

COMPARATIVE EVALUATION OF ANGIOTENSIN RECEPTOR BLOCKERS WITH OR WITHOUT STATINS IN THE TREATMENT OF ESSENTIAL HYPERTENSION IN A TERTIARY HEALTH CARE SETUP

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ABSTRACT

Background: Hypertension has emerged as a leading risk factor for cardiovascular disease, stroke and kidney failure affecting 20% adult population worldwide. In India, the prevalence is reported to be ranging from 10- 30.9% with an average of 25% in urban and 10% in rural inhabitants. There is considerable evidence that hypertension and dyslipidaemia are interrelated metabolically, epidemiologically and clinically.

Aims & Objective: To study the antihypertensive role of statins, apart from their lipid lowering effects. We have compared Angiotensin Receptor Blockers (ARBs) either alone or in combination with statins in essential hypertension patients.

Materials and Methods: The study was conducted in 20 hypertensive patients in Department of Pharmacology and Medicine at SGRIM&HS, Dehradun for 1 year. Initially patients were stabilized for 4 weeks by ARBs and then divided in 2 groups. Group-I: ARBs (n=10) and group-II: ARBs + Statins (n=10). Patients were followed up every 4 weeks for 16 weeks. Change in systolic and diastolic Blood Pressure (SBP, DBP) was the primary efficacy variables. Waist Hip Ratio (WHR), Body Mass Index (BMI) and Lipid profile were secondary end points. Analysis was done by student T-test and P value ≤ 0.05 was significant.

Results: At 4 and 16 weeks SBP in group-I was 133.6 ± 3.7 mmHg and 124 ± 2.56 mmHg ($p < 0.05$) and in group-II was 135.8 ± 2.5 mmHg and 125.4 ± 2.08 mmHg ($p < 0.01$) respectively. At 4 and 16 weeks DBP in group-I was 80 ± 2.56 mmHg and 80.8 ± 0.7 mmHg ($p > 0.05$) and in group-II was 81.8 ± 2.31 mmHg and 81 ± 1.9 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 ($p > 0.05$), group-II ($p < 0.05$), BMI and WHR in group-I and group-II ($p > 0.05$) respectively.

Conclusion: Both the groups showed significant improvement in SBP. But no significant difference was seen on intergroup comparison. Larger studies with more patients are needed to establish the role of Statins in hypertension.

Key Words: Angiotensin Receptor Blockers (ARBs); Statins; Blood Pressure; Essential Hypertension

Introduction

Hypertension has emerged as a leading risk factor for cardiovascular disease, stroke and kidney failure affecting 20% adult population worldwide.^[1,2] In India, the prevalence is reported to be ranging from 10- 30.9% with an average of 25% in urban and 10% in rural inhabitants. There is considerable evidence that hypertension and dyslipidaemia are interrelated metabolically, epidemiologically and clinically.^[3] Owing to this correlation, Statins have been used in patients with hypertension with an attempt to counter dyslipidaemia which is itself an independent risk factor for cardiovascular and cerebrovascular diseases.^[4] 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" or pleiotropic effects.^[5] Several short term studies have shown that statins can improve endothelial function and the endothelium dependent arterial vasodilatation by stimulation of nitric oxide (NO)

synthase activity and mediate antioxidant effects that result in enhanced NO bioavailability.^[6] Statins inhibit production of superoxide anions and may limit oxidation of low density lipoprotein (LDL) and contribute to increase NO bioavailability by limiting oxidative degeneration of NO.^[7] 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 are the drugs which act on Renin Angiotensin System, i.e. Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers.^[8] They are currently the most commonly used drugs for treating hypertension in all subsets of patients. Therefore, we have compared Angiotensin Receptor Blockers (ARBs) either alone or in combination with Statins in essential hypertension in a tertiary health care health setup in Dehradun, Uttarakhand.

Aim: Comparative evaluation of essential hypertension

with Angiotensin Receptor Blockers, either alone, or in combination with Statins.

Materials 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 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 suffering from essential hypertension as per JNC VII guidelines^[9] were included in the study.

Inclusion Criteria: The hypertensive patients of either sex were included in the study if they were aged between 20 to 60 years.

Exclusion Criteria: Patients aged < 20 years and > 60 years, secondary hypertension, having hypersensitivity to statins, pregnant and lactating women, 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.^[9] The BP of patients was stabilized initially by giving Olmesartan 40mg once daily (OD) for a period of 4 weeks. After stabilization period of 4 weeks, patients were further subdivided in 2 groups. Group I: Olmesartan 40mg OD (n =10) and Group II: Olmesartan 40mg OD+ Atorvastatin 10 mg OD (n=10).The patients were called for follow up after every 4 weeks for a period 16 weeks. Measurement of Systolic and Diastolic Blood Pressure, Waist Hip Ratio and Body Mass Index was done at every visit. Lipid profile was done at 4 weeks and at the end of 16 weeks. Primary end point were change in SBP and DBP, change in Waist Hip Ratio, Body Mass Index 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

Patients included in the study had a mean age of 55.8 ± 1.37 years. The values were expressed in Mean ± SEM.

Male: Female ratio was 11:9. Family history of Hypertension was seen in 6 (30%) patients, suggesting positive correlation of hypertension with familial inheritance. Out of 20 patients, 13 patients were old hypertensive and 7 patients were new hypertensive with a mean duration of illness of 4.88±0.61years. The mean Systolic Blood Pressure of patients at the start of the study was 145.3 ± 2.49 mmHg, mean Diastolic Blood Pressure 88.8 ± 1.7 mm Hg, mean Body Mass Index 25.62 ± 0.73 kg/m² and mean Waist to Hip Ratio was 0.96 ± 0.008. All values were expressed in Mean ± SEM (Table 1). The patients underwent the titration phase of 4 weeks. The SBP and DBP significantly decreased at 4 weeks as compared to day 0 and the difference was highly significant (p <0.01) (Figure 1). At 4 weeks, comparison of SBP and DBP was done between group-I and group-II. The SBP of group-I and group-II were 133.6 ± 3.7 mm Hg and 135.8 ± 2.5 mm Hg respectively (p > 0.05). The DBP of group-I and group-II were 80± 2.56 mm Hg and 81.8±2.31mm Hg (p >0.05). No significant difference was seen in Systolic and Diastolic Blood Pressure between the groups at 4week. Patients were followed up every 4 weekly till the end of study period (16 weeks). At 16 weeks, the comparison of change in Systolic and Diastolic Blood Pressure was done between 4 weeks and 16 weeks in group-I and group-II. The systolic BP at 16 weeks in group-I was 124 ± 2.56 mm Hg (p <0.05) and in group-II was 125.4 ± 2.08 mm Hg (p value<0.01) (Figure 2). The improvement was more significant in the group that received ARBs + statins (group-II) than in the group which received only ARBs (group-I). The diastolic BP at the end of 16 weeks in group-I was 80.8 ± 0.73 mm Hg (p>0.05) and in group-II was 81 ± 1.99 mm Hg (p>0.05). There was no significant change in DBP in both the groups (Figure 3). Both the study groups showed improvement in systolic and diastolic BP in 16 week period. At 16 weeks the comparison of fall in Systolic and Diastolic BP was done between groups-I and group-II. The systolic BP in group-I was 124 ± 2.56 mm Hg and in group-II was 125.4 ± 2.08 mm Hg (p>0.05). The diastolic BP in group-I was 80.8 ± 0.73 mm Hg and in group-II was 81 ± 1.99 mm Hg (p > 0.05). No significant difference was seen between the groups with respect to systolic and diastolic blood pressures at the end of 16 weeks (Figure 4).

There was a significant improvement in lipid profile at the end of study period in the group that received statins as compared to the group that did not receive statins (Table 2).

Table-1: Baseline characteristics of patients

Parameters	Numbers/ Percentage
Total number of patients	20
Mean age (years)	55.8 ± 1.37
Men : Women	11:9
Positive Family History of Hypertension	6 (30%)
Newly diagnosed patients	7 (35%)
Mean duration of illness (years)	4.88±0.61
Mean SBP (mm Hg)	145.3 ± 2.49
Mean DBP (mm Hg)	88.8 ± 1.7
Mean BMI (kg/m ²)	25.62 ± 0.73
Mean WHR	0.96 ± 0.008

Table-2: Comparison of lipid profile between 4 weeks and 16 weeks

Groups (n=10)	S. Chol (mg/dl)		TG (mg/dl)		HDL (mg/dl)		LDL (mg/dl)	
	4 wk	16 wk	4 wk	16 wk	4 wk	16 wk	4 wk	16 wk
I	193.4 ± 3.12	196.8 ± 3.24	118.6 ± 3.53	115.4 ± 2.87	42.8 ± 1.5	40.8 ± 1.8	114.8 ± 3.0	122 ± 3.0
II	189.8 ± 4.9	172.5 ± 4.36*	117.2 ± 3.41	100.6 ± 2.1***	40.4 ± 1.7	47.2 ± 1.3*	112.8 ± 3.1	93.3 ± 2.6***

p ≤ 0.05 is significant; * p < 0.05; ** p < 0.001; *** p < 0.001; Group I: ARBs; Group II: ARBs + Statins; S. Chol: Serum Cholesterol; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins

Table-3: Comparison of BMI and WHR between 4 weeks and 16 weeks

Group (n=10)	BMI		P value	WHR		P value
	4 wks	16 wks		4 wks	16 wks	
I	25.11±0.8	25.11±0.81	>0.05	0.96±0.03	0.97±0.03	>0.05
II	26.11±1.2	26.07±1.18	>0.05	0.95±0.03	0.94±0.01	>0.05

p ≤ 0.05 is significant; Group I: ARBs; Group II: ARBs + Statins; BMI: Body Mass Index; WHR: Waist Hip Ratio

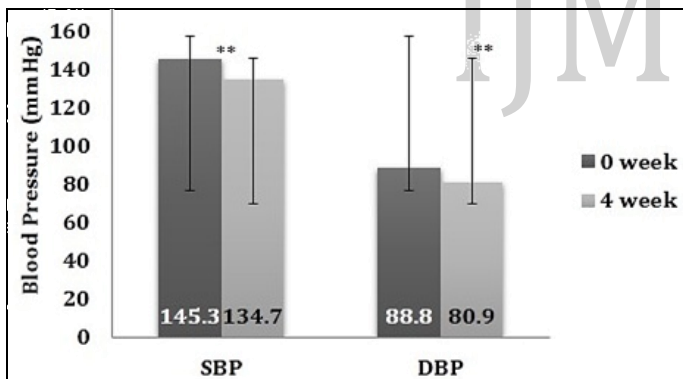


Figure-1: Comparison of SBP & DBP between 0 and 4 weeks (p ≤ 0.05 is significant; * p < 0.05; ** p < 0.01)

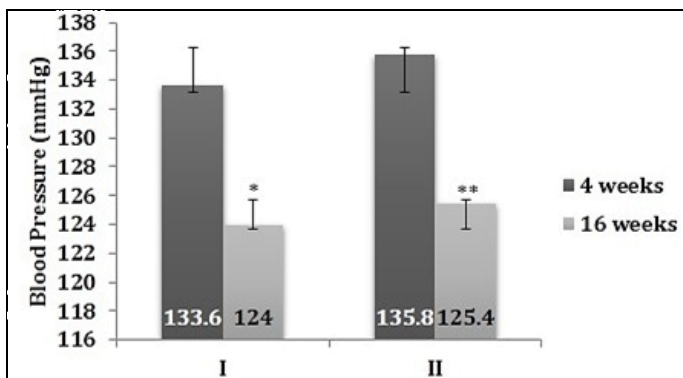


Figure-2: Comparison of SBP between 4 and 16 weeks (p ≤ 0.05 is significant; * p < 0.05; ** p < 0.01; Group I: ARBs; Group II: ARBs + Statins; SBP: Systolic Blood Pressure)

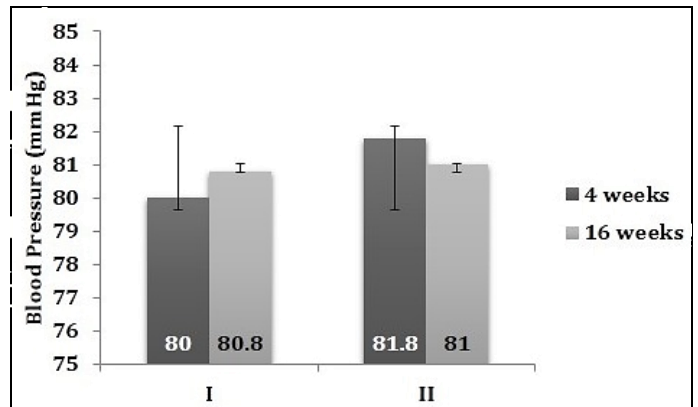


Figure-3: Comparison of DBP between 4 and 16 weeks (p ≤ 0.05 is significant; * p < 0.05; ** p < 0.01; Group I: ARBs; Group II: ARBs + Statins; DBP: Diastolic Blood Pressure)

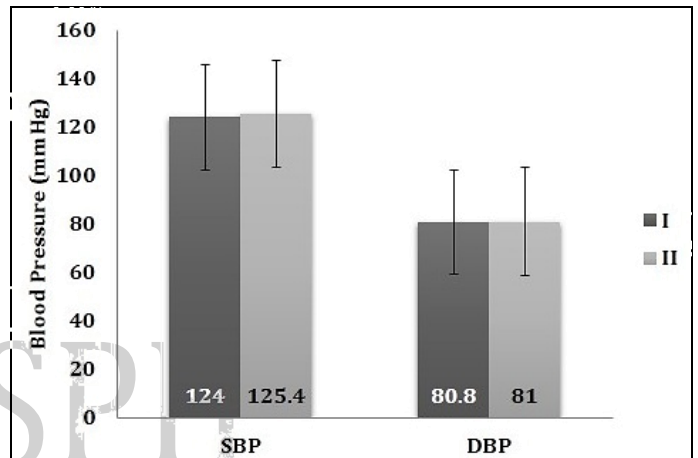


Figure-4: Intergroup comparison of BP at 16 weeks (p ≤ 0.05 is significant; * p < 0.05; ** p < 0.01; Group I: ARBs; Group II: ARBs + Statins; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure)

There was no significant change in BMI and WHR between 4 weeks and 16 weeks in both the groups (Table 3). Overall 4 adverse drug reactions were seen in the study period. 2 in group-I and 2 in group-II. Nausea in 2 patients, dry cough in 1 patient and generalized body weakness in 1 patient were seen. Adverse effects were mild and did not require any modification or withdrawal of study medications.

Discussion

Essential hypertension is commonly seen in middle aged individuals; especially after 50 years of age.^[10] The average age of patients in the present study was 52.28 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.^[11] Hypertension was more prevalent in males in our study which was comparable to that observed in earlier studies on hypertensive patients.^[11,12] Hypertension though commonly

associated with obesity in developed nations, is also associated with non-obese population especially in developing nations.^[13] 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 decrease in BP, seen with the study groups (Table 3). This was comparable with previous study by Radhika G, Sathya RM et al.^[14] A positive family history was seen in 6 patients out of 20 in this study, because of the probable multi factorial inheritance, the familial association in hypertension has not been proven yet, but there are epidemiological evidences linking hypertension to a positive family history^[10] (Table 1).

The present study showed a significant improvement in BP in titration period. Earlier studies have shown that ARBs are highly effective in the treatment of essential hypertension in reducing both systolic and diastolic BP.^[15] In the present study the group which received ARBs + Statins showed a more significant fall in SBP as compared to the groups which received ARBs alone (Figure 2) Our results were consistent with other studies in which also greater significant fall in Systolic BP was seen in statin user than non-user groups. A retrospective study using antihypertensive drug database by Hashimoto S. et al showed a greater reduction in SBP in hypertensive patients.^[16] Sposito et al compared BP reduction between hypertensive patients receiving ACE inhibitors alone and those in whom a statin was added.^[17] The statin treated group showed a greater reduction in Blood Pressure. Ikeda et al observed an additional lowering effect of pravastatin only on SBP in patients undergoing long-term treatment with antihypertensive agents.^[18] A meta-analysis of antihypertensive effects of Statins by Alexandros et al also showed a significant reduction in SBP and DBP in patients taking statins.^[19] However in the present study, such results were not observed with respect to DBP in either group (Figure 3). At 16 weeks, comparison was done between group-I and group-II. No intergroup difference was found between the groups (Figure 4). 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 fosinopril) with or without addition of statin (pravastatin).^[20] A significant improvement in lipid profile was observed in all patients who received statins. These findings were consistent with many previous

studies where lipid lowering effects of atorvastatin have been well proven^[21] (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. These adverse effects were mild and were comparable to those reported in other clinical studies.^[22]

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. Secondly the sample size was small. Only 20 patients were included in the study which may not be sufficient enough to demonstrate intergroup differences in efficacy of study drugs. Thirdly the duration of follow up was just 16 weeks. A longer follow up period with larger sample size may have yielded different results. Hence keeping these limitations in view, further studies with larger sample size and longer duration are needed to evaluate the magnitude of the antihypertensive effects of statins.

Conclusion

To conclude, the patients who received Antihypertensives + Statins had a more significant fall in Systolic Blood Pressure than the patients who received only antihypertensives. But no intergroup difference was found on comparing the study groups at the end of study period. But further larger studies with more number of patients and longer duration are needed to establish the role of statins in hypertension.

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