

HEART RATE MANIPULATION IN IDIOPATHIC DILATED CARDIOMYOPATHY: ASSESSING THE ROLE OF IVABRADINE

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ABSTRACT

BACKGROUND

The prevalence of chronic heart failure (HF) in the general population has been estimated to be around 2–3%.¹ Dilated cardiomyopathy (DCM) is the most common cause of HF in young adults.² The recognition of elevated heart rate as a risk factor for cardiovascular morbidity and mortality and its association with sudden cardiac death has made lowering the heart rate in HF patients one of the most important therapeutic approaches.

The aim of the study is to assess the role of ivabradine in idiopathic dilated cardiomyopathy by modulating heart rate, based on functional class, and echocardiographic parameters.

MATERIALS AND METHODS

In this study, a prospective, non-randomised, double arm, open label, longitudinal one, 80 patients of DCM (idiopathic) were taken into study after exercising the inclusion and exclusion criteria as per the study protocol. Subjects were selected from those attending Cardiology OPD or admitted to Cardiology ward of S.C.B. Medical College, Cuttack, Odisha during period of Aug 2016-Aug 2017. They were divided into Ivabradine group (cases/group A) and standard tt. Group (controls/group B).

RESULTS

The baseline data of the 40 cases and 40 controls are presented. The reasons for patients not receiving target doses of carvedilol were hypotension, asthma, chronic obstructive airway disease, and fatigue. The reasons for not achieving target doses of ACEI were development of hypotension and severe dizziness. As shown in the table the baseline HR, blood pressure, exercise tolerance, Minnesota questionnaire score, and LV systolic function were all comparable between the two groups ($p > 0.05$) for all.

CONCLUSION

To conclude the addition of Ivabradine in patients with dilated (idiopathic) cardiomyopathy resulted in significant improvement in functional capacity, Minnesota questionnaire score and LV dimension. The lack of improvement in NYHA class and EF(%) may be due to limitations of the study like small sample volume and short duration of follow up. However, it should be remembered that all patients must receive the maximally tolerated doses of beta blockers, ACEI/ARBs, MRAs before starting Ivabradine; and Ivabradine should not be used as an alternative of beta blockers.

KEYWORDS

Ivabradine; Heart failure; Dilated cardiomyopathy.

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BACKGROUND

The prevalence of chronic heart failure (HF) in the general population has been estimated to be around 2–3%.¹ Dilated cardiomyopathy (DCM) is the most common cause of HF in young adults.² The recognition of elevated heart

rate as a risk factor for cardiovascular morbidity and mortality and its association with sudden cardiac death has made lowering the heart rate in HF patients one of the most important therapeutic approaches.

Heart rate reduction has been proven to be beneficial in patients of chronic heart failure (HF).^{3,4} HR is usually increased in chronic HF and correlates positively with mortality.⁵ It was speculated that HR lowering is beneficial by possibly increasing left ventricular (LV) filling, preventing LV ischemia. However, HR reduction-related decrease in cardiac output can be harmful and not necessarily offset by the previously mentioned effects.

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The current guidelines from the American College of Cardiology/American Heart Association and European Society of Cardiology all recommend β -blockers for all patients with HF along with other standard treatment. Unfortunately, β -blockers are contraindicated in patients with bronchial asthma and patients with critical limb ischemia. β -blockers also have a significant number of adverse effects including bronchospasm, lethargy, hypotension, worsening of AV conduction, therefore are not suitable for use in these patients.^{6,7}

Ivabradine is a selective sinus rate slowing agent which inhibits the cardiac if current that is responsible for spontaneous diastolic depolarisation in the sinus node.

Aims and Objectives

The aim of our study is to assess the role of ivabradine in idiopathic dilated cardiomyopathy by modulating heart rate, based on functional class, and echocardiographic parameters.

MATERIALS AND METHODS

In this study, a prospective, non-randomised, double arm, open label, longitudinal one, 80 patients of DCM (idiopathic) were taken into study after exercising the inclusion and exclusion criteria as per the study protocol. Subjects were selected from those attending Cardiology OPD or admitted to Cardiology ward of S.C.B. Medical College, Cuttack, Odisha during period of Aug 2016-Aug 2017. They were divided into Ivabradine group (cases/group A) and standard tt. group (controls/group B).

The assessment was done at base line, and at 6 months follow up.

Inclusion Criteria

Cases were selected who were >18 yrs., had LVEF <40%, in NYHA class \geq II and in sinus rhythm with resting HR \geq 70 bmp.

Exclusion Criteria

Patients with baseline resting heart rate <70/min, sick sinus syndrome, atrial fibrillation/flutter, Pacemaker or cardiac resynchronisation therapy, renal impairment (ser. creat>3 mg/dl), pregnancy, hemoglobin \leq 10 gm/dl, uncontrolled thyroid disease, significant valvular or congenital heart disease, with history of CAD or CAG showing \geq 50% stenosis were excluded from the study.

Study Protocol

Pts were divided into two groups group A (cases - even numbers) that received ivabradine as an add on therapy to standard optimal medical treatment and group B (controls - odd numbers) that received only standard optimal medical treatment.

The cases (gr A or ivabradine group) received ivabradine (dose 2.5 BD to 7.5 BD) in addition to standard therapy (beta blockers, ACE inhibitors, diuretics) whereas controls (gr B or standard tt group) received only standard therapy.

The ivabradine dose was gradually titrated upward till reaching a resting HR of 60 bpm or reaching target dose of 7.5 mg twice daily. The starting dose was 2.5 mg every 12 hours for 2 weeks, then 5 mg every 12 hours for another 2 weeks, then 7.5 mg every 12 hours till the end of 6 months.

All the selected patients were be subjected to detailed history (NYHA class), complete physical examination, exercise tolerance by modified Bruce protocol, MLWHF (Minnesota Living with HF questionnaire). Relevant investigations such as Routine investigations, ECG, Holter monitoring if necessary, BNP levels, Echocardiographic parameters including LV size, LVEF were done.

Statistical Analysis

All the demographic, anthropometric data and laboratory values were compiled into a master chart. Data were analysed using the Graph pad software. Values are expressed as mean \pm S.D. The differences in mean values of the variables between cases and controls were tested using student t-test and t-test with adjustment for variables with unequal variances (Welch’s test) to check for significance. Categorical variables were described with absolute and relative (percentage) frequencies. Difference between proportions was tested using Chi-square test. Wilcoxon rank-sum test was used to detect the differences between cases and controls. Pearson’s correlation coefficient test was performed to study the correlation between HR at 6 months on one hand; and exercise tolerance and quality of life, on the other hand. A bivariate analysis followed by multiple logistic regression was carried out to estimate odds ratio (OR) and 95 per cent confidence interval (95% CI). P \leq 0.05 was considered as significant.

RESULTS

The baseline data of the 40 cases and 40 controls are presented in following table 1.

Parameters at Base Line	Ivabradine Group (Cases) (Gr A) n= 40	Standard tt Group (Controls) (Gr B) n=40	P Value
Age (years)	46.83 \pm 1.83	45.33 \pm 1.95	0.58
Male gender	23 (57.5%)	28 (70%)	
Smoking	3 (7.5%)	5 (12.5%)	
Hypertension	4 (10%)	3 (7.5%)	
Diabetes	5 (12.5%)	8 (20.5%)	
ACEI (% of target dose	40 (100%)	40 (100%)	0.73
Ramipril	53.5 \pm 28%	56 \pm 29.3%	
Enalapril	26 (65%)	28 (70%)	
Telmisartan	9 (22.5%) 5 (12.5%)	10 (25%) 2 (5%)	
Beta blockers Carvedilol dose (mg)	39 (97.5%) 18.1 \pm 14.2	40 (100%) 17 \pm 16.3	0.91

NYHA class: II III IV	12 (30%) 24 (60%) 4 (10%)	10 (25%) 25 (62.5%) 5 (12.5%)	0.84
Resting Heart Rate (bpm)	86.78 ± 11.94	88.90 ± 12.97	0.448
SBP (mm Hg)	102.25 ± 11.95	100.35 ± 9.72	0.437
LV EDD (mm)	62.50 ± 5.31	62.38 ± 4.54	0.91
EF (%)	32.28 ± 5.63	32.33 ± 5.29	0.96
Left Atrial dimension	42 ± 6	40 ± 5	0.17
Total exercise duration(min)	3.87 ± 2.17	3.97 ± 1.9	0.84
Minnesota questionnaire score	59.18 ± 12.03	61.10 ± 11.56	0.55
Table 1. Baseline Characteristics of the Two Study Groups			

The reasons for patients not receiving target doses of carvedilol were hypotension, asthma, chronic obstructive airway disease, and fatigue. The reasons for not achieving target doses of ACEI were development of hypotension and severe dizziness. As shown in the table the baseline HR, blood pressure, exercise tolerance, Minnesota questionnaire score, and LV systolic function were all comparable between the two groups ($p > 0.05$) for all.

At the end of a 6-month follow-up, 32 (80%) patients of the ivabradine group were on 7.5 mg twice daily, 6 (15%) on 5 mg twice daily, and 2(5%) on 2.5 mg once daily (severe visual symptoms). The mean dose of ivabradine received was 6.8 mg twice daily. The main reasons for patients not reaching the target dose of ivabradine were development of symptomatic bradycardia, and visual symptoms.

The following table - 2 shows the change in parameters at 6 month follow up.

Parameters at 6 Months	Ivabradine group (Gr A) n= 40	Standard tt group (Gr B) n=40	p value
NYHA class			
I	0 (0%)	1 (2.5%)	> 0.05
II	20(50%)	18 (45%)	
III	16 (40%)	17 (42.5%)	
IV	2 (5%)	3 (7.5%)	
Death	2 (5%)	1 (2.5%)	
Resting Heart rate (bpm)	69.58 ± 10.21	80.36 ± 11.07	< 0.001
SBP (mm Hg)	101.47 ± 7.26	102.62 ± 9.99	0.569
LVEDD (mm)	61.32 ± 5.28	63.92 ± 5.27	0.03
EF (%) at 6 month	32.83 ± 4.7	31.28 ± 5.70	0.65
Total exercise duration (mim)	5.51 ± 2.54	4.15 ± 2.50	0.02
Minnesota questionnaire score	47.68 ± 9.27	54.90 ± 12.01	0.004
Table 2. Changes at 6 months follow up			

As we can see there was no significant difference in NYHA class, Systolic BP or Ejection fraction between the two groups at 6 months follow up. HR was reduced by a

mean of 17 bpm in the ivabradine group compared with baseline; and HR reduction in the ivabradine group was 9 bpm in comparison to standard tt group. So at 6 months there was significant reduction in resting heart rate between the two groups. There was statistically significant improvement in LV dimension, Total exercise duration and Minnesota score between the both groups.

Abbreviations -

- ACEI - Angiotensin-converting enzyme inhibitor
- AF - Atrial fibrillation
- ARB - Angiotensin receptor blocker
- DCM - Dilated cardiomyopathy
- EF (%) Ejection fraction
- ESC - European Society of Cardiology
- GRACE Registry- Global Registry of Acute Coronary Events
- HF - Heart failure
- HFmrEF - HF with mid-ranged LVEF
- HFNEF - Heart failure with normal ejection fraction
- HFpEF - HF with preserved LVEF
- HR - Heart rate
- HFrEF - HF with reduced LVEF
- MRAs - Mineral corticoid receptor antagonists
- NYHA Class - New York Heart Association classification
- QoL - Quality of life
- SBP - Systolic blood pressure

DISCUSSION

Increased resting HR is a known risk factor for worse clinical outcome in patients with HF, and chronic stable angina.^{8,9} Evidence suggests that HR reduction is associated with improved clinical outcome in patients with HF and LV systolic dysfunction;¹⁰ the magnitude of benefit is related to the extent of HR reduction.^{8,10} Unfortunately, in most patients with HF receiving beta-blockers, HR remains substantially elevated and in many patients the target beta blocker dose could not be achieved because of poorly tolerated adverse effects including hypotension.^{11,12} Ivabradine, which is a selective If current inhibitor; is very effective in reducing the HR while having minimal effect on blood pressure.

Our study demonstrated that in symptomatic patients with idiopathic dilated cardiomyopathy who are already receiving the maximally tolerated doses of beta-blockers and ACEI, the administration of ivabradine as add-on therapy reduced HR & LV dimensions, improved exercise tolerance, and quality of life, compared with placebo, at short-term follow-up of 6 months. Yet, no effect on blood pressure, NYHA class or LV function (EF %) was observed when compared to standard therapy. To the best of our knowledge, this is the first piece of evidence for a beneficial effect of ivabradine on exercise tolerance and quality of life in patients with idiopathic dilated cardiomyopathy.

In the SHIFT trial which included patients with systolic HF (2/3 ischemic) and a sinus HR ≥ 70 bpm, ivabradine reduced the composite endpoint of cardiovascular death or hospitalization for HF. However the benefit was largely

driven by reduction of HF hospitalization only.^{11,13} Based on this the ESC in 2012 recommended to consider ivabradine in patients with symptomatic HF, LVEF \leq 35%, and a sinus HR \geq 70 bpm, despite the maximally tolerated doses of evidence-based therapy (class IIa, level of evidence B) and in patients unable to tolerate a beta-blocker (class IIb, level of evidence C).¹⁴

In our study, it was not possible to achieve the recommended target dose of beta-blockers in all patients, because of intolerance to beta-blockers, mostly hypotension. About 1/3rd (34%) patients received the target dose of beta blocker compared to that in SHIFT trial in which 26% of patients received the target dose. The mean baseline HR were 86 bpm and 88 bpm in study and control groups respectively. The mean HR reduction in our study was 9 bpm at 6 months with ivabradine treatment (mean dose 6.8 mg). In the multicenter SHIFT trial there was reduction of HR of 11 bpm with mean ivabradine dose of 6.5 mg.¹³ In the current study, the exercise tolerance and quality of life correlated well with the final HR at follow-up. The lack of significant improvement of the NYHA class in the current study might be attributed to the small sample size of the study.

Heart rate reduction with ivabradine was not associated with any hemodynamic deterioration and correlated well with improvement in LV dimension. The improvement may be explained by changes at molecular and cellular level that leads to improvement in myocyte function and changes in extracellular matrix as a result of sustained HR reduction.

CONCLUSION

To conclude the addition of Ivabradine in patients with dilated (idiopathic) cardiomyopathy resulted in significant improvement in functional capacity, Minnesota questionnaire score and LV dimension. The lack of improvement in NYHA class and EF (%) may be due to limitations of the study like small sample volume and short duration of follow up. However, it should be remembered that all patients must receive the maximally tolerated doses of beta blockers, ACEI/ARBs, MRAs before starting Ivabradine; and Ivabradine should not be used as an alternative of beta blockers.

REFERENCES

- [1] Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis, treatment of acute, chronic heart failure 2008. The Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;10(10):933-989.
- [2] Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006;355(18):1873-1884.
- [3] Benetos A, Rudnichi A, Thomas F, et al. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. *Hypertension* 1999;33(1):44-52.
- [4] Chang M, Havlik RJ, Corti MC, et al. Relation of heart rate at rest and mortality in the Women's health and aging study. *Am J Cardiol* 2003;92(11):1294-1299.
- [5] Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352(19):1951-1958.
- [6] Ragueneau I, Laveille C, Jochemsen R, et al. Pharmacokinetic-pharmacodynamic modelling of the effects of ivabradine, a direct sinus node inhibitor, on heart rate in healthy volunteers. *Clin Pharmacol Ther* 1998;64(2):192-203.
- [7] Singh BN. Impact of heart rate on cardiovascular disorders: focus on chronic stable angina. In: Fox K, ed. *Selective and specific if channel inhibition in cardiology*. London: Science Press Ltd 2004:25-36.
- [8] Böhm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;376(9744):886-894.
- [9] Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;372(9641):817-821.
- [10] Flannery G, Gehrig-Mills R, Billah B, et al. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008;101(6):865-869.
- [11] Swedberg K, Komajda M, Böhm M, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012;59(22):1938-1945.
- [12] Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme: a survey on the quality of care among patients with heart failure in Europe. Part 2: Treatment. *Eur Heart J* 2003;24(5):464-474.
- [13] Swedberg K, Komadja M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376(9744):875-885.
- [14] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33(14):1787-1847.