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ORIGINAL RESEARCH

Effects of Carvedilol and Bisoprolol on Inflammation and Oxidative Damage in Patients with Chronic Heart Failure

J. Jacob Justin[1], Sabu Augustine[2]

[1]Associate Professor, Department of General Medicine, Dr. Somervell Memorial C.S.I Medical College, Trivandrum, Kerala, India

[2]Associate Professor, Department of General Medicine, Dr. Somervell Memorial C.S.I Medical College, Trivandrum, Kerala, India

ABSTRACT

Background: Inflammation and oxidative stress contribute to persistent heart failure (CHF). Bisoprolol is better than carvedilol at protecting CHF patients' myocardium, according to our earlier clinical trial. Low high-sensitivity cardiac troponin T showed this (hsTnT).

Materials and Methods: From the 87 people who took part in the trial, 48 (26 in the bisoprolol group and 22 in the carvedilol group) were included in this study because they had measurements of derivatives of reactive oxygen metabolites (d-ROMs) as an indicator of oxidative stress at the beginning and end of the trial.

Results: High-sensitivity C-reactive protein (hsCRP), a marker of inflammation, went down in both groups, but the drop in the bisoprolol group was bigger than the drop in the carvedilol group. Both groups also had a drop in d-ROMs, but the drop in the bisoprolol group was not as big as the drop in the carvedilol group. The change in hsTnT was linked to the change in hsCRP for all 48 patients ($R = 0.467$, $p = 0.003$).

Conclusion: Bisoprolol might be better than carvedilol at reducing inflammation, but carvedilol might be better at reducing oxidative stress than bisoprolol. Patients with CHF could benefit from the right use of bisoprolol or carvedilol based on their own pathophysiology.

Keywords: Bisoprolol, carvedilol, inflammation, heart failure, and oxidative damage.

Corresponding Author: Dr J. Jacob Justin, Associate Professor, Department of General Medicine, Dr. Somervell Memorial C.S.I Medical College, Trivandrum, Kerala, India

INTRODUCTION

Chronic heart failure (CHF) patients with impaired left ventricular function have been investigated.[1–4] Japanese guidelines approve only carvedilol and bisoprolol for treatment CHF.[5] Bisoprolol selectively blocks beta-1 receptors, while carvedilol blocks alpha receptors.[6] No clinical data reveals how to utilise these two drugs. Bisoprolol is better than carvedilol at protecting CHF patients' myocardium, according to our recent clinical trial. High-sensitivity cardiac troponin T (hsTnT) dropped.[7]

Inflammation and oxidative stress may contribute to CHF's progression. Inflammatory mediators affect CHF in several ways. They affect cardiac myocytes, fibroblasts, and beta-adrenergic receptors, producing hypertrophy, fibrosis, and decreased heart contractility. By activating the proper genes, they might cause apoptosis.[8] In CHF, more free radicals that damage lipids, proteins, and nucleic acids are generated. Chronic increases in mitochondrial oxygen radical generation can damage mitochondrial DNA, reduce function, and harm cardiac cells in CHF.[9] Inflammation and oxidative stress aren't proven CHF treatments. It's

unknown what carvedilol's antioxidant effects on failing hearts mean for CHF patients. Anti-inflammatory therapy may be added to standard medications to aid CHF patients. N-terminal pro-brain-type natriuretic peptide (NT ProBNP) and high-sensitivity troponin T are indicators of inflammation and oxidative stress (hsTnT). In this subanalysis, we examined how carvedilol and bisoprolol impact inflammation and oxidative stress in CHF patients.[10,11]

MATERIALS AND METHODS

Study population

The study was designed as a prospective, open label, randomized trial. Study subjects included hospitalized patients with CHF who were not on beta-blockers and fulfilled the following inclusion criteria:

- Age 20 years;
- Left ventricular ejection fraction 45% by echocardiography;
- Stability of heart failure symptoms as demonstrated by New York Heart Association (NYHA) functional class, for one month prior to enrollment; and
- Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Exclusion criteria were as follows:

- Severe heart failure, definedas NYHAclassIV;
- Seriousarrhythmias such as ventricular tachycardia or sustained brady-cardia(<60/min),includingsecond-degreeatrioventricularblockwithout pacemaker implantation;
- Acute coronary syndromewithin 3 months of enrollment;
- Sustained hypotension (restingsystolic blood pressure <90 mmHg);
- Serious hepatic or renaldysfunction (serum alanine aminotransferase level50 IU/L and/orserum creatininelevel3.0 mg/dL);
- Acontraindicationtobeta-blockers, suchasbronchial asthma;and
- The treatingphysician'sobjectiontoinclusioninthestudy.

Study protocol: Patients who were eligible were given either bisoprolol or carvedilol by chance. Patients in the bisoprolol group took bisoprolol once a day, starting with 0.625 mg/day and increasing by 1.25, 2.5, and 3.75 mg/day every two weeks, up to a maximum of 5 mg/day. Patients in the carvedilol group took carvedilol twice a day, starting with 2.5 mg/day (1.25 mg per dose) and increasing by 5 and 10 mg/day every two weeks as tolerated, up to a maximum of 20 mg/day. Patients' NYHA functional class, heart rate, blood pressure, cardiothoracic ratio on the chest roentgenogram, blood levels of different biomarkers, and echocardiographic parameters were measured at the start of treatment and after 24 weeks. We looked at the estimated glomerular filtration rate (eGFR), the amount of haemoglobin in the blood, and the amount of NT-ProBNP and hsTnT in the blood. We also looked at high-sensitivity C-reactive protein (hsCRP), which is a biomarker for inflammation, and derivative of reactive oxygen metabolites, which is a biomarker for oxidative stress (d-ROMs). Patients who stopped taking the study drugs for any reason were taken out of the final analysis of the data.[12–14]

Echocardiography:

Transthoracic echocardiography was done on patients who were lying on their left side. A SONOS 7500 or a Vivid 7 system was used to get two-dimensional and M-mode images. Two cardiologists who were not involved in the study were in charge of getting the images. Wall movement was seen in images that were only two dimensions. With the modified Simpson's method, the left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were found in the four-chamber and two-chamber apical views. The left ventricular ejection fraction (LVEF) was then calculated as [(LVEDV-LVESV)/LVEDV]

100 (%). These parameters were found by keeping track of three heartbeats in stable conditions and taking the average of the measurements.[15–18]

Measurementofspecificbiomarkers:

Blood samples were spun at 1500 g for 15 minutes at room temperature right away. The serum was put in a freezer and kept at 80°C until it could be tested. The Roche Diagnostic NT-ProBNP electrochemiluminescent immunoassay kit on an Elecsys 2010 analyzer was used to measure NT-ProBNP according to the instructions from the manufacturer.[19] The NT-ProBNP test at our institute is 3.9% different from one test to the next. Elecsys Troponin T High Sensitive immunoassay was used to measure hsTnT in the blood. In our study, the measurement of hsTnT met the precision guidelines for the universal definition of myocardial infarction. An increased value for cardiac troponin was defined as a measurement above the 99th percentile of a normal reference population, and the optimal precision (coefficient of variation) at the 99th percentile decision limit was set at 10% [20]. In a group of healthy adults, the normal range for hsTnT is 0.014 ng/mL (99th percentile).[21] The lowest concentration that can be reliably measured by an analytical procedure is 0.003 ng/mL.[22] The hsCRP was measured using particle-enhanced technology on a Behring BN II nephelometer with monoclonal anti-CRP antibodies and a calibrator that was traceable to WHO Reference Material. With this method, the coefficients of variation between runs were 6.4%, 3.7%, and 2.9% at hsCRP concentrations of 0.047, 1.05, and 5.49 mg/dl, and the detection limit was 0.001 mg/dL (0.1 ng/mL).[23] Last, we used the d-ROMs test,[24] to measure d-ROMs. The test for d-ROMs uses a photometric method based on the radical reaction of Fenton, which Haber and Weiss,[25] explained in detail. This test finds out how many hydroperoxides are in serum. Hydroperoxides, which come from free radicals, have a close relationship with the amount of ROMs. In the d-ROMs test, hydroperoxides in a sample of serum react with a chromogenic substrate to make a coloured derivative. The temperature of the reaction is 37 C. At a wavelength of 505 nm, a photometer can find the coloured complex and measure how much of it there is. The d-ROMs test results are given in arbitrary units called "Caratelli Units" (U.CARR), where 1 U.CARR is equal to 0.08 mg/100 mL of H2O2.[26]

Statistical Analysis: For continuous variables, data are given as the mean and standard deviation. For categorical variables, data are given as the number (or percentage) of patients. NYHA class I, II, III, and IV were given scores of 1, 2, 3, and 4, respectively. The Shapiro-Wilk test was used to check if the distribution of continuous variables was normal. Since the distributions of NT-ProBNP, hsTnT, and hsCRP values were skewed, they were logarithmically changed so they could be analysed. For comparisons within a group and between groups, paired and unpaired t-tests were used to compare continuous variables. A chi-square test was used to compare categorical variables from different groups. Simple linear regression analysis was used to find the link between two variables. SAS software, Version 9.4, was used for all statistical analyses. A p-value of less than 0.05 was thought to be significant.[27]

RESULTS

Patientcharacteristics: In this trial, a total of 87 people took part. 44 were in the bisoprolol group and 43 were in the carvedilol group. This study looked at 48 of these patients (26 in the bisoprolol group and 22 in the carvedilol group; 9 of these patients had ischemic heart failure) whose d-ROMs were measured both at the start of the study and 24 weeks later. Both groups had similar age, gender, cause of heart failure, and other health problems at the start of the study. Both groups took similar medications at the same time, like ACE inhibitors or ARBs, aldosterone blockers, loop diuretics, anti-arrhythmic agents, and statins. But more digitalis was used in the group that took carvedilol. One person in the bisoprolol group and one person in the carvedilol group stopped taking statins after 24 weeks of follow-up. But all

of the people in each group kept taking the other drugs. At 24 weeks, the final dose of beta-blockers in the bisoprolol group was 2.5–1.6 mg/day, while the dose in the carvedilol group was 6.1–4.0 mg/day.

Changesinmeasuredparameters: Baseline values of measured parameters were the same for the 26 people in the bisoprolol group and the 22 people in the carvedilol group. Both groups got better after 24 weeks of treatment. The NYHA class, heart rate, cardiothoracic ratio, LVEDV, LVESV, and LVEF all got better. The bisoprolol group had a bigger drop in heart rate than the other groups, but the other changes were the same for both groups. At 24 weeks, the bisoprolol group had a significantly lower heart rate, and the carvedilol group had a significantly lower cardiothoracic ratio. The levels of blood pressure, eGFR, and haemoglobin did not change in either group 24 weeks after they were given beta-blockers.

Changeinspecificbiomarkers: At the start of the study, the NT-proBNP levels in the bisoprolol and carvedilol groups were about the same (2.99 pg/ml vs. 2.91 pg/ml). Both groups' NT-ProBNP levels went down after treatment with beta-blockers for 24 weeks, but the decrease in the bisoprolol group [to 2.48 0.61 log (pg/ml), p = 0.014] was less significant than the decrease in the carvedilol group [to 2.11 0.68 log (pg/ml), p 0.001].

The hsTnT level at the start was the same in both the bisoprolol and carvedilol groups (1.28 ng/ml and 1.13 ng/ml, respectively). At 24 weeks, the hsTnT level in the bisoprolol group went down to 0.95 0.39 log (ng/ml) (p = 0.010), but it only went down slightly in the carvedilol group (to 0.91 0.35 log (ng/ml), p = 0.064).

The hsCRP level at the start was the same in both the bisoprolol and carvedilol groups (3.35 ng/ml and 3.38 ng/ml, respectively). At 24 weeks, the hsCRP level went down in both groups, but the drop in the bisoprolol group was more significant than the drop in the carvedilol group [to 2.69 0.44 log (ng/ml), p = 0.001] (401 106 vs 382 84 U.CARR, respectively). At 24 weeks, the d-ROMs level dropped in both groups, but the drop in the bisoprolol group (to 344 82 U.CARR, p=0.015) was less significant than the drop in the carvedilol group (to 312 76 U.CARR, p=0.006).

When both groups were put together (n=48), the relationships between changes (baseline values minus values at 24 weeks) in inflammatory, oxidative stress, and cardiac biomarkers were looked at. Changes in the levels of d-ROMs and hsCRP were linked (R = 0.444, p = 0.005).

DISCUSSION

Inflammatory biomarker hsCRP and oxidative stress biomarker d-ROMs both decreased following 24 weeks of bisoprolol or carvedilol treatment. But hsCRP decreased more in bisoprolol patients and d-ROMs decreased more in carvedilol patients. Interestingly, hsTnT decreased with hsCRP but not d-ROMs. NT- ProBNP did not correlate with hsTnT or d-ROMs.

Inflammation causes, worsens, prolongs, and improves CHF. Proinflammatory cytokines like TNF-alpha and IL-6 rise with CHF severity and can predict its fate. These cytokines slow cardiac function by acting negatively inotropically. They halt beta-receptor activation and slow inducible nitric oxide synthase synthesis. These cytokines produce cardiac cachexia due to skeletal muscle loss, increase vascular permeability, and raise peripheral vascular resistance, making it harder for CHF patients to exercise. Inflammatory cytokines in the blood affect heart failure severity and outlook.[28] Val-HeFT demonstrated that CHF patients had greater levels of hsCRP, which was connected to more severe heart failure and death and disability. Valsartan therapy lowered hsCRP.[29] Beta-blockers may reduce inflammatory cytokine levels in CHF patients. Preventing sympathetic nervous system overactivity may reduce inflammatory reactions in CHF patients.[30] Bisoprolol and carvedilol decreased hsCRP in this study. Bisoprolol seems to suppress inflammatory reactions better than carvedilol. Bisoprolol and carvedilol lowered NT-proBNP levels similarly. Bisoprolol

reduced hsTnT greater than carvedilol. These results match the major study findings we gave you. Injured ventricular myocardium in a failing heart releases cardiac troponin, not NT-proBNP.[31] Myocardial cell death, apoptosis, normal myocardial cell turnover, cellular release of proteolytic troponin breakdown products, enhanced cellular wall permeability, and production and release of membranous blebs.[32] TNF-alpha, IL-1-beta, and IL-6 make cardiac cell membranes more permeable. This can release troponin. In CHF, inflammation may cause troponin release. In this study, all 48 CHF patients administered beta-blockers saw a reduction in hsTnT and hsCRP. This supports the concept that CHF inflammation and myocardial injury are connected. Bisoprolol reduced hsTnT and hsCRP more than carvedilol. Bisoprolol may be better than carvedilol for preventing inflammation-related myocardial damage. Bisoprolol lowered IL-1 beta mRNA expression in the myocardium of rat models of hypertensive diastolic heart failure. Bisoprolol may have a direct anti-inflammatory impact, supporting the present findings.[33]

Overproduction of reactive oxygen species (ROS) compared to antioxidant defences may potentially contribute to CHF.[34] ROS damage cardiac cells, proteins, and lipids, and DNA. This causes persistent damage and death of CHF-linked cardiac cells. ROS accelerate cardiac remodelling, worsening CHF. They change proteins critical for how the heart contracts and relaxes, harming contractile function. They activate hypertrophic signalling kinases, transcription factors, and apoptosis. ROS boosts cardiac fibroblasts and activates matrix metalloproteinases, changing extracellular matrix. CHF is caused by cell changes.[35] Beta-blockers, ARBs, and statins can lower oxidative stress and enhance CHF heart and vascular function. Carvedilol is an antioxidant beta-blocker. Carvedilol stops lipid peroxidation in CHF patients by scavenging free radicals. In a rabbit heart failure model generated by fast pacing, Kawai et al. found that carvedilol was more effective than metoprolol at decreasing 8-oxo-7, 8-dihydro-2'-deoxyguanosine in the myocardium. Interestingly, carvedilol's effect was stronger than propranolol and doxazocin. The result revealed carvedilol's capacity to fight free radicals may not depend on blocking alpha-receptors. Bisoprolol and carvedilol reduced oxidative stress markers d-ROMs in this study. However, carvedilol reduced d-ROMs. This confirms that carvedilol is a superior antioxidant than beta-1 selective blockers.[37] In this investigation, beta-blocker-induced decreases in hsTnT and NT-ProBNP were not associated to d-ROMs. The antioxidant capabilities of beta-blockers may not protect the myocardium directly, but may improve CHF in other ways. Inflammation and oxidative stress are associated pathophysiologies. Both mechanisms are found in numerous illnesses, including CVD. Inflamed cells emit ROS. This exacerbates oxidative stress. ROS can initiate intracellular signalling that enhances proinflammatory gene expression. Inflammation and oxidative stress are connected pathophysiological phenomena. Both can cause the other, therefore which is more essential depends on the pathophysiology.[38] Kamezaki et al. found a link between hsCRP and d-ROMs in coronary artery disease patients. Decreases in hsCRP and d-ROMs after beta-blocker medication were associated in all 48 CHF patients. Bisoprolol and carvedilol both dropped hsCRP and d-ROMs, but bisoprolol did so better for hsCRP. Both bisoprolol and carvedilol diminish inflammation and oxidative stress. Bisoprolol may work better than carvedilol. This study suggests that CHF-caused inflammation may be connected to myocardial damage and that bisoprolol may reduce inflammation better than carvedilol. Carvedilol may reduce oxidative stress better than bisoprolol for treating CHF. Since inflammation and oxidative stress affect how terrible CHF is and how it will turn out, beta-blockers may be beneficial in treating CHF by reducing these pathophysiologic states. Both bisoprolol and carvedilol enhance CHF prognosis. Future CHF treatments may be dependent on an individual's pathophysiology, such as inflammation- or oxidative stress-dominance.

CONCLUSION

Patients with CHF who were treated with both bisoprolol and carvedilol had less cardiac overload and less myocardial damage. Both beta-blockers also reduce inflammation and protect cells from damage. The ability of beta-blockers to protect the heart muscle could be linked to their ability to reduce inflammation. However, bisoprolol and carvedilol are not exactly the same in these ways. In the future, CHF patients might be able to get more benefits by using beta-blockers in the right way based on their own pathophysiology.

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