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Original Article

Effect of Nebivolol on Endothelial Dysfunction in Coronary Artery Disease Patients -An Open Label Randomized Controlled Clinical Trial (NEDCAD)

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ABSTRACT

Background: Coronary artery disease (CAD) is one of the leading causes of mortality and morbidity in India. Oxidative stress and endothelial dysfunction play a major role in the pathophysiology of the disease. Nebivolol a third generation beta blocker is claimed to have additional vasodilatory and antioxidant properties. Studies comparing Nebivolol with older beta blockers such as metoprolol in hypertensive patients have demonstrated improvement in endothelial dysfunction. There are only limited studies showing the effect of Nebivolol on endothelial dysfunction in patients with coronary artery disease. Hence this study aimed to compare the effect of Nebivolol and metoprolol on oxidative stress and endothelial function in patients with coronary artery disease and hypertension. **Methods:** A total of 62 patients participated in the study, out of which 32 patients received Nebivolol 5 mg/day and 30 patients received metoprolol 50 mg/day. 5 ml of blood was taken at baseline and after 4 weeks of therapy to estimate concentration of malondialdehyde, total antioxidant status and intercellular adhesion molecule-1. Brachial artery ultrasonography was done to assess the flow mediated dilation before and after study drug therapy. **Results:** The reduction in MDA was detected after 4 weeks of therapy with both Nebivolol (1.4 ± 0.54 vs 1.2 ± 0.55, p=0.03) and metoprolol (1.6 ± 0.32 vs 1 ± 0.60, P = 0.0003). Brachial artery ultrasonography done in 15 patients did not show any significant increase in the lumen diameter or FMD after one month of therapy in both arms of the study. Fatigue was reported less commonly in patients receiving Nebivolol (3 vs 12, p=0.007). **Conclusion:** Nebivolol (5 mg/day) has antioxidant benefit in patients with coronary artery disease and hypertension. The drug is well tolerated. The improvement in endothelial function could not be demonstrated in our study. Larger studies need to be carried

Key words: Endothelial Function, Metoprolol, Nebivolol, Oxidative Stress.

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INTRODUCTION

Coronary artery disease (CAD) is one of the major causes of disease related mortality and morbidity worldwide. In the last decade several trends have emerged showing that Indians are at a greater risk for CAD owing to changing dietary patterns and genetic predispositions.[1] Various factors have been conclusively established to play a contributory role in the etiopathogenesis of CAD such as advancing age, smoking, presence of coexisting diseases namely hypertension, diabetes, hypercholesterolemia and hyperhomocysteinemia. Atherosclerosis, the pathologic hallmark of coronary artery disease is known to be strongly influenced by oxidative stress. In a study done in healthy population, plasma malondialdehyde (MDA), a biomarker of oxidative stress was shown to be associated with intima media thickness, presence of plaques and total atheroma burden. All the above findings were found to be associated with oxidative stress independent of age, sex, ethnicity, smoking, body mass index and visceral adipose tissue (VAT).[2] Oxidized phospholipids are considered as predictors of the presence as well as extent of carotid and femoral atherosclerosis, development of new lesions and increased risk of cardiovascular events.[3] The disruption of pro-oxidant and antioxidant balance has been found to have a major contributory role in the progression of atherosclerosis.[4] Plasma levels of MDA were found to be higher in patients with unstable angina and myocardial infarction compared to patients with stable angina.[5] Hence, the role of oxidative stress in worsening the progression of atherosclerosis is increasingly more evident.

Nebivolol, a third generation beta blocker with vasodilatory potential has been shown to be effective in improving endothelial function in patients with hypertension.[6] However, the evidence for its anti-oxidant potential is relatively sparse. A study in patients with Cardiac Syndrome X found that Nebivolol reduced serum myeloperoxidase activity and MDA to a significant extent compared to metoprolol.[7] Another study done in hypertensive patients by Serg M *et al*, had shown reduction of oxidized LDL and 8-isoprostanes following administration of Nebivolol.[8] However there is sparse data in the literature regarding the benefit of Nebivolol on oxidative stress in CAD patients. Hence, this study aimed to appraise the efficacy of Nebivolol in reducing oxidative stress compared to metoprolol in coronary artery disease patients with hypertension.

METHODS

Eligible patients were recruited from the out-patient department of cardiology, JIPMER, Puducherry. Written informed consent was obtained from all the patients and the study was done in accordance with the prin-

ciples of ethical conduct of research as outlined by Declaration of Helsinki and ICMR ethical guidelines for biomedical research in humans. The study was approved by the Institute Human Ethics Committee, JIPMER and study was registered under the Clinical Trials registry, India (CTRI/2012/01/002384).

Patients of either gender with angiographically proven coronary artery stenosis with >50% block in at least one of the major arteries or with past history of acute coronary syndrome and known cases of hypertension on treatment for at least 6 months were included in the study. Patients with history of acute coronary syndrome in the preceding three months, those already on Nebivolol, uncontrolled hypertension (systolic blood pressure (SBP) > 180mm Hg or Diastolic blood pressure (DBP) > 90mmHg), patients with left ventricular ejection fraction <35%, known history of hypersensitivity to Nebivolol, pregnant and lactating women, contraindication to beta blocker therapy such as asthma, sick sinus syndrome, peripheral vascular disease, variant angina, uncontrolled dyslipidemia, patients unwilling to participate in the study, past history of liver disease, known case of alcohol abuse, or elevated liver enzymes defined as ALT, AST or ALP greater than thrice the upper limit of normal were excluded from the study.

Eligible patients were randomized to receive either Nebivolol 5 mg or metoprolol 50 mg using a computer generated randomization sequence. The allocation concealment was maintained using serially numbered opaque sealed envelopes. At baseline and after 4 weeks of study period, 6 ml blood was collected from the patients to assess plasma ICAM (intercellular adhesion molecule), MDA (Malondialdehyde) and TAS (total antioxidant status). Brachial artery ultrasonography was done to assess the flow mediated dilation before and after study drug therapy. During the study period of 4 weeks, patients were followed up every two weeks to measure blood pressure (BP) and heart rate for dose adjustment or change in drug therapy. Adherence and adverse drug reactions were also monitored during the follow up visits.

All the data were analyzed using Graph Pad Instat version 3.06. The baseline characteristics between the groups were compared using Fisher's exact test for nominal data and student's t test for quantitative data. The change in MDA, total antioxidant status and ICAM-1 after 4 weeks of therapy was compared using paired t test. The change in heart rate and BP after 4 weeks of therapy was analyzed using paired t test. The frequency of adverse drug reactions between the groups was compared using Fisher's exact t test. P value <0.05 was considered as statistically significant.

RESULTS

82 patients with coronary artery disease and hypertension were enrolled in the study based on the eligibility criteria. Of this 20 patients were unwilling to participate in the study. Out of the 62 patients who participated in the study, 32 patients received tab Nebivolol 5 mg and 30 patients received tab metoprolol 50 mg as per the randomization schedule. Baseline demographic and clinical characteristics were found to be similar among both the groups. **(Table 1)**. Patients in both study groups showed significant reduction in MDA after 4 weeks of therapy **(Table 2).** However the reduction in MDA was more pronounced in the metoprolol group (p=0.003) than in the Nebivolol group (p=0.02). There was no significant improvement in the TAS or reduction in the plasma ICAM-1 in either arms of the study (p>0.05).

The reduction in heart rate, systolic and diastolic blood pressure was found to be similar in both groups**.** None of the patients in the study experienced any serious adverse event. The frequency of fatigue was significantly less in Nebivolol group when compared to metoprolol (p=0.007). There was no significant difference in the frequency of other common adverse drug reactions namely dizziness, dyspepsia, nightmares, erec-

Table 1: Baseline characteristics of the patients

Characteristic	Nebivolol (n=32)	Metoprolol (n=30)	P value
Age (years)	57.81 ± 8.69	58.9 ± 9.58	NS
Male sex (%)	90%	96%	
Parameters	**Nebivolol group (5mg/day)**	**Metoprolol group (50 mg/day)**	
Body-mass index (Kg/m2)	24.43 ± 3.91 (23 to 25)	23.31± 2.84 (22 to 24)	NS
Diabetes	19%	15%	NS
Smokers	6%	7%	NS
Past acute coronary syndrome	61%	80%	NS
Systolic blood pressure (mmHg)	135.53 ± 21.81 (127 to 143)	132.43 ± 18.71 (125 to 139)	NS
Diastolic blood pressure (mmHg)	83.66 ± 10.33 (80 to 88)	80.71 ± 8.13 (76 to 84)	NS
Baseline Heart rate(beats/min)	68.69 ± 9.49 (65 to 72)	68.96 ± 6.95 (66 to 72)	NS
Drug therapy (%)			
Aspirin	78 %	73%	NS
Clopidogrel	59 %	43%	NS
Atorvastatin	68 %	70%	NS
Enalapril	81 %	77%	NS
Nitrates	44%	33%	NS
Furosemide	13%	30%	NS
Amlodipine	25 %	17 %	NS
Angiotensin Receptor blockers	3 %	0 %	NS

Data are expressed as mean ± SD or percentage. Values in parenthesis indicates confidence intervals. NS – not significant, SD – standard deviation

Table 2: Effect of Nebivolol and metoprolol on malondialdehyde, total anti-oxidant status and intercellular adhesion molecule-1.

Parameters	Nebivolol group (5mg/day)		Metoprolol group (50 mg/day)	
	Baseline (n=31)	After 4 weeks (n=24)	Baseline (n=29)	After 4 weeks (n=16)
Malondialdehyde (μM/L)	1.4 ± 0.54 (1.21 to 1.62)	1.2 ± 0.55* (0.97 to 1.48)	1.6 ± 0.32 (1.43 to 1.74)	1 ± 0.60* (0.69 to 1.32)
Total Antioxidant status (μM)/L	846.2± 205.73 (766 to 926)	784.4 ±160.53 (716 to 852)	700 ± 251.5 (591 to 808)	742 ± 245.44 (611 to 872)
ICAM – 1(ng/mL)	394.2 ±120.02 (321 to 466)	367.3 ±71.87 (313 to 429)	375.1 ± 62.89 (338 to 411)	373 ± 66.72 (266 to 479)

Data expressed as mean ± SD, Values in parentheses represents 95% confidence interval, SD – standard deviation, * P value < 0.05

Table 3: Adverse drug reactions among patients during the study

	Nebivolol group (n=32)	Metoprolol group (n=30)
Fatigue	3	12*
Headache	1	2
Paresthesia	4	0
Dizziness	2	2
Dyspepsia	4	4
Constipation	1	0
Insomnia	6	7
Nightmares	3	1
Erectile dysfunction	2	2
Dry cough	1	1
Orthostatic hypotension	1	0
Myalgia	0	1
Pruritus	0	1

*P=0.007, Fisher's exact test

tile dysfunction etc between Nebivolol and metoprolol groups **(Table 3).** Brachial artery ultrasonography done in 15 patients did not show any significant increase in the lumen diameter or FMD after one month of therapy in both arms of the study.

DISCUSSION

Our study has shown that four weeks of therapy with Nebivolol 5 mg once daily in patients with coronary artery disease and hypertension causes significant reduction in the MDA. These findings are consistent with data from previous studies that have demonstrated the antioxidant potential of Nebivolol.[7-9] In a study done in 32 patients with slow coronary flow, six months of Nebivolol therapy was found to improve various oxidative stress parameters such as malondialdehyde (MDA) and serum nitric oxide (NO) levels, erythrocyte catalase (CAT) and erythrocyte superoxide dismutase (SOD).[9] Similarly another study done in 30 patients with cardiac syndrome X using metoprolol as control, showed reduction in malondialdehyde, myeloperoxidase and increased superoxide dismutase levels following 12 weeks of Nebivolol therapy.[7] Elevated myeloperoxidase enzymes have been found to deplete endothelium-derived nitric oxides by utilizing them as a substrate for oxidative reactions. Hence increased myeloperoxidase levels is implicated in the reduction of bioavailability and function of nitric oxide resulting in endothelial dysfunction.[10] Although the above mentioned studies were done for longer duration, our study was able to demonstrate the reduction of MDA within 4 weeks of Nebivolol therapy.

There was no significant improvement in the TAS after one month of Nebivolol therapy. There are conflicting data in the literature on the effect of Nebivolol on total anti oxidant status. In hypertensive patients, treatment with Nebivolol for 12 weeks did not improve the total antioxidant status as compared to carvedilol.[11] Although the patients in our group had coronary artery disease and hypertension, these findings are in support of our data. On contrary, Nebivolol given for eight months in patients with heart failure and diabetes, showed a significant improvement in antioxidant protection as assessed by increase in SH group level.[12] The lack of improvement seen in total antioxidant status after one month of Nebivolol therapy in our study could be attributed to the fact that most patients in our study had advanced coronary artery disease as evidenced by the past history of acute coronary syndrome. Besides this, the shorter exposure of Nebivolol in our study as compared to earlier studies could have been a reason for lack of benefit in TAS level. It is hypothesized that longer treatment with Nebivolol for more than 12 weeks may be effective in restoring the anti-oxidant status in patients with hypertension and advanced coronary artery disease.

Our study did not detect any favorable change in the ICAM-1 levels after one month of Nebivolol therapy. Preclinical studies have shown strong evidence of Nebivolol's potential in reducing biomarkers of endothelial dysfunction. Incubation of human umbilical vein endothelial cells (HUVEC) that are exposed to oxidative stress with Nebivolol resulted in reduced ICAM, P- selectin mRNA expression.[13] A reduction in VCAM-1 (vascular cell adhesion molecule 1), ICAM-1, PDGF-B (Platelet-derived growth factor subunit B), E-selectin and P-selectin mRNA expression

was observed in human coronary artery endothelial cells and smooth muscle cells that were incubated with Nebivolol for 72 hours, but similar finding was absent in those cells exposed to metoprolol.[14] However, there are conflicting clinical reports in the literature on the effect of Nebivolol on biomarkers of endothelial dysfunction. Long term use of Nebivolol in hypertensive patients for one year was shown to reduce ICAM-1.[8] This is the only other clinical study reported in the literature on the effect of Nebivolol on ICAM-1. The lack of benefit in our study could possibly be attributed to the short exposure of patients to Nebivolol as compared to earlier studies.

There was no difference in the blood pressure or heart rate and this could be due to the fact that many of the patients in both arms of the study had well controlled blood pressure at baseline and were already receiving beta blocker at therapeutic dosage prior to the study. The frequency of fatigue was lesser among patients on Nebivolol as compared to those on metoprolol. This is in accordance with the data from earlier clinical trials on the improved quality of life and tolerance of patients to Nebivolol as compared to atenolol and metoprolol.[15,16] There were no differences in the angina episodes between the two groups.

The results of the study show that one month of therapy with Nebivolol in coronary artery disease patients with hypertension causes significant reduction in MDA. Randomized controlled trials in a larger population should be done to evaluate if these additional antioxidant benefits of Nebivolol could translate into improved long term outcomes such as reduction in mortality and morbidity in coronary artery disease patients.

Limitations of the study

The major limitation of the study was exposure to treatment drug for a short period of 4 weeks. The beneficial effects of Nebivolol would have been better demonstrated if the drug was given for at least 12 weeks. Similarly stress perfusion imaging to assess microcirculation of heart was not performed. Brachial artery ultrasonography was done only in 15 patients for measuring flow mediated dilatation (FMD) due to lack of man power. Although patients were adequately counselled to take the study drug, we did not perform any objective assessment for adherence to study drug.

CONCLUSION

Nebivolol at a dose of 5 mg/day given in coronary artery disease patients with hypertension is effective in reducing MDA, one of the parameters of oxidative stress. The drug is well tolerated and has a lesser incidence of fatigue as compared to metoprolol. The improvement in endothelial function could not be demonstrated in our study. Thus Nebivolol with its antioxidant effect and better tolerability may be of special benefit in patients with coronary artery disease and hypertension.

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Nil

CONFLICT OF INTEREST

Nil

ABBREVIATION USED

CAD: coronary artery disease; MDA: malondialdehyde; TAS: total antioxidant status; VAT: visceral adipose tissue; SBP: systolic blood pressure; DBP: diastolic blood pressure LDL: low density lipoprotein; NO: nitric oxide; CAT: catalase; SOD: superoxide dismutase; HUVEC: human umblical vein endothelial cells; ICAM: Intercellular adhesion molecule; VCAM-1: vascular cell adhesion molecule-1; PDGF-B: Platelet derived growth factor subunit B; FMD: Flow mediated dilatation.

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