ORIGINAL ARTICLE

Comparison of Nebivolol with Metoprolol in controlling heart rate and improving left ventricular ejection fraction in patients with congestive cardiac failure

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ABSTRACT

Objective: To compare nebivolol versus metoprolol therapy in controlling heart rate and improvement in left ventricular ejection fraction in patients with congestive cardiac failure.

Study Design: Randomized controlled trial.

Place and Duration of Study: Out-patient department of Cardiology, Pakistan Institute of Medical Sciences (PIMS), Islamabad from 1st March 2016 to 28th February 2017.

Materials and Methods: A total of 262 cases were included. A detailed clinical examination, electrocardiography and echocardiography were done by blinded operators. Randomization of patients into group A and group B via random number table was done. Group A received nebivolol and group B received metoprolol tartrate for six months. Patients of all age groups, of either gender or all socioeconomic strata, with the clinical diagnosis of cardiac failure were included in this study. Decompensation of heart failure requiring hospitalization and bradycardia or atrioventricular blocks developing during the study was taken as a criterion for drop out. History of diabetes, hypertension, and smoking was recorded. Left ventricular ejection fraction and heart rate were documented and compared amongst the two groups. Chi square test was applied for comparison between qualitative variables while the independent samples *t*-test was used to compare quantitative variables between groups. Analysis of data was done using SPSS version 21. A *p*-value of ≤ 0.05 was considered significant.

Results: Our study population was 262 patients with a mean age of 49.25 ± 31.74 years, range between 18 and 80 years. Patients in group A, on nebivolol demonstrated a significant improvement in left ventricular ejection fraction (p=0.00031) and heart rate (p=0.00163) when compared to patients in group B, on metoprolol.

Conclusion: Nebivolol was found to more effective in improving left ventricular ejection fraction and heart rate in patients with congestive cardiac failure.

Key Words: *Congestive Cardiac Failure, Heart Rate, Left Ventricular Ejection Fraction, Metoprolol, Nebivolol.*

Introduction

Congestive Cardiac Failure (CCF) is a disease in which patients have breathlessness at rest or during exercise, easy fatiguability, or signs of fluid accumulation, which are associated with an objective dysfunction of the heart due to a structural or functional abnormality.[1,2] In diastolic cardiac failure, more than 50% of the ejection fraction is preserved despite signs and symptoms of failure. Diminished left ventricular ejection fraction (LVEF) with clinical features is usually associated with systolic cardiac dysfunction.[3,4]

Tachycardia associated with cardiac failure carries a grim prognosis. An elevated heart rate serves as a trigger for the development of cardiac complications in various ailments including cardiac failure, myocardial infarction, and hypertension. Patients with poorly controlled tachycardia have increased cardiovascular morbidity and mortality.[5,6] The risk of cardiac failure development in the general population is 1 in 5 at the age of 40 years.[7] Data regarding the pattern and outcome of heart failure from developing countries is sparse. Cardiac failure affected approximately 6.6 million population in America in 2010 with a total expenditure in

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healthcare services on the disorder of 34.4 billion dollars.[8]

There are three types of receptors controlling cardiac functions: β_1 & β_2 adrenergic receptors produce a positive chronotropic and inotropic effect as opposed to β_3 adrenergic receptor producing a negative inotropic effect via nitric oxide synthesis pathway.[9,10] In cardiac failure, β blockers have been recommended as the main treatment modality as it has both prognostic and symptomatic benefits. β blockers have been proven to be effective in decreasing the number of death and improving morbidity.[11] Moreover, the β blockers which cause vasodilatation may be better in treating cardiac failure because it results in a decrease in after-load when compared to drugs of the same class that do not have this function.[12] Nebivolol is on the latest β blockers developed and has a significant arteriolar dilatory effect. It lacks sympathomimetic activity and is a highly selective β_1-adrenergic blocker as compared to other drugs in this class.[13]This study was conducted to compare nebivolol versus metoprolol therapy in controlling heart rate and improvement in left ventricular ejection fraction in patients with congestive cardiac failure

Materials and Methods

This randomized controlled trial was conducted from 1 March 2016 to 28th February 2017 at the Out-Patient Cardiology Department of Pakistan Institute of Medical Sciences (PIMS), Islamabad. The sample size was calculated using the World Health Organization (WHO) sample size calculator using the formulae for hypothesis test for two population proportions (one-sided), keeping a level of significance of 22.1%, a power of the test of 80.5%, a population portion 1 of 26.4%, and a population proportion 2 of 35.7%, giving us a sample size of 131 patients in each group or 262 total patients.[14] Approval from the ethical committee of the hospital was obtained (letter no HEC 2240, 05/05/2014). The study population included those patients who had congestive cardiac failure based on the clinical history and confirmed on echocardiography as having either systolic or diastolic dysfunction, having sinus rhythm. Adults of 18 years or above and of both genders were included. The patients with co-morbidities like asthma, chronic obstructive airway disease (COPD), peripheral arterial disease, heart blocks, and acute decompensated cardiac failure were not included in the study.

A detailed history was taken. History of diabetes, hypertension, and smoking were recorded. The New York Heart Association classification was used to stratify patients according to the severity of dyspnoea at the index visit and subsequently thereafter. Clinical examination was done after five minutes of rest to record heart rate, and blood pressure was recorded using mercury sphygmomanometers.

Detailed echocardiography was done by a blinded operator. Other medications being taken according to guideline-directed medical treatment (including Angiotensin converting enzyme (ACE) inhibitors, Angiotensin receptor blockers, diuretics, digoxin, nitrates) by the patients were noted. Left Ventricular end-diastolic and end-systolic dimensions, volumes and ejection fraction were recorded with the M-Mode and Simpson's method and a mean of three values was taken on echocardiography. Diastolic function was recorded with echocardiography by measuring E and A mitral inflow waves with pulsed wave Doppler. E prime was recorded with Tissue Doppler from the lateral mitral annulus. Isovolumic relaxation time (IVRT) and deceleration times were recorded with Doppler echocardiography.

Randomization was done, with the patients being sorted into two groups to get either metoprolol tartrate (Group B) or nebivolol (Group A) according to a random number table. The procedures were reconducted at one-, three- and six-months after drug administration by blinded operators. At each visit, an electrocardiogram (ECG) was performed to note the PR interval and history and physical examination was done. Dose titration of β blockers was done at two weekly intervals keeping in view the symptoms, heart rate and PR interval with a target of 60 to 70 bpm.

After entering data, analysis was done with SPSS software version 21.0. The categorical variables like gender, diabetes, hypertension, smoking, and efficacy were analysed as frequencies and percentages. The mean baseline LVEF and heart rate values were compared with post-intervention values after 6 months using the independent samples *t*-test. Independent sample *t*-test was also used to compare mean change in heart rate and LVEF between two

groups. A *p*-value≤ .05 was considered significant.

Results

A total of 262 patients were included in the study. The mean age of the patients was 49.25 ± 31.74 years that ranged from 18 to 80 years. Most of the patients in group A i.e., 46 (35.2%) were aged between 61-70 years, while in group B, 35 (26.7%) were also in the same age group. A total of 78 (60%) of patients in Group A were male, while this number was 73 (56%) in Group B. Patient distribution according to age group and the presence of risk factors is exhibited in Table I.

In group A, the mean and standard deviation of pre-treatment LVEF in our study was 45.23 ± 24.77% with a range of 20-70%. The mean and standard deviation of pre-treatment heart rate in our study was 50.13 ± 34.86 bpm with a range of 50-120 bpm, while in group B, the mean and standard deviation of pre-treatment LVEF in our study was 43.13 ±17.07% with a range of 24-62%. The mean and standard deviation of pre-treatment heart rate in our study was 85.10± 25.16 bpm with a range of 60-110 bpm.

Table I: Distribution of Patients According to age and Risk Factors

Age (years)	Group A n= 131	%Age of Patients	Group B n= 131	%Age of Patients
18 to 20	0	0%	0	0%
21 to 30	02	1.5%	04	3%
31 to 40	07	5.3%	18	13.7%
41 to 50	23	17.6%	22	16.8%
51 to 60	37	28.2%	35	26.7%
61 to 70	46	35.2%	31	23.7%
71 to 80	16	12.2%	21	16%
Risk Factors	**Group A n= 131**	**% Age of patients**	**Group B n= 131**	**% Age of patients**
DM	51	45.8%	66	50.4%
HTN	44	32%	39	29.8%
SMOKING	36	22.1%	26	19.9%
DM + HTN	64	48%	61	46.6%
DM + HTN + SMOKING	57	43.5%	47	36%

In group A, LVEF increased after the 6 months nebivolol therapy in patients up to the age of 60 years while it decreased after the age of 60 years while in group B, LVEF increased after 6 months metoprolol therapy in patients up to the age of 60 years while it is decreased after the age of 60 years. LVEF increase was increased to a greater degree in the nebivolol group as compared to metoprolol group. In group A, heart rate deceleration was more after the 6 months of nebivolol therapy than when compared with the metoprolol group with the same duration of therapy. Heart rate deceleration was more in patients having ages less than 60 years in both groups. Data for this variable is displayed in Table II.

In Group A, the average deceleration of heart rate was more in patients having diabetes, hypertension, and smokers, while in group B, the average deceleration of heart rate was more in smokers and those who had diabetes and hypertension. The data for these variables is displayed in Table III.

Table II: Age-wise Distribution of Patients having According to LVEF and Heart Rate

Age (years)	Group A (Nebivolol) n= 131	%Age Improvement After Nebivolol Therapy	Group B (Metoprolol) n= 131	%Age of LVEF Improvement After Metoprolol Therapy	*p*-value
18 to 20	0	0 %	0	0%	0.00031
21 to 30	02	7%	04	06%	
31 to 40	07	11%	18	04%	
41 to 50	23	11%	22	07%	
51 to 60	37	10%	35	05%	
61 to 70	46	-05%	31	-09%	
71 to 80	16	- 09%	21	-06%	
Age (years)	**Group A n= 131**	**Average HR Deceleration after Nebivolol therapy**	**Group B n= 131**	**Average HR Deceleration After Metoprolol therapy**	***p*-value**
18 to 20	0	16	0	12	0.00163
21 to 30	02	26	04	13	
31 to 40	07	20	18	20	
41 to 50	23	18	22	17	
51 to60	37	23	35	12	
61 to 70	46	19	31	16	
71 to 80	16	16	21	19	
18 to 20	0	16	0	12	

In group A, the average improvement in LVEF was more in hypertensive and diabetics, while in group B the average improvement in LVEF was 9% in hypertensive. The average improvement of LVEF was higher with nebivolol in each age group when

Table III: Average Heart Rate Improvement in Patients having CCF in According to different Risk Factors.

	Group A (Nebivolol) n= 131	Average HR Deceleration after Nebivolol therapy	Group B (Metoprolol) n= 131	Average HR Deceleration after Metoprolol therapy	*p*-value
DM	51	09	66	02	0.000351
HTN	44	16	39	06	
Smoking	36	11	26	10	
HTN + DM	64	08	61	12	
HTN + DM Smoking	57	09	47	07	

compared to metoprolol. This data is displayed in Table IV.

Table IV: Average LVEF (%) of patients having CCF in different Risk Factors.

	Group A (Nebivolol) n= 131	Average LVEF (%) Improvement after Nebivolol therapy	Group B (Metoprolol) n= 131	Average LVEF (%) Improvement after Metoprolol therapy	*p*-value
DM	51	11%	66	08%	0.001132
HTN	44	13%	39	09%	
Smoking	36	06%	26	05%	
DM + HTN	64	07%	61	05%	
DM + HTN + SMOKING	57	03%	47	02%	

Discussion

In our study, **t**he mean and standard deviation of LVEF was 45.23 ± 24.77% with a range of 20-70%. The mean and standard deviation of heart rate in our study was 50.13 ± 34.86 bpm with a range of 50-120 bpm. There were 2 (0.8%) patients of the age range of 18-20 year, in whom the LVEF decreased to 3% after the 6 months nebivolol therapy. A total of 9 (3.5%) patients belonged to the age range of 21-30 years and LVEF increased in them to 06% after the 6 months nebivolol therapy. 19 (7.2%) patients of the age range of 31-40 years had an LVEF increased to 04% after the 6 months nebivolol therapy, 42 (16%) patients of the age range of 41-50 years had an increase in LVEF of 7% after the 6 months nebivolol therapy, while 72 (27.5%) patients of the age range of 51-60 years saw LVEF increased to 5% after the 6 months nebivolol therapy. Lastly, 64 (24.4%) patients of the age range of 61-70 years developed an LVEF decrease of 9% after the 6 months nebivolol therapy.

In a study Brehm et al, the average improvement of cardiac rate was noted in 63% study population having EF of 13-39% in a double-blinded randomized controlled trial. Exertion time, cardiac rate, LVEF and tolerability were noted at initiation and after 3 months of administration of nebivolol (2.5 and 5 mg, n = 6) or placebo (n = 6).[15] In 4 patients nebivolol was better tolerated resulting in improvement of dyspnoea. Heart rate decreased while the maximum exercise duration and performance remained stable. LVEF increased (ejection fraction 31.5 ± 10.11 to 42.0 ± 10.99%, $p \leq 0.01$) after treatment with nebivolol.[15] The left ventricular end-systolic diameter decreased in the nebivolol-group from 56.5 ± 9.40 to 50.2 ± 9.43 mm ($p \leq 0.02$). This show that with nebivolol treatment LVEF may improve.[15]

The ENECA (efficacy of nebivolol in the treatment of elderly patients with chronic heart failure as add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis) study showed that nebivolol treatment had markedly increased LVEF in comparison to placebo in all subgroups of population under study.[14] In a double blinded randomized control study by Shibata et al wherein they studied the benefits of nebivolol and compared it with placebo. It was inferred that the nebivolol group demonstrated a greater improvement despite the poor conditions like age, gender, ejection fraction, diabetes, or prior ischemic cardiac insult. Moreover, it was shown that to prevent death and hospital admission, nebivolol should be continued for 2 years.[16]

There are very few comparative studies in treating cardiac failure with β-adrenergic blockers.[17] In two small clinical trial where in nebivolol was compared with carvedilol in terms of exercise tolerance, both the drugs had beneficial effect in improving exercise tolerance after twelve months of treatment. Conversely, in a trial by Patrianakos et al, there was no difference in improvement in LVEF and left ventricular end systolic volume.[17] Both carvedilol and nebivolol had beneficial effect on exercise tolerance and neither drug had declined exercise tolerance at earlier assessment. The drawback of this study was its low power, more over Patrianakos and colleagues conducted their study in patients with non-ischemic dilated cardiomyopathy so extrapolating it to other cardiac failure patient due ischemic disease is inappropriate.[18] In order to establish the benefit of one β blocker over the other in treatment of cardiac failure more head-to-head comparative studies should be done. Moreover, these should be high

power studies before jumping to any concrete conclusions. Furthermore, Sim et al have noted that Nebivolol is beneficial even in low doses, providing benefits at the roughly the same degree as higher doses without the added risk of side effects.[19] Lastly, Seleme et al noted that Nebivolol was of great use in the management of hypertension that was comparable in its effectiveness to more established drug classes such as ACE inhibitors and calcium channel blockers.[20]

Limitations

Our study was limited by the duration of follow-up i.e., up to six months: heart failure is a chronic condition and, the effects of nebivolol need to be observed for a longer duration against standard treatment, to determine whether short-term benefits translate into long-term ones. Secondly, our study did not look at the side-effects of both study-arms in detail, which is another aspect that should be adequately reviewed before changing established clinical practices. Lastly, this was a single-center study, with patients being drawn from ethnic groups, so the results may not be generalizable to the rest of the country.

Conclusion

Nebivolol was found to improve LVEF and cardiac rate in this cohort of patients presenting with heart failure and further collective studies at a larger scale are required to establish its non-inferiority and subsequently, its superiority over other beta-blockers so that such prescribing may be inculcated into local and international practice guidelines.

REFERENCES

1. Malik A, Brito D, Vaqar S, Chahbra L. Congestive Heart Failure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430873/.
2. Hajouli S, Ludhwani D. Heart Failure and Ejection Fraction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553115/.
3. Sarwar M, Majeed SM, Khan MA. Types and frequency of cardiac arrhythmias in patients with heart failure. J Pak Armed Forces Med J 2014;1(1):S109-13.
4. Sanhoury M, Mohamed F, Sadaka M, Abdel-Hay MA, Sobhy M, Elwany M. The impact of asymptomatic ventricular arrhythmias on the outcome of heart failure patients with reduced ejection fraction. Egypt Heart J. 2022 16;74(1):11.
5. Khan MA, Majeed SM, Sarwar M. Screening of High Risk Patients with Mitral Valve Prolapse – Role of Heart Rate Variability. J Islam Int Med Coll. 2013;9(3):59-62.
6. Zhao W, Zhao J, Rong J. Pharmacological Modulation of Cardiac Remodeling after Myocardial Infarction. Oxid Med Cell Longev. 2020 ;2020(1):8815349.
7. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017 Apr;3(1):7-11
8. Seemi S, Iffat S, Ahmed Sana JS. Diagnostic Accuracy of Electrocardiography in Diagnosis of Left Ventricular Hypertrophy. J Islam Int Med Coll. 2014;9(3):63–8.
9. Ali DC, Naveed M, Gordon A, Majeed F, Saeed M, Ogbuke MI, et al. β-Adrenergic receptor, an essential target in cardiovascular diseases. Heart Fail Rev. 2020 ;25(2):343-354.
10. Raja GS, Khan HF, Siddiqui A. Cardiac Autonomic Modulation in Psychologically Stressed Subjects as Reflected by Heart Rate Variability. J Islam Int Med Coll. 2015;10(3):199–203.
11. Silverman DN, de Lavallaz JD, Plante TB, Infeld MM, Goyal P, Juraschek SP, et al. Beta-Blocker Use in Hypertension and Heart Failure (A Secondary Analysis of the Systolic Blood Pressure Intervention Trial). Am J Cardiol. 2022 ;165(1):58-64.
12. Alvi AA, Khan MA, Ali W. Control of Oral Anticoagulant Therapy using INR in Patients with Artificial Heart Valves. J Islam Int Med Coll. 2014;9(2):3–6.
13. Priyadarshni S, Curry BH. Nebivolol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551582/.
14. Edes I, Gasior Z, Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. Eur J Heart Fail [Internet]. 2005;7(4):631–9.
15. Brehm BR, Wolf SC, Gorner S, Buck-muller N. Effect of nebivolol on left ventricular function in patients with chronic heart failure : a pilot study. 2002;4(5):757–763.
16. Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. Eur J Heart Fail [Internet]. 2011;3(3):351–7.
17. Veverka A. Nebivolol in the treatment of chronic heart failure. 2017;3(5):647–54.
18. Patrianakos AP, Parthenakis FI, Mavrakis HE, Diakakis GF, Chlouverakis GI, Vardas PE. Comparative efficacy of nebivolol versus carvedilol on left ventricular function and exercise capacity in patients with nonischemic dilated cardiomyopathy. A 12-month study. Am Heart J. 2015;150(5):985-985.
19. Sim DS, Hyun DY, Jeong MH, Kim HS, Chang K, Choi DJ, et al. Effect of Low-Dose Nebivolol in Patients with Acute Myocardial Infarction: A Multi-Center Observational Study. Chonnam Med J. 2020 ;56(1):55-61.
20. Seleme VB, Marques GL, Mendes AE, Rotta I, Pereira M, Júnior EL, et al. Nebivolol for the Treatment of Essential Systemic Arterial Hypertension: A Systematic Review and Meta-Analysis. Am J Cardiovasc Drugs. 2021;21(2):165-180.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.