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ORIGINAL ARTICLE

Efficacy of ivabradine in idiopathic dilated cardiomyopathy patients with chronic heart failure

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KEYWORDS

Ivabradine;
Heart failure;
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Abstract *Background:* The aim of this study was to investigate the effect of ivabradine on symptoms, quality of life, effort tolerance, and echocardiographic parameters in patients with idiopathic dilated cardiomyopathy presenting with New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms.

Methods: We screened 167 patients hospitalized for NYHA class III or IV chronic HF symptoms and left ventricular (LV) ejection fraction $<40\%$. Of these, 53 were randomly assigned to either guidelines-based medical therapy alone (23 patients, control group) or ivabradine as add-on therapy (30 patients) for 3 months with about 1 year follow up.

Results: After 3 months' treatment, adding ivabradine significantly reduced the heart rate from 96 to 72 bpm ($p < 0.0001$ versus control group), with more improvement in echocardiographic LV dimensions, LV volumes, LV ejection fraction ($p = 0.045$), NYHA class symptoms ($p = 0.004$), exercise tolerance ($p = 0.03$), and quality of life ($p = 0.02$). The average number of hospitalizations for HF over a mean longer-term follow-up of 13.5 months was 1.0 ± 1.4 in the ivabradine group versus 2.1 ± 1.1 in the control group ($p = 0.003$). Heart rate reduction was significantly correlated

Abbreviations: ACE, angiotensin-converting enzyme; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association.

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with better exercise tolerance, quality of life, LV ejection fraction, and NYHA class, together with fewer HF hospitalizations. Multivariate analysis showed heart rate reduction to be a stronger predictor for better LV ejection fraction ($p = 0.024$) and decreased hospitalizations than ivabradine use.

Conclusion: Adding ivabradine to optimal medical treatment in HF patients improved symptoms, quality of life, effort tolerance, and echocardiographic parameters, and reduced hospitalization. This beneficial ivabradine effect is probably due to its heart rate–reducing properties.

1. Introduction

The prevalence of chronic heart failure (HF) in the general population has been estimated to be around 2–3%.[1] Dilated cardiomyopathy (DCM) is the most common cause of HF in young adults.[2] Despite recent advances in the treatment of HF, it remains a disabling disorder that can severely affect the patient's quality of life, and the prognosis remains poor.[3–5] It is therefore crucial to develop novel therapeutic approaches to the treatment of chronic HF. The recognition of elevated heart rate as a risk factor for cardiovascular morbidity and mortality[6–8] and its association with sudden cardiac death[9–11] has made lowering the heart rate in HF patients one of the most important therapeutic approaches. Beta-blockers are known to improve morbidity and mortality in patients with DCM.[12] However, the use of beta-blockers in advanced HF patients is limited due to side effects, including negative inotropic effects and associated hypotension, which could worsen the HF,[13,14] slow intra-cardiac conduction, and their effect on the peripheral vasculature and the airways.

A new class of selective heart rate–reducing agents has been discovered, the If channel inhibitors, of which ivabradine is the only currently available member. Ivabradine selectively inhibits cardiac pacemaker activity, thus allowing heart rate reduction without affecting myocardial contractility, conduction velocity, and refractoriness, or arterial blood pressure.[15] Ivabradine has been shown to improve remodeling of extracellular matrix in animal models of HF.[16] Ivabradine has been demonstrated to have some benefit in coronary artery disease,[17] but its role in HF of non-ischemic origin is not yet established.

The aim of the study described here was to investigate the effect of ivabradine on clinical and echocardiographic parameters in patients with idiopathic DCM presenting in New York Heart Association (NYHA) classes III or IV.

2. Methods

2.1. Patients

Patients suffering from symptomatic HF referred to the Department of Cardiology of Ain Shams University were screened and examined for left ventricular (LV) cardiomyopathy. Initial screening for all patients included assessment for ischemic heart disease by history, perfusion study or angiography, routine laboratory test for liver and renal functions, and specific investigations for thyrotoxicosis and collagen disease. The study protocol was approved by the committee of research and medical ethics of the cardiology department of Ain Shams University in October 2008, and informed consent was obtained from all patients.

Inclusion criteria were idiopathic DCM patients with NYHA class III or IV on presentation and ejection $< 40\%$ by echocardiography. Patients were in sinus rhythm with resting heart rate > 70 bpm as measured on 12-lead electrocardiogram (ECG) performed after at least 5 min rest. Exclusion criteria included NYHA class I, coronary artery disease, significant rheumatic valvular heart disease, thyrotoxic heart disease, atrial fibrillation, severe renal impairment with serum creatinine > 3 mg/dL, and severe hepatic impairment with signs of liver cell failure.

2.2. Study design

Prior to randomization, all patients received diuretics according to symptoms plus spironolactone (at least 25 mg/day), digoxin, angiotensin converting enzyme (ACE) inhibitor uptitrated to the maximally tolerated dose, and carvedilol also uptitrated to the maximally tolerated dose. All patients had to be on stable treatment for at least 4 weeks before randomization.

A computer-driven randomization program was used to allocate the remaining patients to receive either optimal medical treatment for LV systolic HF according to the European Society of Cardiology guidelines[1] (control group), or optimal medical treatment with ivabradine added on top (ivabradine group) for 3 months. Ivabradine was slowly uptitrated according to the following sequence: (i) Half a 5-mg tablet once daily for 1 week; (ii) half a 5-mg tablet twice daily for 1 week; (iii) one 5-mg tablet in the morning and half a 5-mg tablet daily in the evening for 1 week; (iv) one 5-mg tablet every 12 h for 1 week; (v) one 7.5-mg tablet in the morning and half a 7.5-mg tablet in the evening 1 week; and (vi) one 7.5-mg tablet every 12 h. This uptitration of ivabradine was guided by the patients' heart rate in each visit and their tolerance of the preceding dose. The target dose was not the maximum dose of 15 mg per day, but rather the dose that slowed the resting heart rate to < 70 bpm provided that the patient tolerated that dosage.

2.3. Assessments

Baseline assessments at randomization included verification of inclusion and exclusion criteria, relevant medical history, physical examination including blood pressure (systolic and diastolic) recording of concomitant treatments, and assessment of NYHA class. Echocardiographic assessment was performed using vivid5 (Vingmed, GE) system in a core echocardiographic laboratory by an operator blinded to the patient's clinical data. Images were acquired in left lateral position in which standard apical four-chamber, two-chamber, parasternal short-axis views were acquired. LV dimensions were measured by M-mode of short axis, then fraction shortening and ejection fraction were calculated by Techoliz formula. LV volumes were measured in apical four-chamber views by