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A Comparative Study of Bisoprolol with Carvedilol on LV Systolic Function in Patients with Chronic Heart Failure

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Abstract:

Background: *Chronic heart failure (CHF) is the most common and prognostically unfavorable outcome of many diseases of the cardiovascular system. Recent data suggest that beta-blockers are beneficial in patients with CHF. Among β-blocker class of drugs, bisoprolol is a highly selective β_1-adrenergic receptor blocker whereas Carvedilol is non-selective. Many large-scale trials have confirmed that both these β-blockers are superior to placebo and other β-blockers. This study was designed to compare the effects of carvedilol and bisoprolol in patients with chronic HF in a single center.*

Methods: *It was a quasi experimental study. A total of 288 cases of heart failure were selected by purposive sampling, from January 2017 to June 2017. Each patient was allocated into either of the two groups, and was continued receiving treatment with either bisoprolol (Group-I) or carvedilol (Group-II). Each patient was evaluated clinically and echocardiographically at the beginning of treatment (baseline) and at the end of 3rd month. Echocardiography was performed to find out change in left ventricular systolic function.*

Result: *After 3 months of treatment, ejection fraction was found higher in the bisoprolol group (42.6 ± 6.5 versus 38.3 ± 4.6%; P < 0.05). Ejection fraction (EF) changes were 8.4% in bisoprolol group and 4.1% in carvedilol group. A significant reduction in left ventricular end-systolic volume (21.9±2.5 in group I versus 14.9±5.7 in group II; P < 0.05) and left ventricular systolic diameter (3.2±0.1 in group I versus 2.3±0.5 in group II; P<0.05) occurred after 3 months of treatment. But no significant differences were observed in left ventricular end-diastolic volume (10.1±3.2 versus 6.1±6.4; P=0.101) and left ventricular diastolic diameter (1.7±0.8 versus 1.3±0.8; P=0.081) between groups. Three months after treatment, heart rate was reduced in the bisoprolol group from 87.7±9 to 74.5±8.1 and carvedilol group from 88.8±9.1 to 80.1±8.7. Differences in heart rate responses between 2 groups were not statistically significant (P=0.113). Assessment of blood pressure three months later of treatment shows, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were improved in both group but difference between two groups were statistically non significant (p>0.05).*

Conclusion: *In this study, bisoprolol was superior to carvedilol in increasing left-ventricular ejection fraction, improving left ventricular end systolic volume and left ventricular end systolic diameter but no significant difference was observed in LV end diastolic volume, LV end diastolic diameter, heart rate and blood pressure.*

Keywords: *Chronic Heart Failure, Bisoprolol, Carvedilol, LV Systolic Function.*

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Introduction:

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[26] Chronic heart failure carries a major health burden, with significant morbidity and mortality. Accurate diagnosis, treatment of reversible causes and institution of proven medical and device therapies are key facets of management.[20] HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF. EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies.[3]

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Controlled clinical trials have shown that b-blockers produce consistent benefits in patients with chronic heart failure. As a result, these agents are now recommended for use in all patients with stable heart failure caused by left ventricular (LV) systolic dysfunction who do not have contraindications.[13]

Bisoprolol is highly selective β_1-adrenergic receptor blocker where as carvedilol is a non-selective β and ±1-adrenergic receptor blocker with an antioxidant effects that improves the state of HF. The major HF-guidelines do not recommend any of the approved β-blockers over the other, thus implying equal efficacy. Nonetheless, there are pharmacologic differences between β-blockers (for example, β-receptor selectivity, vasodilator activity, and bioavailability), which raises the possibility that differences in clinical effectiveness may exist.[11] Aim of our study was to compare the left ventricular systolic function in chronic heart failure patient treated with bisoprolol and carvedilol in our setting.

Methods:

Study design and patiens

This Quasi Experimental Study was conducted at the University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Dhaka. The centre has consistently being ranked as the one of the top hospital in Bangladesh. Total duration was six months from January, 2017 to June, 2017. We studied 288 adult patients (age >15 years) of heart failure with reduced EF due to ischemic cause. All patients had New York Heart Association class I to IV symptoms for ≥3 months and an LV ejection fraction ≤0.40 by echocardiography. Patients were excluded if they had decompensated heart failure, obstructive lung disease like asthma or reactive airways disease, brady-arrhythmia like advanced AV block, sick sinus syndrome or symptomatic bradycardia (≤60 beat/min) and Prior history of β-blockers hypersensitivity. The protocol was approved by the local ethics committee and Institutional Review Board (IRB). Written informed consent was obtained from all study patients after careful explanation of the study procedures.

Study Procedure

The study was a prospective, non-randomized, single center trial. All patients with chronic heart failure were enrolled consecutively following the inclusion and exclusion criteria. Detailed history, physical examination and an echocardiogram were done on admission and outpatient consultation. On the basis of history, examination and investigations the patient other than chronic heart failure due to ischemic cause were excluded. Among these patients who were getting study drugs either bisoprolol or carvedilol was eligible for the study. After enrollment the study subject were divided into 2 groups depending on the agent administered: bisoprolol (group I) and carvedilol (group II). The choice of these agents was left to the discretion of the attending physician. In addition to study drug, standard treatments for CHF according to the ACC/AHA HF Guideline 2013 were permitted. Up and down titration of the index drug was done according to patients need. At the end of the 3rd month of treatment, LV systolic function of all cases was compared with their baseline echocardiographic data. Detail clinical evaluation and echocardiographic assessment of LV systolic function of all the cases were performed at baseline and after 3 months of treatment with bisoprolol or carvedilol group. Echocardiographic assessment was done by using 2D and M-mode echocardiography. The LV ejection fraction (LVEF) was calculated using a standard method (modified Simpson method) in Vivid E9 (GE Healthcare) echo machine with 3.5 MHz transducer. During echocardiography the following parameters were assessed; left ventricular end diastolic dimension (LVIDd), left ventricular end systolic dimension (LVIDs), left ventricular end diastolic volume and left ventricular end systolic volume. Two independent, blinded observers will review these echocardiograms. After completion of the data collection, comparison was done between two (baseline and after 3 months of treatment) echocardiographic finding and inference was drawn regarding superiority of the drugs.

Statistical analysis

The primary end point of the study was LV study: Left ventricular end diastolic dimension (LVIDd), Left ventricular end systolic dimension (LVIDs), Left ventricular end diastolic volume (EDV), Left ventricular end systolic volume (ESV), The LV ejection fraction (LVEF). Secondary efficacy end point variables were effect on heart rate and blood pressure.

Keeping the research topic in concern, a preset easily understandable data sheet was used for data collection. After collection of all information, these data were checked, verified for consistency and edited for finalized result. Continuous variables are expressed as mean value±standard deviation or as median. Categorical variables are expressed as absolute number and percentages which were presented as frequency tables and charts. After normality test we compared symmetrical continuous data by t-test and asymmetrical data by Mann-Whitney U Test. The chi-square test was used to compare categorical variables. Differences were considered significant was defined as P value less than 0.05.

Results:

A total 288 patients were selected for study. Each patient was allocated into one of the two groups, and continued receiving treatment with either bisoprolol once daily

(Group-I) or carvedilol twice daily (Group-II). Each patient was evaluated clinically and echocardiographically at the beginning of treatment (baseline) and at the end of 3rd month. The number of patients who lost to follow-up was 9 in bisoprolol group and 15 in carvedilol group. As shown in Table 1, there were no significant differences between the two groups in terms of socio-demographic data including age, gender, body weight, occupations, hypertension, diabetes mellitus, hyperlipidemia and smoking at baseline. With regard to cardiac medications, administration of diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), nitrates, statins and antiplatelet was similar in both groups.

Left ventricular volume, dimension and function

Left ventricular volumes and function data are presented in Table 2. After 3 months of treatment, significant improvement of left ventricular ejection fraction was observed in bisoprolol treated group (42.6 ± 6.5 in group I versus 38.3 ± 4.6% in group II; $P < 0.05$). Ejection fraction (EF) changes were 8.4% in bisoprolol group and 4.1% in carvedilol group.

A significant reduction in left ventricular end-systolic volume (21.9±2.5ml in group I versus 14.9±5.7ml in group II; $P < 0.05$) and left ventricular systolic diameter (3.2±0.1mm in group I versus 2.3±0.5mm in group II; P<0.05) occurred after 3 months of treatment. But no significant differences were observed in reduction of left ventricular end-diastolic volume (10.1±3.2ml versus 6.1±6.4ml; P=0.101) and left ventricular diastolic diameter (1.7±0.8 versus 1.3±0.8; P=0.081) between groups.

Effects on heart rate and blood pressure

Three months after treatment, heart rate was reduced in the bisoprolol group from 87.7±9 to 74.5±8.1 and carvedilol group from 88.8±9.1 to 80.1±8.7. The effect of bisoprolol appeared more pronounced than those of carvedilol. But differences in heart rate responses between 2 groups were not statistically significant (P=0.113).

Assessment of blood pressure three months later of treatment shows, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were improved in both group but difference between two groups were statistically non significant (p>0.05) Table 3.

Table-I

Baseline characteristics of study patients

	Bisoprolol (n=144)	Carvedilol (n=144)	P-value
Age (mean±SD)	52.1±8.3	52.5±9.83	0.172
SexMale (%)	95 (65.9%)	99 (68.7%)	0.283
Female (%)	49 (34.1%)	45 (31.2%)	
BMI (mean±SD)	25.59±3.17	26.34±3.52	1.000
Heart Rate (mean±SD)	87.7±9	88.8±9.1	0.113^{ns}
Blood Pressure (mean±SD)			
Systolic	116.3±14.8	115±13.3	0.09^{ns}
Diastolic	75.5±10.1	73.7±9.3	1.00^{ns}
Occupation			0.251^{ns}
Service holder	16 (11.1%)	23 (15.9%)	
Businessman	43 (29.8%)	49 (34.0%)	
Teacher	12 (8.3%)	5 (3.4%)	
House wife	30 (20.8%)	32 (22.2%)	
Retired	27 (18.7%)	23 (15.9%)	
Others	16 (11.1%)	12 (8.3%)	
Hypertension	112 (77.7 %)	104 (72.2%)	0.487^{ns}
Diabetes	81 (56.2%)	87 (60.4%)	0.342^{ns}
Dyslipidaemia	98 (68.0%)	118 (81.9%)	0.193^{ns}
Smoker	73 (50.6%)	83 (57.6%)	0.312^{ns}
Medication			
Diuretics	144 (100.0%)	144 (100.0%)	0.119^{ns}
ACEI	79 (54.8%)	75 (52.0%)	0.172^{ns}
ARB	48 (33.3%)	53 (36.8%)	0.312^{ns}
Nitrate	19 (13.1%)	22 (15.2%)	0.103^{ns}
StatinAntiplatelet	104 (72.2%)117 (81.2%)	107 (74.3%)105 (72.9%)	$0.479^{ns}0.212^{ns}$

Table-II

Changes in left ventricular function, volumes and dimensions after 3 months of treatment.

	Bisoprolol		Difference	Carvedilol		Difference	p-value
	Baseline	After 3 months		Baseline	After 3 months		
LVIDd (mm)	62.4±5.0	61.0±4.9	1.7±0.8	61.3±5.3	60.1±4.5	1.3±0.8	0.0818^{ns}
LVIDs (mm)	52.0±4.8	48.5±4.9	3.2±0.1	51.1±4.9	48.7±4.0	2.3±0.5	0.0002^{s}
LV end systolic volume (ml)	131.1±27.6	108.6±26.8	21.9±2.5	125.9±28.2	110.9±20.5	14.9±5.7	0.0007^{s}
LV end diastolic volume (ml)	198.7±35.7	188.1±33.9	10.1±3.2	193.9±37.7	187.8±30.4	6.1±6.4	0.101^{ns}
LVEF(%)	34.1±3.6	42.6±6.5	8.4±0.7	34.7±2.9	38.3±4.6	3.9±0.5	0.0001^{s}

Table-III

Changes of blood pressure and heart rate amongst the study patients

	Bisoprolol		Difference	Carvedilol		Difference	p-value
	Baseline	After 3 months		Baseline	After 3 months		
SBP (mmHg)	116.3(14.8)	108.6(12.9)	7.6(1.6)	115.7(13.3)	109.8(11.1)	5.8(1.9)	0.09^{ns}
DBP (mmHg)	75.5(10.1)	72.3(8.5)	3.2(0.7)	73.7(9.3)	73.1(7.8)	0.6(0.8)	1.00^{ns}
HR (beats/min)	87.7(9.0)	74.5(8.1)	13.2(3.3)	88.8(9.1)	80.1(8.7)	8.7(2.5)	0.113^{ns}

Discussion:

The main objective of the study was to compare the left ventricular systolic function in chronic heart failure patients treated with bisoprolol and carvedilol. In the present study, the baseline characteristics of the two treatment groups were same; therefore, the effectiveness of carvedilol and bisoprolol is clearly comparable.

The present study demonstrates that bisoprolol improves cardiac performance to a greater extent than carvedilol during the 3 month treatment of patients with chronic heart failure. When compared with the carvedilol group, the bisoprolol group showed larger increases in LV ejection fraction and LV systolic dimension (volume and diameter) at rest. In addition, bisoprolol produced greater decreases in mean heart rate than carvedilol. In contrast, no significant difference of improvement was observed in left ventricular diastolic dimension (LVIDd and LVEDV) and blood pressure between 2 groups. But the 2 drugs improved symptoms, exercise tolerance, and quality of life to a similar extent.

Most previous studies that evaluate the hemodynamic response in 3 to 6 months of beta-blockade therapy have reported benefits, including improvements in left ventricular ejection fraction and reduced ventricular volumes. Our findings are consistent with most of these studies, as measures of left ventricular end-diastolic volume, left ventricular end systolic volume, and ejection fraction tend to improve in both groups but more with bisoprolol, although the reductions in end-diastolic volume did not reach statistical significance.

Importantly,[4] showed most of these hemodynamic changes occurred during the later 6 months of the study, which suggests that 3 months duration may not have been long enough to observe the full extent of the effects of beta blockade.

The hemodynamic effects of bisoprolol fumarate have previously been studied in a subset of patients in the CIBIS trial. 5 months of bisoprolol fumarate therapy had no significant effects on end-diastolic or end-systolic dimensions. Although left ventricular ejection fraction increased with bisoprolol fumarate and this improvement was related to improved survival rate. The differences in our findings and those of the CIBIS trial may be the result of differences in study duration (5 months versus 3 months) or measurement techniques.

Our findings in accordance with result of other study,[8] which reported that in both groups, blood pressure, heart rate, LVEF, and BNP levels improved significantly. In the bisoprolol group, the change in HR was greater than in the carvedilol group.

Three randomized controlled trials have compared carvedilol and metoprolol head-to-head. The largest[13] included 150 subjects with ejection fractions below 35% who were randomized to 1 of the 2 drugs and followed for more than 3 years. Symptom scores and quality of life assessments were similar in the 2 groups but the carvedilol group had a statistically greater improvement in ejection fraction (+10.9 ± 11.0 vs +7.2 ± 7.7 at rest). Despite this difference, the overall cardiac outcome were not significantly different between the 2 groups.

Bristow et al also reported that carvedilol produces dose-related improvements in HF patients, whereas a study by Dungen et al showed that the potency of carvedilol at a target dose of 50 mg per day and bisoprolol at 10 mg per day is approximately equal. The dosages of the two β-blockers in our study were lower than the common dosages found in many large-scale trials.

There is wide consensus about the benefits of beta-blockers in systolic heart failure.[19] However, it is not clear if one specific beta--blocker is superior to the others. Carvedilol might have different physiological properties, commonly referred as pleiotropic effects, which might confer it's superiority against the other beta-blockers.

The present data showed that heart rate (HR), one of the most relevant parameter to determine clinically effective β-blockade, was decreased by both carvedilol and bisoprolol. The effects of bisoprolol appeared more pronounced than those of carvedilol. However, this difference was not statistically significant between two groups in reducing HR.

Regarding blood pressure comparison, after 3 months of treatment, the reduction of both systolic and diastolic blood pressure between two groups was not statistically significant. All findings were consistent with results of other studies.[1,9]

The differences we observed in the LV function and hemodynamic effects of bisoprolol and carvedilol may be explained by the greater antiadrenergic activity of bisoprolol. Bisoprolol acts selectively on β1-receptors where as carvedilol blocks non-selective β and α_1-adrenergic receptor on the heart and peripheral blood vessels. The findings obtained with carvedilol might possibly be explained by a decrease in blood pressure caused by the α-blocking effects of the drug. The decrease in blood pressure may be expected to cause a compensatory increase in sympathetic tone, thus increasing the HR. On the other hand bisoprolol, which lacks α-blocking effects, significantly decreased heart rate. These data suggest that carvedilol is rather weak as a β-adrenergic antagonist. The greater improvement in LV performance in the bisoprolol group may have been related to its ability to provide more comprehensive protection against the deleterious actions of the sympathetic nervous system on the heart. The molecular and electrophysiological mechanisms of these beneficial effects are still unclear and further studies are required regarding this issue.

Refereces:

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