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Blood pressure lowering effect of statin drugs with an application to rosuvastatin

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Hyperlipidemia and hypertension are among the major risk factors for cardiovascular disease (CVD) and they often co-exist within a single patient. Recently, many studies published results regarding the potential role of statins in decreasing blood pressure (BP) however there is still a controversy over the efficacy of statin therapy on BP. This study aimed to investigate the potential role of rosuvastatin in BP lowering properties in Korean population. Data were taken from three randomized, multiple-dose cross over studies for rosuvastatin, angiotensin II receptor blocker (ARB) and metformin monotherapies and the combined therapy of rosuvastatin and ARB, in total of 91 healthy male normotensive subjects. Measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) at the baseline before treatment begins and for 24 hours after the last dose were used in the analysis. The analysis variables used were (i) the mean change in steady-state BP from the baseline, symbolized as ΔBP, and (ii) the difference in ΔBP between the ARB monotherapy and the combined therapy, symbolized as ΔBP,d. The △BP and ΔBP,d for SBP from each study varied in -0.1 ~ -1.3 mmHg and 1.2 ~ 1.6 mmHg, respectively, and were not significantly different from zero. The △BP and ΔBP,d for DBP from each study varied in -2.8 ~ -1.4 mmHg and -2.9 ~ -1.8, respectively, which were statistically significant for △BP ($p < 0.05$) but was not for ΔBP,d ($p > 0.05$). These results indicated that the rosuvastatin monotherapy may produce small blood pressure lowing effect in DBP.

Introduction

Hyperlipidemia and hypertension are among the major risk factors for cardiovascular disease (CVD) and they often co-exist within a single patient.[1] Statins are the lipid-lowering agent inhibiting 3-hydroxy-3-methygluaryl coenzyme A reductase and is used to treat hyperlipidemia, leading to a reduction in low density lipoprotein cholesterol (LDL-C) and circulating total cholesterol (TC).[2] Recently, many studies have demonstrated the potential role of statins in decreasing blood pressure (BP) among hypertensive patients.[2-5]

There have been several experimental studies to study the mechanism underlying the antihypertensive effect of statin therapy.[6-8] From the literature, statins have been shown to promote the actions that may contribute to vasodilation such as increase in endothelial production of nitric oxide (NO) and inhibition of reactive oxygen species (ROS) production.[7,8]

However there is still a controversy whether statin use leads to any significant blood pressure lowering properties,[8-11] possible due to heterogeneity of study groups including different level of dyslipidemia types, different types of antihypertensive drugs and different patient population. So far, only one study has been carried out to examine the BP lowering efficacy of rosuvastatin in combination with valsartan in Korean population[1] but no other studies have been carried out to examine the efficacy of rosuvastatin monotherapy in Korean population.

Therefore the aim of this study was to investigate the potential role of rosuvastatin in BP lowering properties in Korean population

Methods

Subjects

Data were taken from three different clinical trials, conducted

at Severance Hospital. All the clinical trials were multiple-dose cross over study, and eligible subjects were male and aged between 20 to 50 years. A brief description of design, dosage and duration of each trial is reported in Table 1. Detailed descriptions of each clinical trial were reported elsewhere.[12-14] Subjects received rosuvastatin, angiotensin II receptor blocker (ARB) and metformin monotherapies and the combined therapy of rosuvastatin and ARB or rosuvastatin and metformin, with ARB specifically indicating olmesartan and telmisartan. Then, vital signs of SBP and DBP were measured at predose during the multiple dose periods in an outpatient clinic. On the last day of the study, subjects were hospitalized and SBP and DBP were measured up to 72 hours after the last dose. Of these BP measurements, data collected only up to 24 hours were used for the analysis, with those obtained from the combination therapy with metformin being excluded.[12-14]

Analysis variable

The analysis variable used in this work was the mean change in steady-state BP from the baseline, symbolized as ΔBP, which was defined as:

$$\Delta BP = BP_{ss,ave} - BP_{base} \quad (1)$$

· $BP_{ss,ave}$: mean steady-state BP (= mean BP over the last dosing interval of 24 hours)
· BP_{base} : baseline or pre-drug BP measured on day 1 before the treatment begins

Statistical analyses

After ΔBP is obtained for each subject, using a t-test, BP lowering effect of rosuvastatin was tested using the following hypothesis:
For monotherapy,

$$H_0:\ \mu_{\Delta BP} = 0 \ \text{ and } \ H_1:\ \mu_{\Delta BP} < 0 \quad (2)$$

For combination therapy,

$$H_0:\ \mu_{\Delta BP,d} = 0 \ \text{ and } \ H_1:\ \mu_{\Delta BP,d} < 0 \quad (3)$$

where μ denotes the mean value and ΔBP,d is the difference in ΔBP between the 2 therapies, defined as $\Delta BP,d = \Delta BP_{Com} - \Delta BP_{Mono}$ with subscripts "Com" and "Mono" denoting combination and mono therapy, respectively. Thus, H_1 indicates that rosuvastatin has an effect in BP reduction. Significance level of the test was chosen as 5%. The reason that one-sided t-test was used here is that our main concern is to test if rosuvastatin has blood pressure lowering effect and thus blood pressure raising effect, if any, had to be considered to be statistically insignificant. In doing a t-test, normality test was conducted for data to check if the distribution satisfies the assumption underlying the t-test.

Results

Overall, 91 subjects from the 3 clinical trials were analyzed in this work. As the dose (10 to 20 mg) and duration (5 to 7 days) of each clinical trial differs from each other, the analysis and hypothesis test were performed separately for each trial. The assumption of a normal distribution of BP data was satisfied when normality test was conducted using Q-Q plot and Shapiro-Wilk normality test (data not shown).

Rosuvastatin monotherapy

Figure 1(a) plotted the mean SBP measurements at the baseline and for 24 hours after the last dose of rosuvastatin for the 3 clinical trials cited. Each trial has a different duration of rosuvastatin monotherapy, 5 days for Lee et al,[12] 7 days for Roh et al[13] and 6 days for Son et al.[14] A common trend is seen in the graph where SBP initially decreases up to 8 hours after the last dose and then increases thereafter, yielding the measurement at 24 hours higher than the pre-dose value at the beginning of last dosing interval. T-test results from each trial are shown in Table 2. The mean change in steady-state BP from the

Table 1. Characteristics of clinical trials included in the analysis

Study, Design	Subjects (no. of subjects)	Dosage per day	Duration of study	BP sampling Schedule
Randomized, open-label, 3-period, multiple-dose crossover study[13]	Healthy normotensive male subjects[35]	20 mg	7 days	At predose on days 1 through 6 and at 0, 2, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 7
Randomized, open-label, 2-part, 2-period, multiple-dose crossover study[14]	Healthy normotensive male subjects[23]	20 mg	6 days	At predose on days 1 through 5 and at 0, 2, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 6
Randomized, open-label, 6-sequence, 3-period, multiple-dose crossover study[12]	Healthy normotensive male subjects[33]	10 mg	5 days	At predose on days 1 through 4 and at 0, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 5

baseline (ΔBP) from each study was -0.1, -1.3 and -0.1 mmHg for Lee et al,[12] Roh et al[13] and Son et al,[14] respectively. The results show that P-value for each study is bigger than 0.05, indicating that the rosuvastatin monotherapy does not show SBP lowering properties.

Figure 1(b) plotted the mean DBP at baseline and the following 24 hours of DBP measurements after the last dose of rosuvastatin, in the same format as in Figure 1(a). Similarly to SBP, a common trend is seen where DBP decreases up to 8 hours after the last dose and almost returned to the pre-dose value at 24 hours after the dose. The ΔBP from each study is -1.8, -1.4 and -2.8 mmHg for Lee et al,[12] Roh et al[13] and Son et al[14] respectively (Table 2). The results show that P-value is less than 0.05 in all studies thus null hyphothesis can be rejected, indicating that the rosuvastatin monotherapy decreases DBP signifcnatly in relative to baseline DBP.

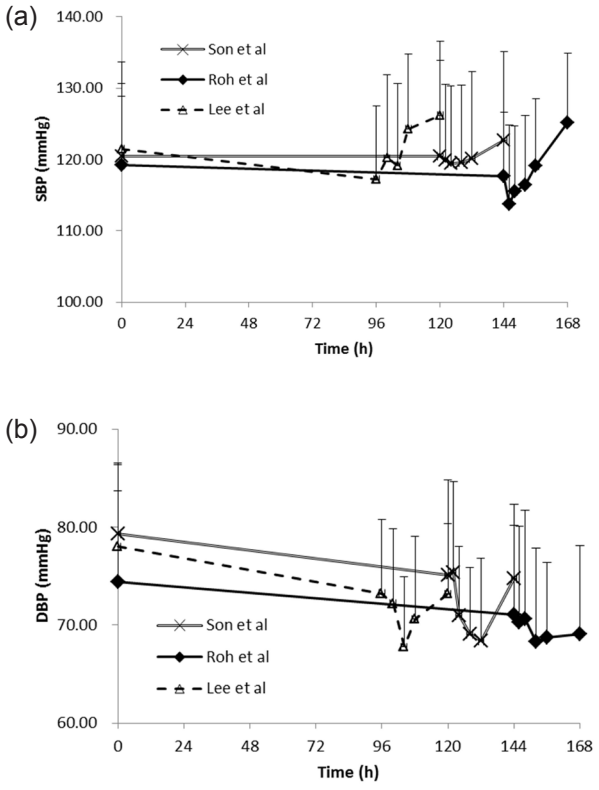

Figure 1. Mean (SD) BP profile at baseline and for 24 hours after the last dose for SBP (a) and DBP (b) for rosuvastatin monotherapy

Combination therapy of rosuvastatin and olmesartan or telmisartan

Figure 2(a) plotted the mean SBP measurements at the baseline and for 24 hours after the last dose of combination therapy of rosuvastatin and olmesartan (upper) and rosuvastatin and telmisartan (lower) with SBP measurements for ARB monotherapy being superimposed for the comparison purpose. The figure shows that the blood pressure decrease from the baseline for the combination therapy looks similar to that for the monotherapy. Table 3 shows that, for SBP, the ΔBP,d, the difference in ΔBP between ARB monotherapy and co-administration with rosuvastatin, is 1.2 and 1.6 mm Hg for olmesartan and telmisartan therapy, respectively, with both statistically being insignificant ($p > 0.05$), indicating rosuvastatin has no additional blood pressure lowering effect when co-administered with an ARB.

Figure 2(b) plotted the mean DBP measurements at the baseline and for 24 hours after the last dose of combination therapy of rosuvastatin and olmesartan (upper) and rosuvastatin and telmisartan (lower) with DBP measurements for ARB monotherapy being superimposed for the comparison purpose. Somewhat differently from Figure 2(a), the figure shows that the blood pressure decrease from the baseline for the combination therapy looks greater than that for the monotherapy. However,

Table 2. T-test results for rosuvastatin monotherapy

	△BP for SBP (mmHg)			△BP for DBP (mmHg)		
	μ	CI	p-value	μ	CI	p-value
Lee et al[12]	-0.1	-3.4 ~ 3.3	0.4867	-1.8	-3.3 ~ -0.3	0.0269
Roh et al[13]	-1.3	-3.7 ~ 1.2	0.1910	-1.4	-2.5 ~ -0.3	0.0219
Son et al[14]	-0.1	-2.4 ~ 2.2	0.4786	-2.8	-4.9 ~ -0.7	0.0165

Table 3. T-test results for combination therapy of rosuvastatin and olmesartan (Roh et al) or telmisartan (Son et al)

	△BP,d for SBP (mmHg)			△BP,d for DBP (mmHg)		
	μ	CI	p-value	μ	CI	p-value
Roh et al[13]	1.2	-3.2 ~ 5.6	0.6799	-2.9	-6.1 ~ 0.3	0.0655
Son et al[14]	1.6	-4.9 ~ 7.4	0.4623	-1.8	-7.3 ~ 3.7	0.2868

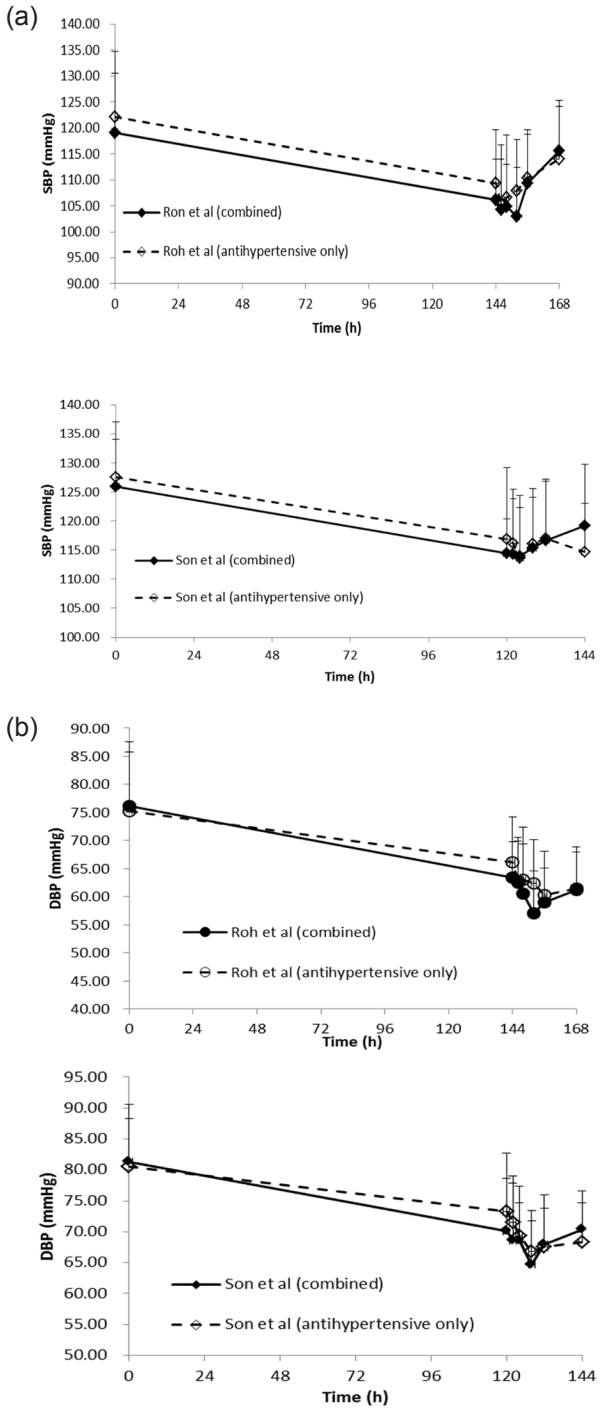

Figure 2. Mean (SD) BP profile at baseline and for 24 hours after the last dose for SBP (a) and DBP (b) for combination therapy of rosuvastatin and olmesartan (upper) and rosuvastatin and telmisartan (lower)

this seemingly different degree of blood pressure decrease between the 2 therapies was found to be statistically insignificant (P-value > 0.05) for both ARBs as reported in Table 3, indicating rosuvastatin has no additional blood pressure lowering effect as for DBP.

Discussion

Several studies have reported that statins may exert a BP lowering effect as an additive effect to antihypertensive agents.[1,4,11] Jang et al. carried out a randomized clinical trial with 123 patients and the results show that the combined therapy of valsartan and rosuvastatin exhibited additive blood lowering effect in both SBP and DBP where the mean change of SBP further decreased by 3.9 mmHg and 2.4 mmHg for DBP as compared to valsartan monotherapy. Strazzullo et al. had a similar conclusion with Jang et al. that combined therapy of antihypertensive drugs and statins resulted in additive BP lowering effect (-1.9 mmHg for SBP and -0.9 mmHg for DBP). Additive BP lowering effect of statin therapies were greater in patients who have baseline SBP of 130 mmHg or higher or baseline DBP of 80 mmHg or higher where the mean difference from the baseline were -4.0 mmHg and -1.2 mmHg for SBP and DBP respectively. Briasoulis et al. conducted a meta-analysis of prospective controlled studies to evaluate the antihypertensive effects of statins and found small but statistically significantly BP reduction of -2.62 mmHg for SBP and -0.94 mmHg for DBP in patients taking statins. In addition, decrease of BP with statin therapy was most often significant among patients with hypertension.[3,9,11]

On the other hand, studies reporting that statins do not have a BP lowering effect are also found. Banach et al carried out a meta analysis of published literature studies to evaluate the antihypersntive effect of statins in normotensive subjects. Effect size was calculated to be the differences between rosuvastatin monotherapy and placebo administration. Summary of effect size on SBP from 11 different trials was 0.03 with the p value of 0.95 for SBP and -0.28 with a p value of 0.29 for DBP, indicating that the statin does not lower blood pressure in normotensive subjects.[2]

Current study investigated blood pressure lowering effect of rosuvastatin monotherapy in normotensive subjects in Korean population and found that the effect is not significant in SBP in rosuvastatin monotherapy and in both SBP and DBP in combination therapy with rosuvastatin and an ARB, as tested by ΔBP and ΔBP,d. For DBP in rosuvastatin monotherapy, there was significant blood pressure lowering effect in all cases ($p < 0.0005$), ΔBP of which, however, was small, ranging from -2.8 to -1.4 mmHg only. It is suggested that the reason that blood pressure lowering effect for DBP in combination therapy was not significant whereas it was in rosuvastatin monotherapy is that since the blood pressure drop in rosuvastatin monotherapy is rather small, it was most likely masked by the huge blood pressure drop caused by antihypertensive drugs when given together.

All the literature that investigated the possibility of additive effect of statins therapy in BP reduction measured BP as primary or secondary outcome in the clinical trials. Mean changes in SBP and DBP from baseline were then the key outcomes of in-

terest to evaluate the role of statin therapy in BP lowering properties. Therefore, the ΔBP was selected as an analysis variable in rosuvastatin monotherapy and ΔBP,d in combination therapy.

The additive blood pressure lowering effect of statin therapy was considered to be the results of pleiotropic effect of statins.[4,15] There have been a growing number of evidence from both in vitro and animal studies that statins show pleiotropic effect such as increasing bioavailability of nitric oxide, improving endothelial-dependent vasodilation and reducing levels of endothelin-1, leading to reducing cardiovascular risk.[7,8,15,16] This phenomenon is deemed to be clinically important as hypertension and hyperlipidemia often co-exist within single patient and reducing cardiovascular risk would eventually lead to reduction in morbidity and mortality in patients.[4]

In conclusion, our results show that the rosuvastatin monotherapy may produce small blood pressure lowing effect in DBP. However, given that BP data analyzed in this work were taken from clinical studies comprised of a relatively small number of subjects (e.g., n=35 in the largest study), the studies were carried out from healthy subject only, rather short duration of period (less than a week) and the unavailability of changes of BP with placebo effect, the result obtained in this work should be treated with caution.

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Conflict of interest

The author declared no conflict of interest.

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