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Original Article

A comparative study of ivabradine and atenolol in patients with moderate mitral stenosis in sinus rhythm

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ABSTRACT

Background: Beta-blockers are frequently used in patients with mitral stenosis to control the heart rate and alleviate exercise-related symptoms. The objective of our study was to examine whether ivabradine was superior to atenolol for achieving higher exercise capacity in patients with moderate mitral stenosis in sinus rhythm. We also evaluated their effects on left ventricular myocardial performance index (MPI).

Methods and results: Eighty-two patients with moderate mitral stenosis in sinus rhythm were randomized to receive ivabradine ($n = 42$) 5 mg twice daily or atenolol ($n = 40$) 50 mg daily for 6 weeks. Transthoracic echocardiography and treadmill test were performed at baseline and after completion of 6 weeks of treatment. Mean total exercise duration in seconds markedly improved in both study groups at 6 weeks (298.57 ± 99.05 s vs. 349.12 ± 103.53 s; $p = 0.0001$ in ivabradine group, 290.90 ± 92.42 s vs. 339.90 ± 99.84 s; $p = 0.0001$ in atenolol group). On head-to-head comparison, there was no significant change in improvement of exercise time between ivabradine and atenolol group ($p = 0.847$). Left ventricular MPI did not show any significant change from baseline and at 6 weeks in both drug groups (49.8% ± 8% vs. 48.3% ± 7% in ivabradine group, 52.9% ± 10% vs. 50.9% ± 10% in atenolol groups; $p = 0.602$).

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Conclusion: Ivabradine or atenolol can be used for heart rate control in patients with moderate mitral stenosis in sinus rhythm. Ivabradine is not superior to atenolol for controlling heart rate or exercise capacity. Left ventricular MPI was unaffected by either of the drugs.
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1. Introduction

Rheumatic mitral stenosis is the commonest valvular heart disease in developing countries.[1] Beta-blockers or calcium channel blockers are used in patients with mitral stenosis for heart rate control.[2] These drugs act by reducing exercise-induced rise in heart rate and cardiac output and thereby decreasing pulmonary venous pressure and improving effort-related symptoms.[3,4] Results from various clinical and hemodynamic studies with beta-blocker have been conflicting.[3,5–12] Studies with tissue Doppler imaging have shown left ventricular dysfunction in patients with isolated rheumatic mitral stenosis.[13,14] These studies did not discuss negative chronotropic agents, the use of which may also have contributed for higher prevalence of ventricular dysfunction.

Ivabradine is a pure heart rate lowering drug that acts by inhibiting the I_f current, an important ionic current that determines the pacemaker activity of sinus node. It has selective action on the sinus node and is thus devoid of the usual side effects of beta-blockers.[15] Ivabradine seems as an attractive option for heart rate reduction in patients with mitral stenosis in sinus rhythm. One recent study has shown that patients with rheumatic mitral stenosis on ivabradine have higher total exercise duration and a lower peak heart rate during exercise than patients on atenolol.[16] The present study was undertaken to evaluate the effects of ivabradine on exercise capacity and left ventricular function in patients with moderate mitral stenosis in sinus rhythm.

2. Methods

This study was designed as a randomized, open-label, parallel group trial of ivabradine and atenolol in patients with moderate mitral stenosis in sinus rhythm. The study was approved by institutional ethics committee. A written informed consent was obtained from patients included in the study. The trial was registered at http://ctri.nic.in (identifier: CTRI/2012/10/003076). The study period was from November 2012 to February 2014.

3. Protocol

We included consecutive patients (age between 18 and 60 years) with moderate mitral stenosis (2-D mitral valve area 1–1.5 cm^2) in sinus rhythm in NYHA functional class I–II. Patients were excluded if they had other significant valvular lesions, NYHA functional class III–IV, inability to perform treadmill test (TMT)/contraindication for TMT, urgent need for surgical treatment or balloon mitral valvotomy, pregnancy, known allergy/intolerance to study drugs, known coronary artery disease, or left ventricular ejection fraction (EF) less than 50%. For those patients who were on heart rate reducing medication, the drug was discontinued for a period of five half-lives. Baseline transthoracic echocardiography and TMT were performed. The patients were randomized according to computer-generated random number sequence. Participants randomized to ivabradine arm received 5 mg twice daily and those randomized to atenolol arm received 50 mg once daily for a period of 6 weeks. Echocardiography and TMT were repeated at 6 weeks. Primary outcome was change in total duration of exercise from baseline TMT and at 6 weeks. Secondary outcome was change in the LV myocardial performance index (MPI) by tissue Doppler imaging. The trial protocol is depicted in Fig. 1.

Detailed clinical evaluation of all study subjects was done. Transthoracic echocardiography was done to assess mitral valve area, mean gradient across the mitral valve, left atrial size, tricuspid regurgitation, pulmonary artery pressure, and EF as per recommendations of the American Society of Echocardiography.[17] Bruce TMT protocol was used to assess heart rate response, exercise duration, and peak heart rate achieved. Operators who were blinded to the treatment arm performed TMT. Exercise was terminated on development of symptoms or attainment of more than 10 metabolic equivalents.

Tissue Doppler indices like isovolumic contraction time (ICT), isovolumic relaxation time (IRT), and ejection time (ET) were measured for obtaining MPI at septal and lateral mitral annulus in apical 4-chamber view and at anterior, posterior mitral annulus in apical 2-chamber view, respectively. Consecutive 3 values were taken for calculation of mean of each parameter. MPI was calculated using the formula, MPI = (ICT + IRT)/ET.

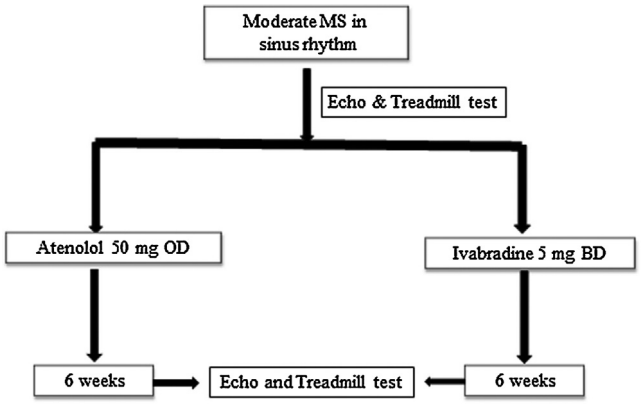

Fig. 1 – Trial protocol-flow chart.

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