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Protective effects of bisoprolol against myocardial injury and pulmonary dysfunction in patients with chronic heart failure

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ABSTRACT

Objectives: This study was designed to elucidate differences in effects of 2 beta blockers, bisoprolol and carvedilol, in patients with chronic heart failure.
Background: Although the beta blockers bisoprolol and carvedilol are commonly used in patients with chronic heart failure, differences in the efficacy and safety of these medications have not been established in this patient population.
Methods: Patients with chronic systolic heart failure, defined as ≤45% ejection fraction, who had received intensive medical therapy with the exception of beta blockers, were randomly assigned to receive either bisoprolol or carvedilol for 24 weeks.
Results: A total of 67 patients were enrolled in the study (bisoprolol: 38 patients, carvedilol: 29 patients). No difference was observed in the improvement of NYHA class, ejection fraction, or N-terminal pro-brain-type natriuretic peptide level between groups. In contrast, the level of high sensitivity troponin T decreased in the bisoprolol group [−4.1 ± 0.9 to −4.5 ± 0.8 log (ng/ml), P = 0.003], but did not change in the carvedilol group [−4.4 ± 1.1 to −4.6 ± 0.8 log (ng/ml), P = 0.161]. Forced expiratory volume in the first second increased in the bisoprolol group [2.26 ± 0.70 to 2.40 ± 0.70 (L), P = 0.014], but did not change in the carvedilol group [2.53 ± 0.71 to 2.59 ± 0.78 (L), P = 0.127].
Conclusion: Bisoprolol might be superior to carvedilol in providing protection from myocardial injury and preserving pulmonary function in patients with chronic systolic heart failure.

1. Introduction

The effects of beta blockers on long-term morbidity and mortality have been established in patients with chronic heart failure with reduced left ventricular function [1–4]. Among various beta blockers, only carvedilol and bisoprolol are approved by Japanese guidelines for treatment of patients with chronic heart failure [5]. Bisoprolol is highly selectivity for the beta-1 receptor, while carvedilol is a non-selective beta blocker with simultaneous alpha receptor antagonist effects [6].

Brain-type natriuretic peptide (BNP) and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) are established biomarkers used in the diagnosis and prognosis of chronic heart failure [7,8]. Recently, high sensitivity troponin T (hsTnT), which is released by injured myocardial tissue, has also been investigated as a marker of heart failure [11]. Although several reports have compared bisoprolol and carvedilol in patients with chronic heart failure in Japan [12] as well as in western countries [13], these reports did not focus on hsTnT levels. We thus designed the "Bisoprolol Improvement Group for chronic heart failure treatment study in Dokkyo Medical University" (BRIGHT-D) to directly compare drug tolerability, heart failure symptoms, biomarkers, and cardiac and pulmonary function between bisoprolol and carvedilol in patients with chronic heart failure with reduced ejection fraction.

2. Methods

2.1. Study population

The study was designed as a prospective, open label, randomized trial and was conducted at Dokkyo Medical University (UMIN000011261). The study protocol was approved by the Institutional Review Committee on Human Research, Dokkyo Medical University, and informed consent was obtained from each patient prior to enrollment.

Study subjects included hospitalized patients with chronic heart failure who were not being treated with beta blockers and who fulfilled the following inclusion criteria: 1) age ≥ 20 yrs. old, 2) left ventricular ejection fraction ≤45% by echocardiography, 3) stability of heart failure symptoms, as demonstrated by New York Heart Association (NYHA) functional class, for one month prior to study initiation, and 4) receiving angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Exclusion criteria were as follows: 1) severe heart failure, defined as NYHA class IV, 2) serious arrhythmias such as ventricular tachycardia or sustained bradycardia (<60/min), including

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second-degree atrio-ventricular block without pacemaker implantation, 3) acute coronary syndrome within 3 months of study initiation, 4) sustained hypotension (resting systolic blood pressure < 90 mm Hg), 5) serious hepatic or renal dysfunction (serum alanine aminotransferase level ≥ 50 IU/L and/or serum creatinine level ≥ 3.0 mg/dL), 6) contraindication to beta blockers, such as bronchial asthma, and 7) the treating physician's objection to inclusion in the study.

2.2. Study protocol

Eligible patients were randomly assigned to receive either bisoprolol or carvedilol. Patients in the bisoprolol group received a once-daily dose of bisoprolol, starting at 0.625 mg/day, and increased every two weeks as tolerated (1.25, 2.5 and 3.75 mg/day) to a final maximum dose of 5 mg/day. Patients in the carvedilol group received twice-daily carvedilol, starting at 1.25 mg twice daily (2.5 mg/day), and increased every two weeks as tolerated (5 and 10 mg/day) to a final maximum dose of 20 mg/day. Patients were assessed at baseline and after 24 weeks of treatment for the following parameters: NYHA functional class, heart rate, blood pressure, cardiothoracic ratio on the chest roentgenogram, estimated glomerular filtrating rate (eGFR), blood hemoglobin level, and serum levels of NT-ProBNP and hsTnT. Echocardiographic and pulmonary function parameters were also assessed (Fig. 1). Patients who discontinued the study drugs for any reason were eliminated from the final data analysis.

2.3. Measurement of NT-ProBNP and hsTnT levels

Blood samples obtained for measurement of NT-ProBNP and hsTnT were immediately centrifuged at 1500 × *g* for 15 min at room temperature. The serum was frozen and stored at −80 °C until analyzed. NT-ProBNP determinations were performed using the Roche Diagnostic NT-ProBNP electrochemiluminescent immunoassay kit on an Elecsys 2010 analyzer (Roche Diagnostics Ltd., Rotkreuz, Switzerland) according to the manufacturer's recommendations [14]. The intra-assay variability of the NT-ProBNP test at our institute is 3.9%. Serum hsTnT was measured by Elecsys Troponin T High Sensitive immunoassay (Roche Diagnostics Ltd., Rotkreuz, Switzerland). The hsTnT measurements in our study conformed to guideline precision requirements for the universal definition of myocardial infarction: an increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population, and optimal precision (coefficient of variation) at the 99th percentile decision limit should be defined as ≤10% [15]. The normal range of the hsTnT troponin marker in a healthy adult population is ≤0.014 ng/ml (99th percentile) [16]. The limit of detection, that is, the smallest concentration that can be reliably measured by an analytical procedure, is 0.003 ng/ml [17].

2.4. Echocardiography

Transthoracic echocardiography was performed with patients in the left lateral decubitus position. 2D, M-mode, and color- and tissue-Doppler images were obtained using a SONOS 7500 (Philips Ultrasound, Bothell, Washington, WS, USA) or Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) system. Image acquisition was performed by 2 independent cardiologists who were unaware of the study design. Wall and valve motion were observed in the 2D image, and valvular regurgitation was evaluated by color-flow imaging. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were determined in the four- and two-chamber apical views using the modified Simpson's method, and left ventricular ejection fraction (LVEF) was calculated as [(LVEDV − LVESV) / LVEDV] × 100 (%) from these results. Left ventricular diastolic transmitral flow was recorded at the tip of the mitral valve leaflet in the pulsed-Doppler apical view. The peak early diastolic flow velocity (E wave) was determined based on the flow patterns. The early diastolic mitral annular velocity (E′) was determined at the mitral annular septum by tissue Doppler in the four-chamber apical view, and the E to E' ratio (E/E') was calculated. Right ventricular dimension (RVD) was also measured as a basal right ventricular dimension, i.e., maximal transversal dimension in the basal one third of right ventricular inflow at end-diastole in the right ventricle-focused apical 4 chamber view. These parameters were determined by recording 3 cardiac cycles under stable conditions, and the mean of the measurements was used for analysis.

2.5. Pulmonary function testing

Spirometry was performed in our pulmonary function laboratory using standard procedures for grading the quality of the test and its interpretation, using a pulmonary function test system, FUDAC-77N (Fukuda Denshi, Tokyo, Japan). The subjects, who were seated and wearing nose clips, performed a forced exhalation, which yielded the forced expiratory volume in the first second ($FEV_{1.0}$). Each subject was allowed to perform up to 15 forced expiratory maneuvers, in order to obtain three acceptable maneuvers with the highest $FEV_{1.0}$.

2.6. Statistical analysis

Clinical data were expressed as the mean ± standard deviation for continuous variables or the number (percent) of patients for categorical variables. Normality for distribution of continuous variables was assessed using the Shapiro–Wilk test. Inter-group comparison of the categorical variables was performed using the chi-square test or the Fisher's exact test. The normally distributed continuous variables were compared using the paired and unpaired t-tests for intra-group and inter-group comparisons, respectively. If variables were not normally distributed, paired or unpaired Mann–Whitney U-tests for intra-group and inter-group comparisons were used. Since the values of NT-ProBNP and hsTnT exhibited a skewed distribution, the log transformation was used for analysis. Inter-group comparison of the change in log transformed hsTnT levels was also analyzed after adjustment for the change in heart rate, using a mixed model analysis of variance (ANOVA). All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute, Cary, NC, USA). A P value < 0.05 was considered significant.

3. Results

3.1. Patient outcome analysis

A total of 84 patients (42 in the bisoprolol group and 42 in the carvedilol group) were enrolled in the trial. However, 17 patients (4 in the bisoprolol group and 13 in the carvedilol group) were eliminated from data analysis. Among these 17 patients, 11 patients (4 in the bisoprolol group and 7 in the carvedilol group) discontinued taking the study drugs because of the following adverse outcomes: coronary bypass graft surgery in 3 (carvedilol group), percutaneous coronary

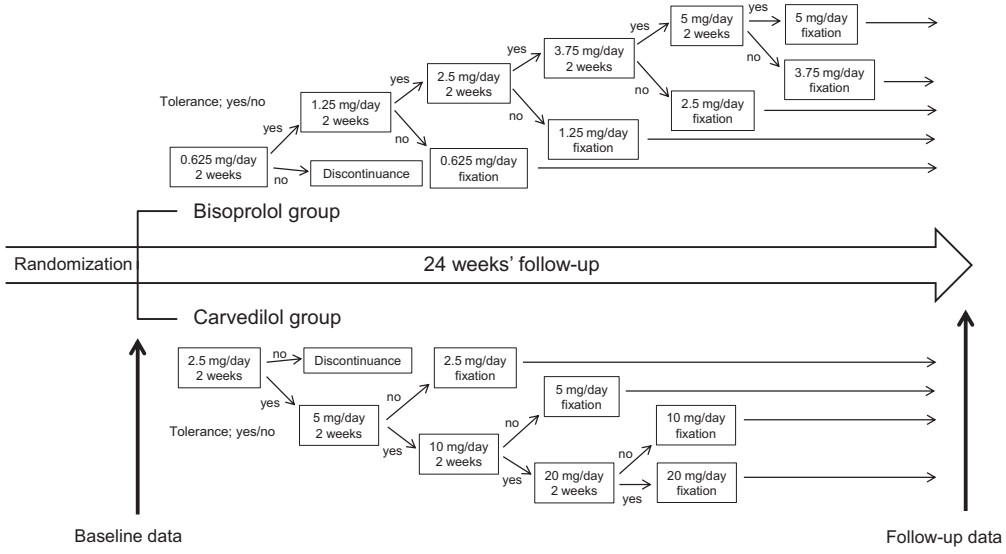

Fig. 1. Study protocol. After randomization, patients were started on low doses of either bisoprolol or carvedilol. Medication doses were gradually increased every 2 weeks, based on drug tolerance, to a maximum dose target for each medication. Data were acquired at baseline and after 24 weeks of treatment.