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Research Article

A study of atenolol and nebivolol in prehypertension

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ABSTRACT

Background: Patients with prehypertension have an increased risk of cardiovascular disease. The coexistence of prehypertension with risk factors increases cardiovascular morbidity and mortality. That's why it is important to treat pre-hypertensive patients having risk factors. The objective was to evaluate the effect of atenolol and nebivolol in pre-hypertensive patients.
Methods: Pre-hypertensive patients having risk factors were selected, and non-pharmacological therapy was advised to all patients. Those patients who were not able to follow strictly non-pharmacological guidelines and remained pre-hypertensive were included in this study. Pre-hypertensive patients were divided into three groups. One group received atenolol 50 mg orally, once daily. Second group received nebivolol 5 mg orally, once daily. Third group received placebo orally, once daily. All groups received treatment for 1 month.
Results: In the nebivolol group after 1 month of study, the mean reduction in systolic blood pressure (SBP) was 134.2±3.07-118.26±4.66 and mean reduction in diastolic BP (DBP) was 87.13±1.87-80.73±1.99. Reduction in SBP and DBP in the nebivolol group was significant ($p \leq 0.0001$). In the placebo, and atenolol group results were not significant.
Conclusion: Nebivolol produces a significant reduction in SBP and DBP in pre-hypertensive patients. Atenolol and placebo did not show beneficial results.

Keywords: Atenolol, Nebivolol, Prehypertension, Mean systolic blood pressure, Mean diastolic blood pressure

INTRODUCTION

Hypertension is a major problem leading to morbidity and mortality. "Prehypertension also has become an important public health issue in China because it identifies people at higher risk for hypertension and cardiovascular diseases."[1] "The prevalence rates of prehypertension and hypertension were 13.9% and 19.4% respectively, among adolescent high school girls in Tabriz, Iran."[2] "Starting at a blood pressure (BP) of 115/75 mm of Hg, risk of cardiovascular diseases doubles with rise of every 20/10 mmHg of BP. Pre-hypertensive patients have an increased risk of cardiovascular disease."[3] According to seventh U.S. Joint National Committee on prevention, detection, evaluation and treatment of high BP, prehypertension is considered when systolic BP (SBP) is between 120 and 139 mmHg or diastolic BP (DBP) is between 80 and 90 mmHg.

"Even within the prehypertension BP category, an increased risk of cardiovascular events and death is associated with higher BP values."[4] The risk of cardiovascular disease, disability and death in hypertensive patients is also increased by concomitant cigarette smoking, diabetes, obesity, genetic predisposition, and elevated low-density lipoprotein. The coexistence of hypertension with these risk factors increases cardiovascular morbidity and mortality. That's why, it is important to treat pre-hypertensive patients having risk factors. Therefore, "a large proportion of a family practice's patients need close surveillance of BP because of the prevalence of prehypertension."[5]

Prehypertension with risk factors should be managed to maintain good cardiovascular health. "The recently published Trial of Preventing Hypertension is the first study of pharmacologic intervention among those with prehypertension. Results from this trial demonstrated that

angiotensin receptor blockers retard age-related BP increase in pre-hypertensive patients."[6] "Another study revealed that early pharmacological intervention had strong beneficial effects on aortic elasticity in patients with prehypertension."[7] The present study was planned with the objective to evaluate the effect of atenolol and nebivolol in pre-hypertensive patients.

METHODS

The present study was undertaken in the Department of Pharmacology and Department of Medicine, S.S. Medical College and S.G.M. Hospital Rewa. The research protocol had the clearance of S.S. Medical College Rewa Ethics Committee. Written consents were obtained from all the participants.

Single blind placebo-controlled study is designed to evaluate the effect of atenolol and nebivolol on pre-hypertensive patients. Pre-hypertensive patients (SBP is between 120 and 139 mmHg or DBP is between 80 and 90 mmHg) having one or more risk factors (obesity, smoking, sedentary lifestyle, family history of cardiovascular problems) were selected from general out-patient department (OPD). These patients came in the hospital OPD for treatment of tropical disease. We did not select any patient who was taking treatment of non-tropical diseases. Non-pharmacological treatment was advised for 3 months to them. In non-pharmacological therapy, "Weight reduction; a diet rich in fruits, vegetables and low-fat dairy products with a reduced content of saturated and total fat; reduced dietary sodium intake, and regular physical activity (at least 30 mins/day, most days of the week) were advised in life style modification program."[1]

After completing lifestyle modification program of 3 months, BP was measured. Out of 146, 37 patients became normotensive. A total of 109 patients remained in pre-hypertensive group. They were not able to follow strictly non pharmacological guideline to control BP. This study included these 90 pre-hypertensive patients and remained 19 patients refused to take part in this study.

Ninety pre-hypertensive patients were divided into three groups, 30 patients in each group. To ensure randomness of division of 90 patients into three groups, we have adopted lottery method, irrespective of age, sex, and risk factor. One group received atenolol 50 mg orally once daily. Second group received nebivolol 5 mg orally once daily. Third group received placebo orally once daily. All groups received treatment for 1 month. At the end of the study, SBP and DBP of all the patients were taken. To know the significance of the observation, ANOVA test was used for calculations. Patient sex, age, and family history were recorded (Table 1). Any adverse effects during the treatment were noted. BP was recorded at baseline and after 1 month of treatment. There was no any funding source. Patients themselves purchased their medicine as advised. For placebo treatment, we provided blank capsules filled with glucose.

After completion of 1-month study, we advised all ninety pre-hypertensive patients to follow medical guideline to control BP strictly and visit the hospital OPD for routine BP monitoring.

RESULTS

In the placebo group, the mean SBP prior to treatment was 133.46±2.894, and 133.46±2.62, after 1 month of placebo therapy. The reduction in SBP was found to be statistically insignificant (p=0.6253). The mean DBP in the placebo group prior to treatment was 87±1.94 and 86.46±1.31 after 1 month of placebo therapy. The reduction in DBP was found to be statistically insignificant (p=0.2122) (Tables 2 and 3).

In the atenolol group, the mean SBP prior to treatment was 134.13±3.19 and 132.6±3.11, after 1 month of atenolol therapy. The reduction in SBP was found to be statistically insignificant (p=0.652). The mean DBP in atenolol group prior to treatment was 87±1.94 and 86.4±1.1, after 1 month of atenolol therapy. The reduction in DBP was found to be statistically insignificant (p=0.1474) Patients receiving atenolol showed an insignificant fall (p=0.652) in mean SBP (Table 2) and (p=0.1474) in mean DBP (Table 3) in pre-hypertensive patient. Atenolol and placebo drug did not reduce mean SBP and mean DBP significantly.

In the nebivolol group, the mean SBP prior to treatment was 134.2±3.07, and 118.26±4.66, after 1 month of nebivolol therapy. The reduction in SBP was found to be statistically significant (p=0.0001). The mean DBP in the nebivolol group prior to treatment was 87.13±1.87 and 80.73±1.99, after 1 month of nebivolol therapy. The reduction in DBP was found to be statistically significant (p=0.0001) (Tables 2 and 3).

This study showed nebivolol is highly effective in the management of pre-hypertensive patients while atenolol is not effective in its management.

Mild side-effects in the patients taking atenolol and nebivolol were observed. Cold extremities, fatigue and sleep disturbances and weakness were the common side effects in all three groups. In the placebo group, 6% patients reported headache and 6% patients reported weakness. Remaining patients of the placebo group did not report any other complaints. In atenolol group, fatigue was observed in 6% patients, weakness was observed in 10% patients, and 12% patients reported a nightmare. In the nebivolol group, 6% patients reported sleep disturbances, and 6% patient reported headache, fatigue.

DISCUSSION

"β-receptor antagonists generally do not reduce BP in patients with normal BP. However, these drugs lower BP in patients with hypertension".[8] In hypertension, release of

Table 1: Distribution of cases managed by non-pharmacological therapy.

Age group (years)	Male	Female	Total number	Non-pharmacological therapy (cured-cases)			Non-pharmacological therapy (failure-cases)		
				Male	Female	Total	Male	Female	Total
21-30	16	08	24	08	07	15	08	01	09
31-40	45	20	65	07	10	17	37	13	48
41-50	27	21	48	02	03	05	20	11	43
51-61	07	02	09	00	00	00	07	02	09
Total patients	95	51	146	17	20	37	72	27	109

Table 2: Effect of drugs on SBP.

Parameter	Placebo	Atenolol	Nebivolol
Baseline (mean±SD)	133.8±2.89	134.13±3.19	134.2±3.07
After 1 month of Rx (mean±SD)	133.46±2.62	132.6±3.11	118.26±4.66
p value	0.625	0.065	0.0001

Nebivolol showed a significant fall in SBP (p=0.0001) by using ANOVA test. SBP: Systolic blood pressure, SD: Standard deviation

Table 3: Effect of drugs on DBP.

Parameter	Placebo	Atenolol	Nebivolol
Baseline (mean±SD)	87±1.94	87±1.94	87.13±1.87
After 1 month of Rx (mean±SD)	86.46±1.31	86.4±1.1	80.73±1.99
p value	0.2122	0.1474	0.0001

Nebivolol showed a significant fall in DBP (p=0.0001) by using ANOVA test. DBP: Diastolic blood pressure, SD: Standard deviation

renin and norepinephrine is increased and β-blockers reduce release of renin and norepinephrine, which are suggested mechanism of antihypertensive action of β blockers. Atenolol is not effective in prehypertension. It suggests that in prehypertension, concentration of renin and norepinephrine is not increased in comparison to hypertension. Nebivolol is effective in prehypertension because "it has different hemodynamic profile, different from classic β-receptor antagonists such as atenolol, propranolol. It actually lowers arterial BP without depressing left ventricular function and reduces systemic vascular resistance."[5] It also suggested "nebivolol reverses endothelial dysfunction"[9] and "it also activates vasorelaxation through activation of inositol-phosphate metabolism and constitutive nitric oxide synthase activity in endothelial cells."[10] In one study, "nebivolol caused vasodilatation, which was antagonized by N(G)-monomethyl-L-arginine (LNMMA), whereas atenolol did not, suggesting that such a mechanism could also operate in human veins."[11] Nebivolol relaxation is antagonized by inhibition of nitric oxide (NO) synthase by LNMMA, implicating the endothelial L-arginine/NO mechanism. It clarifies that this reduction in systemic vascular resistance is due to a direct vasorelaxant effect that is mediated by NO. There are many studies for management of mild, moderate and severe hypertension. We studied management of prehypertension to reduce cardiovascular morbidity and mortality in earlier ages. Further studies are required for its clinical implications.

CONCLUSION

Nebivolol produces a significant reduction in SBP and DBP in pre-hypertensive patients. Atenolol and placebo did not show beneficial results. Nebivolol actually lowers arterial BP without depressing left ventricular function and reduces systemic vascular resistance. It also suggested that nebivolol reverses endothelial dysfunction, and it also activates vasorelaxation through activation of inositol-phosphate metabolism and constitutive nitric oxide synthase activity in endothelial cell.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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