COMPARATIVE STUDY OF EFFECTS OF ATENOLOL AND IVABRADINE ON LEFT ATRIAL APPENDAGE FLOW VELOCITIES IN PATIENTS WITH RHEUMATIC MITRAL STENOSIS IN SINUS RHYTHM

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ABSTRACT

BACKGROUND

Cardioembolic episodes are reported in patients with rheumatic mitral stenosis. Impaired function of left atrial appendage secondary to left atrial pressure and volume overload facilitates thrombus formation inside. Beta blockers used for symptom relief can worsen the left atrial appendage function further. Ivabradine, a selective rate reducing drug is unlikely to have such an effect and may be a better alternative. Objective of the study was to compare the effects of these two drugs on left atrial appendage velocities.

MATERIALS AND METHODS

This study is a sub study of a trial which compared the effectiveness of atenolol and ivabradine for rate control. Out of 82 patients randomised to atenolol (50 mg once daily) or ivabradine (5 mg twice daily) in the original study, 20 patients were selected (9 in the atenolol group and 11 in the ivabradine group).

RESULTS

These patients underwent transoesophageal echo at baseline and 6 weeks after treatment with assigned drug and left atrial appendage emptying velocities (LAAEV) and left atrial appendage filling velocities (LAAFV) were estimated. Baseline velocities were comparable in both groups. Peak LAAEV were 29.224 (5.678) cm/s and 24.557 (5.103) cm/s (p value 0.069), early LAAEV were 15.778 (3.002) cm/s and 16.410 (1.750) cm/s (p value 0.564) and LAAFV were 34.265 (6.605) cm/s and 30.031 (6.606) cm/s (p value 0.206) in atenolol group and ivabradine group respectively. Post drug treatment, peak LAAEV and LAAFV decreased significantly while early LAAEV did not change significantly in the atenolol group (29.224(5.678) cm/s v/s 27.771 (5.774) p value 0.018 for peak LAAEV and 34.265 (6.605) cm/s v/s 32.382 (5.789) cm/s with p value 0.009 for LAAFV). None of the three velocities changed significantly in the ivabradine group.

CONCLUSION

Atenolol significantly reduced peak LAAEV and LAAFV in patients with rheumatic mitral stenosis in sinus rhythm. Ivabradine did not have such an effect.

KEYWORDS

Mitral Stenosis, Left Atrial Appendage, Atenolol, Ivabradine.

HOW TO CITE THIS ARTICLE: Kalathingathodika S, Vellani H, Nair RG. Comparative study of effects of atenolol and ivabradine on left atrial appendage flow velocities in patients with rheumatic mitral stenosis in sinus rhythm. J. Evid. Based Med. Healthc. 2019; 6(5), 277-279. DOI: 10.18410/jebmh/2019/57

BACKGROUND

Rheumatic heart disease (RHD) still continues to be an important cause for valvular heart disease in developing countries like India. Mitral stenosis (MS) is the commonest lesion in chronic rheumatic heart disease. Though there is high prevalence of atrial fibrillation in these patients, majority of the patients remain in sinus rhythm. High incidence of spontaneous echo contrast (SEC) and intracardiac thrombi especially in left atrium (LA) and left atrial appendage (LAA) is reported in these patients even in sinus rhythm predisposing to systemic embolization.[1] Heart rate lowering drugs like beta blockers and calcium channel blockers (CCB) are used in these patients for symptomatic improvement and to increase exercise tolerance. Active contraction and relaxation of LAA avoids blood stasis and hence the thrombus formation in normal hearts. LAA filling and emptying are impaired due to both pressure and volume overload in MS patients.[2] Beta blockers used for rate control of heart rate can worsen the LAA function further.[3,4,5,6] Ivabradine, a selective sinus nodal rate reducing drug with no significant effect on myocardial contraction and relaxation may be a better alternative in this setting. This

Financial or Other, Competing Interest: None.
Submission 11-01-2019, Peer Review 19-01-2019,
Acceptance 26-01-2019, Published 02-02-2019.
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study was undertaken to look for the effects of atenolol and ivabradine on LAA flow velocities in patients with rheumatic MS in sinus rhythm.

MATERIALS AND METHODS

The present study is a sub study of a trial undertaken to compare the effectiveness of atenolol and ivabradine for heart rate control in rheumatic mitral stenosis, the results of which are published.[7] It was an open labelled randomised parallel group comparison trial with each group receiving either atenolol or ivabradine for a period of six weeks. The dose of ivabradine was 5 mg twice daily and that of atenolol was 50 mg once daily. Every third patient in each group was considered for inclusion into the study of LAA velocities and those patients who were giving consent were included.

LAA flow velocities were measured by trans oesophageal echocardiography (TEE) before starting the study drug. TEE was repeated after the completion of six weeks of treatment and LAA velocities were re estimated. The LAA velocities were estimated from mid oesophageal position using any view which gives good visualisation of LAA and allows parallel placement of cursor for velocity estimation. The positive deflection immediately after the P wave is taken as the peak left atrial appendage emptying velocity (LAAEV) and the negative deflection immediately following it is taken as the left atrial appendage filling velocity (LAAFV). The positive deflection before the peak LAAEV is taken as early LAAEV. The change in each of these parameters from baseline to post treatment was analysed and was compared between the groups. The study was approved by institutional ethics committee and was registered in the clinical trial registry of India (CTRI 2012/10/003076).

RESULTS

Original study cohort consisted of 82 patients (40 in the atenolol group and 42 in the ivabradine group. Of them 20 patients were taken for the present study (9 in the atenolol group and 11 in the ivabradine group). LAA velocities could be estimated satisfactorily in all patients by TEE before and after the treatment. More than 90% of the whole study group were females. So it happened that all patients recruited for the present study were females. Baseline characteristics of the patient are given in table 1. Baseline characteristics including the LAA velocities were matching for both the groups.

All of the patients completed the 6 weeks of treatment with assigned drug and underwent TEE before and after the treatment. In the atenolol group, peak LAAEV and LAAFV showed a statistically significant decline from baseline while early LAAEV showed an increase which was not significant. In the Ivabradine group, none of the three velocities showed any significant variation between baseline and post drug. LAA velocities before and after treatment are given in the table 2.

	Atenolol (n=9)	**Ivabradine (n=11)**	**p-Value**
Age in Years	38.11 (8.667)	37.91 (8.420)	0.959
Resting HR	72.44 (3.127)	77.36 (8.857)	0.131
LA Size in mm	37.33 (1.936)	37.18 (1.601)	0.850
Mean Gradient in mmHg	7.644 (1.331)	9.183 (2.333)	0.054
LV EF in Percentage	66 (7.98)	62.09 (5.78)	0.225
Early LAAEV cm/s	15.778 (3.002)	16.410 (1.750)	0.564
Peak LAAEV cm/s	29.224 (5.678)	24.557 (5.103)	0.069
LAAFV cm/s	34.265 (6.605)	30.031 (6.606)	0.206

Table 1. Baseline Characteristics

	Atenolol			**Ivabradine**		
	Baseline	Post Drug	p-Value	Baseline	Post Drug	p-Value
Early LAAEV	15.778 (3.002)	18.831 (8.240)	0.464	16.410 (1.750)	16.200 (1.671)	0.199
Peak LAAEV	29.224 (5.678)	27.771 (5.747)	0.018	24.557 (5.103)	24.791 (4.861)	0.349
LAAFV	34.265 (6.605)	32.382 (5.789)	0.009	30.031 (6.606)	30.220 (7.757)	0.634

Table 2. Drug Effect on LAA Velocities

DISCUSSION

Left atrial appendage velocities reported in patients with mitral stenosis are highly variable in various studies probably reflecting the variability in the population studied as well as the duration and severity of the lesion. Study by Golbasi et al[2] showed peak emptying velocity of 40± 1.5 cm/s and filling velocity of 42±2.1 cm/s which are considerably higher than our values. A study by Vijeyvargia et al[8] on Indian population had values similar to our values (22.45±4.11 cm/s for peak emptying velocity, 15.29±2.26 cm/s for early emptying velocity and 28.52±4.37 cm/s for filling velocity). The study by Yilmaz et al[3] showed peak emptying velocity of 27.18±6.01 cm/s. Another Indian study by Reddy et al[9] also showed similar but slightly lower values. All these values are lower compared to values in normal subjects. A value of less than 20 cm/s for peak LAAEV has been found to be correlating with risk of thrombus formation in some studies. Most of our patients had values above than this. In the study

by Vijeyvargia et al,[8] the LAA velocities improved significantly after percutaneous transvenous mitral commissurotomy (PTMC) but remained significantly lower than reported values in normal population even after 6 months follow up. This may indicate persistent LAA dysfunction due to chronic re modelling even after the improvement in the pressure and volume overload of mitral stenosis. Many of these patients will be on chronic therapy with heart rate lowering drugs which can cause further reduction in LAA function.

The studies regarding the influence of drugs on LAA function are very limited in number. Study by Yilmaz et al [3] showed reduction in LAA velocities demonstrated by TEE after 2 weeks of treatment with 100 mg atenolol in patients with symptomatic mitral stenosis. Karaca et al[6] studied the acute effects of intravenous infusions of metoprolol and diltiazem on LAA velocities in patients with symptomatic mitral stenosis. Metoprolol infusion acutely produced no changes in LAA velocities while diltiazem infusion produced reduction in LAA velocities, though statistically not significant. We could not find any study about the effects of ivabradine on LAA function. In the present study, even with small number of patients, there was significant reduction in LAA peak emptying velocity and LAA filling velocity in patients on atenolol while no significant changes were observed in patients on Ivabradine.

Though the presence of LAA dysfunction and improvement after PTMC is well documented, the clinical significance of this including the future development of atrial fibrillation or thrombo embolism is not well established with prospective studies. Hence the impact of this further deterioration of LAA function with drugs cannot be predicted. Major contribution to the burden of embolic episodes in patients with mitral stenosis comes from those in atrial fibrillation. Though beta blockers worsen LAA function in these patients, the Ivabradine has no role in this setting.

CONCLUSION

In female patients with moderate rheumatic mitral stenosis in sinus rhythm, atenolol used for symptom control will worsen already existing left atrial appendage dysfunction. Ivabradine used in the same setting was not shown to have such effect.

Limitations

Small sample size is the main limitation of the study which might have been insufficient to reveal the effect of Ivabradine. But with similar sample size, atenolol was demonstrated to worsen LAA dysfunction. A cross over study design would have been better in this setting, but the need for multiple transoesophageal examinations pre-empted this approach.

Only female patients were studied. But the results are unlikely to be different in males.

Clinical impact of the findings is not well established enough to recommend any management changes.

What is Already Known?

Left atrial appendage velocities are impaired in patients with rheumatic mitral stenosis in sinus rhythm. Few small-scale studies have shown that beta-blockers can impair LAA velocities. Impact of Ivabradine on LAA velocities is not well studied.

What this Study Adds?

Study confirmed the impairment of LAA velocities by beta blockers. Ivabradine did not show any change in LAA velocities.

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