained from all subjects after being given a full explanation of the study.

Materials

Insamsansa-eum (Renshenshanzha-yin, ISE) isa capsulated water extract (300 mg per one capsule) of Ginseng Radix and Crataegii Fructus (Table 1). Each herbal medicine was extracted twice with boiling water for 2 h. These extracts were filtered and evaporated in a rotary vacuum evaporator and then finally lyophilized with a freezing dryer. To standardize the quality of ISE, ginsenoside Rg1 in Ginseng Radix was quantitatively assayed according to the previous methods[17].

Study protocol

Subjects'general characteristics were recorded and diagnosis were confirmed when the World Health Organization Diagnostic Criteria were fulfilled or they had prior treatment history. Patterns of subjects were identified with diagnostic scoring system for Yin-Yang and the condition of Excess-Deficiency[18] (Table 2, 3) before treatment.

Subjects were administered ISE with the dose of 600 mg three times a day for 4 weeks. Any dietary advice was not given to the subjects, so they could maintain their life style on diet and exercise.

Serum lipids including total cholesterol (TC), triglyceride (TG), total lipid (TL), phospholipid (PL), high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol were measured at baseline and after 4 weeks of medication. For each subject, 10-15 mL of blood was collected in blood collection tubes containing heparin after overnight fasting, and the analysis of serum lipids was performed using an enzymatic method (Hitachi 7600-110, Japan).

Any possible adverse effect was monitored by physical examination during the treatment period. Hepatic and renal toxicity were assessed by Aspatate transaminase (AST), Alanine transaminase (ALT), Blood urea nitrogen (BUN), and Creatinine (Cr).

Table 4. Subjects' general Characteristics

		(n=20)
Male, n (%)		9(45)
Age, y (range)		47±13.2(28-69)
Coronary artery disease, n (%)		0(0)
Hypertension, n (%)		5(25)
Total Cholesterol		267.7±13.8
Yin-Yang pattern identification	*Yin*, n (%)	0(0)
	Yang, n (%)	8(40)
	Not-*Yin*-not-*Yang*, n (%)	12(60)
Deficiency-Excess pattern identification	*Deficiency*, n (%)	4(20)
	Excess, n (%)	8(40)
	Not-Deficiency-not-Excess, n (%)	8(40)

Statistical analysis

All results are expressed as mean ± SD unless otherwise stated. Data were analyzed by one-way ANOVA, paired t-test and independent t-test. A value of $P<0.05$ was considered significant. All calculation was performed by SPSS for windows, version 11.5 (SPSS Inc., Chicago, Illinois, USA).

Results

Initial subjects' characteristics

The characteristics of the subjects are summarized in Table 4. At first, 25 subjects were recruited but 5 subjects dropped out during the study. Therefore, 20 subjects were included in the final analysis. In Yin-Yang pattern identification, 8 subjects showed Yangpattern and 12 subjects showed not-Yin-not-Yang. 4 subjects showed Deficiency pattern, 8 showed Excess and 8 showed not-Deficiency-not-Excess in Deficiency-Excess pattern identification.

Lipid lowering effect of ISE

ISE lowered TC, TL, TG, PL, and LDL significantly. But, HDL was not lowered significantly (Table 5).

Comparison of lipid-lowering effects among the groups

This study is not a case-controlled trial so we compared ISE's lipid-lowering effect with the data of our previous study[19]. There were no significant differences in the subjects' general characteristics and the baseline assessment of lipid levels among three groups (data not shown). ISE was less effective than Atorvastatin in lowering TC and LDL. But, there were no significant differences in lipids-lowering effects between ISE and Chunghyul-dan (Qingxue-dan, CHD) (Table 6).

Changes of serum lipids according to the pattern identification

In Yang pattern group, ISE was less effective in lowering TG and LDL than it was in not-yang-not-Yin pattern group (Table 7). But, in Excess-Deficiency pattern identification, there were no significant differences in ISE's lipids-

lowering effects among the groups (data not shown).

Safety assessment

There was no clinical adverse effect during 4 weeks of medication. Table 8shows there was no significant elevation of ALT, AST, BUN, and Cr.

Discussion

ISE is a new medicine developed to treathyperlipidemia and CVD. In this study, ISE significantly lowered TC, TL, TG, PL, and LDL after 4 weeks of treatment. The mechanism by which ISE decreases serum cholesterols remains unclear. Serum cholesterol can be lowered at several metabolic points including decreased synthesis, activation of LDL receptors, inhibition on absorption of dietary cholesterol, and conversion of cholesterol to bile acids. It was previously reported that ginseng may decrease blood cholesterol levels by increasing cholesterol excretion through bile acid formation[20-21], and increase LDL receptors by promoting the synthesis of LDL receptors in rats[22]. Muwalla and Abuirmmeileh reported that 3-hydroxy-3-

Table 5. Lipids-lowering Effects of *Insamsansa-eum*

(mg/dL)	Baseline	4 weeks
TC	267.7±13.8	238.8±23.1**
TL	722.9±95.0	681.6±110.8**
TG	154.6±43.7	134.1±34.8*
PL	290.9±26.0	271.6±26.5**
HDL	62.4±11.1	61.8±9.5
LDL	163.8±42.0	150.2±20.0*

Values are mean ± standard deviation.
TC, TG, TL, PL, HDL, and LDL are total cholesterol, triglyceride, total lipid, phospholipids, high density lipoprotein cholesterol, and low density lipoprotein cholesterol, respectively.
* and ** are P<0.05 and 0.01 by paired t-test vs. baseline

Table 6. Comparison of the Lipid-lowering Effects between the Groups

	Changes during 4 weeks		
(mg/dL)	*Insamsansa-eum*	*Chunghyul-dan*	Atrovastatin
TC	-28.9±29.1	-14.5±31.4	-83.8±28.2*
TL	-41.3±56.7	-26.2±158.3	-86.4±293.9
TG	-20±33.2	6.2±118.0	27.8±226.8
PL	-19.3±28.1	-13.9±31.6	-39.6±38.4
HDL	-0.6±6.4	-3.57±6.61	0.08±6.54
LDL	-13.6±40.7	-12.1±30.6	-64.3±22.8*

Values are mean ± standard deviation.
TC, TG, TL, PL, HDL, and LDL are total cholesterol, triglyceride, total lipid, phospholipids, high density lipoprotein cholesterol, and low density lipoprotein cholesterol, respectively.
* is P<0.01 by independent t-test vs. *Insamsansa-eum* group

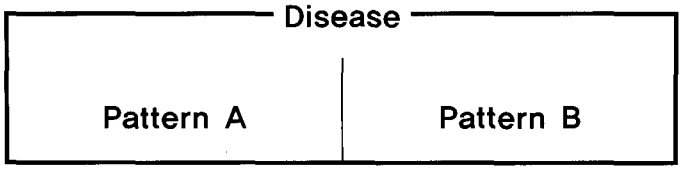

Fig. 1. Hypothesis of the relationship between the name of disease used in modern western medicine and the pattern in the system of oriental medicine.

methylglutaryl coenzyme A (HMG-CoA) reductase activity was significantly lowered by ginseng, which shows the mechanism of the hypocholesterolemic action of ginseng involves the suppression of cholesterol biosynthesis[12]. Hawthorn (Crataegus) fruit was reported to increase LDL-receptor activity of hepatic membrane in rats[23]. In addition to the activation of LDL receptors, it was also reported to increase excretion of bile acids through up-regulation of hepatic cholesterol 7α-hydroxylase activity, and inhibit cholesterol absorption through down-regulation of intestinal acyl CoA: cholesterol acyltransferase activity[14]. Based on the studies reported, it was thought that those action mechanisms of Ginseng Radix and Crataegii Fructus on lipid metabolism might be involved in the present study.

This study is not a case-controlled trial. Therefore, we compared ISE's lipid-lowering effect with the data of our previous study[19]. It was less effective than Atorvastatin but showed equal lipids-lowering effect with CHD. Although Atorvastatin is highly effective, it has been reported to have several kinds of side effects[24-26]. Therefore, it is worthy to develop new effective agents from natural products, which are generally safer than conventional chemical agents. And moreover Ginseng Radix and Crataegii Fructus have been reported to improve cardiac function and decrease peripheral resistance [27-31]. Thus we could expect ISE's additional effect, preventing chronic heart failure or treating early stage of chronic heart failure.

In the present study, ISE's lipid-lowering effect

Table 7. Changes of serum lipids according to the pattern identification

	Changes during 4 weeks	
(mg/dL)	*Yang* pattern	Not *Yin* not *Yang* pattern
TC	-18.8±23.8	-35.7±31.3
TL	-21.6±54.9	-54.5±56.2
TG	-2±27.8	-32.8±31.6*
PL	-10.5±27.9	-25.2±27.8
HDL	-2.3±2.9	0.5±7.9
LDL	-10.4±51.1	-29.6±22.4*

Values are mean ± standard deviation.
TC, TG, TL, PL, HDL, and LDL are total cholesterol, triglyceride, total lipid, phospholipids, high density lipoprotein cholesterol, and low density lipoprotein cholesterol, respectively.
* is $P<0.05$ by independent t-test vs. Yang pattern group

Table 8. Safety assessment

(mg/dL)	Medication		P-value*
	Before	After	
AST(U/L)	19.0±4.7	16.7±3.9	N.S
ALT(U/L)	19.3±9.0	17.8±9.1	N.S
BUN(mg/dL)	14.8±5.2	12.4±2.5	N.S
Cr(mg/dL)	0.9±0.3	0.9±0.2	N.S

Values are mean ± deviation.
AST: aspatate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, Cr: creatinine
*: tested by paired t-test.

was compared according to the pattern identification. In Yang pattern group, ISE was less effective in lowering TG and LDL than it was in not-yang-not-Yin pattern group (Table 7). Traditional oriental medicine has used Ginseng Radix and Crataegii Fructus, especially Ginseng Radix, to treat patients with Yinpattern. So this result is thought in agreement with the tradition of oriental medicine. It appears that there are no direct links between the name of disease used in modern western medicine and the pattern (the condition of the patient) in the system of oriental medicine. But when we treat a disease especially with herbal medicine, it is thought to be more effective and safe when diagnosis is made by not only the name of disease but also the pattern identification (Figure 1). For example, when hyperlipimemia is treated, ISE could be used for patients with Yin pattern and CHD, composed of Scutellariae Radix, Coptidis Rhizoma, Phellodendri Cortex, Gardeniae Fructus, and Rhei Rhizoma, could be used for patients with Yang pattern.

There are two limitations in this study. First, this study is small and not a case-controlled trial so we can not make a concrete conclusion. Even though we compared ISE's effect with the data of our previous study, large randomized controlled trial should be followed. Secondly, treating a disease according to the pattern identification is a kind of hypothesis that should be tested. And there are many kinds of pattern identifications in oriental medicine. Further studies using various pattern identifications will be necessary to test this hypothesis.

In conclusion, we suggest that ISE is a safe and useful herbal medicine for hypercholesterolemia, and moreover it could be more useful when it is used for patients with not Yang pattern.

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