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Research Article

To study the comparative effects of nebivolol and metoprolol on lipid profile in patients of essential hypertension

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ABSTRACT

Background: Hypertension and certain alteration in serum lipoproteins are complementary coronary risk factors. The effect of antihypertensive agents on lipid metabolism exhibits a wide range. Numerous studies have established that vasodilating beta-blockers are associated with more favorable effects on glucose and lipid profiles than non-vasodilating beta-blockers. The study was conducted to study the comparative effects of nebivolol and metoprolol on lipid profile in patients of essential hypertension.

Methods: A prospective, randomized open label single center study was conducted in the Department of Pharmacology in collaboration with Department of Medicine, MGM's Medical College and Hospital, Aurangabad in newly diagnosed patients of essential hypertension. Sixty patients of either sex in the age group of 30-65 years with blood pressure (BP) of ≥140/90 mmHg with deranged lipid parameters according to National Cholesterol Education Program were randomized into two groups. Group I received metoprolol (50 mg) and Group II received nebivolol (5 mg), both given once daily for 12 weeks. BP and lipid parameters were evaluated at baseline as well as at the end of 12 weeks.

Results: There was significant reduction in BP values ($p<0.0001$) as compared to baseline in both the groups, however no significant difference was observed between two drugs revealing that their efficacy in reducing systolic BP/diastolic BP is comparable. Furthermore, both the drugs had a favorable effect on lipid profile, but more significant results on lipid profile were observed in the nebivolol group as compared to metoprolol group ($p<0.0001$).

Conclusions: In our comparison study, it is seen that the favorable effect of nebivolol on serum lipids and its good tolerability profile make it a good choice for control of hypertension as well as preventing the long-term cardiovascular morbidities and mortalities.

Keywords: Essential hypertension, Beta-blocker, Metoprolol, Nebivolol, Lipid profile

INTRODUCTION

Essential or primary hypertension is the most prevalent type, affecting between 90% and 95% of patients diagnosed with hypertension.[1] It has been reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.[2] Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025.[3] However, prevalence of hypertension in India, for the last three decades has increased by about 30 times among urban residents and by about 10 times among rural residents.[4]

Hypertension and certain alteration in serum lipoproteins are complementary coronary risk factors. Several studies have indicated that high concentrations of low-density lipoprotein (LDL) cholesterol and triglyceride (TG) are strong risk factors for the development of cardiovascular disease (CVD).[5,6] It has been reported that the effect of antihypertensive agents on lipid metabolism exhibits a wide range. Some have adverse effect on the lipid profile whereas others have a neutral or favorable effect on it.[7] Beta-adrenergic receptor antagonists (beta-blockers) are widely used for the management of CVDs and have been proved efficacious in the treatment of hypertension, coronary heart disease, including angina pectoris, myocardial infarction, and heart failure.[8]

Metoprolol is a selective β_1 receptor blocker, devoid of intrinsic sympathomimetic activity. It has an established role in the management of essential hypertension and angina pectoris, and in patients with chronic heart failure. It has been observed that metoprolol in doses which significantly reduce raised arterial blood pressure (BP) had milder effects[9] or neutral effects[10] on lipid parameters. However, in some studies, metoprolol increased high-density lipoproteins (HDL) cholesterol levels and lowered total cholesterol (TC) and TG levels.[11]

Nebivolol is a third-generation, highly selective β_1 blocker and is devoid of intrinsic sympathomimetic activity. It achieves BP control through nitric oxide (NO)–mediated vasodilation in addition to conventional beta-blocking.[12] Its endothelium vasodilatory properties are exerted via the activation of the L-arginine/NO pathway and have proven the BP-lowering capability and a favorable tolerability profile.[13] Furthermore, antioxidant properties of nebivolol have been found responsible for neutral or even favorable effects on lipid and carbohydrate metabolic profile.[14]

Further, numerous studies have established that vasodilating beta-blockers are associated with more favorable effects on glucose and lipid profiles than non-vasodilating beta-blockers.[15] Hence, the study was planned to study the comparative effects of nebivolol and metoprolol on lipid profile in patients of essential hypertension.

METHODS

A prospective, randomized open label single center study was conducted in the Department of Pharmacology in collaboration with Department of Medicine, MGM's Medical College and Hospital, Aurangabad in patients of essential hypertension. It was conducted from 20.11.2012 to 24.2.2013. Ethics clearance was obtained from Institutional Ethics Committee. All patients gave their written and informed consent at the time of enrolment after being fully explained about the nature and purpose of the study. Sixty patients of either sex in the age group of 30-65 years with BP of ≥140/90 mmHg were included in the study. Only newly diagnosed patients of essential hypertension without prior antihypertensive treatment and with deranged lipid parameters according to National Cholesterol Education Program were selected. The patients with secondary hypertension, bronchial asthma and with clinical evidence of cerebrovascular, cardiac, renal, hepatic, gastrointestinal or endocrinologic disease, hypersensitivity to metoprolol, nebivolol or related drugs, history of smoking, alcohol intake, substance abuse or mental illness were excluded. Besides, patients taking any concomitant medication that might interact with the trial drugs and pregnant or lactating females were also excluded. We also excluded patients who were concurrently taking the drugs known to affect BP and serum levels of parameters of lipid metabolism. After screening eligibility for enrollment, patients were randomly allocated using random number table into two groups of 30 each. Group I received metoprolol 50 mg OD and Group II received nebivolol 5 mg OD.

Patients were recruited and at the initial visit, medical history and detailed physical examination were performed. Routine hematology, biochemistry, and urinalysis were undertaken and a 12 lead electrocardiogram was recorded. At baseline and after 12 weeks, systolic BP (SBP), and diastolic BP (DBP) was measured with an appropriate sized cuff in right arm with the patient seated and after 15 mins of rest. Three readings were taken 5 mins apart and the mean of these readings was taken. Furthermore, blood test data, including serum TC, HDL cholesterol, and TG, were collected for each individual at the baseline and at 12 weeks after the start of metoprolol or nebivolol monotherapy. Estimation of serum lipids were carried out with Automated Random access clinical chemistry analyzer ERBA Chem 7 with ERBA TEST REAGENT (Transasia Bio-medicals Ltd., India), TC by cholesterol oxidase peroxidase method, glycerol phosphate oxidase method for TG, and phosphotungstate precipitation method for HDL. LDL cholesterol and very LDL (VLDL) cholesterol were calculated from the estimated values of TC, TG, and HDL, using Friedewald's formula. Compliance was assessed by interview and pill count.

Statistical analysis was done using paired and unpaired Student's t-test to compare results within the group and between groups, respectively. For all the tests, a value of $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 60 patients were enrolled for the study, 3 patients were lost during follow-up. 57 patients completed the study, with 28 patients (14 male and 14 female) in the metoprolol group and 29 patients (14 male and 15 female) in nebivolol group. Patient's age for both groups ranged between 30 and 65. Table 1 summarizes the baseline characteristics of the patients enrolled for this study. There were no significant differences between the groups at baseline.

BP

After 12 weeks of treatment, mean supine SBP/DBP in metoprolol group decreased from 161.36 ± 5.81/98.5 ± 3.11 mmHg to 136.07 ± 3.1/95.21 ± 2.85 mmHg (Table 2 and Figure 1). In nebivolol group, mean supine SBP/DBP decreased from 162.76 ± 3.56/98.07 ± 2.7 mmHg to 135.03 ± 4.13/94.55 ± 2.44 mm Hg over 12 weeks period (Table 2 and Figure 1). A statistically significant fall in mean SBP and DBP was observed in both the groups when compared to the baseline ($p<0.0001$). However, unpaired t test did not show any difference between two drugs revealing that their efficacy in reducing SBP/DBP is comparable ($p>0.10$) (Table 3).

Table 1: Baseline characteristics of patients.

Variables	Group I (Metoprolol) n=28 (%)	Group II (Nebivolol) n=29 (%)
Age (years)*	49.07±7.58	47.51±7.68
Sex		
Male	14 (50)	14 (48)
Female	14 (50)	15 (52)
Mean supine SBP (mmHg)*	161.36±5.81	162.76±3.56
Mean supine DBP (mmHg)*	98.5±3.11	98.07±2.7
TC (mg/dl)*	263.27±32.23	260.26±29.11
TG (mg/dl)*	262.26±34.39	252.43±27.08
HDL (mg/dl)*	43.65±4.6	44.08±5.56
LDL (mg/dl)*	167.5±31.73	165.68±28.4
VLDL (mg/dl)*	52.45±6.87	50.45±5.36

*Values are expressed as mean±SD. No statistically significant differences were present at baseline. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, SD: Standard deviation

Serum lipids

Table 2 and Figure 2 show lipid levels in the two study groups at baseline and after 12 weeks of therapy. Metoprolol significantly decreased levels of TC (3.2%), TG (3.9%), LDL (5.5%), VLDL (3.9%) and significantly increased HDL level (6.13%) ($p<0.0001$ vs. baseline). Similarly, nebivolol group also observed significant lowering in TC by 16.9%, TG by 11.8%, LDL by 30.6%, VLDL by 11.8%, and significant increase in HDL level (28.7%) ($p<0.0001$ vs. baseline).

When both the groups were compared by unpaired t-test, it was observed that more significant results on lipid profile were observed in the nebivolol group as compared to metoprolol group ($p<0.0001$) (Table 3).

Adverse effects

Both the drugs were well tolerated. Patients of metoprolol group experienced nausea, headache, dizziness, and fatigue whereas reported mild fatigue. The number of patients with adverse effect events was higher in the metoprolol than in the nebivolol group (3.44% of nebivolol vs. 14.28% of metoprolol).

Table 2: Comparative effects of metoprolol and nebivolol on SBP, DBP, and serum lipids before and after 12 weeks of therapy using paired t-test.

Parameter	Group I (Metoprolol)		Group II (Nebivolol)	
	Baseline	12 weeks	Baseline	12 weeks
Mean supine SBP (mmHg)	161.36±5.81	136.07±3.10****	162.76±3.56	135.03±4.13****
Mean supine DBP (mmHg)	98.5±3.11	95.21±2.85****	98.07±2.7	94.55±2.44****
TC (mg/dl)	263.27±32.23	254.94±29.47****	260.26±29.11	216.16±20.11****
TG (mg/dl)	262.26±34.39	251.97±32.9****	252.43±27.08	222.5±15.91****
HDL (mg/dl)	43.65±4.6	46.33±4.87****	44.08±5.56	56.75±5.12****
LDL (mg/dl)	167.5±31.73	158.19±28.88****	165.68±28.4	114.91±18.98****
VLDL (mg/dl)	52.45±6.87	50.41±6.73****	50.45±5.36	44.5±3.18****

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 was considered significant in comparison to baseline. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

Table 3: Comparative effects of metoprolol and nebivolol on SBP, DBP, and serum lipids after 12 weeks of therapy by unpaired t-test.

Parameters	Group I (Metoprolol)	Group II (Nebivolol)	t value	p value
Mean supine SBP (mmHg)	136.07±3.10	135.03±4.13	1.069	0.289
Mean supine DBP (mmHg)	95.21±2.85	94.55±2.44	0.944	0.349
TC (mg/dl)	254.94±29.47	216.16±20.11	5.821	<0.0001*
TG (mg/dl)	251.97±32.9	222.5±15.91	4.328	<0.0001*
HDL (mg/dl)	46.33±4.87	56.75±5.12	7.863	<0.0001*
LDL (mg/dl)	158.19±28.88	114.91±18.98	6.709	<0.0001*
VLDL (mg/dl)	50.41±6.73	44.5±3.18	4.264	<0.0001*

*Extremely significant differences were found statistically between the two groups ($p>0.0001$). SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

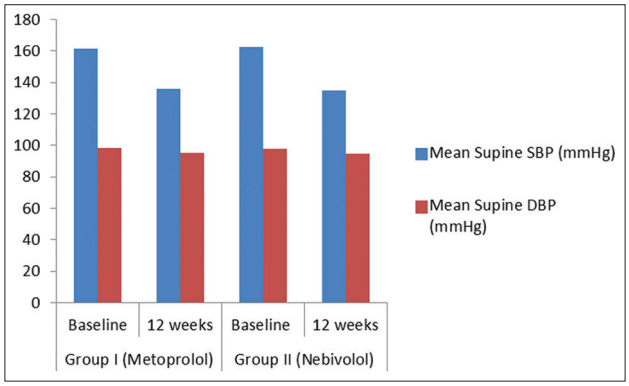

Figure 1: Comparative effects of metoprolol and nebivolol on systolic blood pressure and diastolic blood pressure before and after 12 weeks of therapy.

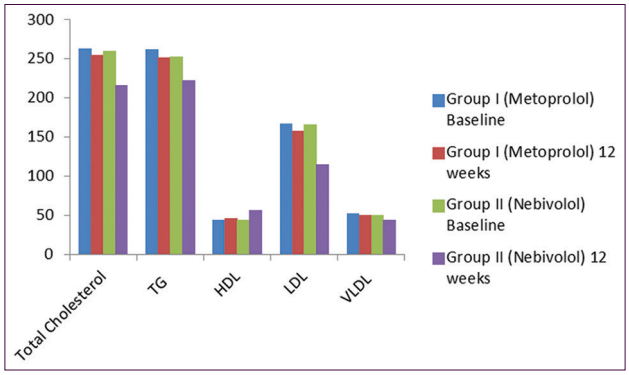

Figure 2: Comparative effects of metoprolol and nebivolol on serum lipids before and after 12 weeks of therapy.

DISCUSSION

Hypertension is emerging as a silent killer in the Indian population as compared to the west where there is awareness of the disease and its complications. It is recognized globally as a major risk factor for CVD, stroke, diabetes, and renal diseases.[16] Ideally, an antihypertensive agent should have a neutral effect or, preferably, produce a favorable shift in the serum lipid and lipoprotein profile, which is associated with a decrease in coronary heart disease risk. The effects of beta-blockers on blood lipids have been studied extensively. Variability has been observed in effects of nonselective and cardioselective beta-blockers on lipid profile in different studies as well as among the agents of cardioselective beta-blockers also.

Our study demonstrated that both metoprolol and nebivolol effectively reduced BP, but their effects of lowering BP are not significantly different from each other, i.e., both drugs have comparable efficacy.

Through this study, it has been revealed that metoprolol significantly decreased the levels of serum TC, serum TGs, LDL, and VLDL and increased levels of HDL ($p<0.0001$). These results were comparable to the study conducted by Gupta et al.[17] However, earlier studies such as Waal-Manning,[18] showed that administration of higher doses of metoprolol (100 mg twice daily) increased plasma TGs. On the other hand, Beinart et al. study which was conducted at Clinical Pharmacology Unit, Royal Northern Hospital, London showed that metoprolol had no effect on serum TG or cholesterol concentrations.[19]

Similarly, administration of nebivolol also significantly decreased the levels of serum cholesterol, serum TGs, LDL, VLDL while increased the levels of HDL after 12 weeks of treatment ($p<0.0001$). These results correlate to the study done by Van Bortel[13] with the exception that no significant changes in HDL cholesterol and TGs were observed in the respective study. However, our findings are in contrast with Pesant et al.[20] and Badar et al.[21] who showed in their studies that there was no change in lipid parameters in patients on treatment with nebivolol. Similarly, a study by Peter et al. in patients of type 2 diabetes with mild to moderate hypertension exhibited no significant changes in serum cholesterol or TGs following treatment with nebivolol, but a significant increase in HDL cholesterol was noted.[22]

The advantage of using nebivolol 5 mg OD can be clearly seen in Group II as it reduced serum TC, TG, LDL, and VLDL and increased HDL to a greater extent. The results of our study show that nebivolol produced a more beneficial influence on plasma lipids than metoprolol. Hence, nebivolol appears rather to decrease than increase the lipid-mediated risk for developing or accelerating coronary atherosclerosis. The antioxidant property of nebivolol and increase in NO by reducing its oxidative inactivation is probably responsible for beneficial lipid metabolic profile. Moreover, its affordable cost also benefits the hypertensive patients to have a long term control of lipid profile and, thus helps in the overall reduction of secondary complications.

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