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EFFECT OF NEBIVOLOL AND METOPROLOL ON PLATELET ACTIVATION IN HYPERTENSIVE PATIENTS

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Abstract: Objective: To evaluate the effects of nebivolol and metoprolol on platelet activation in hypertensive patients by measuring mean platelet volume (MPV) and platelet count. **Study Design:** This was an open labelled, prospective, single centric study. Sixty newly diagnosed hypertensive patients with stage 1 hypertension were enrolled in this study. After baseline assessment, all eligible patients were divided into two groups. One group received 5 mg daily dose of nebivolol and second group received 100 mg daily dose of metoprolol and were treated for 8 weeks with two follow up visits. Blood pressure, heart rate, mean platelet volume, platelet counts and lipid profile were measured before and after treatment. Results were expressed as the mean ± SD and percentage and were analysed using paired and unpaired student t test. **Results :** At the end of 8 weeks, mean platelet volume and platelet count were significantly reduced with nebivolol group (10.36 ± 3.03 Vs 8.75 ± 2.46 and 236.63 ± 9.73 Vs 226.96 ± 9.38 respectively) compared with those of metoprolol group (10.57 ± 3.69 Vs 9.80 ± 3.49 and 236.66 ± 9.67 Vs 232 ± 9.57 respectively). **Conclusion:** Beneficial effect of nebivolol on platelet activation was more potent than those of metoprolol which might play a role to reduce thrombotic risk in hypertensive patients.

Keywords: Hypertension, Platelet Activation, Metorprolol, Nebivolol, Mean Platelet Volume

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INTRODUCTION

Hypertension is defined as the consecutive elevation of blood pressure above 140 mm Hg systolic BP or 90 mm Hg diastolic BP when measured in an office setting. Normal or optimal BP is classified as being systolic BP less than 120 mm Hg and diastolic BP less than 80 mm Hg [1]

Essential hypertension is associated with an increased risk of thrombotic complications such as stroke and myocardial infarction [2]. Some previous studies showed that platelets get activated in hypertension and have a role in the pathogenesis of atherosclerotic complications. Some previous study revealed that β- blocker had an inhibitory effect on platelet activation [3, 4]. Nebivolol is a selective β_1 adrenergic receptor antagonist which differs from conventional β-adrenergic blockers by inducing nitric oxide (NO) synthesis in the endothelium [5]. Nebivolol has been shown to relax human forearm vasculature via the L-arginine/nitric oxide pathway in both normotensive and hypertensive subjects [6, 7]. Platelet activation can be assessed by various methods, such as platelet morphology, function, and plasma markers. MPV is a marker of platelet function. Moreover, higher MPV levels have been identified as an independent risk factor not only for myocardial infarction in patients with coronary heart disease but also for death or recurrent vascular events after myocardial infarction [8]. It has been proved that higher mean platelet volume is associated with increased platelet activity. In present study, we evaluated the effect of nebivolol and metoprolol on platelet activation using mean platelet volume in hypertensive patients.

METHODS

The study protocol was approved by the Ethics Committee of Sanjivani Super Speciality Hospital. Written informed consent was obtained from all patients prior to enrolment in the study.

Patients

Both male and female patients aged between 18-75 yrs of age with SBP between 149-159 mm-Hg and DBP between 90- 99 mm-Hg were enrolled in this study. We excluded patients with all other clinical conditions. We also excluded patients who had a history of allergy or hypersensitivity to study medication or who required dose titration during study.

Study design

This was an open labelled, prospective, non-randomized, parallel group, single centric 8 week study. Total 60 patients were enrolled in this study. After detailed explanation of the study and involved procedures to the patients, eligibility assessment, informed consent and investigations were carried out to screen the patients. After that, patients were allocated in two experimental

groups. The patients received either 5 mg of nebivolol (Group I) or 100 mg of metoprolol (Group II) orally once daily. Blood Pressure, heart rate, mean platelet volume, platelet count and lipid profiles were measured in each patient at each scheduled visit (week 4 and week 8).

Statistical analysis

Data were collected in paper case report form and were converted into excel spreadsheet. Results were expressed as mean ± SD and percentage. The statistical differences between two groups were tested by using unpaired t test. Two tailed t test was used to compare continuous variables before and after drug therapy. *p* value<0.05 was considered as statistically significant.

RESULTS

Total 60 patients (47 male, 13 female) who met all inclusion criteria and none of the exclusion criteria were enrolled in the study. Among these, 30 patients received nebivolol (group I), whereas 30 patients received metoprolol (Group II).

The demographic characteristic of patients is shown in Table 6.1 and fig 6.1. Mean (±SD) age of patients in nebivolol group was found to be 56.06 (±9.22) and in metoprolol (group-II) mean (±SD) age of patients was 54.46 (±9.18). There were 22 males and 08 females in nebivolol group as compared to 25 males and 05 females in metoprolol group.

Baseline characteristics of patients

During screening, baseline characteristics like systolic and diastolic blood pressures, heart rate, mean platelet volume, platelet count and metabolic parameters (LDL, HDL, TG, TC) were recorded in both groups as mentioned in Table: 6.2. There were no statistically significant difference observed between nebivolol (group-I) and metoprolol (group-II).

Change in SBP, DBP and in Heart rate from baseline to week-8

As shown in Table 6.3, both nebivolol and metoprolol had significant antihypertensive effect. Systolic and diastolic blood pressures were significantly decreased with nebivolol and metoprolol though there was no significant difference between two groups regarding decrease in BP. In both the groups, heart rate was significantly lowered but metoprolol caused higher decrease in heart rate as compared to that of nebivolol.

Percentage reduction in SBP, DBP and in Heart Rate from baseline to weeks-8

Percentage reduction in SBP, DBP and in heart Rate was shown in figure 6.2. Both the groups showed reduction in SBP, DBP and heart Rate. Percentage reduction in SBP and DBP by nebivolol was 16.11% and 13.68% respectively which was higher than that seen with

metoprolol 12.83% and 10.79% respectively. But percentage decrease in heart rate was more in metoprolol group as compared to nebivolol group (9.94%. and 8.69% respectively).

Change in MPV and Platelet Count from baseline to week 8

As shown in Table: 6.4, nebivolol significantly decreased mean platelet volume and platelet count. Metoprolol also decreased mean platelet volume and platelet count but it is not statistically significant indicating that nebivolol showed greater inhibition of platelet activation than that of metoprolol which might play a role in reducing thrombotic risk in hypertensive patients.

Percentage reduction in MPV and Platelet Count from baseline to weeks-8

As shown in fig: 6.3, percentage reduction in mean platelet volume and platelet count by nebivolol was 15.54% and 4.08% respectively and were higher than percentage reduction in mean platelet volume and platelet count by metoprolol which was 7.28% and 1.96% respectively.

Change in Lipid profile from baseline to week 8

As shown in Table 6.5, there was no statistically significant difference in the reduction of LDL in both the groups. Metoprolol significantly decreased HDL level from baseline to week 8. Nebivolol also decreased HDL level but it was not significantly significant. Both TG and TC levels were significantly elevated with metoprolol indicating that on long term usage it may cause undesired effect on lipid profile.

Percentage change in Lipid Profile from baseline to weeks-8

As shown in figure 6.4, both the drugs showed effect on lipid profile. Percentage reduction in LDL in nebivolol group was 0.64% where as in metorolol group, it was 0.34%. Percentage reduction in HDL by nebivolol was 1.19% which was comparatively less than that of metoprolol (4.66%). Percentage increase in TG and TC levels by nebivolol was 0.60% and 0.64% respectively wherein metoprolol group, it was 4.61% and 4.40% respectively.

DISCUSSION

This single centric, non randomized, observational study was designed to compare the effect of nebivolol and metoprolol on platelet activation in hypertensive patients. The results of this study indicate that nebivolol is superior in terms of reducing mean platelet volume and platelet count in the patients having hypertension.

Weiss et al (2011) conducted a study to evaluate the efficacy and tolerability of nebivolol in stage I and II hypertension. They found that overall mean reduction in SBP and DBP were significantly greater with nebivolol at recommended dosage compared with placebo. Nebivolol treatment was associated with significantly greater proportion of responders suggesting that nebivolol is an efficacious and more tolerated agent for the reduction of BP in the patients with stage I and II hypertension [9].

Neuten et al (1997) evaluated the effect of nebivolol and atenolol on essential hypertension. They found that both active drugs caused highly significant reduction in systolic and diastolic BP. Both active drugs were well tolerated but nebivolol was better tolerated than atenolol. Moreover, nebivolol, a long acting cardioselectve, vasodilating β-blocker which acts via L-arginine/ nitric oxide pathway, appears potentially valuable in the treatment of hypertension [10].

In our study, we observed that both nebivolol and metoprolol had significant antihypertensive effect. Systolic and diastolic blood pressures were significantly decreased with nebivolol and metoprolol though there was no significant difference between the two groups regarding decrease in BP. In both the groups, heart rate was significantly lowered but metoprolol caused higher decrease in heart rate as compared to that with nebivolol.

Boos et al (2007) evaluated assessment of platelet activation indices amongst high risk hypertensive patients by measuring mean platelet volume and platelet count. They concluded that there is a stepwise increase in platelet activation with increasing severity of hypertensive disease which may contribute to the pathogenesis of thrombosis related complication in hypertension [11].

Celik et al (2006) conducted a study to evaluate the effect of nebivolol and metoprolol on platelet activation by measuring mean platelet volume. They found that mean platelet volume was significantly decreased with nebivolol compared with those of metoprolol group indicating that beneficial effect of nebivolol on platelet activation was more potent than those of metoprolol [12].

In the present study, we observed that nebivolol significantly decreased mean platelet volume and platelet count. Metoprolol also decreased mean platelet volume and platelet count from baseline to week 8 but the difference was not statistically significant indicating beneficial effect of nebivolol on platelet activation which might play a role in reducing thrombotic risk.

Badar et al (2011) carried out a study to evaluate the effect of nebivolol and atenolol on metabolic parameters (lipid profile and blood sugar) in patients with essential hypertension. They concluded that mean blood sugar and lipid profile were found to be significantly elevated

with atenolol but it was not significantly elevated with nebivolol indicating that it is better β-blocker due to its less metabolic adverse events [13].

In the present study, we observed that lipid profile was not significantly altered with nebivolol group but in metoprolol group it was altered significantly which indicates that on long term usage metoprolol may cause undesirable effect on lipid profile.

Our result suggests that nebivolol seems to be better therapeutic option due to inhibitory effect on platelet activation which might play a role in reducing thrombotic risk as well as less metabolic adverse events. But since it is a single centric study of short duration and only few studies are available which determine the effect of both the drugs on platelet activation, more evidences are required to obtain satisfactory results.

CONCLUSION

The result of this study shows that nebivolol and metoprolol had significant antihypertensive effect. Beneficial effect of nebivolol on platelet activation was more potent than those of metoprolol which might play a role to reduce thrombotic risk in hypertensive patients. But decrease in heart rate and alteration in lipid profile were greater with metoprolol group as compared with nebivolol group, which on long term use may cause metabolic syndrome. Thus, from this study it is concluded that nebivolol is a better therapeutic option for hypertensive patients not only in terms of controlling blood pressure but also in terms of inhibiting platelet activity.

Table 1: Demographic details

Characteristics	Nebivolol (Group I) (n=30) Mean ± SD	Metoprolol (Group II) (n=30) Mean ± SD
Age (yr)	56.06 ± 9.22	54.46 ± 9.18
Sex		
Male	22	25
Female	08	05
Height (cm)	161.90 ± 9.09	163.16 ± 8.91
Weight (kg)	62.6 ± 9.23	60.4 ± 8.94

Table 2: Baseline characteristics of the patients

Parameters	Nebivolol group (n=30) Mean ± SD	Metoprolol group (n=30) Mean ± SD
SBP (mmHg)	155.60 ± 7.17	152.13 ± 5.32
DBP (mmHg)	95.93 ± 7.07	95.06 ± 7.09
Heart Rate (/ min)	75.93 ± 6.37	78.4 ± 6.91
Mean Platelet Volume (MPV)(/cum)	10.36 ± 3.03	10.57 ± 3.69
Platelet Count (/cmm)	236.63 ± 9.73	236.66 ± 9.67
LDL (mg/dl)	127.06 ± 10.53	128.2 ± 13.33
HDL (mg/dl)	46.76 ± 6.15	47.16 ± 6.06
TG (mg/dl)	126.86 ± 13.16	129.2 ± 12.36
TC (mg/dl)	186.53 ± 8.38	184.66 ± 10.16
LDL= Low Density Lipoprotein, HDL= High Density Lipoprotein Cholesterol TC= Total Cholesterol, TG= Triglyceride		

Table 3: Change in SBP, DBP and in Heart rate from baseline to weeks-8

Parameters	Nebivolol (Group I) (n=30) Mean ± SD		Metoprolol (Group II) (n=30) Mean ± SD	
	Baseline	Week 8	Baseline	Week 8
SBP	155.60 ± 7.17	130.53 ± 6.62*	152.13 ± 5.32	132.6 ± 5.15*
DBP	95.93 ± 7.07	82.80 ± 6.44*	95.06 ± 7.09	84.8 ± 6.33*
HR	75.93 ± 6.37	69.33 ± 6.17*	78.4 ± 6.91	70.6 ± 6.30*
*p value <0.0001 week 8 versus baseline, paired t-test.				

Table 4: Change in MPV and Platelet Count from baseline to week 8

Parameters	Nebivolol (Group I) (n=30) Mean ± SD		Metoprolol (Group II) (n=30) Mean ± SD	
	Baseline	Week 8	Baseline	Week 8
MPV	10.36 ± 3.03	8.75 ± 2.46*	10.57 ± 3.69	9.80 ± 3.49
Platelet Count	236.63 ± 9.73	226.96 ± 9.38*#	236.66 ± 9.67	232 ± 9.57#

*p value <0.0001 (at week 8 compared to Baseline), paired t-test.
p value <0.05 between groups (at week 8 compared to week 8), unpaired t-test.

Table 5: Change in Lipid profile from baseline to week 8

Parameters	Nebivolol (Group I) (n=30) Mean ± SD		Metoprolol (Group II) (n=30) Mean ± SD	
	Baseline	Week 8	Baseline	Week 8
LDL	127.06 ± 10.53	126.26 ± 10.36	128.2 ± 13.33	127.76 ± 13.28
HDL	46.76 ± 6.15	46.20 ± 6.04	47.16 ± 6.06	44.96 ± 5.75*
TG	126.86 ± 13.16	127.63 ± 13.37#	129.2 ± 12.36	135.16 ± 12.69*#
TC	186.53 ± 8.38	187.73 ± 9.16#	184.66 ± 10.16	192.8 ± 10.41*#

*p value <0.0001 (at week 8 compared to Baseline), paired t-test.
p value <0.05 (at week 8 compared to week 8), unpaired t-test.

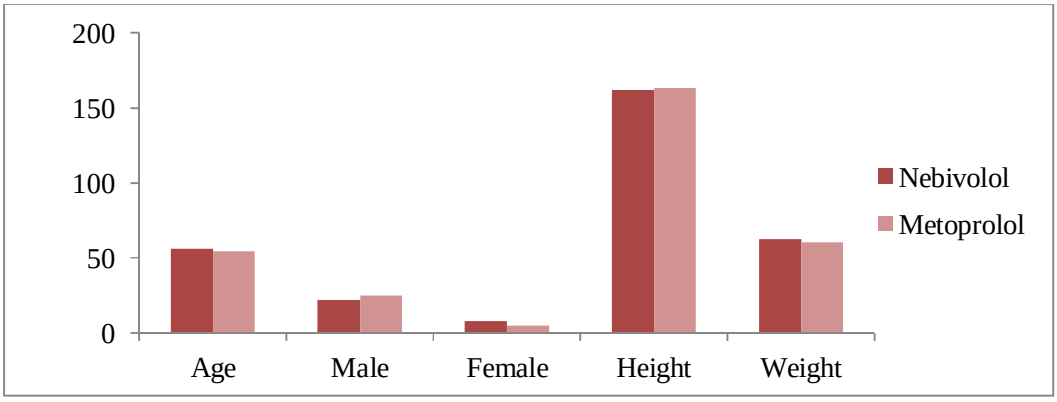

Fig. 1: Demographic Characteristics

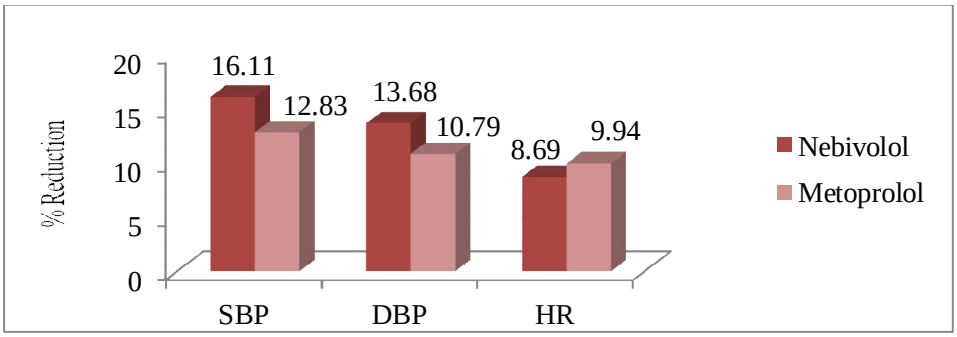

Fig. 2: Percentage reduction in SBP, DBP and Heart Rate from baseline to week-8.

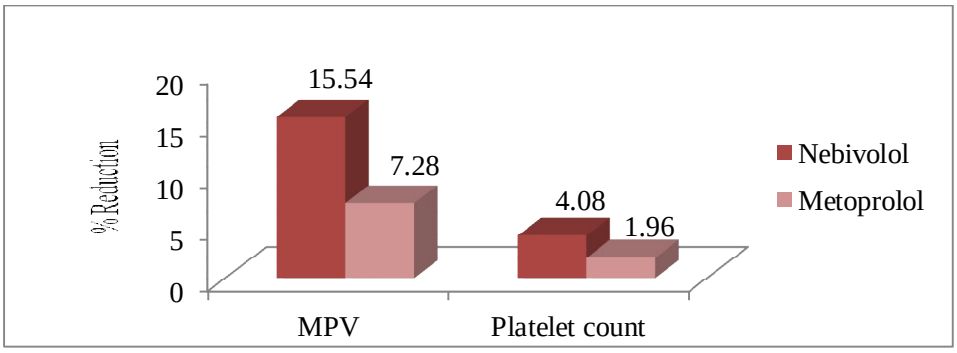

Fig. 3: Percentage reduction in Mean Platelet Volume and Platelet Count from baseline to week-8

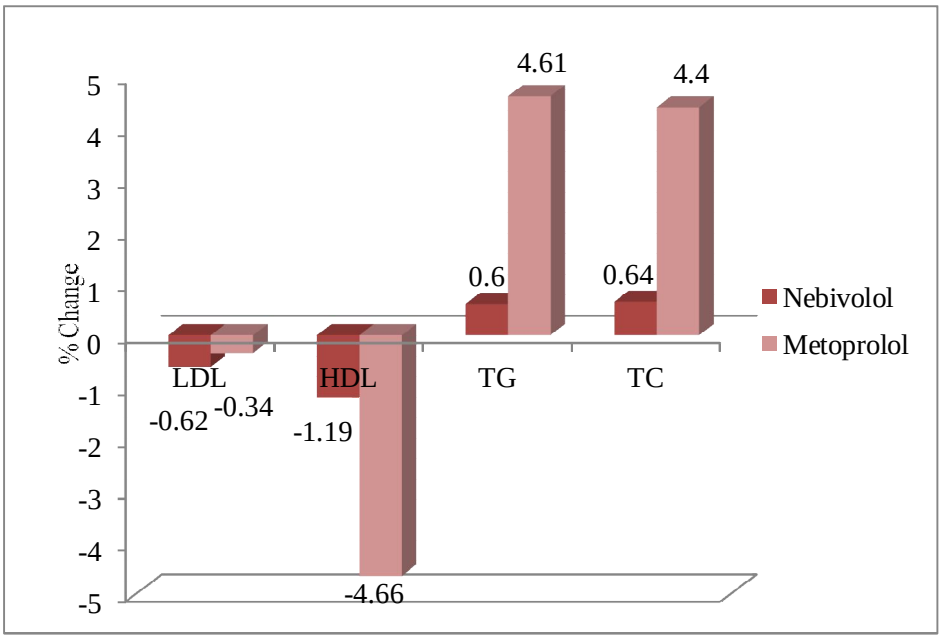

Fig. 4: Percentage change in lipid profile from baseline to week- 8

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