Effect of Ivabradine on Heart Rate and Duration of Exercise in Patients With Mild-to-Moderate Mitral Stenosis: A Randomized Comparison With Metoprolol

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Background: Symptoms in mitral stenosis (MS) are heart rate (HR) dependent. Increase in HR reduces diastolic filling period with rise in transmitral gradient. By reducing HR, beta-blockers improve hemodynamics and relieve symptoms, but the use may be limited by side effects. The present randomized crossover study looked at comparative efficacy of ivabradine and metoprolol on symptoms, hemodynamics, and exercise parameters in patients with mild-to-moderate MS (mitral valve area, 1–2 cm^2) in normal sinus rhythm.

Material and Methods: Baseline clinical assessment, treadmill stress testing, and an echocardiographic Doppler evaluation were performed to determine resting HR, total exercise duration, mean gradient across mitral valve, and mean pulmonary artery systolic pressure (PASP). Patients were then allocated to either metoprolol or ivabradine to maximal tolerated doses over 6 weeks (metoprolol: 100 mg twice a day, ivabradine: 10 mg twice a day). Reevaluation was done at the end of this period, and all drugs stopped for washout over 2 weeks. Thereafter, the 2 groups were crossed over to the other drug that was continued for another 6 weeks. Assessment was again performed at the end of this period.

Results: Thirty-three patients of 34 completed the protocol. Fifteen were male, mean age was 28.9 ± 6.6 years, all were in New York Heart Association class 2, and mean resting HR was 103.5 ± 7.2/min. Mean mitral valve area was 1.56 ± 0.16 cm^2, mean PASP was 38.1 ± 5.1 mm Hg, and mean gradient across mitral valve was 10.6 ± 1.6 mm Hg. Significant decrease in baseline and peak exercise HR was observed at the end of follow-up with both drugs. Reduction in mitral valve gradient after ivabradine (42%) and metoprolol (37%) and reduction in PASP after both ivabradine (23%) and metoprolol (27%) were to a similar extent. Significant reduction in total exercise duration after both ivabradine and metoprolol therapy was observed. One patient developed blurring of vision with ivabradine therapy but did not require discontinuation of drug. An improvement in dyspnea of one grade was observed in all the patients by treatment with both ivabradine and metoprolol.

Conclusions: Both metoprolol and ivabradine reduced symptoms and improved hemodynamics significantly from baseline to a similar extent. Ivabradine thus can be used effectively and safely in patients with MS in normal sinus rhythm who are intolerant or contraindicated for beta-blocker therapy.

Key Words: mitral stenosis, normal sinus rhythm, ivabradine, metoprolol

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INTRODUCTION

The hemodynamic consequences of mitral stenosis (MS) have been extensively studied both at rest and during exercise.[1] Transmitral gradient increases with heart rate (HR) during exercise and results in elevated pulmonary venous pressure, precipitating dyspnea. These may be attenuated by HR-reducing agents.[2,3] Beta-blockers have been shown to improve clinical and hemodynamic profile significantly in symptomatic patients of MS.[1,4] However, side effects of beta-blocker limit its use in some patients.

The novel rate-lowering drug ivabradine results in a dose-dependent HR reduction at rest and during exercise.[5–7] It has been used for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm (NSR) who have contraindication or intolerance to beta-blockers.[7] It is currently being recommended in treatment of heart failure where HR remains more than 70 beats per minute despite beta-blocker therapy.[8] There are very limited clinical data on the benefit of ivabradine therapy for reducing HR in patients with MS and NSR. This study was therefore undertaken to evaluate the effects of ivabradine and metoprolol on hemodynamic parameters and effort intolerance in patients with MS and NSR and to compare the effects of ivabradine and metoprolol.

METHODS

Patients

This study was approved by institutional review board, and all the patients provided written informed

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consent for the study. Consecutive 34 patients of mild-to-moderate MS (mitral valve area, 1–2 cm^2) in NSR were included in this prospective, open-label crossover study. All were in functional class 2 of the New York Heart Association classification. The diagnosis of MS was made clinically and confirmed by 2D and Doppler echocardiography (ECHO) in every patient. A baseline 2D and Doppler ECHO was done to measure mean and peak gradients across mitral valve and pulmonary arterial systolic pressure by tricuspid regurgitation velocity.[9] An exercise stress test was done in all patients on Bruce's protocol until the point of exhaustion, fatigue of leg muscles, dizziness, or intolerable dyspnea was reached, and parameters noted were peak exercising HR and total exercise duration (TED).

Study Protocol

All patients were subjected to a 2-phase crossover study with each phase lasting 6 weeks. They were divided into 2 groups. Group A was assigned to ivabradine 5 mg twice daily, increased to maximum dose of 10 mg twice daily over 2 weeks, and continued for next 4 weeks. Group B was assigned to metoprolol 50 mg twice daily, increased to maximum dosage of 100 mg twice daily over 2 weeks, and continued for next 4 weeks. Patients from both groups were reevaluated clinically after 6 weeks for New York Heart Association symptomatic class. A repeat clinical evaluation, exercise stress test, and 2D and Doppler ECHO were performed at the end of 6 weeks.

After a drug-free interval of 2 weeks, crossover was conducted with group A switched to metoprolol and group B switched to ivabradine. Reevaluation was done on the previously mentioned lines again after 6 weeks. All patients received secondary prophylaxis for rheumatic fever and oral diuretic therapy throughout the study period.

Statistics

Paired *t* test was used for statistical analysis, and *P* values of less than 0.05 were considered significant. The data are presented as mean ± SD. We have performed per-protocol analysis, ie, only those patients who have completed both the treatment phase were analyzed.

RESULTS

Thirty-four patients with mild-to-moderate MS (mean mitral valve area, 1.56 ± 0.16 cm^2) constituted study group. Of the 34 patients, 33 completed the protocol. One patient was lost to follow-up after basal test and was excluded from the study. Out of 33, 18 (54.5%) were female. Mean age was 28.9 ± 6.6 years (male and female: 28.3 and 29.4 years, respectively). One patient developed blurring of vision with ivabradine therapy but did not require discontinuation of drug. An improvement in dyspnea of one grade was observed in all the patients by treatment with both ivabradine and metoprolol. There was significant reduction in baseline and peak exercise HR at the end of follow-up after both the drugs, and difference between the 2 drugs was not significant (Table 1). Both drugs resulted in significant reduction in resting mitral valve gradient as assessed by Doppler evaluation; however, reduction in mitral valve gradient after ivabradine (42%) and metoprolol (37%) was to a similar extent. Reduction in pulmonary artery systolic pressure after both ivabradine (23%) and metoprolol (27%) was significant as compared with baseline but was to a similar extent with both the drugs. Increase in TED after both ivabradine and metoprolol therapy was also statistically significant as compared with baseline and similar with both drugs.

DISCUSSION

The present 2-phase crossover study demonstrated that ivabradine significantly decreases both resting and exercise-induced HR and improves mean gradient across mitral valve and pulmonary arterial systolic pressure along with TED in patients with mild-to-moderate MS and intact sinus node function in a similar manner as metoprolol.

Patients with symptomatic MS usually suffer from pulmonary congestion due to left atrial and pulmonary venous hypertension. They are often in sinus rhythm, and cardiac output is usually well maintained at rest. Symptoms occur most often with increase in HR, cardiac output, or both, as increase in cardiac output or a decrease in diastolic filling period results in an exponential rise in gradient.[10]

Beta-blockers have been shown to decrease the pulmonary capillary pressure and, thus, the gradient across the mitral valve because of their inherent ability to reduce resting

TABLE 1. Baseline and Exercise Parameters in Both Groups

Parameters	Baseline (Mean ± SD)	Metoprolol (Mean ± SD)	*P* (B vs. M)	Ivabradine (Mean ± SD)	*P* (B vs. I)	*P* (M vs. I)
HR, beats per minute						
Resting	103.5 ± 7.2	61.8 ± 3.8	0.001	65.9 ± 5.7	0.001	NS
Exercise	172.5 ± 23.7	130.3 ± 24.1	0.001	132.9 ± 24.3	0.001	NS
MG, mm Hg	10.6 ± 1.6	6.3 ± 1.7	0.006	6.0 ± 1.6	0.001	NS
PASP, mm Hg	38.1 ± 5.1	27.7 ± 4.4	0.004	28.4 ± 4.2	0.006	NS
TED, min	7.9 ± 1.6	10.3 ± 1.7	0.001	10.6 ± 1.6	0.002	NS

Table showing decrease in baseline and peak exercise HR at the end of follow-up after both the drugs; reduction in mitral valve gradient after ivabradine (42%) and metoprolol (37%) was to a similar extent; reduction in PASP after both ivabradine (23%) and metoprolol (27%) was to a similar extent; increase in TED after both ivabradine and metoprolol therapy was statistically significant but to a similar extent.

B, baseline; I, ivabradine; M, metoprolol; MG, mean gradient across mitral valve; PASP, pulmonary artery systolic pressure.

and exercising HR.[10,11] However, potential adverse effects of beta-blockers that include cardiac effects (severe bradycardia, sinus arrest, atrio-ventricular block, reduced left ventricle contractility), bronchoconstriction, fatigue, mental depression, nightmares, gastrointestinal upset, sexual dysfunction, intensification of insulin-induced hypoglycemia, and cutaneous reactions limit their use in some patients. Ivabradine, which is a specific and selective inhibitor of the I_f ion channel, reduces the spontaneous firing rate of sinoatrial pacemaker cells and thus slows HR through a mechanism that is not associated with negative inotropic effects. Therefore, it would be expected to reduce the transmitral pressure gradient and pulmonary wedge pressure in patients with MS in sinus rhythm.

As metoprolol has already proved its favorable hemodynamic effects in patients with MS in a number of clinical trials,[10,11] this study with ivabradine points toward a similar beneficial effect in patients of MS.

A recent crossover study comparing the effect of ivabradine versus atenolol in a similar population of patients of MS showed that ivabradine was superior to atenolol with respect to HR reduction.[12] However, dose of atenolol (a noncardioselective beta-blocker) used was 50 mg twice a day, and we used metoprolol (a cardioselective beta-blocker) with maximum dose of 100 mg twice a day. Thus, ivabradine has a potential role in medical management of patients of MS in sinus rhythm, especially in a beta-blocker intolerant or contraindicated patient.

Study Limitations

Total number of patients recruited in this study was small, and we could not test a hemodynamic response to exercise after study drugs (ivabradine and metoprolol) in our patients.

CONCLUSIONS

Present study shows beneficial effects of both ivabradine and metoprolol at the end of study protocol in patients with mild-to-moderate MS in NSR in terms of improvement in symptomatic status, exercise parameters, and hemodynamic parameters significantly from baseline, and their effects were similar.

Based on our results, we propose that ivabradine is a potentially useful alternative in patients with MS in NSR where metoprolol is not tolerated or contraindicated because of side effects.

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