American Journal of Chinese Medicine, Vol. XXVI, No. 2, pp. 199-209

Effect of Red Ginseng on Blood Pressure in Patients with Essential Hypertension and White Coat Hypertension

Ki Hoon Han, Seong Choon Choe, Hyo Soo Kim, Dae Won Sohn, Ki Yeul Nam*,
Byung Hee Oh, Myoung Mook Lee, Young Bae Park, Yun Shik Choi, Jung Don Seo and Young Woo Lee

Division of Cardiology, Department of Internal Medicine,
Seoul National University College of Medicine,
**Korea Ginseng & Tobacco Research Institute, Seoul, Korea*

(Accepted for publication June 24, 1997)

Abstract: The objective of this study is to evaluate the changes of diurnal blood pressure pattern after 8 weeks of red ginseng medication (4.5 g/day) by 24 hour ambulatory blood pressure monitoring. In 26 subjects with essential hypertension, 24 hour mean systolic blood pressure decreased significantly ($p = 0.03$) while diastolic blood pressure only showed a tendency of decline ($p = 0.17$). The decrease in pressures were observed at daytime (8 A.M. - 6 P.M.) and dawn (5 A.M. - 7 A.M.). In 8 subjects with white coat hypertension, no significant blood pressure change was observed. We suggest that red ginseng might be useful as a relatively safe medication adjuvant to current antihypertensive medications.

Hypertension, a major high-risk factor that accelerates arteriosclerosis, is known to result in ischemic cerebrovascular disease and angina pectoris due to infarction or embolism of the cerebral artery; ischemic heart disease such as myocardial infarction; and sudden cardiac arrest as well as peripheral and occlusive disease of the blood vessel (Australian therapeutic trial, 1980; MRC trial, 1985; HDFP experience, 1980) (IPPPSH Collaborative Group, 1985).

The effects of red ginseng (Ginseng Radix Rubra) biochemical and pharmacological effect are being gradually disclosed. Ginseng's influence on blood pressure, however, is still a subject of controversy. Reports on the antihypertensive effect of red ginseng as a result of clinical trial are rare. According to Sokabe *et al.* (1984), after administration of 3 g of red ginseng powder every day for three months to 19 idiopathic hypertensive patients, who were treated with antihypertensive agent, a distinct antihypertensive effect was not observed. However, 89% of the patients revealed improvement in subjective symptoms

such as fatigue, insomnia, sexual life and mood. A comparatively large scale clinical trial by Yamamoto *et al.* (1990) on 316 random cases from 15 hospitals, administered (3 - 6 g, taken separately each day before meal) Korean red ginseng powder on a long term basis (10 months on the average), which showed the following results: 51% of 74 hypertensive patients showed antihypertensive effect, 43% remained unchanged in blood pressure, and 5% showed elevation in blood pressure; whereas 95% of the normotensive patients showed steadiness in blood pressure, 2% showed decrease in blood pressure and 3% marked the opposite; in hypotensive patients, 63% out of 35 showed no change in blood pressure, 31% had elevation in blood pressure and 6% proved the opposite. Trivial side effects were recognized in vicinity of 3% out of the total subjects but were improved through discontinuation of the medication.

It was thought that since the above mentioned clinical studies methodically employed data from clinic-based blood pressure measurements, a basic bias might underlie the process of analyzing the antihypertensive effect of red ginseng. Thus, this study is designed as a placebo controlled study. We also tried to analyze more objectively the blood-pressure controlling effect of red ginseng by monitoring 24 hour ambulatory blood pressure rather than clinic-based blood pressure.

Materials and Methods

Selection of Primary Subjects

Patients who came to the Seoul National University Hospital (Seoul, Korea) from June to December 1994 and who were diagnosed with idiopathic hypertension were screened as primary subjects. Patients who were mild or moderate idiopathic hypertensives with blood pressure measured over 140/90 mm Hg, and diastolic blood pressure (DBP) below 110 mm Hg before any antihypertensive medication were initially included for the study.

Criteria for exclusion were as follows:

1. patients under 18 or above 70 years of age;
2. patients who were pregnant or who are planning to get pregnant;
3. patients with secondary hypertension;
4. patients with malignant or accelerated hypertension;
5. patients with nephrotic syndrome;
6. patients with a history of cerebrovascular disease within a period of 3 months;
7. patients with acute myocardial infarction or unstable angina pectoris within a period of 3 months;
8. patients with congestive heart failure;
9. patients with renal diseases or renal impairment of above moderate degree (serum creatinine level > 1.5 mg/dl);
10. patients with hepatic diseases (enzyme level of AST and ALT measuring twice the normal level);
11. patients with senile dementia;
12. alcoholics or other drug abusers;

13. patients assessed to be inappropriate for drug administration during the study period due to other diseases.

Classification of subjects (Figure 1)

First, all subjects were asked to discontinue all antihypertensive agents for at least 4 weeks. Then, patients with clinic-based DBP measuring over 90 mm Hg and below 110 mm Hg were included in the study. When the DBP exceeded 110 mm Hg, one of the following two options was chosen and the change in blood pressure was observed for more than 4 weeks. That is 50 mg of atenolol, a ß-blocker, was administered once a day; or 40 mg of nicardipine, a calcium channel blocker, was applied twice a day. After administering one of the above drugs for a minimum of 4 weeks, only those whose clinic-based diastolic blood pressure measured between 90 mm Hg and 110 mm Hg were included in the study group.

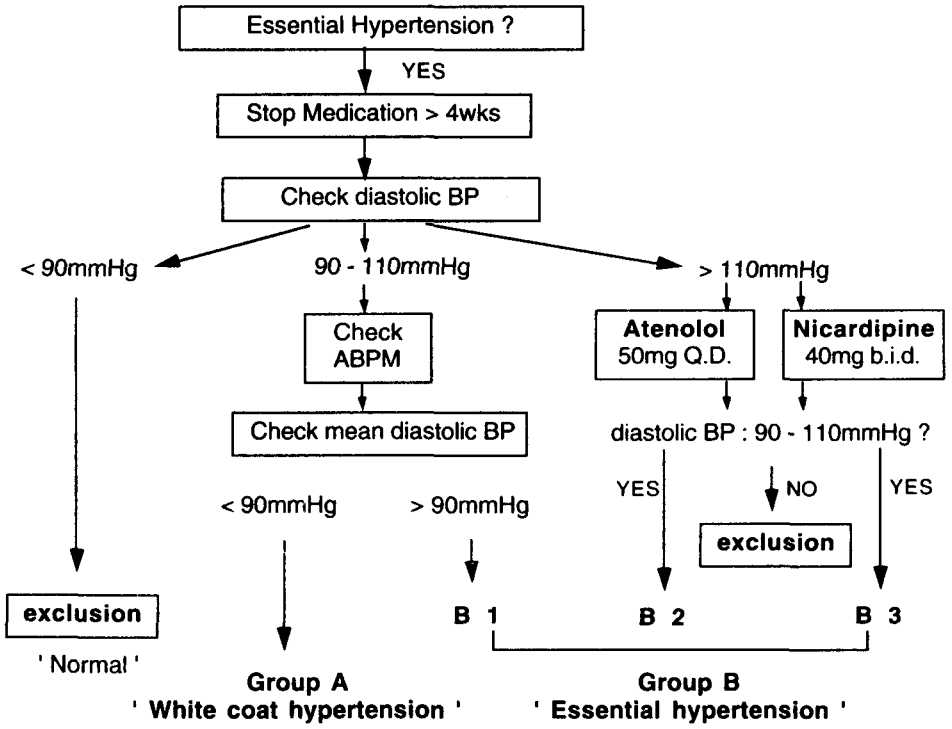

Figure 1. Classification of study subjects

At the starting point of this study, 24 hour ambulatory blood pressure monitoring (ABPM) was performed on all subjects. Based on the result of 24 hour ABPM, all 34 subjects were classified into 4 subgroups.

Group A (subjects with white coat hypertension, n = 8):

Patients whose clinic-based DBP measured above 90 mm Hg and below 110

mm Hg after discontinuation of antihypertensive agent, but mean 24 hour DBP measured below 90 mm Hg by 24 hour ABPM.

Group B (26 subjects with essential hypertension)

Subgroup B1 (administered with red ginseng only, n = 12):
Patients whose clinic-based DBP measured over 90 mm Hg and below 110 mm Hg after discontinuation of antihypertensive agent, and also whose mean 24 hour DBP measured above 90 mm Hg by 24 hour ABPM.

Subgroup B2 (administered with red ginseng and ß blocker, n = 8):
Out of the cases whose clinic-based DBP measured over 110 mm Hg after discontinuation of antihypertensive agent and who were presently taking ß-blocker, these were the ones whose clinic-based DBP measured between 90 mm Hg and 110 mm Hg while taking the ß-blocker.

Subgroup B3 (administered with red ginseng + calcium channel blocker, n = 6):
Out of the cases whose clinic-based DBP measured over 110 mm Hg after discontinuation of antihypertensive agent and who were presently taking calcium channel blocker, these were the ones whose office-based DBP measured between 90 mm Hg and 110 mm Hg while taking the calcium channel blocker.

Administration of Red Genseng and Placebo

After classifying the above subjects, medication of placebo was administered for 4 weeks, and red ginseng medication for 8 weeks. Subjective side effects were monitored through the out patient clinic every four weeks.

All subjects were asked to take a total of 4.5 grams of red ginseng (Ginseng Radix Rubra, obtained from Korean Tobacco & Ginseng Corporation, Taejeon, Korea) per day (1.5 gram t.i.d., each capsule containg 300 mg of red ginseng). The placebo was made into the same capsule shape as the red ginseng so the study subjects could not discern the difference. The medication time was fixed at 8-9 A.M., 1-2 P.M. and 6-7 P.M.

The following cases were excluded from the study. (1) When significant adverse reaction surfaced during medication or when the study subject was observed in potential life threatening danger; (2) when the patient rejected medication; (3) when the patient's clinic-based DBP rose above 110 mm Hg during the study period.

Monitor of 24 Hour Ambulatory Blood Pressure

24 hour ambulatory blood pressure monitoring (ABPM) of all subjects was done in three stages. The timing of measuring the 24-hour ABPM is as follows: 1. starting point of research - Basal level (Basal); 2. period of placebo medication- 4 weeks after administered placebo (Placebo); 3. period of red ginseng medication - 8 weeks after administration of red ginseng (Medication).

Blood pressure was measured at the interval of every 30 minutes from 8 A.M. until 8 A.M. the following day. An A&D TM 2421 apparatus (A&D Co. Ltd., Tokyo, Japan) was employed as measuring device and the oscillometric method was used as a blood pressure measuring method (Kronig *et al.*, 1996).

Measurement of Variables

In every respect, 24 hour blood pressure measuring points, 24 hour mean systolic and diastolic blood pressure, mean blood pressure and mean heart rate were measured. According to time table starting from 8 A.M. until 11 P.M., a total of 16 hours was defined as daytime and 11 P.M. to 8 A.M. of the next morning was defined as nighttime.

Pressure load, the fraction representing over 140 mm Hg in the case of SBP and over 90 mm Hg in the case of diastolic blood pressure from the 24-hour blood pressure measurements are defined, respectively, as systolic pressure load and diastolic pressure load. The variability of blood pressure and heart rate was analyzed by obtaining the respective standard deviation.

Statistical Analysis

Before and after medication of red ginseng and during follow-up examination, changes in hemodynamic profiles were analyzed with paired t-test. Frequency was observed in case of drug side effect. Statistical significance was defined as $p<0.05$.

Results

Clinical Characteristics of the Subjects

Out of the 45 subjects initially recruited in this study, 11 dropped out due to the following: 2 complained of upper abdominal discomfort and constipation; 5 refused blood pressure measurement by 24-hour blood pressure measuring device; and 4 were excluded from the study due to high DBP which was over 110 mm Hg during the medication of placebo.

The remaining 34 subjects were 17 men and 17 women with average age of 58.8 ± 8.8. The mean period of hypertension was 6.8 ± 4.2 years (2-15 years). According to electrocardiography, 17 were normal, 9 showed nonspecific ST segment change in precordial leads, and 8 showed left ventricular hypertrophy. There was no finding of acute or old myocardial infarction and cardiomegaly on the chest x-ray in any of the subjects. Five showed moderate hypertensive retinopathy over third degree on funduscopic examination according to the Kaith Wagener classification. 15 were diagnosed as normal, 6 showed first-degree, and 8 showed second-degree hypertensive change. There was no correlation between fundus finding and the degree of hypertension or electrocardiographic finding. Fourteen showed obesity marking over 30.0 in the body mass index and smoking history was observed in 4 males.

Change in Blood Pressure

1. Systolic blood pressure (SBP)

The 24 hour mean SBP of 8 subjects with white coat hypertension (Group A) was 138.0 ± 15.1 mm Hg before red ginseng medication (Basal), 134.3 ± 17.2 mm Hg after the medica-

tion of placebo (Placebo) and 127.3 ± 11.3 mm Hg after administering red ginseng for 8 weeks (Medication). There was no statistical difference between these treatments (p = 0.395 by paired t-test) (Table 1).

Table 1. Changes of Blood Pressure Profile, Heart Rate and Pressure Load before and after Red Ginseng Medication

	Basal	Placebo	Medication	P value
White coat hypertension (Group A, n = 8)				
Systolic BP (mmHg)	138.0 ± 15.1	134.3 ± 17.2	127.3 ± 11.3	0.395
Diastolic BP (mmHg)	79.0 ± 6.1	78.0 ± 7.8	74.7 ± 7.5	0.214
Mean BP (mmHg)	98.3 ± 8.9	96.0 ± 10.6	92.0 ± 8.5	0.373
Heart Rate (/min)	64.3 ± 2.3	61.0 ± 5.3	59.0 ± 4.6	0.074
Systolic Pressure Load (%)	43.1 ± 38.3	42.9 ± 39.1	27.6 ± 17.9	0.489
Diastolic Pressure load	18.5 ± 15.2	18.4 ± 10.6	15.9 ± 12.3	0.128
Essential hypertension (Group B, n = 26)				
Systolic BP (mmHg)	147.9 ± 14.2	149.3 ± 12.1	143.6 ± 10.3*	0.030
Diastolic BP (mmHg)	91.6 ± 8.6	91.3 ± 6.8	87.8 ± 5.7	0.173
Mean BP (mmHg)	110.1 ± 9.9	110.1 ± 7.8	106.1 ± 6.5	0.088
Heart Rate (/min)	67.6 ± 10.8	68.7 ± 7.2	64.0 ± 9.1	0.077
Systolic Pressure Load (%)	64.9 ± 23.6	69.1 ± 22.1	62.6 ± 22.6	0.138
Diastolic Pressure load	60.3 ± 25.1	58.2 ± 20.6	43.9 ± 19.0	0.065

All data are expressed as mean ± S.D. P value: (Placebo vs. Medication),
*: $p<0.05$ by paired t-test

The 24 hour mean SBP of all 26 subjects from the essential hypertensive groups (B1, B2, B3) was 147.9 ± 14.2 mm Hg before red ginseng medication (Basal) and 149.3 ± 12.1 mm Hg after the medication of placebo (Placebo). The difference was not significant. The 24 hour mean SBP measured after red ginseng treatment for 8 weeks (Medication) was 143.6 ± 10.3 mm Hg, a significant decline due to the medication of red ginseng, regardless of other medications taking in addition to red ginseng (p = 0.030 vs. 'Placebo' by paired t-test) (Table 1).

2. Diastolic Blood Pressure (DBP)

Profiles of the 24 hour mean DBP of the white coat hypertensive group (Group A) and the essential hypertensive groups (B1, B2, B3) showed no significant difference before the red ginseng medication (Basal) and after the medication of placebo (Placebo). A decline tendency was shown after administered red ginseng for 8 weeks (Medication), however, the difference was insignificant (p = 0.214, p = 0.173 vs Placebo for group A and group B, respectively). Also, there was no significance difference between the subgroups B1, B2 and B3 ($p>0.05$, data not shown).

3. Heart Rate

There was no statistical significant difference between Group A and Group B after the medication of placebo and after the 8-week red ginseng medication ($p = 0.074$, $p = 0.077$ vs. Placebo by paired t-test, respectively) (see Table 1).

4. Variability Analysis

The variability can be expressed as the variance of the distribution of each parameter. The changes in variability of systolic, diastolic and mean blood pressure, and heart rate due to the red ginseng medication were not observed in any group ($p>0.05$, F-test).

5. Pressure Load

The fraction(%) representing above 140 mm Hg in SBP and over 90 mm Hg in DBP measured during 24 hours are defined as systolic pressure load and diastolic pressure load, respectively. There was no change in pressure load between the basal level and placebo medication in both groups A and B. But after red ginseng administration, both systolic pressure load as well as diastolic pressure load showed a decline tendency (see Table 1), especially when daytime (8 A.M. to 11 P.M.) and nighttime (11 P.M. to 8 A.M. of the next day) were distingushed when analysis was carried out. This kind of tendency was more obvious during the daytime ($p<0.05$ both systolic and diastolic pressure load), whereas the pressure load during the nighttime showed little change. This decline tendency was more profound in group B than group A (Figures 2A and 2B).

6. Placebo Subtracted Curve (Figures 2A and 2B)

The changes of systolic and diastolic blood pressure before and after red ginseng medication are shown in Figures 2A (SBP) and 2B (DBP). That is, both systolic and diastolic blood pressure mainly decline in the daytime (8 A.M. through 6 P.M.) and at dawn (5 A.M. through 7 A.M.). Meanwhile, changes in blood pressure at night (6 P.M. through 4 A.M. of the following day) are marginal or slightly increased.

7. Effect According to Subjective Symptoms

Besides the two subject who discontinued taking red ginseng due to abdominal discomfort, allergic subjective symptoms were not observed. Other side effects were trivial and temporary such as diaphoresis ($n = 3$) tiredness and drowsiness ($n = 4$) constipation and dyspepsia ($n = 2$).

Discussion

Although the antihypertensive effects of red ginseng have been reported in some studies (Sokabe *et al.*, 1984; Yamamoto *et al.*, 1990), there is no definite established explanatory

theory since the methods for measuring blood pressure and number of subjects were limited, and results varied according to each investigation. This can be attributed to the heterogeneity within the ingredients of the administered red ginseng itself, and differences in research method. Studies carried out before this study were accompanied by several limitations, among them that clinic-based BP measurements could only be measured just one time per each study stage. Since the antihypertensive effects had to be evaluated based solely on this, there is a high likelihood of variability and bias in making assessments of the antihypertensive effect of red ginseng.

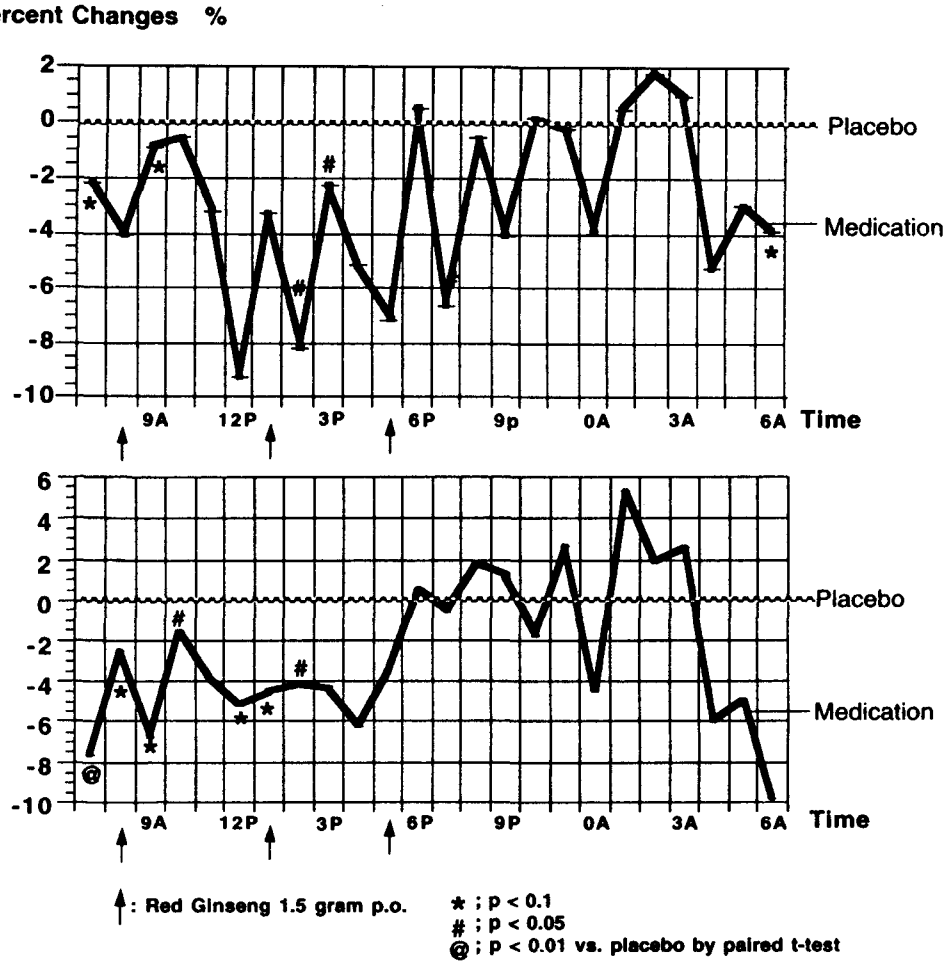

Figure 2. Placebo-subtraction curve of systolic (upper graph) and diastolic (lower graph) blood pressure profile. Both systolic and diastolic blood pressure mainly decline in the day time (8 A.M. through 6 P.M.) and during dawn (5 A.M. through 7 A.M.). Meanwhile, changes in blood pressure at night (6 P.M. through 4 A.M. of the following day) were marginal or slightly increased.

This study utilized the following methods to eliminate any possible limitations in the research. First, each study subject took a 24 hour ABPM after stopping all medications for more than 4 weeks. Secondly, by choosing the placebo controlled study, a placebo effect of the subjects was eliminated. Third, 24 hour ambulatory blood pressure monitoring made possible the discernment and analysis of white coat hypertension that is impossible to be diagnosed through clinic-based BP measurement.

It has been acknowledged that using ABPM (which measures the pressure fifty times in each examination) to analyze blood pressure changes by antihypertensive medication guarantees higher accuracy and reliability than clinic-based BP measurement. The advantage of 24 hour blood pressure monitoring is mainly that the numbers of measurement are much higher than in the clinic, and a rather small number of subjects like this made this study possible (William *et al.*, 1989; Lawrence *et al.*, 1993; Prince *et al.*, 1991; Michael *et al.*, 1994; Kevin *et al.*, 1992).

The results of this study on antihypertensive effects of red ginseng are as follows: (1) A significant decline in SBP from the essential hypertensive group (groups B1, B2, B3) in contrast with the white coat hypertensive group (group A) was observed, (2) its degree was calculated at about 5%, and (3) although statistical significance seems small, the decline in DBP was due to red ginseng medication. As was suggested in the Australian studies, HDFP (1984), MRC (1985) and IPPPSH (1985) the ideal control range of DBP is 90-95 mm Hg in idiopathic hypertensive patients. The decline in DBP in this study can also be regarded as string of the beneficial pharmacological reactions of red ginseng. This is because the number of subjects whose 24 hour mean DBP measured above 90 mm Hg decreased from 26 before the red ginseng medication to 8 after the medication; and the mean DBP in the daytime decreased from 91.1 ± 9.8 mm Hg after placebo to 86.5 ± 9.5 mm Hg after the red ginseng medication in the hypertensive group.

Pressure load is a concept that was introduced when the 24 hour observation of blood pressure changes became possible with the practical use of 24 hour ABPM (Lawrence *et al.*, 1993; Prince *et al.*, 1991). It is a percentage that denotes the number of systolic and diastolic blood pressure exceeding 140 mm Hg and 90 mm Hg, respectively, out of all 24 hour measurements. Presently, there are no standard studies on Koreans, but it is accepted that the risk of end organ damage increases if the pressure load exceeds 40% and the hypertension is essential (William *et al.*, 1989). The pressure load of the essential hypertensive group (group B) was 64.9% and 60.3% for mean systolic and diastolic, respectively, before red ginseng treatment. Although it shows a decrease in pressure load due to red ginseng medication (62.6% and 43.9% for SBP and DBP, respectively), the degree of decrease is insignificant. Consequently, it can be contended that the antihypertensive effect of red ginseng in this study is not potent to prevent organ damage or diminish the rates of mortality and complications.

On the other hand, results of 24 hour blood measurement showed that red ginseng effects on blood pressure fluctuated according to time sequence (Figures 2A and 2B). The decrease in blood pressure due to red ginseng medication is observed mainly during daytime (8 A.M. to 6 P.M.) and from 5 A.M. to 7 A.M. The fact that decrease in blood pressure by red ginseng medication occurs during daytime as well as dawn when the frequency of cerebrovascular disease climbs up is encouraging.

The mechanisms of the antihypertensive effect of red ginseng are reported to enhance the secretion of EDRF (endothelium derived relaxing factor) of red ginseng; enhance sensitivity of atrial natriuretic peptide whose secretion is naturally blunted in aged people like this study subjects, and block calcium channel (Hong *et al.*, 1992; Jiang *et al.*, 1992; Tanado *et al.*, 1992; Takamashi *et al.*, 1992). In order to elucidate this indirectly, we tried to differentiate the group medicated with red ginseng alone (subgroup B1), group treated with red ginseng and ß blocker (subgroup B2), and red ginseng plus calcium channel blocker medicated group (subgroup B3). However, changes in hemodynamic factors appeared equal in all the subgroups. By making allowances for the changes in hemodynamic factors such as decrease in systolic and diastolic blood pressure, tendency of decrease in heart rate, it can be speculated that there might be similar stabilizing effect of the heart to the ß blocker among pharmacological effects of red ginseng. Also, by taking into consideration the fact that blood pressure decreases at dawn, prevention of cortisol and catecholamine surge or down regulation in receptor function can be considered.

The results of this study, and the systolic as well as the diastolic blood pressure lowering by red ginseng medication based on this study can be predicted to reach about 5% of the basal level.

In summary, this study indicated that 24 hour ABPM is more reliable than the blood pressure measured in the outpatient clinic, and is highly correlated with blood pressure in outpatient clinics if that is sufficiently repeated. Mild decrease in systolic as well as diastolic blood pressure was observed without serious side effects and discomfort due to red ginseng medication in idiopathic hypertensive patients. And since these findings are continuously observed in hypertensive subgroups, which were medicated with ß-blocker or calcium channel blocker along with red ginseng, red ginseng can be useful as an adjuvant medication to any antihypertensive agent. Also, since (1) decreasing tendency of pressure load and (2) antihypertensive effect at dawn were observed with red ginseng treatment, onset of cerebrovascular disease in hypertension or end organ damage is less expected. However, this clinical respect awaits further study.

References

1. Hirofumi Sokabe, Koichiro Kishi and Takushi X. Watanabe. Antihypertensive effect of Korean red ginseng. *The Ginseng Review,* 2(1): 3-14, 1984.
2. Hong, M., Y. Jin, Mai Yo, A. Boersma, K.K. Han, M.C. Vantyghen and J. Lefebvre. The decline of atrial natriuretic peptide gene expression in older rats and the effects of ginsenoside on ANP gene expression. *Comp-Biochem Physiol-B* 101(1-2): 35-39, 1992.
3. Hypertension Detection and Follow-up Program Cooperative Research Group. The effect of antihypertensive drug treatment on mortality in the presence of resting electrocardiographic abnormalities at baseline. The MDFP experience. *Circulation* 70: 96-105, 1984.
4. IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: The International Prospective Primary Prevention Study in Hypertension (IPPPSH). *Hypertension* 3: 379-385, 1985.
5. Jiang, Y., G. Zhong, C. Shao and G. Yue. Calcium channel blocking effect of panaxadiol saponins and panaxatriol saponins of cultured cardiac cells. *Chung-Kuo Chung Yao- Tsai-Chi* 17(3): 172-173, 1992.

6. Kevin, A.P., H.G. Richard, R.M. Sunil, S. Kenneth, R.L. Phillip, D.N. James and E. Kristine. Population derived comparisons of ambulatory and office blood pressures. *Arch Intern Med.* 152: 750-756, 1992.
7. Kronig, B. Ambulatory blood pressure monitoring devices. Zeitschift fur Kardiologie. Kardiologie, 85 (suppl) 3: 32-37, 1996.
8. Lawrence, J. Appel and William B. Stason. Ambulatory blood pressure monitoring and blood pressure self-measurement in the diagnosis and management of hypertension. *Annals of Internal Medicine* 118: 867-882, 1993.
9. Management of Committee. The Australian therapeutic trial in mild hypertension. *Lancet*, 1-1261-1265, 1980.
10. Medical Research Council Working Party. MRC trial of treatment of mild hypertension - Principal Results. *Br. Med. J.* 291: 97-103, 1985.
11. Michael, A.W., Joel MN, David HG and William FG. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation* 90: 2291-2298, 1994.
12. Prince KJ and James DK. Clinical use of ambulatory blood pressure monitoring. *Journal of Hypertension* 9: S7-S12, 1991.
13. Takamashi M, Tokuyama S and Kaneto H. Antistress effect of ginseng on the inhibition of morphine tolerance in stressed mice. *Jpn J Pharmacol* 59(3): 399-404, 1992.
14. Tanado T, Aizawa T, Asao-T, Hozumi M and Kisara-K. Pharmacological studies of nutritive and tonic crude drugs on fatigue in mice. *Nippon-Yakurigaku-Zasshi* 100(5): 423-431, 1992.
15. William FG, Jodi LL, Denna GC and Michael AW. Validation of portable noninvasive blood pressure monitoring devices: Comparisons with intra-arterial and sphygmomanometer measurements. *Am Heart J.* 116: 1155-1162, 1988.
16. William B. White, Holley M. Dey and Peter Schulman. Assessment of the daily blood pressure load as determinent of cardiac function in patients with mild to moderate hypertension. *Am Heart J* 118: 782-789, 1989.
17. Yamamoto M., Y. Tamura, K. Kuashima and Y. Immamura. Clinical effects of red ginseng in patients with essential hypertension. *The Ginseng Review*, 9: 15-27, 1990.