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Research Article

Advantage of Nebivolol Use Over Metoprolol in Patients with Acute Myocardial Infarction Complicated by Left Ventricular Dysfunction

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Abstract

Objectives: The aim of the study was to do a comparative analysis of the composite outcomes of Nebivolol and Metoprolol therapy in patients with acute myocardial infarction (AMI) complicated by reduced left ventricular ejection fraction (LVEF).

Subjects and Methods: Patients (n = 192, aged 20 - 65 years) having AMI with LVEF ≤ 45% were randomized to Nebivolol (n = 96) and Metoprolol (n = 96) subgroups.

Baseline demographic and clinical characteristics and composite event rates of non-fatal MI, cardiovascular mortality, hospitalization due to unstable angina pectoris or heart failure during the 01-year follow-up were compared among the groups using the $\chi 2$ test.

Results: A total of 17.7% (n = 17/96) patients were hospitalized in group A and 30.2% (n = 29/96) in group B (P = 0.042). Mortality was reported in 11.5% (n = 11/96) patients in group A and 22.9% (n = 22/96) in group B (P = 0.035).

Conclusion: Rate of hospitalization and mortality during one-year follow up was significantly lesser in patients treated with Nebivolol as compared to those treated with maximum tolerable doses of Metoprolol.

Keywords: *Nebivolol; Metoprolol; Acute Myocardial Infarction (AMI); Left Ventricular Ejection Fraction (LVEF); Beta Blockers (BB)*

Introduction

Oral beta blockers (BB) are administered universally to all patients experiencing AMI, without contraindications. Established effects include reduced infarct size, decreased further ischemic events and mortality after AMI, with greater beneficial effects in those who develop LV dysfunction and/or heart failure [1,2]. These effects are mediated through decreased oxygen demand owing to reduction in heart rate and blood pressure and reduced contractility - all producing a relief in ischemic chest pain as well [3]. Various beta blockers have been reported to be effective in this regard metoprolol, carvedilol, bisoprolol and nebivolol. Metoprolol, bisoprolol and nebivolol are β1 -selective BBs. However, carvedilol has β1 and β2 receptor and α1 receptor blocker and M2 receptor up regulation properties. Nebivolol has nitric oxide-releasing and vasodilatory properties and inhibits endothelial proliferation [4-6].

It has been shown that metoprolol and atenolol are frequently prescribed BBs in patients with MI, though other beta blockers (Carvedilol, Bisoprolol and Nebivolol) have also been used. There is still no consensus as to what should be the BB of choice in patients presenting with AMI with reduced LV-ejection fraction [7,8]. A recent study conducted by Ozaydin., *et al*. evaluated the efficacy of Nebivolol and Metoprolol succinate on the outcome of patients presenting with AMI complicated by left ventricular dysfunction. A lower composite end point of

nonfatal MI, cardiovascular mortality, hospitalization due to unstable angina pectoris or heart failure, stroke or revascularization during the 12-month follow-up with Nebivolol (n = 8, 14.5%) than the metoprolol succinate group (n = 17, 31.5%; p = 0.03) [9]. There is still no agreement on the beta blocker of choice, in patients presenting with AMI complicated by reduced left ventricular ejection fraction [4,7,8]. Present study was designed to evaluate two different beta blockers (Nebivolol and Metoprolol) in our local population.

Subjects and Methods

This was a single-center, randomized and end point-blinded study based on consecutive non-probability sampling technique. Patients with a diagnosis of AMI based on clinical, electrocardiographic and cardiac biomarker criteria and an echocardiographic LV ejection fraction ≤ 0.45 were included. A total of 192 patients (121 males and 71 females, with age range (20 - 65 yrs.) were enrolled. The exclusion criteria being bradycardia (< 60 bpm), systolic blood pressure of < 90 mm Hg, second- or third-degree atrioventricular block, symptomatic peripheral arterial disease, documented prior MI, documented previous Bundle Branch Blocks, α-blocker use, severe chronic obstructive pulmonary disease and severe asthma.

Of the 192 eligible patients, 96 were enrolled in the Nebivolol Group (69 males, 27 females) and 96 patients were included in the Metoprolol Group (54 males and 42 females) randomly. The Nebivolol group received a dose of nebivolol 1.25 mg once daily and the Metoprolol Group received metoprolol in a dose of 25 mg once daily. The treatment continued for one year and the respective doses was titrated up to a tolerable dose by monitoring blood pressure and heart rate daily during the hospital stay. Nebivolol was increased to 2.5, 5 and 10 mg once daily and Metoprolol was increased gradually to 50, 100 and 200 mg once daily. Rest of the care and treatment was same in both groups as per standard guidelines. All the patients were followed up for one year and primary outcome was measured in terms of rates of hospitalization due to unstable angina/non-fatal MI and cardiovascular related mortality during follow up period.

Patient data was analyzed in terms of age, gender, baseline comorbidities and composite outcomes (hospitalization rate due to unstable angina/non-fatal MI and mortality). Chi-square test was applied to assess the significance of difference in both groups. P-value of ≤ 0.05 was considered significant. Effect modifiers like age, gender and baseline comorbidities were controlled by stratification and post stratified chi-square test was applied and P-value of ≤ 0.05 was considered significant.

Results

Age distribution and age groups have been highlighted in table 1 and figure 1 respectively. Comorbidities in both groups are recorded in figure 2.

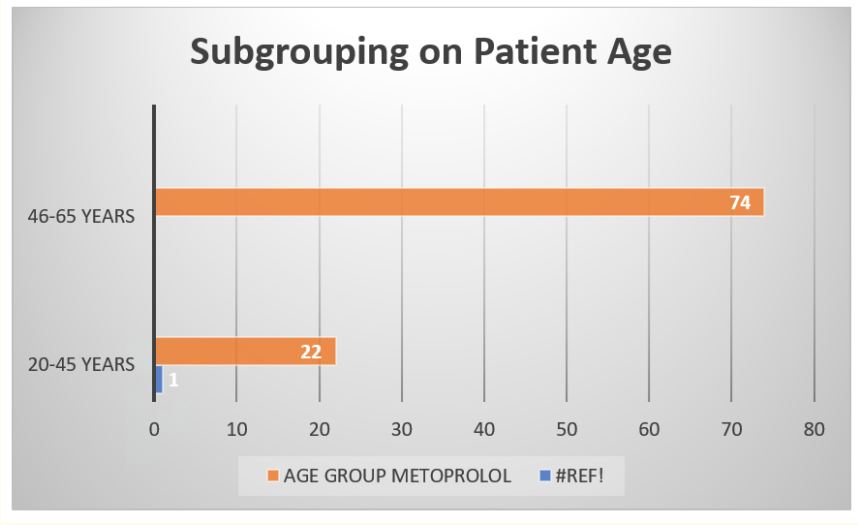

Figure 1: *Subgroups in the 2 groups depending upon patient's age.*

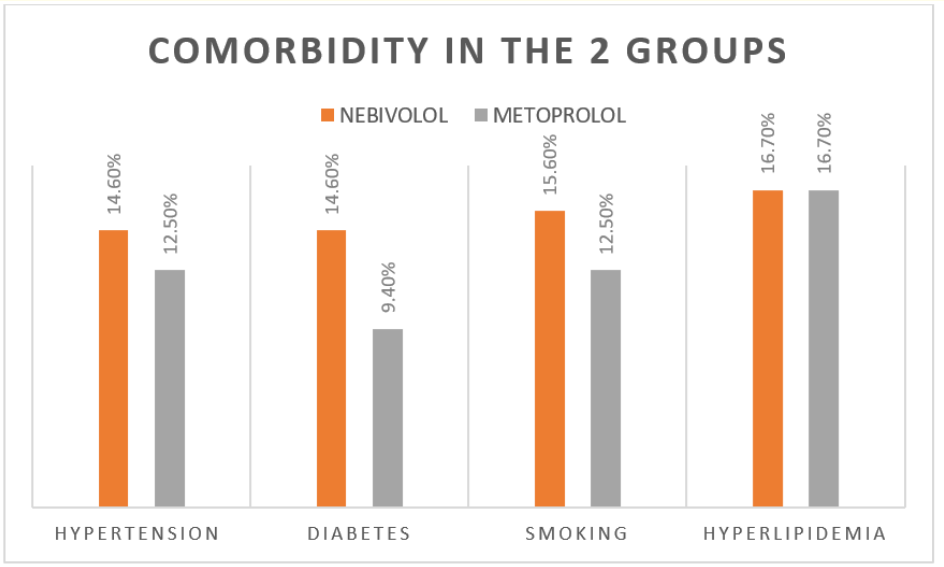

Figure 2: *Baseline co-morbidities in both groups.*

Group	Gender	Mean age	Std. Deviation
Nebivolol	Males	50.3	9.6
	Females	46.5	9.8
	Total	49.2	9.7
Metoprolol	Males	50.9	7.4
	Females	48.8	7.3
	Total	49.9	7.4

Table 1: *Age distribution in both groups.*

Outcomes in both groups

During the follow up period, a total of 17.7% (n = 17/96) patients were hospitalized in group A and 30.2% (n = 29/96) in group B (P = 0.042). Results are shown in table 1. During the follow up period, mortality was reported in 11.5% (n = 11/96) patients in group A and 22.9% (n = 22/96) in group B (P = 0.035). Rate of hospitalization and mortality was significantly lesser in Group A patients (P < 0.05), highlighted in figure 3.

Stratification for effect modifiers

Analysis of outcomes specific outcomes and mortality stratified for rate of hospitalization, age, gender and baseline comorbidities and revealed a lesser incidence of these factors in the Group A i.e. the group on nebivolol treatment as compared to Group B (on metoprolol treatment).

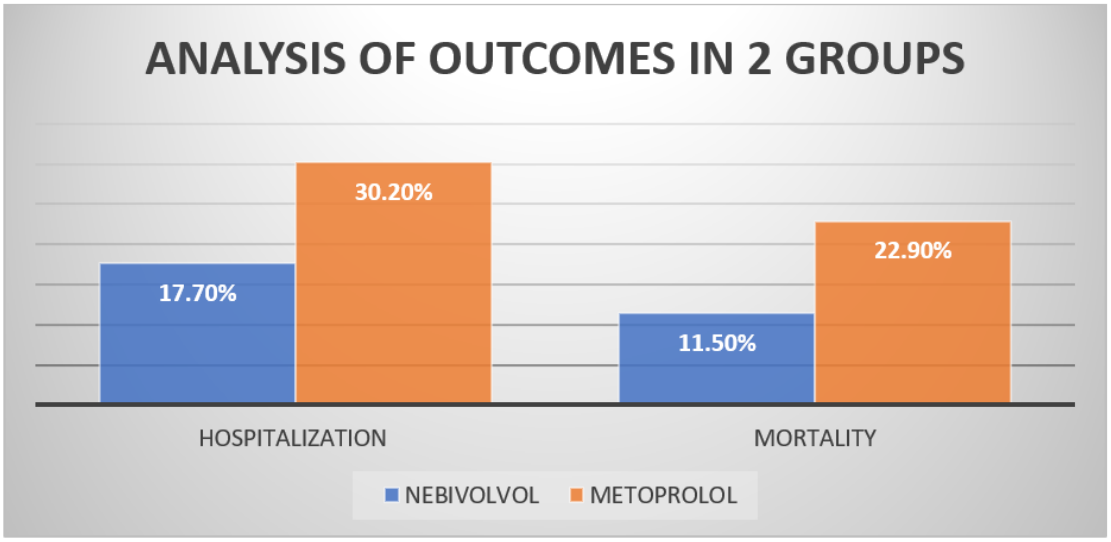

Figure 3: *Comparative percent analysis of specific outcomes and mortality in the 2 groups.*

Discussion

B-blocker (BB) has constituted one of the mainstays of evidence-based therapy for patients with AMI. The optimal duration of β-blocker therapy in patients with AMI is unknown. The beneficial effect of β-blocker therapy after AMI may be limited until 1 year after AMI. This study was designed to evaluate Nebivolol and Metoprolol in patients with AMI and reduced left ventricular ejection fraction; in terms of hospitalization rate due to unstable angina/non-fatal MI and frequency of mortality during 12-month follow up. Our results showed that a total of 17.7% (n = 17/96) patients were hospitalized in Nebivolol group and 30.2% (n = 29/96) in Metoprolol group (P = 0.042). Mortality was reported in 11.5% (n = 11/96) patients in Nebivolol group and 22.9% (n = 22/96) in Metoprolol group (P = 0.035).

Nebivolol plays an important role in patients with reduced endothelial dysfunction, especially for those who have AMI, as it has nitric oxide-induced vasodilatory properties and may offer anti-atherosclerotic activity by its inhibitory effects on oxidative stress and vascular smooth muscle proliferation [10]. By its vasodilatory effects, nebivolol decreases peripheral vascular resistance and increases stroke volume, which is very beneficial in heart failure [11]. Our results are similar with the already published date on this subject. In a similar study, Ozaydin M., *et al.* aimed to evaluate the efficacy of nebivolol, carvedilol or metoprolol succinate on the outcome of patients presenting with AMI complicated by left ventricular dysfunction. They randomized patients (n = 172, aged 28 - 87 years) with AMI and left ventricular ejection fraction ≤ 0.45 were to the nebivolol (n = 55), carvedilol (n = 60) and metoprolol succinate (n = 57) groups. Baseline demographic and clinical characteristics and composite event rates of nonfatal MI, cardiovascular mortality, hospitalization due to unstable angina pectoris or heart failure, stroke or revascularization during the 12-month follow-up were compared among the group. Their results showed that baseline demographic and clinical characteristics were similar in the three groups. The composite end point during follow-up was lower in the patients treated with nebivolol than those treated with metoprolol (14.5 vs. 31.5%; p = 0.03). However, event rates were similar between the patients treated with carvedilol and those treated with the metoprolol (20.3 vs. 31.5%, p > 0.05) and between the patients treated with nebivolol and carvedilol (14.5 vs. 20.3%, p > 0.05). Authors concluded that patients treated with nebivolol experienced 12-month cardiovascular events at a lower rate than those treated with metoprolol succinate. However, event rates were similar between the carvedilol and the metoprolol succinate groups and between the nebivolol and the carvedilol groups [9].

In a recent systematic review and meta-analysis on randomized, controlled, direct-comparison trials that included adults receiving atenolol, bisoprolol, metoprolol, nebivolol, or carvedilol to evaluate their effects of carvedilol compared to other BBs on mortality, cardiovascular events, and hospital readmissions in the setting of AMI or systolic heart failure (HF). Authors reported that nebivolol was better than metoprolol in reducing all-cause mortality in systolic HF patients, Overall carvedilol was superior when compared against atenolol, bisoprolol, metoprolol and nebivolol [12].

Seo GW., *et al.* determined the comparative effectiveness of nonselective BB carvedilol and the most frequently prescribed β1-selective BBs (bisoprolol, metoprolol, and nebivolol) in patients with AMI undergoing PCI. They enrolled a total of 7,863 patients were selected from the prospective national AMI registry, and patients were divided into carvedilol group (n = 6,231) and β1-selective BB group (n = 1,632) at hospital discharge. The primary end point was all-cause death or MI during follow-up. During a mean follow-up of 243 ± 144 days, all-cause death or MI they found nebivolol was more effective than metoprolol, however, the difference was not statistically significant. They also reported no significant differences in the risk of all-cause death or MI were observed between the carvedilol and β1-selective BB groups in contemporary practice of the treatment for AMI [13].

The fact is strongly highlighted in these studies that metoprolol and not nebivolol decreased cardiac output, increased systemic vascular resistance and pulmonary capillary wedge pressure in patients with systolic dysfunction [14]. Similarly, nebivolol but not metoprolol inhibited cardiac Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation and improved LV dysfunction and nebivolol had a significantly more pronounced inhibitory effect than metoprolol on cardiomyocyte hypertrophy after MI [15]. Nebivolol was also found to be superior to atenolol in improving diastolic functions and the maximal exercise duration of patients with ischemic LV dysfunction [16]. However, in patients with non-ischemic heart failure, both nebivolol and carvedilol improved LV diastolic functions and also performed similarly on follow-up [17].

Another recent study showed that lung diffusion and exercise performance were higher with nebivolol than carvedilol, but carvedilol allowed better ventilation efficiency than nebivolol during exercise [18].

In synchrony with limited available clinical trials comparing efficacy of nebivolol with other beta blockers in post MI patients with systolic dysfunction, the data analysis in our study yielded useful clinical inference of advantages of using nebivolol over metoprolol.

We recommend further randomized controlled trials with larger sample size and with longer duration of follow up before adopting nebivolol in routine clinical practice.

Conclusion

Rate of hospitalization and mortality during twelve-month follow up was significantly lesser in AMI patients with reduced LVEF treated with Nebivolol as compared to those treated with maximum tolerable doses of Metoprolol.

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