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Original Research Article

Ivabradine versus Metoprolol in Patients with Mitral Stenosis in Sinus Rhythm- A Randomized Comparison on Efficacy and Impact on Quality of Life

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Abstract:

Background: Beta-blockers are widely used in patients with mitral stenosis (MS) for heart rate (HR) control that alleviate exercise-related symptoms but with many limitations. Ivabradine, a novel selective bradycardic drug, may be promising outcomes in terms of safety and efficacy in rest and exercise. Our study examined comparative efficacy of ivabradine and metoprolol on clinical, hemodynamic and exercise parameters with quality of life (QOL) in patients with MS in normal sinus rhythm.

Material and Methods: Randomized single blind trial randomized 65 patients of different severity to BETA (n=33, metoprolol 50 mg BD) or IVA group (n=32, ivabradine 5 mg BD). After clinical evaluation, treadmill stress testing, Echocardiography, ECG at baseline, patients were re-evaluated after six months. EQ-5d-3L questionnaire evaluated QoL at 0,6 months.

Results: Mean Resting HR in bpm significantly decreased over 6 months in both groups (88.59±12.77 to 71.75±6.04 in IVA; 88.30±12.37 to 72.61±9.9 in BETA) as well peak exercise HR (IVA 171.91±28.07 to 130.09±24.21 and BETA 167.55± 31.02 to 132.30±25.97) (p<.001) but was comparable intergroup (p>.05). on head to head, total exercise duration(TED) increased significantly in IVA(p=.002). In BETA minimum HR at Holter were significantly low (p<.001) with adverse bradycardic symptoms. No serious safety issues noted in IVA. QoL score (EQVAS) was significantly improved from baseline for both interventions (p<.001) as well as for IVA group (p<.001) whereas NYHA class improvement not significant.

Conclusions: Metoprolol and ivabradine significantly improved clinical, hemodynamic, and exercise, QOL parameters from baseline. Ivabradine was superior in TED and Qol scores than metoprolol without significantly lowering minHR or BP. Ivabradine thus is an independent choice in rate control in MS with NSR.

Keywords: Mitral Stenosis, Normal Sinus Rhythm, Ivabradine, Metoprolol, Beta Blocker.

Introduction

Mitral stenosis (MS), the commonest valvular heart disease, is characterized by obstruction to left ventricular inflow due to structural abnormality of mitral valve apparatus1. Progressive MS is generally asymptomatic but during exercise and episodes of increased heart rate symptoms aggravate. Patients with higher severity often experience disabling dyspnea in less than the ordinary activities or at rest. Besides surgical treatment like balloon mitral valvuloplasty (BMV) medical management plays a vital role in treatment. [1]

Decreasing heart rate is reasonably recommended as medical management that prolongs the diastolic filling period and facilitates ventricular inflow through the stenosed mitral valve and thus relieves symptoms at rest as well as in exercise. [1,2] β-blockers are used conventionally but can result many undesirable actions that can limit their use. [3] Additionally, β-blockers may cause bronchoconstriction in patients with obstructive airway disease [4]. A selective bradycardic agent, which does not produce these undesirable hemodynamic and adverse effects, could thus be of therapeutic interest.

Ivabradine, a novel drug, selectively blocks If current acting on SA node and decreases cardiac pacemaker depolarization [5,6]. It has no effect on

the cardiac contractile force, ventricular repolarization, intracardiac conductance. [5] This selective and specific bradycardic effect at rest and during exercise with a safe therapeutic profile is clinically promising in symptomatic mitral stenosis patients in sinus rhythm [1,2].

In recent clinical trials, the efficacy of ivabradine as a superior alternative to beta-blockers has not been proved unquestionably. Some concluded that ivabradine controls exertional symptoms more than beta-blockers [7,8,9], while some studies demonstrated only comparable results in some parameters [10,11]. No study has addressed the subjective and emotional dimensions of the health of patients treated with ivabradine compared to beta-blockers.

The present study has compared the efficacy of drug ivabradine with beta-blockers in MS patients with sinus rhythm in terms of subjective and objective parameters (clinical, hemodynamic and exercise parameters) in a randomized clinical trial.

Methods

Primary Endpoint: To compare the efficacy of Ivabradine to Metoprolol in terms of subjective (QOL) and objective (clinical and hemodynamic and exercise) parameters.

Secondary Endpoint: To document any adverse drug events in both treatment groups.

Present study was a randomized participant blinded clinical trial based on tertiary hospital setting. It was approved by IEC and registered to CTRI (CTRI/2020/07/026401). Eligibility requirements included an age of at least 18 years, documented/newly diagnosed mitral stenosis in normal sinus rhythm (heart rate ≥70 bpm). Exclusion criteria included very severe MS in urgent need for surgical treatment, other significant valvular lesions (more than mild aortic stenosis/ aortic regurgitation/ mitral regurgitation/ Tricuspid regurgitation/ Tricuspid stenosis), presence of significant noncardiac comorbidities, e.g., chronic obstructive pulmonary disease, renal failure, malignancy, pregnancy, Known allergy/ intolerance to study drugs, known coronary artery disease, cardiomyopathies, congenital heart diseases, HTN etc., marked anemia (Hb < 8 g/dl). Sample size estimated using for each group was 26.

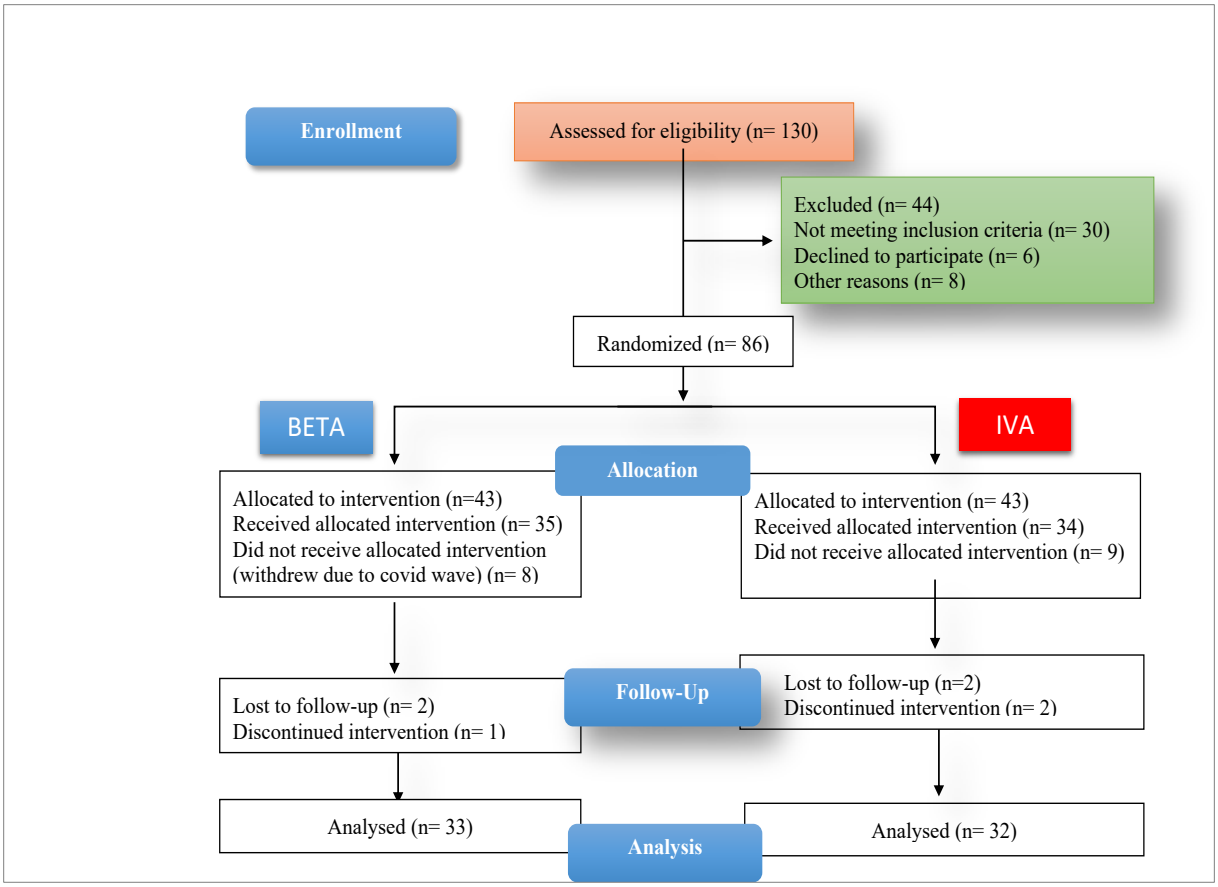

Figure 1: consort diagram for the clinical trial

Trial Procedures: After written informed consent and a 14-day screening period assigned during which selection criteria were checked and baseline information gathered. Patients were randomly

assigned to receive either metoprolol (metoprolol 25 mg to 50 mg twice daily dose selected according to body weight and resting heart rate with gradual up titration and down titration as per cardiologists review of heart rate) or Ivabradine (5mg twice daily up titrated to max 7.5 mg twice daily doses) into BETA or IVA groups respectively. Central assignment confirmed allocation concealment. (Consort diagram Figure 1). Both the group participants were blinded on which medication they received.

Recruitment phase was for 18 months and after median study period of six months, participants were followed up in OPD or virtually per month with regular history, clinical examination, requisite investigations and data were collected and documented.

Outcomes: Clinical and hemodynamic parameters were HR reduction, effect on blood pressure, exercise parameters (Max HR, total exercise duration), echocardiographic parameters (MDG/ EF/MVA), Minimum attained heart rate (Holter monitoring). Exercise parameters were not meant for patients unable to have TMT evaluation or contraindicated due to severe disease. Holter monitoring was meant to evaluate and corroborate major events with lower heart rates. The QoL scores assessed on EQ-5D-3L Questionnaire, a standardized and valid scoring system of five dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression with 3 levels each (no, some and extreme problems) and self-estimated total score (EQ-VAS) [14]. Safety analyses included adverse events associated with the discontinuation of trial treatment, drug related specific events. Safety data collected by means of continuous scrutiny over the study period and later.

Statistical Analysis: IBM SPSS Statistics for Windows version 26 [15] was used for statistical analysis. The study was done per- protocol. Data were analysed using paired, unpaired t tests for parametric data, for non-parametric data like scores and non-normally distributed data Wilcoxon signed rank test (related data) and Mann Whitney's test for paired data were used. Graphs charts and tables were constructed with SPSS and Microsoft excel and word. Level of significance declared if p-value was <0.05.

Results

Among 65 patients, 47.69% (n=31) were male and 52.31% (n=34) were female. Mean age was 38.14±1.47 years. More than 80% of the population was below 50 years old.

Majority of patients (67.7%; n=44) was from low socioeconomic group. Asymptomatic and symptomatic participants were grouped as per echocardiography as mild 26.2% (n=17), moderate 40% (n=26), and severe cases 33.8% (n=22). Baseline parameters are summarized in table 1.

Table 2 depicts hemodynamic, exercise and echo parameters. On Holter monitoring, minimum heart rate was significantly lower in BETA (p= 0.0002; extremely significant) with mean min HR 55.53bpm (SEM 1.28; 95% C.I=52.82 to 58.24 bpm)) that corroborated with adverse outcomes of Metoprolol.

Table 1: Baseline characteristics of both intervention groups

characteristics	IVA Ivabradine (n=32)		BETA Metoprolol (n=33)		P value intergroup
	Mean	SEM	Mean	SEM	
Age (yrs)	37.36	1.9	38.94	2.2	0.597
Gender					
Male^	15		16		
Female^	17		17		
Hemoglobin (gm/dl)	10.106	0.24	10.067	0.23	0.904
Serum creatinine (mg/dl)	1.015	0.03	1.279	0.24	0.295
HR (bpm)	88.59	2.26	88.30	2.15	0.926
SBP (mm Hg)	122.28	1.75	122.91	1.5	0.786
DBP (mmHg)	74.25	1.42	73.64	1.2	0.744
MBP (mmHg)	90.26	1.34	90.06	1.11	0.911
Max HR at TMT (bpm)	171.91	5.85	167.55	6.94	0.631
total Exercise duration (s)	298.35	5.11	293.85	6.29	0.578
Mitral valve area (cm^2)	1.22	0.07	1.09	0.06	0.159
Mean gradient (mmHg)	15.96	1.12	18.52	1.40	0.160
Ejection fraction (%)	54.11	1.36	53.95	1.47	0.933

Significance based on unpaired t test between IVA and BETA groups; significant if p<.05
^ data presented in number (not mean)
SEM=standard error of mean, HR=Heart rate, SBP=systolic blood pressure, MBP=Mean BP, DBP=Diastolic BP

Table 2: changes in Hemodynamic, Exercise, echo parameters in different treatment groups

Characteristics	IVA (Ivabradine)		BETA (Metoprolol)		P value intergroup
	Baseline	6 months	Baseline	6 months	
Hemodynamic parameters					
Resting HR	88.59 ±12.77	71.75± 6.04**	88.30± 12.37	72.61±9.9 **	0.677
Minimum HR at Holter monitoring	70.23± 4.28 (1.73)	62.71±3.71 (0.95)**	71.86± 5.33(1.88)	55.53±5.27 (1.28)**##	0.0002
MBP(mm hg)	90.26±7.6 (1.34)	89.08±7.68 (1.36)	90.06±6.361 (1.11)	79.96±6.96**## (1.21)	<0.0001
Exercise Parameters@					
Max HR at TMT	171.91±28.07 (5.85)	130.09**±24.2 (5.05)	167.55±31.02 (6.94)	132.3**±25.97 (5.8)	0.775
TED (s)	298.35±24.52 (5.11)	293.85**##±28.11 (6.28)	340.96±14.79 (3.08)	317.55**±26.47 (5.9)	0.002
Echo parameters					
Ejection fraction (%)	54.11±7.69 (1.36)	57.43± 6.57 (1.16)	53.95± 8.47 (1.47)	55.59±8.41 (1.46)	0.328
MVA (cm^2)	1.22±0.38 (0.07)	1.23±0.36 (0.064)	1.09±0.35 (0.06)	1.11±0.32 (0.056)	0.188
Mean gradient (mmHg)	15.96±6.36 (1.12)	13.71**±5.6(0.99)	18.52±8.05 (1.4)	16.22**±7.49 (1.3)	0.132

Significance based on unpaired t test between IVA and BETA groups; data presented as mean and SD (SEM in bracket), *intragroup significance based on paired t test from baseline, * means p<.05, ** p<0.001. #intergorup significance based on unpaired t test at the end of treatment, ## p<.001(high significance)

@exercise parameters for participants excluding severe MS patients who were unable to run in TMT (n IVA =23, n BETA=20)
SD=Standard deviation, SEM=Standard error of mean, MBP=Mean blood pressure, TED= total exercise duration expressed in seconds (s); HR=heart rate expressed in beats per minutes (bpm), MVA=Mitral valve area,

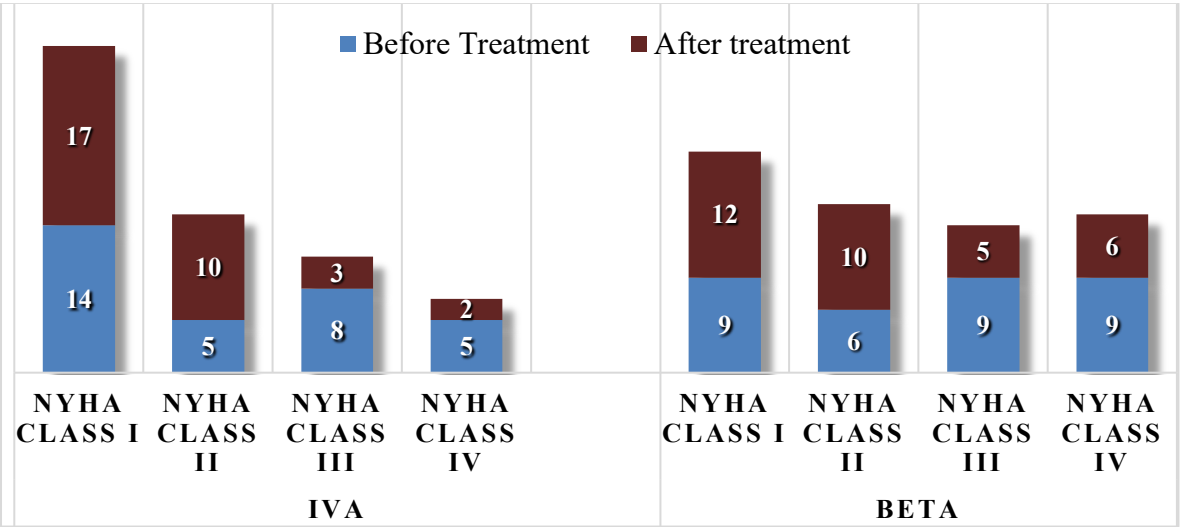

Figure 2: NYHA classification of cases of both groups before and after treatment

More inclusion after treatment to class I and II and decrease in class III, IV significant from baseline (p=.006; Wilcoxon signed Rank Test), but comparable on intergroup comparison (Mann Whitney U test; p=.08).

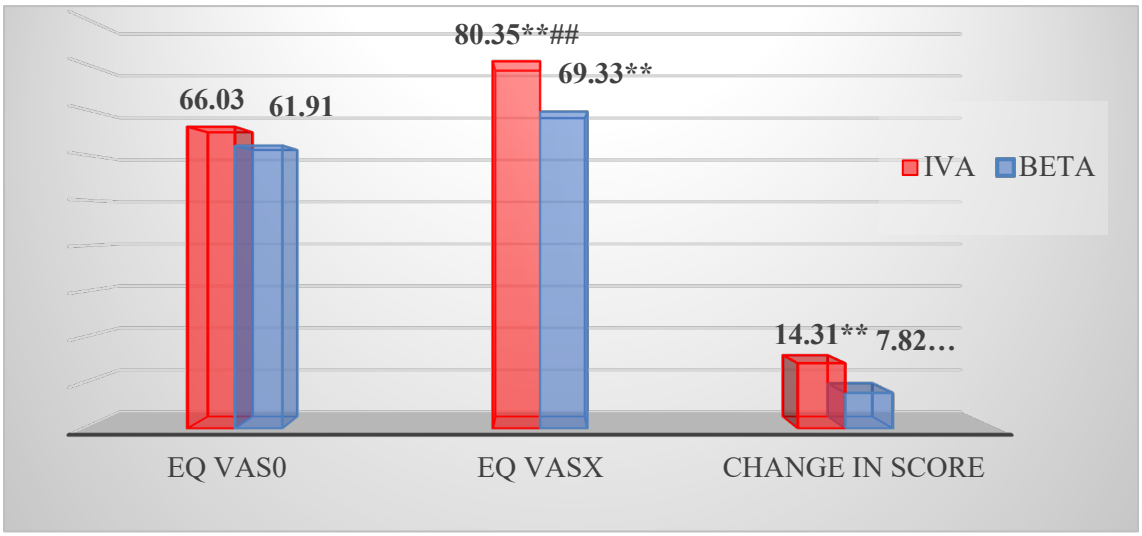

Figure 3: group wise distribution of Mean EQVAS scores at baseline vs 6months of treatment with change in score

**intragroup significance from baseline (p<.001), intergroup significance (p<.005##), here p=0.0002, $EQVAS_0$= baseline, $EQVAS_x$= after treatment score of EQVAS

Table 3: difference from intergroup and intragroup scoring in EQ-5D-3L questionnaire from baseline to after drug treatment

5D	Mobility	Self-care	Usual activities	Pain discomfort	Anxiety depression
p (b vs T/t)	<0.001	<0.001	<0.001	<0.001	<0.001
p (I vs B)	0.456	0.325	0.808	0.025	0.418
b vs t/t -baseline vs 6 months based on Wilcoxon Signed Rank Test, t/t- after 6 months treatment based on Mann Whitney U test , I vs B- IVA vs BETA, significance @ p<.05, highly significant p<.005 (highlighted)					

NYHA classification categorizes symptoms of heart failure in four functional groups. After the study both the groups showed increased frequency of class I, II and decrease in class III, IV. This improvement in NYHA classification was significant over baseline (p=.006; Wilcoxon signed Rank Test), but comparable on intergroup comparison (Mann Whitney U test; p=.08). See (Fig-2).

EQ-5D-3L scores in 5 dimensions with 3 levels and overall subjective scoring (EQVAS) were evaluated at 0 and 6 months. Five dimensions are evaluated including Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Table 3 depicts intra and intergroup differences of scoring. The overall scoring is shown in fig 3.

Table 4: frequency distribution of adverse effects in both intervention groups

Adverse effects	IVA (n=32)		BETA (n=33)	
Symptomatic bradycardia^	0		2	(6.06)
Asymptomatic bradycardia^	0		3	(9.09)
Headache	2	(6.25)	2	(6.06)
Hypoglycemia	0		1	(3.03)
Hypotension	0		6	(18.18)
Breathlessness	0		1	(3.03)
Lethargy	5	(15.6)	4	(12.12)
Palpitation	2	(6.25)	0	
Phosphenes	3	(9.38)	0	
Syncope	0		1	(3.03)
Head reeling	0		1	(3.03)
Other ECG changes	0		0	
total	12	(37.5)	15(21)[&]	(45.5)
Data expressed as n (% of group participants). No serious severe ADR reported, no drug discontinuation. [&]more than 1 adverse effect was reported by few so total ADR is higher than participants in BETA group. ^ bradycardia based on ECG criteria.				

Safety: In terms of adverse events out of 27 participants reported for 33 adverse events during the 6 months of treatment (41.5%), 12 were from IVA group (18.5% of all ADR) and 15 (23.1% of all ADRs) were from BETA group (Table 4). No serious or severe events needed hospitalization or drug discontinuation. For BETA group participants complained mainly of weakness, symptomatic bradycardia, hypotension etc. Holter monitoring corroborated the finding with low resting HR in the beta blocker treated group

Discussion

The role of beta-blockers for rate control in mitral stenosis has been evaluated in various studies and a well-established fact [2,3,6], but the use of ivabradine as alternate has been debated. Conflicting results are there when both drugs were compared head on head. [7-11] Negative inotropic effect and tolerability issues are also there with beta blockers. So, we look for an equal or not inferior selective alternative for rate control. Lowering heart rate improves ventricular filling against stenosed mitral valve and improves myocardial perfusion, prevents build-up of pulmonary wedge pressure.13Also exercise tolerance improves and exertional symptoms of MS are ameliorated. [1,16]

Ivabradine independently decreased resting heart rate significantly at the end of 3 months onwards (p<.001) and was comparable to metoprolol (p=.567). Dhanger et. Al [9] also showed non-significant difference between 2 groups in context of resting HR, whereas Agarwal et.al [7] and Saggu et al [11] showed ivabradine was inferior to beta blockers in terms of resting HR.

Unwanted alteration of BP was significant for BETA group (p<0.001). IVA group showed no change. This statistical inferiority obviously confirms the selective bradycardic effect of ivabradine. Many patients treated with beta blockers presented with lethargy with documented hypotension. On that point definitely Ivabradine is superior clinically than beta blockers.

Exercise relates to symptoms in progressive MS. Rate control is a strategy to improve exercise tolerance. Peak exercise HR was significantly reduced with both drugs at 6 months from baseline (p<.001). Head to head, ivabradine was not statistically significant (p=.774) like finding of other RCTs; p<.001 (Agarwal 2016) [7]; p =0.04 (Parakh et al [8]). TED that directly signifies exercise tolerance was highly significant in favor of ivabradine (p =0.0032). Parakh et al [8] showed similar results. Meta-analysis by Ramos J et al [18] demonstrates superior outcome with Ivabradine than beta blocker (mean difference 32.73s 95% CI:12.19-53.27; p=.002).

Holter monitoring showed mean minHR for BETA group was significantly lower 55.53(1.28) than IVA was 62.71(0.95). (p=.0002). That corroborates with the higher incidence of weakness, syncope, history of fall associated with Beta blockers. This statistical superiority was thus clinical inferiority in terms of safety for Beta blockers. Our findings are also in line with Agarwal [7], Saggu et al [11] and Muhammad et al. [17]

Echo parameters were not reflected any substantial changes in terms of MVA or ejection fraction. Although the change in mean gradient across mitral valve from baseline to 6 months was highly significant (p<.001). Ivabradine was comparable in effects on MDG of Beta blockers here (p=.936) in line with studies of Dhanger et. Al [9], Saggu et al. [11] these changes were attributed possibly due to change in heart rate as the transmitral pressure gradient (MDG) is dependent on HR, with a quadrupling of transvalvular pressure for a doubling of the HR1. With effective rate control MDG improved allowing less exertional symptoms in both treatment groups significantly.

In terms of ivabradine all the safety events were minor and related to pharmacologic profile of drugs with no new adverse effects detected. Symptomatic bradycardia and hypotension were major events in BETA group that justifies our study rationale of selecting selective bradycardic drug like ivabradine for rate control in MS.

In terms of QOL, for IVA group improvement over baseline in EQVAS score was highly significant over BETA group. This finding adds on a new dimension of the drug ivabradine in medical management of MS targeted at rate control and goes in line with the efficacy, safety, and clinical roles established by various RCT and meta-analyses. [7-11, 17-19]

Lastly, to wrap up the discussion, definitive treatment for symptomatic or severe MS still remains surgery or vulvoplasty1,2 Medical managements are targeted to heart failure management and rate control for those who are symptomatic with exertion-induced tachycardia and dyspnoea, and those with progressive (mild to moderate) lesions. [1,2,16]

Limitations

We have identified our limitations. Safety and tolerability profile needed more participants and time to evaluate. Cost factor could not be evaluated due to some logistic issues.

Conclusions

Based on the results, both the drugs were similar in improving hemodynamic, echo parameters as well as in terms of symptomatic improvement (NYHA class). Statistical superiority of Ivabradine over

beta blockers is established in aspects of total exercise duration and quality of life.

Clinically ivabradine showed superiority as effect on BP, lesser min HR proved problematic for beta blocker. Quality of life improvement adds a new dimension to the findings of available literatures. So why as an alternative to failed beta blocker therapy, we can recommend ivabradine as a primary therapy for rate control in mitral stenosis with normal sinus rhythm. Although, a larger non-academic trial for Ivabradine in MS for rate control avoiding the limitations in recent future.

Ethical Issues: Ethical considerations emerged during the trial as follows: Severe symptomatic cases or patients whose condition deteriorated to a very severe state during the trial were promptly excluded from the study to undergo urgent surgical intervention. In the case of severe patients, surgical treatment was prioritized, and no participant was required to remain only for the sake of the trial for the full 6-month study duration. However, due to various factors such as external circumstances, infrastructural limitations, patient-specific reasons, and the challenges posed by the COVID-19 situation, surgical treatments were delayed in certain instances. In summary, the study was conducted with due attention to ethical considerations, and no other ethical issues were identified. A higher attrition rate was allowed.

References

1. Zipes D, Libby P, Bonow R, Mann D, Tomaselli G, Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Vol II Philadelphia: Elsevier; 2018;1415-24.
2. Nishimura R, Otto C, Bonow R, Carabello B, Erwin J, Guyton R et al. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. Journal of the American College of Cardiology. 2014; 63(22): e57-e185.
3. Kumar R, Saran RK. Beneficial effects of long-term metoprolol therapy on cardiac hemodynamics in patients with mitral stenosis in sinus rhythm—a randomized clinical trial. Indian Heart J. 1994; 46:297–301.
4. Tattersfield AE. Respiratory function in the elderly and the effects of beta-blockade. Cardiovasc Drugs Ther. 1991; 4 (Suppl. 6): 1229–32.
5. Sulfi S, Timmis A. Ivabradine - the first selective sinus node If channel inhibitor in the treatment of stable angina. International Journal of Clinical Practice. 2006;60(2):222-228.
6. Goodman L, Gilman A, Brunton L, Hilal-Dandan R, Knollmann B. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York [etc.]: McGraw Hill Education; 2018.
7. Agrawal V, Kumar N, Lohiya B, Sihag B, Prajapati R, Singh T Et al. Metoprolol vs ivabradine in patients with mitral stenosis in sinus rhythm. International Journal of Cardiology. 2016; 221:562-566.
8. Parakh N, Chaturvedi V, Kurian S, Tyagi S. Effect of Ivabradine vs Atenolol on Heart Rate and Effort Tolerance in Patients with Mild to Moderate Mitral Stenosis and Normal Sinus Rhythm. Journal of Cardiac Failure. 2012;18(4):282-288.
9. Dhanger M, Isser H, Bansal S, Chakraborty P, Gupta P, Sharma N. Comparative study of Ivabradine versus atenolol in symptomatic mitral stenosis patients. Indian Heart Journal. 2014;66: S133.
10. Rajesh G, Sajeer K, Sajeev C, Bastian C, Vinayakumar D, Muneer K et al. A comparative study of ivabradine and atenolol in patients with moderate mitral stenosis in sinus rhythm. Indian Heart Journal. 2016;68(3):311-315.
11. Saggu D, Narain V, Dwivedi S, Sethi R, Chandra S, Puri A et al. Effect of Ivabradine on Heart Rate and Duration of Exercise in Patients with Mild-to-Moderate Mitral Stenosis. Journal of Cardiovascular Pharmacology 2015; 65(6):552-4.
12. Mitral stenosis in 2019: changing approaches for changing times. (2020). Expert Review of Cardiovascular Therapy. Retrieved from https://www.tandfonline.com/doi/full/10.1080/1
13. Carapetis, J., Beaton, A., Cunningham, M., Guilherme, L., Karthikeyan, G., & Mayosi, B. et al. Acute rheumatic fever and rheumatic heart disease. Nature Reviews Disease Primers, 2016; 2(1).
14. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001; 33:337–343.
15. IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp
16. O'Gara P, Loscalzo J. Mitral Stenosis. In: Jameson J, Fauci A, Kasper D, Hauser S, Longo D, Loscalzo J, ed. by. Harrison's principles of internal medicine. 20th ed. México D. F: McGraw-Hill Education.; 2018. p. 1813-1817.
17. Muhammad F, Nazeer A, Rehman Z. The comparison of effects of ivabradine and atenolol on heart rate and symptoms in patients with mild-to-moderate mitral stenosis. Pak J Med Health Sci. 2016;10(2):345–7.
18. Ramos, J., Cunanan, E., Abrahan, L., Tiongson, M., & Punzalan, F. Ivabradine Versus Beta-Blockers in Mitral Stenosis in Sinus Rhythm: An Updated Meta-Analysis of Ran-

domized Controlled Trials. Cardiology Research, 2018;9(4), 224-230.
19. Ghadimi, N., Kaveh, S., Shabaninejad, H., Lijassi, A., Mehr, A., & Hosseinifard, H. Comparative efficacy of ivabradine versus beta-blockers in patients with mitral stenosis in sinus rhythm: systematic review and meta-analysis. International Journal of Clinical Pharmacy, 2019; 41(1): 22-29.
20. Tanboga IH, Topcu S, Aksakal E, Gulcu O, Aksakal E, Aksu U, Oduncu V, et al. The risk of atrial fibrillation with ivabradine treatment: a meta-analysis with trial sequential analysis of more than 40000 patients. Clin Cardiol. 2016;39(10):615-620.
21. Otto C, Nishimura R, Bonow R, Carabello B, Erwin J, Gentile F et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5).