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Original Research Article

A Comparative Study of Efficacy and Safety of Nebivolol and Metoprolol in Post Myocardial Infarction Patient

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Abstract

The aim of the present study was to study the efficacy and safety of Nebivolol and Metoprolol in post-myocardial infarction patient and to compare the efficacy and safety of Nebivolol and Metoprolol in post-myocardial infarction patients. This randomized, open-label and comparative study was done in the Department of General Medicine, Kakatiya Medical College, and MGM Hospital Warangal. A total of n=110 patients were selected based on inclusion and exclusion criteria. Patients were randomized to two groups N-groups of n=55, M-group to receive once-daily Nebivolol 5 mg and Metoprolol 50mg twice-daily respectively for 2 months. Clinical laboratory parameters were measured at day (0), and at day 56. Results The standing baseline mean systolic blood pressure 166±9 mmHg was reduced to 139±10 mmHg after 2 months treatment with Nebivolol, whereas in case of Metoprolol standing baseline systolic blood pressure 161±11 mmHg reduced to 143±14 mmHg after 2 months treatment. In case of standing, baseline mean diastolic blood pressure 103±7 mm Hg reduced to 84±4 mmHg after 2 months of treatment with Nebivolol, whereas with Metoprolol standing baseline diastolic blood pressure 100±6 mmHg reduced to 87±7 mmHg after 2 months treatment. Heart rate in case of N-group baseline 87±9 beats/min reduced to 74±6 beats/min after 2 months treatment, whereas in M-group baseline heart rate 82±7 beats/min reduced to 76±5 beats/min after 2 months treatment. Conclusion: it can be concluded that Nebivolol is superior to Metoprolol in control of blood pressure in post-myocardial infarction patients with hypertension. The distinct advantages of Nebivolol include lower incidences of adverse effects and since the dose is single there is better compliance as compared to Metoprolol

Keywords: Nebivolol, Metoprolol, Post Myocardial Infarction.

INTRODUCTION

Myocardial infarction is the leading cause of mortality and morbidity across the world [1]. In India, it is estimated that approximately 31.7% of deaths occur due to myocardial infarction. Incidence of cardiovascular diseases was approximately about 7% in the 1970s and has increased up to 32% in the year 2011 in India [2]. Many studies have found that in India there is an increasing tendency of the prevalence of coronary artery disease (CAD) in urban India [3-10]. It has been estimated that India had the highest number of deaths in the world due to coronary artery disease in 2002 which is double from 1985 to 2015 [11-13]. Around the world, the USA is leading with 31% mortality ratio many other countries are also presenting with a similar ratio of mortality rate compared to their total population. Patients who survive MI are treated with surgical procedures that include percutaneous Transluminal coronary intervention or angioplasty (PTCI), coronary angiobypass graft (CABG) after thrombolysis. Prognosis in post-myocardial infarction varies greatly, depending on the patient's risk factors, tolerance, the extent of ischemia and the treatment available to the patient. Form the period of 2005-2008 in the United States, the median mortality at 30 days was 16.6% with a range from 10.9% to 24.9% depending on the hospital [14]. Using variables in the emergency room, people with a higher risk of the adverse outcome can be identified. One study found that 0.4% of patients with a low-risk profile died after 90 days, whereas in high-risk people it was 21.1 days [15]. Assessment of left ventricular ejection fraction may increase the predictive power of higher risk [16]. Prognosis is significantly worsened if a mechanical complication such as papillary muscle or myocardial wall ruptures [17]. Morbidity and mortality from MI have improved over the years, by the administration of cardio-selective beta$_1$blockers which prolong the expectancy of a patient. Carvedilol is a non-selective β blocker with the additional property of vasodilatation

like α_1 receptor antagonism, blockade of calcium entry; antioxidant activity is the recent advancement in the prescription for AMI patients. Metoprolol the gold-standard, second generation, cardio-selective beta$_1$blocker, anti-hypertensive agent and also prescribed in heart failure for many years in MI patients. In this study we intended to be compared with Nebivolol third generation, a novel cardio-selective beta$_1$ blocker with additional Nitric Oxide (NO) vasodilation property with Metoprolol in post-MI patients in our tertiary care Hospital.

MATERIAL AND METHODS

It is a randomized, open-label and comparative study was done in the Department of General Medicine, Kakatiya Medical College, and MGM Hospital Warangal. The institutional ethical committee approved the protocol, and all patients provided written informed consent before undergoing any study-related procedure. This clinical study is conducted in patients with post-myocardial infarction of duration one month since the acute attack, presenting with hypertension in the Department of Medicine only those cases with post-myocardial infarction treated with thrombolysis, surgical intervention (PCI/CABG), presenting with hypertension were evaluated. Inclusion criteria were; age above 30yrs and within 80 yrs, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg. Exclusion criteria were; cases of secondary hypertension, other comorbidities, renal, hepatic failure, and Known hypersensitivity to Nebivolol or Metoprolol not willing to participate. At the screening visit, patients were examined and medical history was obtained to determine the patient's eligibility for enrollment in the study. The routine investigations like complete blood picture, liver function tests, renal functions tests, lipid profile tests, thyroid profile tests, E.C.G, and the patient's condition is evolved. At the screening period (day 0), baseline and demographic characteristics were recorded and eligible patients were randomized to two groups N-group, M-group to receive once-daily Nebivolol 5 mg and Metoprolol 50mg twice-daily respectively for 2 months. A total of n=110 patients divided into an equal group of n=55 were allotted randomly to each group. Clinical laboratory parameters were measured at day (0), and at day 56. Patients returned to the study unit for assessments on days 14, 28, 42, and 56 of the treatment period, at which time BP and HR were measured, compliance with study medication was monitored. Heart rate, P-R interval, QTc interval from the E.C.G, lipid profile values are recorded after 2 months duration of the study.

RESULTS

A total of n=110 patients were randomized to receive Metoprolol 50mg twice daily or Nebivolol 5 mg once daily for up to 56 days. At the end of the study, eight randomized patients dropped out from the study 4 each from N-group and M-group. n=52; Nebivolol 5 mg, n=52; Metoprolol 50 mg. The standing baseline mean systolic blood pressure 166±9 mmHg was reduced to 139±10 mmHg after 2 months treatment with Nebivolol, whereas in case of Metoprolol standing baseline systolic blood pressure 161±11 mmHg reduced to 143±14 mmHg after 2 months treatment with significance value P ≤0.001. In case of standing, baseline mean diastolic blood pressure 103±7 mm Hg reduced to 84±4 mmHg after 2 months of treatment with Nebivolol, whereas with Metoprolol standing baseline diastolic blood pressure 100±6 mmHg reduced to 87±7 mmHg after 2 months treatment, P ≤0.001.

Table-1: changes in standing position blood pressure

parameters	**Nebivolol 5mg OD**		**Metoprolol 50mg BD**				
Standing Position	**Mean mmHg**	**± SD**	**Mean mmHg**	**± SD**	**SEM**	**T value**	**P value**
Baseline S.B.P	167	9	161	11	1.990	2.705	0.009
Baseline D.B.P	103	7	100	6	1.259	2.872	0.005
After 2 months S.B.P	139	10	143	14	2.34	3.484	0.001
After 2 months D.B.P	84	4	87	7	0.955	2.961	0.004

The primary endpoint was the change in baseline Standing (St) SBP, Supine (Su) SBP, Standing (St) DBP Supine (Su) DBP to study end. Nebivolol significantly reduced baseline St.SBP (up to 30 ±7 mm Hg), St.DBP (up to 19±5 mm Hg), Su.SBP(up to 31 ±6mm Hg), Su.DBP(up to 18 ±5mm Hg), heart rate up to 14 ±8 beats/min compared with St.SBP (up to 18 ±16mm Hg), St.DBP (up to 12 ±4 mm Hg), Su.SBP(up to 18 ±15 mm Hg), Su.DBP(up to 11 ±4 mm Hg), heart rate up to 5 ±3 beats/min with Metoprolol; (P≤0.001). The overall adverse event experience was similar in the Nebivolol and Metoprolol groups.

Supine baseline systolic blood pressure in N-group 161±8 mmHg reduced to 130±7 mmHg after 2 months treatment, whereas in M-group supine baseline

systolic blood pressure 156±12 mmHg reduced to 138±12 mmHg with significance value P ≤0.001. In case of supine baseline diastolic blood pressure, 100±8 mmHg reduced to 81±4 mmHg in N-group after 2 months treatment, while in M-group supine baseline diastolic blood pressure 95±6 mmHg reduced to 84±6 mmHg after 2 months treatment with significance value P ≤0.001. Heart rate in case of N-group baseline 87±9 beats/min reduced to 74±6 beats/min after 2 months treatment, whereas in M-group baseline heart rate 82±7 beats/min reduced to 76±5 beats/min after 2 months treatment. The significance value P≤ 0.001. These results indicate the reduction of cardiac overload by peripheral vasodilatation.

Table-2: changes in supine position blood pressure

Parameters	NEBIVOLOL 5mg OD		METOPROLOL 50mg BD				
Supine Position	Mean mmHg	± SD	Mean mmHg	± SD	SEM	T value	P value
Baseline S.B.P	161	8	156	12	2.016	2.542	0.013
Baseline D.B.P	100	8	95	6	1.342	3.252	0.002
After 2 months S.B.P	130	7	138	12	2.043	3.726	0.0005
After 2 months D.B.P	81	4	84	6	0.955	2.764	0.007

Heart rate in case of N-group baseline 87±9 beats/min reduced to 74±6 beats/min after 2 months treatment, whereas in M-group baseline heart rate 82±7 beats/min reduced to 76±5 beats/min after 2 months treatment. The significance value P≤ 0.001. These results indicate the reduction of cardiac overload by peripheral vasodilatation. The mean baseline P-R interval 0.13±0.01mm increased to 0.14±0.02 mm in N-group after 2 months treatment, whereas in M-group mean baseline P-R interval 0.13±0.13 mm remained unchanged after 2 months treatment. The mean baseline Q-Tc interval 0.37±0.03 mm increased to 0.36±0.04 mm in N-group after 2 months treatment, whereas in M-group mean baseline Q-Tc interval 0.37±0.03 mm remained unchanged after 2 months treatment.

Table-3: changes in heart rate

Parameters	NEBIVOLOL 5mg OD		METOPROLOL 50mg BD				
	Mean Beats/ min.	± SD	Mean Beats/ min.	± SD	SEM	T value	P value
Baseline Heart Rate	87	9	82	7	1.53	3.630	1.7
After 2 months Heart Rate	74	6	76	5	0.01	2.498	1.1

Table-4: changes in E.C.G. parameters

Parameters	NEBIVOLOL 5mg OD		METOPROLOL 50mg BD				
	Mean	± SD	Mean	± SD	SEM	T value	P value
Baseline P- R interval (sec)	0.132	0.017	0.131	0.017	0.79	6.26	0.003
After 2 months P-R interval (sec)	0.14	0.020	0.136	0.02	0.419	0.813	0.004
Baseline QTc interval (sec)	0.37	0.03	0.37	0.03	0.007	0.45	0.65
After 2 months QTc interval (sec)	0.36	0.04	0.36	0.04	0.007	0.33	0.74

In case of mean baseline triglyceride 164±14 mg% increased to 166±15 mg% after 2 months of treatment in N-group while meaning baseline triglyceride 168±9 mg% increased to 168± 8 mg%. Baseline means cholesterol levels 178± 14 mg% increased to 179±11 mg% in N-group after 2 months of treatment, whereas in M-group baseline mean cholesterol 179±12 mg% increased to182±9 mg% after 2 months of treatment. Baseline mean HDL levels in N-group 41±3mg% increased to 46±3mg% after 2 months of treatment, while in M-group baseline mean HDL level 45±4mg% increased to 47±4mg% after 2 months

of treatment. The baseline mean LDL level 113±17 mg% reduced to 102±14mg% after 2 months treatment in N-group, whereas in M-group baseline mean LDL level 114±15mg% increased to 118±8mg% after 2 months of treatment. The baseline mean VLDL level 36±9mg% reduced to 29±5 mg% after 2 months of treatment in N-group, whereas the baseline mean VLDL level 21±6mg% increased to 32±4mg% after 2 months of treatment in M-group.

Table-6: changes in lipid profile before and after treatment

Parameters	NEBIVOLOL 5mg OD		METOPROLOL 50mg BD				
	Mean mg%	± SD	Mean mg%	± SD	SEM	T value	P value
Baseline Cholesterol	178	14	179	12	2.71	0.43	0.66
After 2 Months Cholesterol	179	11	182	9	1.92	1.54	0.12
Baseline Triglycerides	164	14	168	9	2.48	1.60	0.11
After 2 Months TGL	166	15	168	8	2.58	0.83	0.40
Baseline HDL	41	3	45	4	0.74	4.29	0.0001
After 2 Months HDL	46	3	47	4	0.8	1.23	0.22
Baseline LDL	113	17	114	15	3.15	0.21	0.82
After 2 Months LDL	102	14	118	8	2.32	6.91	0.0001
Baseline VLDL	36	9	21	6	1.45	9.84	0.0001
After 2 Months VLDL	29	5	32	4	0.91	6.05	0.0001

DISCUSSION

Pharmacological treatment of hypertension with cardioselective beta$_1$ blockers, inpatient with a one-month history of post-MI underwent PCI /CABG is traditionally the most rational approach. Many studies have shown that subjects treated with cardioselective beta$_1$ blockers reduced the frequency of reinfarction and heart failure [18]. The optimal treatment in post-MI in recent trends is cardioselective beta$_1$blockers. Among that carvedilol, Metoprolol is the most commonly prescribed nowadays [19]. Recent advances are in limelight in case of Nebivolol with its unique NO vasodilation property [20]. The results in the present study suggested that Nebivolol was an effective and well tolerated antihypertensive agent and recent trends show that it helps patients from the postponement of heart failure [21]. In the present study, we found Nebivolol 5mg has greater significance value when compared with Metoprolol 50mg as an antihypertensive agent. The difference in antihypertensive effect between Nebivolol and Metoprolol was statistically very significant for systolic blood pressure, diastolic blood pressure and heart rate with $p \leq 0.001$. The difference between the two drugs in case of P-R interval, QTc interval in E.C.G, and Lipid profile was not statistically significant. Christine Espinola-Klein *et al*; [21]carried out a study to evaluate the effects and tolerability of Nebivolol in comparison with Metoprolol in patients with hypertension they concluded that conclusion, β-blocker therapy was well-tolerated in patients with arterial hypertension during a treatment period of 1 year. However, in the direct comparison, there was no significant difference between Nebivolol and Metoprolol. In this study, we found both drugs produce a similar reduction in heart rate. The difference between these two drugs was statistically significant $p \leq 0.001$. This was similar to the study of Faruqui AA [22] In this study, it seems that Nebivolol possesses similar efficacy and safety as Metoprolol. This was collaborative with the study of EVOLVE [22]. Nebivolol has more advantage than the other selective and non-selective beta blocker drugs. Because of its high b_1 selectivity, it was suitable for use in antihypertensive patients with associated myocardial infarction. There are no serious adverse effects seen in the case of Nebivolol. The commonest reported adverse effects are dizziness, nausea, constipation, headache, tiredness and pedal edema. Cardioselective β_1 blocker Nebivolol with distinctive characteristics has shown safety and efficacy. Nebivolol improves LV dysfunction and survival early after MI likely beyond the effects provided by the conventional β_1 -receptor blockade. Nebivolol induced effects on NO-mediated endothelial function, early endothelial progenitor cells and inhibition of myocardial NADPH oxidase likely contribute to these beneficial effects of Nebivolol early after MI [23].

CONCLUSION

Within the limitations of the present study, it can be concluded that Nebivolol is superior to metoprolol in control of blood pressure in post-myocardial infarction patients with hypertension. The distinct advantages of Nebivolol include lower incidences of adverse effects and since the dose is single there is better compliance as compared to metoprolol.

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