Effect of Fermented Korean Ginseng Extract Fortified with Ginsenoside Rg_3 on Blood Pressure in Individuals with High Normal Blood Pressure or Hypertension

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Background and Rationale

Hypertension is prevalent worldwide. Many of the industrialized nations report that 20% or more of their adult population suffer from this condition. In Canada and the United States the prevalence is 20% (1,2), in England it is as high as 40% (3), and in South Korea it is 20% (4). The combination of hypertensions widespread occurrence and devastating impact on cardiovascular health makes it a priority for treatment.

Hypertension is defined as a systolic blood pressure (BP) >140 mm Hg or a diastolic BP >90 mm Hg (5). The urgency to treat it is paramount since it plays a central role in the pathogenesis of both coronary heart disease (CHD) and stroke (6). Observational studies indicate that every 7.5 mm Hg rise in BP increases the relative risk of CHD by 29% and stroke by 46%. Fortunately, lowering BP through the use of antihypertensive agents can reduce the morbidity and mortality associated with these diseases (7). Reducing systolic BP by 10-12 mm Hg and diastolic BP by 5-6 mm Hg confers relative reductions in the risk of stroke and CHD by 38% and 16%, respectively. Thus, the treatment of hypertension holds great benefit (8).

The current treatment goal for hypertension is a BP <140/90 mm Hg (5). Such control is meagerly achieved amongst hypertensive Canadians and Americans, with a success rate of only 9 and 27%, respectively (1,2). A similarly poor treatment success rate is found in many other countries too (9). Fortunately, however, this grim reality could be improved, in part, through the creation of new BP lowering agents.

Future BP lowering agents may include those that exert their effect by normalizing the metabolism of vasodilators such as nitric oxide (NO) (10). NO is a diatomic free radical that is produced largely by the vascular endothelium through the action of endothelial NO synthase (eNOS; 11).

One of its chief functions is to regulate vascular tone (12,13), but it also contributes to BP control (14). Evidence for this latter point extends from both human and mice studies. When NO production is inhibited in humans a consequential rise in BP occurs (14,15), and when the eNOS gene is knocked-out in mice they become hypertensive (16,17). Further support for NOs association with BP control comes from the finding that whole-body NO production is inversely correlated with daytime ambulatory BP in healthy and hypertensive humans (18). In addition, whole-body NO production is approximately 40% lower in hypertensive humans than in healthy humans (18). Thus, enhancing the production of NO, or directly increasing its *in vivo* concentration could be paramount for improved BP control in hypertension.

Agents that increase *in vivo* levels of NO, and in turn reduce BP, belong to three different classes. First, there are the NO-donors, which directly release NO to the bloodstream, and include compounds such as organic nitrates and metal-NO complexes (10,19,20). Second there is L-arginine the biological precursor of NO (21). Third, there are agents that stimulate NO production independent of increasing the L-arginine concentration (22). This last class is of particular interest, and a prime example is ginseng.

Ginseng is a powerful stimulator of NO production (23). Initial evidence for this came from both rat and rabbit aortic ring studies. They showed that crude extracts of *Panax ginseng* comprised of a mixture of ginsenosides evoked a dose-dependent relaxation of aortic rings (23,24). Further investigation revealed that this relaxation was mediated by increased NO production (23,24). Subsequent research also indicated that only certain ginsenosides contribute to this, and that ginsenoside Rg_3 is the most potent contributor (25). Based on these findings, it is plausible that ginseng containing a high level of Rg_3 could exert a hypotensive effect.

The hypotensive efficacy of ginseng has, in fact, been shown in both animal and human studies. Administration of Korean red ginseng high in Rg_3 to rats caused a BP reduction (26,27). As well, a recent study showed that humans with hypertension who consumed 4.5g of Korean red ginseng for 8 weeks experienced a 4 mm Hg reduction in 24-hour systolic BP (28). These findings indicate that ginseng rich in Rg_3 could have therapeutic value in the treatment of hypertension. However, further research needs to ascertain what level of Rg_3 can exert the strongest hypotensive effect.

In the present study, we sought to determine the effect of a fermented *Panax ginseng* extract with escalating doses of ginsenoside Rg_3 on acute BP changes in humans with high-normal BP and hypertension. Overall, this study should indicate what dose of Rg_3 causes the greatest acute reduction in BP.

Methods and Research Design

Treatments

Four treatments were used in this study. They included 1 placebo and 3 Korean red ginseng powder (KRG) extracts. A single testing dose of placebo or KRG weighed 508 mg and was enclosed within 2 red #00 capsules. The placebo was comprised of cellulose and the KRG powder contained 65.0 mg of total saponins, 18.6 mg of ginsenoside Rb_1, and 4.0 mg of ginsenoside Rg_1. The three KRG powder extracts differed only in their content of ginsenoside Rg_3, with the first containing 606 μg, the second 1816 μg, and the third 5428 μg.

Study Population

Subjects were recruited mainly through newspaper advertisements. The subjects were all diagnosed with high-normal BP or hypertension according to the 6th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Diagnosis of high-normal BP required that the subject had a systolic BP between 130-139 mm Hg or a diastolic BP between 85-89 mm Hg on 3 consecutive visits. Diagnosis of hypertension required the use of antihypertensive drugs or systolic BP >140 mm Hg or diastolic BP >90 mm Hg on 3 consecutive visits.

Men and women between the ages of 25 and 75 years were recruited. Subjects were excluded if they had a glomerular filtration rate <60 ml/min, if liver enzymes were >1.8 times the upper limit of normal, and if they had secondary hypertension, diabetes, unstable angina, or a coronary/cerebrovascular event within the previous 6 months. Subjects were also excluded if they used ginseng or steroid-based anti-inflammatory drugs.

Study Design

A four-way, double-blind, cross-over study approved by the local research ethics committee was completed in 13 individuals with high-normal BP or hypertension. Each subject received the placebo and 3 KRG extracts in a randomized sequence determined from a random number table. Each testing period lasted for 200 minutes, and was separated by a minimum 3-day washout period (Fig. 1).

On four separate mornings, between the hours of 8:00 and 10:00am subjects arrived at the Risk Factor Modification Centre, St. Michaels Hospital after a 10-12 hour fast. Subjects taking medi-

Fig. 1. The treatment sequence for the study.

cations did not take them on the morning of a test. Upon arrival at the clinic, subjects had their weight measured, sat and filled out study questionnaires for 5 minutes, and were fitted with an indwelling cannula in their right forearm vein for blood collection. Subjects were then equipped with an Accutracker II ambulatory BP monitor (ABPM; SunTech, Raliegh NC) on their left arm. Two initial measurements were taken with the monitor, and then discarded. Following this, the monitor took BP readings every 5 minutes for 15 minutes prior to the ingestion of placebo or KRG; these 4 BP readings represented the baseline readings. At time 0-minutes, placebo or KRG was ingested with 300 ml of tap water. Following this, the monitor took BP readings every 15 minutes for 180 minutes. Immediately following the BP measurement at time 60-minutes, a 360-calorie liquid meal replacement (Ensure®, Ross Ltd.) was consumed within a 5-minute period. Blood was taken at time 0-minutes, and at 30-minute intervals thereafter. Subjects remained seated in a quite room for the duration of each treatment day (Fig. 2).

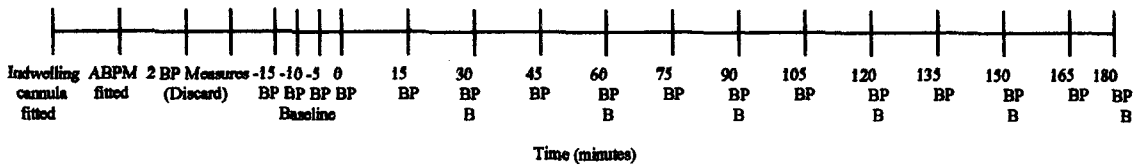

Fig. 2. An overview of the sequence of events and their respective times on the days of study. BP = blood

Outcome Measures

The primary outcome was the change in BP as determined by ABPM. The efficacy of KRG relative to placebo on BP was determined by (i) the change in BP at individual time points and (ii) the change in net area under the BP curve. The change in BP following placebo or KRG ingestion was determined by subtracting the mean of the 4 baseline BP readings from the BP readings taken at each of the 15-minute intervals.

Sample Size Estimation

Calculation of sample size was achieved with power analysis using a two-tailed α of 0.05 and 1-β of 90%.

Statistical Analysis

BP differences between treatments were determined at the individual time points and for area under the BP curve. All differences were analyzed using repeated measures analysis of variance (Number Cruncher Statistical Software). Significance was set at $p<0.05$.

References

1. Burt VL, Cutler JA, Higgins M et al. Trends in the prevalence, awareness, treatment and control of hypertension in the adult US population: data from the health examination surveys, 1960 to 1991. Hypertension 26: 60-69, 1995.
2. Joffres MR, Ghadirian P, Fodor JG, Petrasovits A, Chockalingam A, Hamet P (1997). Awareness, treatment, and control of hypertension in Canada. Am J Hypertens 10:1097-1102.
3. England stats
4. Korea stats
5. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National High Blood Pressure Education Program Coordinating Committee. The 6th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Inter Med 157: 2413-2446, 1997.
6. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J (1990). Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 335:765-774.
7. MacMahon S, Rodgers A (1993). The effects of antihypertensive treatment on vascular disease: reappraisal of the evidence in 1994. J Vasc Med Biol 4: 265-271.
8. Collins R, MacMahon S (1994). Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull 50: 272-298.
9. Other countries
10. Wang PG, Xian M, Tang X, Wu X, Wen Z, Cai T, Janczuk AJ. Nitric Oxide Donors: Chemical Activities and Biological Applications. Chem Rev 102: 1091-1134, 2002.
11. Wilson RI, Yanovsky J, Godecke A, Stevens DR, Schrader J, Haas HL. Endothelial nitric

oxide synthase and LTP. Nature 386: 338-341, 1997.

12. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288: 373-376.
13. Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 1989 Oct 28;2(8670):997-1000
14. Sander M, Chavoshan B, Victor RG. A large blood pressure-raising effect of nitric oxide synthase inhibition in humans. Hypertension 1999 Apr;33(4):937-42
15. Haynes WG, Noon JP, Walker BR, Webb DJ. Inhibition of nitric oxide synthesis increases blood pressure in healthy humans. J Hypertens 1993 Dec;11(12):1375-80
16. Huang PL, Huang Z, Mashimo H, Bloch KD, Moskowitz MA, Bevan JA, Fishman MC. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. Nature 1995 Sep 21;377(6546):239-42
17. Shesely EG, Maeda N, Kim HS, Desai KM, Krege JH, Laubach VE, Sherman PA, Sessa WC, Smithies O. Elevated blood pressures in mice lacking endothelial nitric oxide synthase. Proc Natl Acad Sci U S A 1996 Nov 12;93(23):13176-81
18. Forte P, Copland M, Smith LM, Milne E, Sutherland J, Benjamin N. Basal nitric oxide synthesis in essential hypertension. The Lancet 349:837-842, 1997.
19. Leier CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV. Am J Cardiol 48: 1115-1120, 1981.
20. Marks GS, McLaughlin BE, Jimmo SL, Poklewska-Koziell M, Bien JF, Nakatsu K. Drug Metab Dispos 23:1248-1253, 1995.
21. Higashi Y, Oshima T, Ryoji O, Matsuura H, Kambe M, Kajiyama G. Effect of L-arginine infusion on systemic and renal hemodynamics in hypertensive patients. Amer J Hyper 12: 8-15, 1999.
22. Kim ND, Kang SY, and Schini VB. Ginsenosides evoke endothelium-dependent relaxation in rat aorta. Gen Pharm 25:1071-1077, 1994.
23. Kang SY, Kim SH, Schini VB, Kim ND. Dietary ginsenosides improve endothelium-dependent relaxation in the thoracic aorta of hypercholesterolemic rabbit. Gen Pharmacol 1995 May;26(3):483-7
24. Kang SY, Schini-Kerth VB, Kim ND. Ginsenosides of the protopanaxatriol group cause endothelium-dependent relaxation in the rat aorta. Life Sci 56:1577-1586, 1995.
25. Kim ND, Kang SY, Park JH, Schini-Kerth VB Ginsenoside Rg3 mediates endothelium-

dependent relaxation in response to ginsenosides in rat aorta: role of K+ channels. Eur J Pharmacol 367:41-49, 1999.

26. Animal ginseng
27. Animal ginseng
28. Han KH, Choe SC, Kim HS, Sohn DW, Nam KY. Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. 26: 199-209, 1998.
29. Gerova M, Kristek F. Efficiency of NO donors in substituting impaired endogenous NO production: a functional and morphological study. Physiol Res 2001;50(2):165-73
30. Scrogin KE, Hatton DC, Chi Y, Luft FC. Chronic nitric oxide inhibition with L-NAME: effects on autonomic control of the cardiovascular system. Am J Physiol 1998 Feb;274(2 Pt 2):R367-74
31. Kristec F. Nitric oxide disbalance and structural alterations of the cardiovascular system. Drug Discovery Today. Volume: 4, Issue: 5, May 1, 1999, pp. 243-244
32. Pedraza-Chaverri J, Tapia E, Medina-Campos ON, de los Angeles Granados M, Franco M. Garlic prevents hypertension induced by chronic inhibition of nitric oxide synthesis. Life Sci 1998;62(6):PL 71-7
33. Milei J, Vazquez A, Lemus J. Double-blind controlled trial of molsidomine in hypertension. Eur J Clin Pharmacol 1980 Oct;18(3):231-5
34. Vos J, Dorhout Mees EJ. Clinical evaluation of a new antihypertensive vasodilating agent PR--G 138 Cl. Br J Clin Pharmacol 1979 Aug;8(2):155-62
35. Anwar YA, White WB. Abulatory monitoring of blood pressure. (In Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics, eds White WB), Humana Press Inc, Totowa, NJ, 2001, p57-59.
36. Li Z, Chen X, Niwa Y, Sakamoto S, Nakaya Y Involvement of Ca2+ -activated K+ channels in ginsenosides-induced aortic relaxation in rats. Cardiovasc Pharmacol 2001 Jan;37(1):41-7
37. Tamaoki J, Nakata J, Kawatani K, Tagaya E, Nagai A Ginsenoside-induced relaxation of human bronchial smooth muscle via release of nitric oxide. Br J Pharmacol 130:1859-1864, 2000.
38. Nakajima S, Uchiyama Y, Yoshida K, Mizukawa H, Haruki E (1998). The effects of ginseng radix rubra on human vascular endothelial cells. Am J Chin Med 26:365-373.
39. Yuan CS, Attele AS, Wu JA, Lowell TK, Gu Z, Lin Y (1999). Panax quinquefolium L.

inhibits thrombin-induced endothelin release in vitro. Am J Chin Med 27:331-338.Kim ND, Kang SY, Kim MJ, Park JH, Schini-Kerth VB The ginsenoside Rg3 evokes endothelium-independent relaxation in rat aortic rings: role of K+ channels.Eur J Pharmacol 1999 367:51-57.

40. Nakajima S, Uchiyama Y, Yoshida K, Mizukawa H, Haruki E. The effects of ginseng radix rubra on human vascular endothelial cells. Am J Chin Med 26:365-373, 1998.