Research Article

Comparative evaluation of ACE inhibitors with or without statins in the treatment of essential hypertension in a tertiary care teaching hospital at Dehradun, Uttarakhand

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Abstract

Background: The beneficial effects of statins on the vasculature are present early after statin administration and appear to be independent of their cholesterol-lowering actions. The pleiotropic effects of statins have prompted this study to evaluate their role in hypertension.

Objective: To compare the antihypertensive effects of ACE inhibitors either alone or in combination with statins in a tertiary care teaching hospital at Dehradun, Uttarakhand.

Materials and Methods: The study was conducted in 20 hypertensive patients by the Pharmacology Department in Medicine OPD at Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIM & HS), Dehradun, for 1 year from January 2012 to December 2012. Initially, patients were stabilized for 4 weeks by ACE inhibitors and then subdivided into two groups. Group I: ACE inhibitors (n = 10) and Group II: ACE inhibitors + statins (n = 10). Patients were followed up every 4 weeks for 16 weeks. Systolic blood pressure (SBP), diastolic blood pressure (DBP), waist hip ratio (WHR), and body mass index (BMI) were done every visit. Lipid profile was done at 4 and 16 weeks. Primary end points were changes in SBP and DBP. Secondary end points were changes in BMI, WHR, and lipid profile. Analysis was done by paired and unpaired t test. $p \leq 0.05$ was significant.

Results: At 4 and 16 weeks, SBP in Group I was 131.6 ± 3.42 and 123.8 ± 2.24 mmHg ($p < 0.05$) and in Group II was 138.2 ± 3.13 and 126 ± 1.86 mmHg ($p < 0.01$), respectively. At 4 and 16 weeks, DBP in Group I was 84.4 ± 1.17 and 80.4 ± 0.41 mmHg ($p < 0.05$) and in Group II was 85.6 ± 1.58 and 81.8 ± 0.91 mmHg ($p < 0.05$), respectively. At 16 weeks, intergroup SBP and DBP comparison was done, which was not significant ($p > 0.05$). At 4 and 16 weeks, lipid profile in Group I was insignificant ($p > 0.05$), in Group II was significant ($p < 0.05$). Both BMI and WHR in Groups I and II at 4 and 16 weeks were insignificant ($p > 0.05$).

Conclusion: Both groups showed significant improvement in SBP and DBP. But no significant difference was seen on intergroup comparison at the end of the study period. Longer-duration studies with larger sample size are needed to establish the role of statins in hypertension.

KEY WORDS: ACE inhibitors, statins, hypertension, body mass index, waist hip ratio

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Introduction

Hypertension is an increasingly prevalent chronic condition associated with serious morbidity and mortality. It is an important risk factor for the development and progression of cardiovascular disease, which is predicted to become the leading cause of death and disability worldwide by 2020.[1] In India, 23.10% men and 22.60% women over the age of

25 years suffer from hypertension.[2] There is considerable evidence that hypertension and dyslipidemia are interrelated metabolically, epidemiologically, and clinically.[3] Owing to this correlation, statins have been used in patients with hypertension with an attempt to counter dyslipidemia that is itself an independent risk factor for cardiovascular and cerebrovascular diseases.[4] The remarkable benefit achieved with statin treatment in patients with wide range of cholesterol levels cannot be attributed only to their cholesterol lowering effect. The effectiveness and rapidity of statin-induced decreases in coronary events has led to the assumption that these agents may possess some "cholesterol-independent effects." Statins cause an improvement in endothelial function by activating endothelial nitric oxide synthase, downregulate angiotensin II type I (AT I) receptors, reduce levels of endothelin-1, and decrease the vascular production of reactive oxygen species.[5] The beneficial effects of statins on the vasculature are present early after statin administration and appear to be independent of their cholesterol-lowering actions.[6] Statins upregulate the expression and activity of endothelial nitric oxide synthase via activation of phosphatidylinositol 3-kinase, inhibition of geranyl-geranylation of the small G protein Rho and of vascular Rac-1-mediated activation of NADPH oxidase.[7–9] Furthermore, the effect of statins to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by downregulated AT1 receptor density. Angiotensin II promotes superoxide anion generation and endothelial dysfunction.[10] Statins decrease production of reactive oxygen species and inhibit several angiotensin II-activated intracellular signaling systems, delay hypertension-induced vascular alterations, reduce large artery stiffness, and improve systemic arterial compliance.[11] These mechanisms, may in part, explain the blood pressure (BP) lowering effects of statins. The effect of statins, apart from their role as cholesterol-lowering agents, has prompted this study to evaluate if they can play a role as antihypertensives. The most effective drugs to treat hypertension in most of the patients are the drugs that act on renin–angiotensin system, that is, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers.[12] They are currently the most commonly used drugs for treating hypertension in all subsets of patients. Therefore, we have compared ACE inhibitors either alone or in combination with statins in essential hypertension in a tertiary care teaching hospital at Dehradun, Uttarakhand.

Material and Methods

This open-label study was conducted in the Department of Pharmacology and Medicine at SGRRIM & HS, Patel Nagar, Dehradun, for 1 year from January 2012 to December 2012 and included patients diagnosed with essential hypertension attending the Medicine outpatient department (OPD). Prior to the initiation of the study, approval was taken from Institutional Ethics Committee and written informed consent was obtained from all the patients. A total of 20 consecutive patients with essential hypertension as per JNC VII guidelines[13] were included in the study. Inclusion criteria: the hypertensive patients of either sex aged between 20 and 60 years. Exclusion criteria: patients aged <20 years and >60 years; persons with secondary hypertension; persons having hypersensitivity to statins; pregnant and lactating women; and persons with myopathies, diabetes mellitus, liver diseases, kidney diseases, any other chronic systemic illness, and acute emergencies.

Treatment Protocol

A total of 20 hypertensive patients were included in the study as per JNC VII criteria.[7]. The BP of patients was stabilized initially by giving Ramipril (5 mg) once daily (OD) for a period of 4 weeks. After stabilization period of 4 weeks, patients were further subdivided into 2 groups. Group I: Ramipril 5 mg OD (n = 10) and Group II: Ramipril 5 mg OD + atorvastatin 10 mg OD (n = 10). The patients were followed up after every 4 weeks for a period of 16 weeks. Measurement of systolic and diastolic blood pressures (SBP and DBP), waist hip ratio (WHR), and body mass index (BMI) was done at every visit. Lipid profile was done at 4 weeks and at the end of 16 weeks. Primary end points were change in SBP and DBP. Changes in WHR, BMI, and lipid profile were secondary end points. The patients were examined thoroughly at each follow-up visit for any adverse drug reactions due to the drugs given. The treatment groups were compared and results were analyzed by paired and unpaired t test. p value <0.05 was considered to be significant.

Results

The mean age of the patients included in the study was 52.6 ± 1.86 years. All values were expressed in mean ± SEM. Men and women were in the ratio of 1:1. Thirty-five percent[7] patients had a positive family history of hypertension. Twelve (60%) patients were newly diagnosed as hypertensive. The mean duration of hypertension was 3.84 ± 0.46 years. At the start of the study, the SBP, DBP, BMI, and WHR were 147.2 ± 3.18 mmHg, 90.8 ± 1.46 mmHg, 24.97 ± 0.82 kg/m^2, and 0.96 ± 0.006, respectively (Table 1). The patients underwent a titration phase of 4 weeks during which both SBP and DBP showed significant improvement. The mean SBP of study population at 0 and 4 weeks was 147.2 ± 3.18 and 133.5 ± 1.92 mmHg, respectively ($p < 0.001$). The mean DBP of the study population at 0 and 4 weeks was 90.8 ± 1.46 and 85 ± 0.94 mmHg, respectively ($p < 0.01$). The SBP at 4 weeks in Groups I and II was 131.6 ± 3.42 and 138.2 ± 3.13 mmHg ($p > 0.05$), respectively, and DBP at 4 weeks in Group I and Group II was 84.4 ± 1.17 and 85.6 ± 1.58 mmHg, respectively. Patients were followed up every 4 weeks till the end of the study period (16 weeks). The SBP at 16 weeks in Group I was 123.8 ± 2.24 mmHg ($p < 0.05$) and in Group II was 126 ± 1.86 mmHg ($p < 0.01$) (Figure 1). The DBP

Table 1: Baseline characteristics of study population (All values are expressed in Mean ± SEM)

Parameters	Number (% age)
Total no of patients	20
Mean age (years)	52.6 ± 1.86
Men:women	1:1 (50% vs 50%)
Positive family history of hypertension	7 (35%)
Newly diagnosed patients	12 (60%)
Mean duration of illness (years)	3.84 ± 0.46
SBP (mm Hg)	147.2 ± 3.18
DBP (mm Hg)	90.8 ± 1.46
BMI (kg/m^2)	24.97 ± 0.82
WHR	0.96 ± 0.006

SBP, Systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist hip ratio.

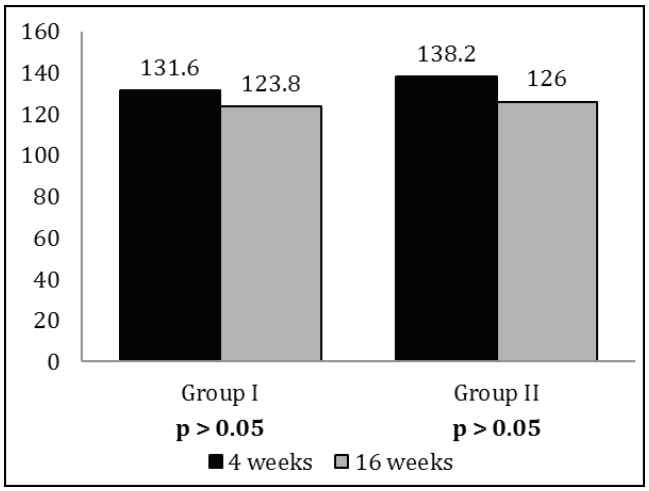

Figure 1: SBP comparison b/w 4 and 16 weeks (Group I: ACE inhibitors Group II: ACE inhibitors + statins).

at the end of 16 weeks in Group I was 80.4 ± 0.41 mmHg ($p < 0.05$) and in Group II was 81.8 ± 0.91 mmHg ($p < 0.05$) (Figure 2). Both the study groups showed improvement in SBP and DBP in 16-week period. At 16 weeks, the comparison of fall in SBP and DBP was done between Groups I and II. No significant difference was seen between the groups with respect to SBP and DBP at the end of 16 weeks ($p > 0.05$) (Figure 3).

There was a significant improvement in lipid profile at the end of the study period in the group that received statins as compared to the group that did not. There was no significant change in BMI and WHR between 4 weeks and 16 weeks in both the groups (Table 2). Overall, eight adverse drug reactions were seen in the study period: five in Group I and three in Group II, respectively. Dry cough in five patients followed by nausea, abdominal pain, and generalized body weakness in one patient each. Adverse effects were mild and did not require any modification or withdrawal of study medications.

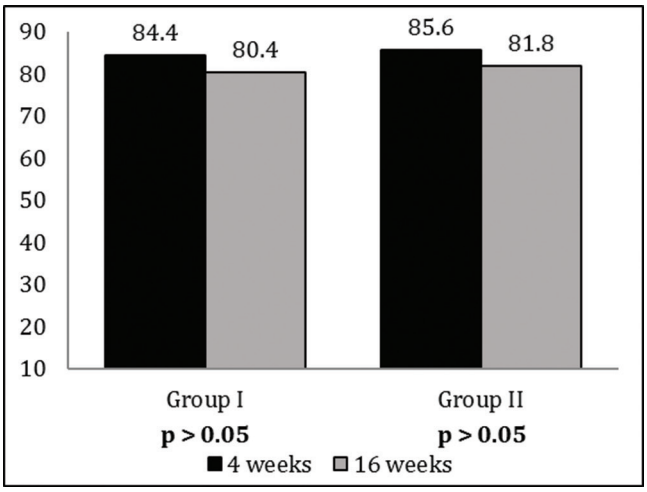

Figure 2: DBP comparison b/w 4 and 16 weeks (Group I: ACE inhibitors Group II: ACE inhibitors + Statins).

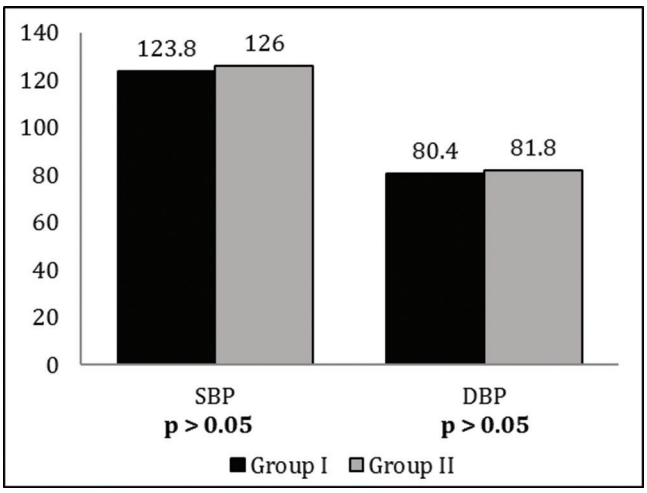

Figure 3: Intergroup BP comparison at 16 weeks (Group I: ACE inhibitors Group II: ACE inhibitors+ Statins).

Discussion

Essential hypertension is commonly seen in middle-aged individuals, especially after 50 years of age.[14] The average age of patients in the present study was 52.6 ± 1.86 years, reflecting the usual age group of disease manifestation. This was comparable to the age of the patients in previous studies where it was reported to be 52.3 years and 52.93 years.[15] Hypertension was equally prevalent in males and females in our study, which was comparable to a previous study that shows equal incidence of hypertension among male and female patients.[16] A positive family history was seen in 7 patients out of 20 in this study. Hypertension has multifactorial inheritance and there are epidemiological evidences linking hypertension to a positive family history[14] (Table 1). Hypertension though commonly observed in obese individuals in developed nations, is also associated with

Table 2: Changes in secondary end points (lipid profile, BMI, and WHR)

Parameters		Group I (ACE inhibitors)		Group II (ACE inhibitors + Statins)	
		4 weeks	16 weeks	4 weeks	16 weeks
Lipid profile	S Chol (mg/dL)	190.3 ± 3.57	195.6 ± 3.73	189.5 ± 4.2	173.9 ± 4.33
	TG (mg/dL)	103.5 ± 3.25	107.6 ± 2.86	113.1 ± 5.72	95 ± 3.89*
	HDL (mg/dL)	47 ± 2.43	49.1 ± 2.42	40.1 ± 2.1	47 ± 2.5
	LDL (mg/dL)	100.3 ± 2.7	99.8 ± 2.9	101.5 ± 2.8	87.9 ± 1.9**
BMI		24.9 ± 1.06	24.9 ± 1.06	25.2 ± 1.24	25.2 ± 1.24
WHR		0.93 ± 0.03	0.95 ± 0.01	0.98 ± 0.03	0.97 ± 0.01

S chol, serum cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; BMI, body mass index; WHR, waist hip ratio.

*$p < 0.05$, **$p < 0.01$.

non-obese population especially in developing nations.[17] The average BMI and WHR of the patients in the present study were in the normal range and both these parameters remained constant throughout the study period, suggesting that they had no role to play in the decrease in BP, seen with the study groups (Figures 4 and 5). This was comparable with previous study by Radhika et al.[18]

The present study showed a significant improvement in BP in titration period. Earlier studies have shown that ACE inhibitors are highly effective in the treatment of essential hypertension in reducing both SBP and DBP.[19] The reduction in BP was significant at the end of 4 weeks (titration phase) ($p < 0.01$) in the study group. At 16 weeks, both the groups showed significant improvement with respect to both SBP and DBP. But the group that received ACE inhibitors + statins showed a more significant fall in SBP as compared to the groups that received ACE inhibitors alone (Figure 1). Our results were consistent with other studies in which greater significant fall in SBP was seen in statin user than non-user groups. Studies by Hashimoto et al.[20] and Ikeda et al.[21] showed a greater reduction in SBP in statin-user hypertensive patients. Another study by Sposito et al.[22] compared BP reduction between hypertensive patients receiving ACE inhibitors alone and those in whom a statin was added. Statin-treated group showed a greater reduction in BP as compared to the group treated with ACE inhibitors alone. A meta-analysis of antihypertensive effects of statins by Alexandro et al.[23] also showed a significant reduction in SBP and DBP in patients taking statins. However, in our study, such results were not observed with respect to DBP in both the groups (Figure 2). At 16 weeks, comparison was done between Group I and Group II. No intergroup difference was found between the groups (Figure 3). This result was consistent with previous study; the PHYLLIS (Plaque Hypertension Lipid Lowering Italian Study) randomized double-blind trial in which intergroup comparison was done between patients receiving antihypertensive treatment (hydrochlorothiazide or lisinopril) with or without addition of statin (pravastatin).[24]

A significant improvement in lipid profile was observed in all patients who received statins. These findings were consistent with previous study where lipid-lowering effects of atorvastatin have been well proven[25] (Table 2). Few adverse effects were noted during the study period, which were mild and did not require any alteration or discontinuation of study drugs and were comparable to those reported in previous clinical study.[26]

Study Limitations

This study was an open-label study. The patients and the doctor were aware of the prescribed drugs. Hence, there are more chances of errors. Second, the sample size was small. Only 20 patients were included in the study, which may not be sufficient enough to demonstrate intergroup differences in the efficacy of study drugs. Third, the duration of follow-up was just 16 weeks.

Conclusion

Both the groups revealed significant improvement in the treatment of hypertension with respect to SBP and DBP. The patients who received ACE inhibitors + statins had a more significant fall in SBP than the patients who received only ACE inhibitors. But no intergroup difference was found on comparing the study groups at the end of study period. Larger studies with more number of patients and longer duration are needed to establish the role of statins in hypertension.

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