International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

A prospective study on the impact of heart rate control achieved with metoprolol on cardiac performance, motor function and quality of life in Chinese chronic heart failure patients

Yong Meng *, Xuelu Liu, Juan Liu, Xianliang Cheng

Department of Cardiology, The Second Affiliated Hospital of Kunming Medical University, No. 374, Dianmian Road, Kunming, Yunnan 650101, China

ARTICLE INFO

Article history:
Received 15 August 2016
Accepted 6 November 2016
Available online xxxx

Keywords:
Metoprolol
Heart rate
Quality of life
Motor function
Cardiac performance
Heart failure

ABSTRACT

Background: To prospectively evaluate the impact of metoprolol achieved heart rate (HR) on cardiac-motor function and quality of life (QoL) in chronic heart failure (CHF) patients.

Methods and results: Between February 2013 to April 2016, association of HR reduction with haemodynamic indices, motor function and QoL in CHF patients with HR > 80 bpm receiving metoprolol 23.75 mg or 47.5 mg q.d was studied. Overall, 154 patients (median age, 66.39 years; males, n = 101; females, n = 53) were enrolled, whose average resting HR decreased significantly from baseline value of 82.72 ± 6.73 to 69.38 ± 3.57, 67.72 ± 2.61, 66.50 ± 3.14 and 64.86 ± 3.21 bpm in the 1st, 3rd, 6th and 12th months post metoprolol intervention, respectively ($P < 0.0001$). Similarly, the ejection fraction ($r = -0.6461$, $P < 0.0001$), cardiac output ($r = -0.5238$, $P < 0.0001$), cardiac index ($r = -0.5378$, $P < 0.0001$) and veterans specific activity questionnaire scores ($r = -0.4088$, $P < 0.0001$) were significantly associated with the reduction in HR after 12 months. The improvement in 6-min walk test was independent of HR reduction ($P = 0.005$). Similarly, QoL as measured by short form-8 questionnaire (SF-8) but not Minnesota Living with Heart Failure was significantly improved at the 12th–month. However, this was not associated with the reductions in HR.

Conclusion: Metoprolol achieved HR control was associated with improvement in cardiac performance and motor function but not QoL in patients with CHF.

1. Introduction

Beta-blockers are known to increase the ventricular function, improve quality of life (QoL) and decrease mortality in Chronic heart failure (CHF) patients, despite their negative inotropic effects, which may lead to deterioration of haemodynamic and HF symptoms [1]. The negative chronotropic effects of these drugs are known to be well correlated with these beneficial changes [2–4]. The results from the meta-analysis of smaller randomized clinical trials have indicated the beneficial effects of beta-blockers in significantly decreasing the total mortality and incidence of sudden death in HF patients [5–10]. Metoprolol, a selective beta-1–adrenergic receptor inhibitor, increased QoL, left ventricular fraction, hospitalizations and exercise tolerance at 12 months compared with placebo [11]. However, heart rate (HR) achievement in CHF patients is suboptimal. A recent study indicated that HR at discharge was significantly elevated in hospitalized HF patients with reduced ejection fraction (EF) [12]. Further, it is reported that reversal of beta-blocker–induced bradycardia had worse outcomes on ventricular function in pacemaker-dependent heart failure patients [13]. These findings suggest that reduction in HR is an important mediator of beta-blocker effects. Moreover, the effect of beta-blockade on exercise tolerance in such patients is uncertain. This uncertainty may be owing to the fact that exercise tolerance is HR dependent and because beta-blockers can significantly reduce the HR. [14] Further, the impact of metoprolol on the QoL of patients is encouraging as studies report an improved QoL which correlated well with the changes in traditional clinical parameters [15–18]. Although unequivocal benefits have been exhibited, beta-blockers may also worsen the condition of HF patients upon initial treatment, which may correlate well with their negative chronotropic and inotropic properties. A recent study reported that aggressive HR control was difficult in CHF patients, which was not associated with improved QoL outcomes [19]. To date, no other prospective studies are conducted to further identify the impact of HR control achieved with metoprolol on the overall cardiac function, motor function and QoL of

Abbreviations: ACEIs, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; CHF, Chronic Heart Failure; CI, Cardiac Index; CO, Cardiac Output; GFR, Glomerular Filtration Rate; HR, Heart Rate; LVEF, Left Ventricular Ejection Fraction; METs, Metabolic Equivalents; MLHFQ, Minnesota Living With Heart Failure Questionnaire; 6MWT, 6-Minute Walk Test; NYHA, New York Heart Association; QoL, Quality of Life; SBP, Systolic Blood Pressure; SF-8, Short Form-8 Questionnaire; VSAQ, Veterans Specific Activity Questionnaire.

* Corresponding author at: Department of Cardiology, The Second Affiliated Hospital of Kunming Medical University, No. 374, Dianmian Road, Kunming, Yunnan 650101, China.
E-mail address: mengyong76@gmail.com (Y. Meng).

http://dx.doi.org/10.1016/j.ijcard.2016.11.115
0167-5273/

patients with chronic heart diseases. Hence, this study was prospectively designed to determine the relative contribution of changes in HR achieved with metoprolol succinate controlled release tablets to the cardiac performance, motor function and QoL observed during the follow-up duration of 12 months in Chinese patients with CHF.

2. Methods

2.1. Study design and patient population

This was a prospectively designed study using patients as their own controls. The protocol was approved by the institutional review board and conformed to the declaration of Helsinki and its subsequent revisions. The study was executed from February 2013 to April 2016 at The Second Affiliated Hospital of Kunming Medical University. Patients with CHF were enrolled into the study. As the study goal was to determine if the HR control (60–70 bpm) achieved with metoprolol succinate controlled release tablets results in better health, improved motor function and QoL outcomes, we included only patients with resting HR > 80 bpm. Patients with HR < 60 bpm, systolic blood pressure (SBP) < 90 mmHg, those who have used metoprolol in the recent 3 months, those with <6 months expected survival, pacemaker-dependent patients, those with contraindications to beta-blockers, those who are currently using class I or class III anti-arrhythmic agents and those who have undergone coronary bypass surgery or experienced a recent heart attack were excluded from the study. All the patients were included in the study only after obtaining a signed informed consent.

2.2. Treatment intervention and follow-up

Baseline data were collected from patients who were on initial 23.75 or 47.5 mg metoprolol continuous release tablets (Betaloc® ZOK, AstraZeneca, Sweden), and the dose was increased by 23.75 mg every 7 days until the target HR level (60–70 bpm) was achieved in some patients during follow-up. The average dose used to reach the target goal was 99.75 mg (47.5–142.5 mg). All patients were followed up at 1, 3, 6 and 12 months from intervention for final outcomes measurement.

2.3. Study outcomes

The primary outcomes were change in cardiac function as measured in terms of EF (%), cardiac output (CO [L/min]) and cardiac index (CI, [L/min $*$ m^2]); exercise tolerance or motor function measured by a standard 6-Minute Walk Test (6MWT) [20] and Veterans Specific Activity Questionnaire (VSAQ); and QoL measured by an 8-item short form questionnaire (SF-8) and Minnesota Living with Heart Failure questionnaire (MLHFQ). The association of the HR control achieved with metoprolol and other clinic pathological findings of the patient with the changes in the above-discussed primary objectives was assessed as the secondary outcome.

2.4. HR and cardiac function measurements

Resting HR at baseline and 1, 3, 6 and 12 months post metoprolol intervention was measured by electrocardiography after 3 min of rest. SBP was also monitored simultaneously using a sphygmomanometer. Other cardiac parameters such as CI, EF and CO were measured using echocardiography.

2.5. Administration of the questionnaires

VSAQ was self-administered by patients before the exercise testing to assess the motor function changes associated with HR changes with the use of metoprolol. VSAQ is a brief questionnaire comprising 13 metabolic equivalents (METs) designed to determine the specific daily activities associated with symptoms of cardiovascular disease (fatigue, chest, pain, claudication or shortness of breath) [21]. Patients were instructed to determine which of the activities could typically cause these symptoms during their daily activities on each follow-up. SF-8 is another generic self-administered 8-item short-form health-related QoL questionnaire designed to determine the metoprolol-associated changes in physical and mental aspects of patients' health [22]. MLHFQ is a disease-specific 21-item questionnaire designed to determine the physical, emotional and socio-economic aspects of health-related QoL. Patients were asked to score the effect of their illness at baseline and during the follow-ups on a particular aspect of their lives on a scale of 0 to 5, in which 0 represents no effect and 5 represents a large effect. The lower the score, the better the patient's health. A score of <24 signifies good health, 24 to 45 signifies moderate health and 45 to 105 (maximum) indicates poor health [22].

2.6. Statistical analyses

Baseline characteristics are reported as descriptive data with counts, percentages and mean ± SD. Differences in 6MWT, SF-8, VSAQ and MLHFQ at different follow-up periods were compared with baseline using repeated measures one-way ANOVA, followed by the post hoc Dunnet's multiple comparison test. The Pearson correlation analysis was performed to estimate the association of HR control achieved with metoprolol with the motor function, QoL and cardiac function. A P value of <0.05 was considered statistically significant for all the analyses.

3. Results

3.1. Baseline characteristics

Of a total of 169 patients included in the study, 11 were excluded, as they were intolerant to metoprolol increments, and 4 patients were lost to follow-up. Finally, data of 154 patients (median age, 66.39 years; males, n = 101; females, n = 53) were obtained in this study. At baseline, the mean glomerular filtration rate (GFR) was found to be 73.9 ± 26.8 mL/min/1.73 m^2 and the mean Body Mass Index was 23.85 ± 3.62 kg/m^2. The majority of the patients were New York Heart Association (NYHA) class III/IV (n = 145, 94.15%), had a previous history of stroke (n = 137, 88.96%) and hypertension (n = 115, 74.67%) and were on angiotensin-convertase-enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) (n = 149, 96.75%) and anti-thrombotic medication (n = 146, 94.80%). Details on the baseline characteristics are reported in Table 1.

3.2. Change in HR and SBP

The average metoprolol dose to reach the target HR goal was 99.75 mg. The average resting HR as measured by resting electrocardiogram decreased significantly from a baseline value of 82.72 ± 6.73 to 69.38 ± 3.57, 67.72 ± 2.61, 66.50 ± 3.14 and 64.86 ± 3.21 bpm at the 1st, 3rd, 6th and 12th months post metoprolol treatment, respectively ($P < 0.0001$). Similarly, there was a significant drop in SBP from a baseline value of 126.73 ± 13.64 to 123.35 ± 12.31 ($P = 0.023$) at the 1st-month follow-up, followed by a slight increase of 124.70 ± 9.67 at the 3rd-month follow-up and 125.11 ± 6.67 at the 6th-month follow-up. At the 12th-month follow-up, the SBP levels reached to a stable level of 123.37 ± 6.88 mmHg ($P = 0.0067$), which was comparable with the levels observed at 1st month following metoprolol treatment (Table 2).

3.3. Cardiac performance, motor function and QoL outcomes post treatment

Post metoprolol treatment, the EF decreased from a baseline value of 37.61 ± 5.95 to 35.08 ± 6.16 ($P = 0.0003$) at the 1st-month follow-up and 35.71 ± 5.09 ($P = 0.0028$) at the 3rd-month follow-up, followed by a stable increase to 47.85 ± 4.49 ($P < 0.0001$) and 50.24 ± 3.63 ($P < 0.0001$) in the 6th- and 12th-month follow-ups, respectively. There was a significant decrease in the CO from a baseline value of 3.17 ± 0.46 to 2.60 ± 0.54 and 2.73 ± 0.58 in the 1st- and 3rd-month follow-ups, respectively, whereas the CO significantly increased to 3.50 ± 0.30 at the 6th-month follow-up and remained stable at 3.54 ± 0.19 ($P < 0.0001$) until the 12th-month follow-up. Similarly, the CI decreased from a baseline value of 1.78 ± 0.21 to 1.72 ± 0.27 at the 1st-month follow-up (non-significant) and then significantly increased to 2.60 ± 0.18, 2.60 ± 0.18 and 2.72 ± 0.18 at the 3rd-, 6th- and 12th-month follow-ups, respectively ($P < 0.0001$).

Similarly, when tested for changes in motor function, the meters walked during the 6MWT significantly decreased from a baseline value of 368.81 ± 33.95 to 341.36 ± 32.56 ($P < 0.0001$) at the 1st-month follow-up, followed by a slight increase to 350.75 ± 33.10 ($P < 0.0001$ vs. 1st-month) at the 3rd-month follow-up and further showed a significantly steady rise to 398.50 ± 21.57 ($P < 0.0001$) and 416.44 ± 15.93 ($P < 0.0001$) at the 6th- and 12th-month follow-ups, respectively. Similarly, the scores of VSAQ decreased from a baseline value of 6.51 ± 1.07 to 4.92 ± 0.88 and 5.53 ± 1.03 at the 1st- and 3rd-month follow-ups, respectively, and significantly increased to 7.85 ± 1.04 and 8.26 ± 0.84 at the 6th- and 12th-month follow-ups, respectively.

The QoL as measured by the SF-8 significantly decreased from a baseline value of 44.01 ± 2.70 to 39.38 ± 2.06 ($P < 0.0001$) and 42.36 ± 3.48 ($P < 0.0001$) at the 1st- and 3rd-month follow-ups, respectively, and showed a significantly sharp increase to 48.87 ± 1.21 ($P < 0.0001$) and 52.09 ± 2.75 ($P < 0.0001$) at the 6th- and 12th-

Please cite this article as: Y. Meng, et al., A prospective study on the impact of heart rate control achieved with metoprolol on cardiac performance, motor function and qualit..., Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.11.115