ORIGINAL ARTICLE

The Comparison of Effects of Ivabradine and Atenolol on Heart Rate and Symptoms in patients with Mild-to-Moderate Mitral Stenosis

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ABSTRACT

Aim: To compare the effect of Ivabradine and Atenolol on heart rate and symptoms (duration of exercise) in patients with mild-to-moderate mitral Stenosis in sinus rhythm.
Methods The prospective, open-label study was performed at DHQ teaching hospital, Sargodha from April 2015 to September 2015. Patients were randomized to two treatment groups. One group was given ivabradine while other was advised antenolol. Resting mitral valve gradient as assessed by Doppler evaluation. Data was collected by proforma aand analyzed using SPSS 20.
Results There was significant reduction in baseline and peak exercise HR at the end of follow-up. Reduction of heart rate from baseline with Atenolol was 42% in resting and 27.7% during exercise. Ivabradine reduces heart rate 38.6% and 24.4% during resting and exercise respectively. Reduction in mitral valve gradient after Ivabradine was (37.7%) and with Atenolol was (39.9%). There was significant Reduction in pulmonary artery systolic pressure after both Ivabradine (29.8%) and Atenolol (32.5%), as compared with baseline.
Conclusion: The study shows beneficial effects of both Ivabradine and Atenolol in patients with mild-to-moderate MS in NSR in terms of improvement in symptoms, during rest and during exercise. Hemodynamic parameters like mitral valve gradient and pulmonary artery pressure were significantly improved.
Keywords: Heart rate, exercise tolerance, mild to moderate mitral Stenosis.

INTRODUCTION

An elevated heart rate is an indicator of high cardiovascular mortality in the general population and among patients with cardiovascular disease. The hemodynamic effects of mitral Stenosis (MS) have been widely studied by different rate lowering drugs both at rest and during exercise[1]. The gradient across the mitral valve increases with rise in heart rate (HR) during exercise and in rest during sudden atrial fibrillation and causes pulmonary edema, as a result of elevated pulmonary venous pressure. The gradient may be reduced by HR-reducing agents, like beta blockers, and rate lowering calcium channel blockers[2,3]. Clinical and hemodynamic profile was significantly improved in symptomatic patients of MS. With Beta-blockers[1,4] but again a side effect of beta-blocker has limited its use in some patients.

The Ivabradine, newer and novel rate-lowering drug results in a dose-dependent HR reduction at rest and during exercise[5,6,7]. It is alternative option to reduce the heart rate in patients intolerant to beta-blockers.

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It is being used for the symptomatic treatment of chronic stable angina[7]. It is recommended by FDA in treatment of chronic heart failure where HR remains more than 70 beats per minute despite beta-blocker therapy[8]. There is no clinical data on the benefit of Ivabradine therapy for reducing HR in patients with MS and NSR and very limited data worldwide. This study was therefore undertaken to evaluate the effects of Ivabradine and Atenolol on hemodynamic parameters and effort intolerance in patients with MS and normal sinus rhythm.

METHODS

The prospective, open-label study was performed at DHQ teaching hospital, Sargodha from April 2015 to September 2015, after taking the written informed consent, Consecutive 50 patients of mild-to-moderate MS (mitral valve area, 1.2 to 2cm^2) in NSR were included. All patients were in NYHA (New York Heart Association functional) class 2 and 3. The diagnosis of MS was made by 2 D and Doppler echocardiography (ECHO) in every patient and to measure mean and peak gradients across mitral valve and pulmonary arterial systolic pressure. A baseline and exercise heart rate was determined by exercise tolerance test on modified Bruce protocol[9].

Study Protocol: All patients were divided into 2 groups. Group A was given Ivabradine 5 mg twice daily, dose was increased to maximum of 10 mg twice daily over a period of 2 weeks, and continued for next 4 weeks. Group B was assigned to Atenolol 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 Atenolol 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, i.e., only those patients who have completed both the treatment phase were analyzed.

RESULTS

Fifty patients with mild-to-moderate MS (mean mitral valve area, 1.56 ±0.16cm^2) constituted study group. Of the 50 patients, 48 completed the protocol. Two patients were lost to follow-up after basal test and were excluded from the study. Out of 48, 25(52%) 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 grade-1 was observed in all the patients by treatment with both Ivabradine and bisoprolol. 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 (Table1). 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 Atenolol (37%) was to a similar extent. Reduction in pulmonary artery systolic pressure after both Ivabradine (23%) and Atenolol (27%) was significant as compared with baseline but was to a similar extent with both the drugs.

Table showing decrease in baseline and peak exercise HR at the end of follow-up after both the drugs; reduction in mitral valve gradient and reduction in PASP after both Ivabradine and Atenolol.

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

Table 1: Parameters in Atenolol group

Parameters	Baseline Mean	Atenolol Mean	%Reduction	P(B vs. A)
Resting HR	101	61	39.6	0.001
Exercise HR	172	128	25.5	0.001
MG, mm Hg	11.4	6.9	39.5	0.006
PASP, mm Hg	36.2	24.4	32.5	0.004

Table 2: Parameters in Ivabradine group

Parameters	Baseline Mean	Ivabradine Mean	%Reduction	P(B vs. I)
Resting HR	99	62	37.3	0.001
Exercise HR	168	127	24.4	0.001
M G, mm Hg	11.4	7.1	39.0	0.001
PASP, mm Hg	39.4	27.4	30.4	0.006

DISCUSSION

It is common that a patient reports about HR during exercise and sometimes even during rest. It was noted that Ivabradine has resulted not only improvement of resting and exercise related HR but also improved the pulmonary artery systolic pressure and mitral valve gradient among all those cases who were symptomatic for mild to moderate MS and intact sinus node function similarly as noted by advice of antenolol.

Left atrial and pulmonary venous hypertension can be a leading cause among all those patients who had developed MS to further devlop pulmonary congestion. There is no fluctuation in the cardiac output, sinus rhythm could be diagnosed among them. Health care specialists are at the opinion that indications could be noted when the case has increased heart rate, increased cardiac output and considerable decrease in diastolic filling period that further goes on increase exponentially[10].

It is documented that beta blockers could put a cause reduction in heart rate weather the case is at rest or doing some exercise and this ability is inherent in the beta blockers. Thus these blockers can be used to reduce the pressure on the pulmonary capillaries[10,11].

It is also a fact that complications are noted in some human so there is less prescription of these blockers. In this condition Ivabradine, a more specific and selective I ion channel inhibitor. It controls the spontaneous firing of the pacemakers residing in the sinoatrial location and ultimately result in the reduction of heart rate by a process that is positively linked with the inotropic effect. Hence, it could be stated and expected from the Ivabradine that it will result in the decrease n pressure of transmitral and pulmonary wedge among those cases who had sinus rhythm accompany the mitral stenosis.

In the previous medical literature it is evident that atenolol has compromising results in terms of controlling hemodynamic in the population suffering from mitral stenosis similarly this study has shown that Ivabradine has the same potential effect on the patients with mitral stenosis[10,11].

Later in a comparative trial run to assess the effect of Ivabradine versus atenolol among the patients of mitral stenosis, it was found that Ivabradine has more positive results as compared to antenolol for terms of control of heart rate[12]. However, dose of Atenolol (a non-cardioselective beta-blocker) used was 50 mg twice a day, and we used Atenolol (a cardioselective beta-blocker) with maximum dose of 100 mg twice a day. Thus, it could be concluded that Ivabradine has potential role in proper management of patient reported with mitral stenosis in sinus rhythm, especially in those who had risk to develop the complications if any other beta blocker is advised.

Study Limitations: Total number of patients recruited in this study were small, and we could not test a hemodynamic response to exercise after study drugs (Ivabradine and Atenolol) in our patients.

CONCLUSION

Present study shows beneficial effects of both Ivabradine and Atenolol 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 Atenolol is not tolerated or contraindicated because of side effects.

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