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Original Research Article

A comparative study of effects of nebivolol and atenolol on blood pressure and lipid profile in patients of mild to moderate hypertension

Monali P. Vakharia, Vijay R. Zad*, Nishikant N. Mankar, Pratik P. Wadivkar

Department of Pharmacology, Dr VMGMC, Solapur, Maharashtra, India

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***Correspondence to:**
Dr. Vijay R. Zad,
Email: monalivakharia88@gmail.com

ABSTRACT

Background: Beta blockers have been used in the treatment of hypertension, since last four decades and are widely accepted as the first-line treatment for hypertension. Nebivolol, a third generation β-blocker has highest β1 selectivity and is devoid of intrinsic sympathomimetic activity. Along with peripheral vasodilatation and nitric oxide (NO)-induced benefits such as antioxidant activity and reversal of endothelial dysfunction, nebivolol promotes better protection from cardiovascular events. The objective of the study was to compare the effects of atenolol and nebivolol on both blood pressure and lipid profile in patients of mild to moderate hypertension.

Methods: This was a prospective, randomized, parallel, open labelled study. Patients were recruited from the medicine out-patient department (OPD) and cardiology OPD. A total of 100 patients were enrolled in the study. 50 patients were allocated to atenolol group and 50 patients to nebivolol group. BP and baseline investigations such as lipid profile were performed. Tests to determine lipid profile were performed on the first visit (Week 0) and at 24 weeks. Continuous variables between the two treatment groups were analyzed by unpaired t-test. Efficacy endpoints within the group were analyzed by using paired t-test.

Results: All the lipid levels except HDL-C were increased with atenolol therapy. At 24 weeks, atenolol therapy led to increase in LDL-C, VLDL-C, TC and TG which was highly significant ($p<0.0001$). HDL levels were decreased at 24 weeks which was also statistically highly significant ($p<0.0001$). The mean values of lipids in nebivolol group at baseline and at 24 weeks. At 24 weeks, nebivolol therapy led to changes in LDL-C, VLDL-C, HDL-C, TC and TG which was not statistically significant ($p>0.05$).

Conclusions: From study it can be concluded that atenolol and nebivolol are equally effective in reducing BP but atenolol worsens lipid profile as compared to nebivolol.

Keywords: Atenolol, Beta-blockers, Lipid profile, Nebivolol

INTRODUCTION

Hypertension is a major public health problem, being one of the leading causes of death and disability worldwide and a major risk factor for cardiovascular diseases.[1] It accounted for 9.4 million deaths and 7% of disability adjusted life years in 2010.[2] In India, the situation is more alarming as hypertension attributes for nearly 10% of all deaths.[3] It is estimated that the worldwide prevalence of hypertension would increase from 26.4% in 2000 to 29.2% in 2025.[4] Hypertension is the principle cause of stroke and a major risk factor for coronary artery disease (CAD) and its attendant complications like myocardial infarction and sudden cardiac death. It is also a major contributor to cardiac failure and renal insufficiency.[5]

Early treatment can reverse and retard the complications associated with hypertension. The main aim of the

treatment is to decrease associated cardiovascular risk and improve the quality of life and encourage a healthy life style.[6] Beta blockers have been used in the treatment of hypertension, since last four decades and are widely accepted as the first-line treatment for hypertension.[7,8] Apart from lowering blood pressure (BP), they have antianginal and anti-arrythmic actions which effectively reduce CAD and death.[9] Many beta blockers, however, have an adverse effect on blood lipids, especially by reducing high-density lipoprotein (HDL) cholesterol and increasing triglycerides resulting in an unfavorable influence on the cholesterol ratio. These cholesterol parameters have been shown to have a strong influence on coronary heart disease (CHD) risk.[10]

Nebivolol, a third generation β-blocker has highest β1 selectivity and is devoid of intrinsic sympathomimetic activity. Along with peripheral vasodilatation and nitric oxide (NO)-induced benefits such as antioxidant activity and reversal of endothelial dysfunction, nebivolol promotes better protection from cardiovascular events. Atenolol is a cardio-selective β-adrenoceptor antagonist which is devoid of significant membrane stabilizing and partial agonist activity.[11] Although it is one of the most widely used β blockers clinically and has often been used as a reference drug in randomised controlled trials of hypertension, it has undesirable effects on lipid profile, blood sugar and heart rate of patients.[12,13]

A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic risk which, in turn, is dependent on abnormalities in plasma lipoproteins and derangement in lipid metabolism.[14] Various epidemiological studies have shown the prevalence of the coexistence of hypertension and dyslipidemia, in the range of 15 to 31%.[15] Studies have demonstrated that the treatment of dyslipidemia, particularly low density lipoprotein cholesterol (LDL-C) lowering, has favorable effects on both coronary and cerebrovascular event rates, over and above the benefits of blood pressure lowering itself.[15] Thus, it would be beneficial if hypertensive patients are prescribed with antihypertensive drugs having favorable effects on lipid profile. Hence the study was planned to compare the effects of atenolol and nebivolol on both blood pressure and lipid profile in patients of mild to moderate hypertension.

METHODS

The study was conducted in a district level tertiary care hospital attached to a medical teaching institute after getting approval from Institutional Ethics Committee vide letter no. IEC/Pharmac/Proposal no. 1114004-4. This was a prospective, randomized, parallel, open labelled study. Patient recruitment was started in the month of January 2015 and completed in March 2016. Patients were recruited from the medicine out-patient department (OPD) and cardiology OPD after initial screening for participating in the study. Screening was based on the following criteria: Inclusion Criteria- Men and women in the age group of 18-60 years with newly diagnosed mild to moderate hypertension (BP ≥140/90mm of Hg to <180/110mm of Hg). Exclusion Criteria Patients with:

1. Severe hypertension (BP ≥180/110mmHg)
2. Secondary hypertension
3. Diabetes mellitus
4. Bronchial asthma and Chronic obstructive pulmonary diseases
5. Hepatic or Renal diseases
6. Sinus bradycardia, sick sinus syndrome, Prinzmetal's angina, heart block, chronic heart failure, myocardial infarction and peripheral vascular disease
7. Patients on lipid lowering agents
8. History of hypersensitivity or allergy to atenolol/nebivolol
9. Pregnant and lactating women.

The formula used to calculate the sample size was:[16]

$$\text{Sample Size (n)} = \frac{(Z\ 1\text{-}\alpha/2)^2\ (p)\ (1\text{-}p)}{d^2}$$

Where,

Z 1-α/2= 1.96 (For 95% confidence interval and 80% power of test) n = minimum sample size to be calculated, p = prevalence of disease under study expressed in terms of 1, d = desired level of precision expressed in terms of 1. Current prevalence of hypertension among 18-60 years old is 19%.[17] So, the prevalence 'p' for our study was considered 19%.

Desired level of precision (d) in this study was 12%. The sample size came out to be 41 in each group using the above formula, yet 50 patients were enrolled in each group. Patients were diagnosed on the basis of history and BP as per the British Hypertension Society guidelines. They were informed about the benefits of the study along with possible risks. After explaining the entire scope of the study, a written informed consent, in a language of their understanding, was obtained from them. The patients were randomly allocated to either group I or group II of the treatment group based on simple random sampling (Chit-Pull method). The patients were examined by the consultant physician to rule out secondary hypertension. Systolic and diastolic blood pressure was measured in right arm, sitting posture by auscultatory method using standard mercury sphygmomanometer. Two recordings of BP were taken at an interval of 15 min by the same physician and the mean BP was recorded. On the first visit (Week 0), patient's characteristics such as age, sex, registration no. and a brief medical history were noted on the case record form. BP and baseline investigations such as lipid profile were performed. Patients were provided with a drug diary to record consumption of medicines and any adverse event. Patients from group I received tablet atenolol 50 mg once a day, orally, and patients from group II received tablet nebivolol 5 mg once a day, orally, daily. All patients were instructed to take the tablet orally once a day with

glass of water in the morning. No patient used any other drug for hypertension, except for those under investigation. Tests to determine lipid profile were performed on the first visit (Week 0) and at 24 weeks. Study treatment was started on the day of randomization and continued for 24 weeks. After randomization, follow up visits were scheduled at 1, 12 and 24 weeks. At each follow up BP was measured, and patients were interviewed and examined for occurrence of any adverse effects. Those patients who did not show the desired anti-hypertensive effect within the stipulated time interval of two weeks were labeled as non-responders and referred to the physician for further treatment. Such patients who did not complete full 24 weeks therapy were not included for statistical analysis.

Efficacy assessment

The primary efficacy end point was the mean change in BP and LDL-C from baseline to final assessment. Along with it, the secondary efficacy end points included the mean change in triglycerides, total cholesterol, VLDL-C and HDL-C from baseline to final assessment. Safety Assessment- At each visit patients were interviewed for occurrence of any adverse effect such as nausea, fatigue, dizziness, headache etc. Patients were also encouraged to enter any side effect they experienced in the drug diary provided to them. These drug diaries were also evaluated for occurrence of side effects. Laboratory analytical methods- All analyses were conducted on fasting venous blood samples at Central Biochemistry Laboratory of the hospital. Total cholesterol, HDL-C and TG were measured using enzyme method. LDL-C and VLDL-C were calculated using Friedewald equation.[18]

Statistical analysis

There were 86- Categorical data in demographic parameters at baseline was analyzed by using 'Z' test for difference between two proportions. Continuous variables between the two treatment groups were analyzed by unpaired t-test. Efficacy endpoints within the group were analyzed by using paired t-test. A 'p' value <0.05 was considered statistically significant.

RESULTS

A total of 100 patients were enrolled in the study. 50 patients were allocated to atenolol group and 50 patients to nebivolol group. During the study period, two patients from atenolol group and one patient from nebivolol group were lost to follow up. One patient from nebivolol group withdrew consent. Hence, two patients from atenolol group and two patients from nebivolol group were excluded from analysis. Thus, 48 patients from each group completed the study and were considered for the analysis of data.

Table 1 shows demographic characteristics i.e. age and gender for both the treatment groups. Both the groups were statistically comparable as regards to age and sex distribution. There was no statistically significant difference between the two groups (p>0.05).

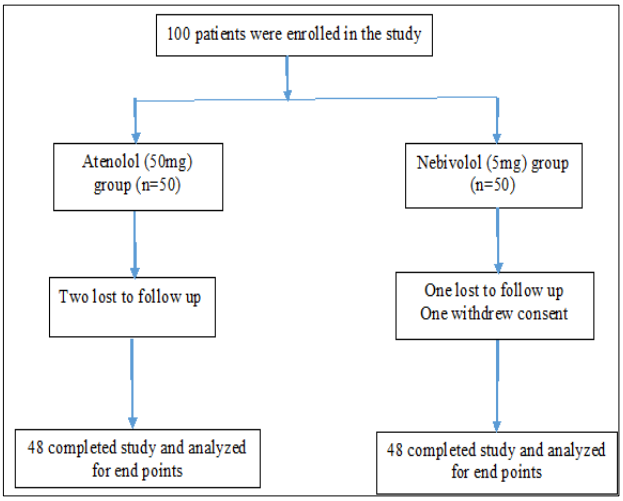

Figure 1: Flowchart of the study.

Table 1: Demographic characteristics of patients in two treatment groups.

Variables		Atenolol (50mg) N = 47	Nebivolol (5mg) N = 47	p value
Age (years) (Mean+SD)#		58.13±7.09	61.08±7.90	0.0599
Gender***	Male	36	35	0.8103
	Female	11	12	

- Unpaired t test, *** - Z test for two proportions

Table 2: SBP (mm/Hg) in two treatment groups.

Group	Atenolol (5 mg)	Nebivolol (5mg)	p value#
Baseline	160.96±8.36	160.5±7.02	0.7733
1 week	145.04±6.02	144.92±5.66	0.9209
12 weeks	121.83±6.42	119.17±6.89	0.0559
24 weeks	119.58±7.03	117.96±6.29	0.2421

#Unpaired t-test, Figures are Mean±Standard Deviation

Table 2 shows reduction in SBP in the two treatment group at baseline, 1 week, 12 weeks and 24 weeks. Although there was greater reduction of SBP in patients treated with nebivolol as compared to those treated with atenolol, the difference was not statistically significant (p>0.05).

Table 3: DBP (mm/Hg) in two treatment groups.

Group	Atenolol (50mg)	Nebivolol (5mg)	p value#
Baseline	97.67±4.73	98.04±5.23	0.7199
1 week	89.75±4.03	88.33±4.07	0.0926
12 weeks	82.79±3.86	81.21±4.48	0.0702
24 weeks	81.17±3.69	80.29±4.48	0.3013

#Unpaired t-test, Figures are Mean±Standard Deviation

Table 3 shows reduction in DBP in the two treatment groups from baseline upto 1 week, 12 weeks and 24 weeks. Although there was greater reduction of diastolic blood pressure in patients treated with nebivolol as compared to those treated with atenolol at each follow up, the difference was not statistically significant at 1 week, 12 weeks and 24 weeks (p >0.05).

Table 4: Lipid profile in atenolol group after treatment.

Lipid (mg/dL)	Baseline	24 weeks	p value**
LDL-C	92.96±15.53	116.79±20.90	<0.0001
HDL-C	44.67±4.15	40.81±3.92	<0.0001
TG	126.65±23.38	147.83±28.97	<0.0001
TC	162.98±16.10	187.15±21.41	<0.0001
VLDL-C	25.35±4.73	29.54±5.82	<0.0001

**Paired t-test, Figures are Mean±Standard Deviation

Table 4 shows the mean values of lipids in atenolol group at baseline and at 24 weeks. All the lipid levels except HDL-C were increased with atenolol therapy. At 24 weeks, atenolol therapy led to increase in LDL-C, VLDL-C, TC and TG which was highly significant (p<0.0001). HDL levels were decreased at 24 weeks which was also statistically highly significant (p<0.0001).

Table 5: Lipid profile in nebivolol group after treatment.

Lipid (mg/dL)	Baseline	24 weeks	p value**
LDL-C	91.42±16.27	90.92±16.07	0.8614
HDL-C	43.19±3.32	43.38±3.30	0.7520
TG	118.04±22.68	113.98±25.53	0.1381
TC	158.23±15.65	157.13±15.09	0.7148
VLDL-C	23.63±4.52	22.83±5.12	0.1547

**Paired t-test, Figures are Mean±Standard Deviation

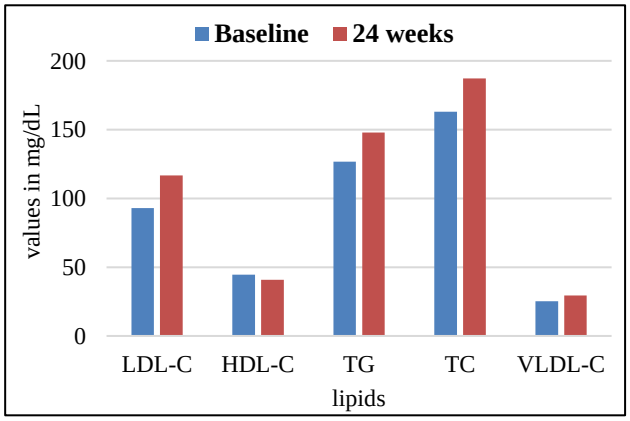

Figure 2: Comparison of lipids at baseline and at 24 weeks in atenolol group.

Table 5 shows the mean values of lipids in nebivolol group at baseline and at 24 weeks. At 24 weeks, nebivolol therapy led to changes in LDL-C, VLDL-C, HDL-C, TC and TG which was not statistically significant (p> 0.05).

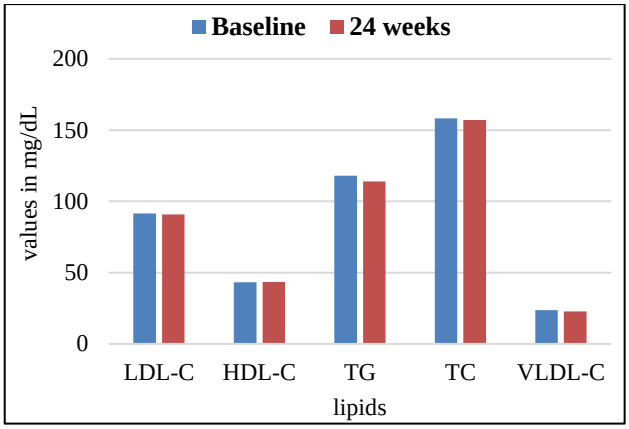

Figure 3: Comparison of lipids at baseline and at 24 weeks in nebivolol group.

Table 6 shows mean differences in various parameters from baseline to 24 weeks in both the treatment groups. This mean difference was statistically significant for LDL-C, TG, TC and VLDL-C (p <0.05) in two treatment groups.

Table 6: Comparison of mean differences in parameters from baseline to 24 weeks in two treatment groups.

Parameters	Atenolol group	Nebivolol group	p value#
SBP (mm/Hg)	41.38±8.94	42.54±7.09	0.4876
DBP (mm/Hg)	16.50±4.26	17.75±4.18	0.1544
LDL-C (mg/dL)	23.83±9.94	16.13±11.15	0.0006
HDL-C (mg/dL)	3.85±1.60	3.48±2.09	0.3377
TG (mg/dL)	21.19±10.02	13.48±13.40	0.0021
TC (mg/dL)	24.17±9.46	16.85±12.00	0.0014
VLDL-C (mg/dL)	4.19±1.97	2.67±2.79	0.0030

#Unpaired t-test, Figures are Mean±Standard Deviation

Table 7 gives the comparative data regarding the percentage of patients who reported a particular adverse effect like fatigue, headache, dizziness, fainting in the two treatment groups. There was no statistically significant difference in the incidence of these adverse effects in the two treatment groups (p >0.05).

DISCUSSION

The β-receptors mediate activation of hormone sensitive lipase in fat cells, leading to release of free fatty acids into the circulation. β-receptor antagonists modify the

metabolism of carbohydrates and lipids by attenuating the release of free fatty acids from adipose tissue.

Table 7: Incidence of adverse effects in the two treatment groups.

Adverse effects	Atenolol group (N=47)		Nebivolol group (N=47)		p Value***
	No. of patients	%	No. of patients	%	
Fatigue	4	9%	1	2%	0.1676
Headache	2	4%	1	2%	0.5552
Dizziness	2	4%	0	0%	0.1527
Hypotension/ fainting	1	2%	1	2%	1.0000

*** Z test for difference between two proportions

Nonselective β-receptor antagonists consistently reduce HDL cholesterol, increase LDL cholesterol, and increase triglycerides. In contrast, β-1 selective antagonists, including celiprolol, carteolol, nebivolol, carvedilol, and bevantolol, improve the serum lipid profile of dyslipidemic patients.[19] Antioxidant property of nebivolol and increase in NO by reducing its oxidative inactivation may be responsible for beneficial lipid and carbohydrate metabolic profile.[20,21] Nebivolol causes vasodilatation by directly secreting NO from endothelial cells by various mechanisms. It has been hypothesized that nebivolol and its metabolites increase the activity of NO synthase enzyme III (NOS III) which increases the synthesis of NO. Nebivolol is also supposed to inhibit degradation of NO due to reactive oxygen species such as super oxides and oxidative stress by its antioxidant property. The improved secretion of NO and antioxidant property of nebivolol helps in the maintenance of normal endothelial functions, prevention of vascular smooth muscle cell hypertrophy, decrease in LDL oxidation, decrease in platelet aggregation and adhesion, prevention of atherosclerotic plaque deposition, and apoptosis. Thus, NO has important therapeutic implications in protecting the cardiovascular system from atherosclerotic complications.[19]

Patients enrolled in the study received either Tab atenolol (50mg) or Tab nebivolol (5mg) orally once a day. Similar doses were used in studies conducted by Badar et al, Bhosale et al, Van Neuten et al, and Dhakam et al, for comparing the efficacy of atenolol versus nebivolol in patients with mild to moderate hypertension.[22-24] In the present study, the mean values of SBP in atenolol group at baseline and at 24 weeks were 160.96mm of Hg and 119.58mm of Hg respectively. This decrease in SBP after atenolol therapy was statistically highly significant (p<0.0001). Similar findings were observed in studies conducted by Sivaji et al, Sahana et al, and Badar et al.[19,25,26] The mean values of SBP in nebivolol group at baseline and at 24 weeks were 160.5 mm of Hg and 117.96 mm of Hg respectively. This decrease in SBP after nebivolol therapy was statistically highly significant (p<0.0001). Similar findings were observed in studies conducted by Sahana et al, and Badar et al.[19,26] In the present study at the end of 24 weeks, it was found that there was no statistically significant difference between atenolol and nebivolol therapy in reduction of SBP. The higher mean difference in this study as compared to that by Bhosale et al, may be due to lesser duration of their study.[22] In the present study, the mean values of DBP in atenolol group at baseline and at 24 weeks were 97.67 mm of Hg and 81.17mm of Hg respectively. This decrease in DBP after atenolol therapy was statistically highly significant. Similar findings were observed in studies conducted by Sivaji et al, and Badar et al.[19,25] The mean values of DBP in nebivolol group at baseline and at 24 weeks were 98.04mm of Hg and 80.29mm of Hg respectively. This decrease in DBP after nebivolol therapy was statistically highly significant (p <0.0001). Similar findings were observed in studies conducted by Sahana et al, and Fogari et al.[26,27] In the present study at the end of 24 weeks, it was found that there was no statistically significant difference between atenolol and nebivolol therapy in reduction of DBP. In the present study, at the end of 24 weeks, there was statistically significant increase in mean LDL-C values as compared to baseline in atenolol group (p<0.0001). Similar results were observed in study conducted by Badar et al.[19] In studies conducted by Fogari et al, Bhosale et al, and Sivaji et al, there was no statistically significant increase in mean LDL-C values after atenolol therapy.[22,25,27]

In the present study, in nebivolol group, there was no statistically significant increase in mean LDL-C values at 24 weeks compared to baseline. These findings were similar to those observed in studies done by Fogari et al, Badar et al, Bhosale et al, and Salve et al.[19,22,27,28] At the end of 24 weeks, in this study, there was statistically highly significant difference between mean LDL-C values in the two group. Similar findings were observed in study by Badar et al.[19] In the present study, at the end of 24 weeks, there was statistically significant increase in mean TC, TG and VLDL-C values as compared to baseline in atenolol group (p <0.0001). In nebivolol group, there was no statistically significant change in mean TC, TG and VLDL-C values at 24 weeks compared to baseline. This finding was similar to those observed in studies done by Fogari et al, Badar et al, Bhosale et al, and Salve et al.[19,22,27,28]

At the end of 24 weeks, in this study, there was statistically highly significant difference between mean TC, TG and VLDL-C values in the two groups. In the present study, at the end of 24 weeks, there was statistically significant decrease in mean HDL-C values as compared to baseline in atenolol group (p <0.0001). In nebivolol group, there was no statistically significant decrease in mean HDL-C values at 24 weeks compared to baseline. These findings were similar to those observed in studies done by Fogari et al, Badar et al, Bhosale et al, and Salve et al.[2,19,27,28] At the end of 24 weeks, in this study, there was statistically highly significant difference between mean HDL-C values in the two groups. The safety and tolerability elicited by both

treatment groups in present study were consistent with the studies conducted by Badar et al, Bhosale et al, and Sahana et al.[19,22,26] There was no statistically significant difference in the incidence of adverse effects in the two treatment groups (p >0.05). The most commonly noted adverse effects were fatigue, dizziness, headache and fainting. The adverse events were mild and none of the patients from either group discontinued the study drugs because of it.

The results of our study suggest that atenolol (50mg) and nebivolol (5mg) are equally efficacious in reducing BP. However, derangement in lipid profile is statistically significant with atenolol as compared to nebivolol. The present study was carried out at a single centre a District level Tertiary Care Hospital in Maharashtra, and hence, large scale multi-centric studies are required to generalize the findings of the present study. The present study could not record and compare the long-term effects of nebivolol and atenolol on blood pressure and lipid profile as it was only of 24 weeks duration.

CONCLUSION

From this study, it can be concluded that atenolol and nebivolol are equally effective in reducing BP but atenolol worsens lipid profile as compared to nebivolol and hence nebivolol is preferable over atenolol for reducing BP.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (IEC/Pharmac/Proposal no. 1114004-4)

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