Indian Heart Journal xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Heart rate manipulation in dilated cardiomyopathy: Assessing the role of Ivabradine

Deep Chandh Raja, Aditya Kapoor*, Archana Sinha, Shiridhar Kashyap, Roopali Khanna, Sudeep Kumar, Naveen Garg, Satyendra Tewari, Pravin Goel

Department of Cardiology, Sanjay Gandhi PGIMS, Lucknow 226014, India

ARTICLE INFO

Article history:
Received 29 April 2017
Accepted 10 August 2017
Available online xxx

Keywords:
Heart failure
Dilated cardiomyopathy
Heart rate
Ivabradine
Beta blocker

ABSTRACT

Background: Heart rate (HR) reduction is of benefit in chronic heart failure (HF). The effect of heart rate reduction using Ivabradine on various echocardiographic parameters in dilated cardiomyopathy has been less investigated.
Methods: Of 187 patients with HF (DCM, NYHA II–IV, baseline HR > 70/min), 125 patients were randomized to standard therapy (beta blockers, ACEI, diuretics, n = 62) or add-on Ivabradine (titrated to maximum 7.5 mg BD, n = 63). Beta-blockers were titrated in both the groups.
Results: At 3 months both groups had improvement in NYHA class, 6 min walk test, Minnesota Living With Heart Failure (MLWHF) scores and fall in BNP, however the magnitude of change was greater in Ivabradine group. Those on Ivabradine also had lower LV volumes, higher LVEF (28.8 ± 3.6 vs 27.2 ± 0.5, p = 0.01) and more favorable LV global strain (11 ± 1.7vs 12.2 ± 1.1, p = <0.001), MPI (0.72 ± 0.1 vs 0.6 ± 0.1, p = <0.001), LV mass (115.2 ± 30 vs 131.4 ± 35, p = 0.007), LV wall stress (219.8 ± 46 vs 238 ± 54) and calculated LV work (366 ± 101 vs 401 ± 102, p = 0.05). The benefit of Ivabradine was sustained at 6 months follow-up. The % change in HR was significantly higher in Ivabradine group (−32.2% vs −19.3%, p = 0.001) with no difference in blood pressure. Resting HR < 70/min was achieved in 96.8% vs 27.9% respectively in the two groups.
Conclusion: Addition of Ivabradine to standard therapy in patients with DCM and symptomatic HF and targeting a heart rate < 70/min improves symptoms, quality of life and various echocardiographic parameters.

1. Introduction

Studies have indicated that lowering heart rate (HR) can help reduce mortality and cardiovascular events by improving the left ventricular filling and favorably affecting the imbalance between myocardial oxygen supply and demand in patients with heart failure (HF).[1–3] Some patients with HF continue to have persistently high HR despite treatment with beta blockers and conventional treatment.[4]

Ivabradine, a novel HR lowering agent, is a selective and specific inhibitor of the "funny" I_f current at concentrations that do not affect other cardiac ionic currents resulting in lack of hemodynamic effects such as reduction of blood pressure, cardiac contractility or atrioventricular conduction, which is often a limitation with beta blockers.[5,6] Improvement in remodeling of the extracellular matrix has also been reported with Ivabradine in animal and experimental models of HF.[7] Despite its benefit being demonstrated in patients with CAD and LV dysfunction,[8,9] the use of Ivabradine in isolated non-ischemic HF has been less studied and only a few studies have reported its use in HF secondary to DCM.[10,11]

This prospective randomized study sought to assess whether addition of Ivabradine to conventional treatment while targeting a heart rate reduction of <70/min would improve functional class, exercise tolerance, and left ventricular function in patients with HF secondary to nonischemic dilated cardiomyopathy.

2. Materials and methods

2.1. End points

The primary end point of the study was to assess the superiority of add-on Ivabradine over conventional medical management on the improvement in various echocardiographic parameters. The

* Corresponding author.
E-mail address: akapoor65@gmail.com (A. Kapoor).

http://dx.doi.org/10.1016/j.ihj.2017.08.009

secondary end point was to assess the superiority of add-on Ivabradine over conventional medical management on heart rate and quality-of-life (QOL-NYHA class, 6 min walk test, MLWHF score, BNP levels) parameters.

2.2. Inclusion and exclusion criteria

The study was conducted at the Department of Cardiology at our institution from January 2014 to July 2015 and conformed to the institutional ethical guidelines. Patients with symptomatic HF secondary to idiopathic DCM, NYHA symptomatic class II–IV and LV ejection fraction ≤40% and resting HR > 70/min were enrolled after obtaining informed consent. Prior to randomization, all patients were on medical therapy (including beta blocker, angiotensin converting enzyme inhibitors, diuretics and digoxin) for at least 12 weeks prior to enrolment into the study. Patients with atrial fibrillation, baseline bundle branch blocks, deranged renal functions (serum creatinine >3 mg/dl), deranged liver functions, significant valvular heart disease, known coronary artery disease (by means of history or prior coronary angiogram), malignancy and inability to provide consent were excluded from the study.

2.3. Randomization, drug titration

Patients were randomized in the sequence of 1:1 by computerized random number generation protocol to either guideline directed optimal medical therapy: (control group)[4] or optimal medical therapy with add-on Ivabradine (Ivabradine group). Ivabradine was initiated in the dose of 2.5 mg bd. Both beta blockers and Ivabradine were up-titrated over next 2–4 weeks (carvedilol and metoprolol were titrated, if tolerated to a maximum dose of 50 or 200 mg respectively, while Ivabradine to 7.5 mg twice daily). The up-titration was guided by the patients' HR and the target dose was not the maximum dose mentioned, but the maximally tolerated dose that produced a resting HR < 70/min. The drug dose was reduced or withdrawn (if needed) in case of intolerance, symptomatic bradycardia (in case of either beta blocker or Ivabradine) or visual disturbances (in case of Ivabradine).

2.4. Data collection

Baseline assessment of symptomatic class was done using the NYHA classification while functional exercise capacity was estimated using the 6 min walk test. The Minnesota Living With Heart Failure questionnaire (MLWHF) was used to assess the quality of life.[12] All patients underwent baseline investigations including complete hemogram, renal and liver functions, blood sugar, serum electrolytes and BNP levels. Levels of BNP were assessed using fluorescence immunoassay with a commercially available kit (Alere Triage Cardio 3 Panel, Alere, Inc., San Diego, CA, USA). All parameters were re-assessed at a follow up of 3 and 6 months.

2.5. Echocardiography

Detailed echocardiography was performed using a GE Vivid 7 ECHO machine (GE Healthcare, Waukesha, WI) by an operator who was blinded to the clinical data. Various 2D Echocardiographic and Doppler indices, including left ventricular end-diastolic dimensions and volumes (LVEDD, LVEDV), left ventricular end-systolic dimensions and volumes (LVESD, LVESV) and LV ejection fraction (LVEF) were recorded. The LV dimensions were obtained from M mode parasternal long-axis views while LV volumes were obtained from the apical four- and two-chamber views. Using the modified Simpson's rule, ejection fraction was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume. Mean LV wall stress (mmhg) was calculated as $(SAP \times (EDD + ESD)/2 \times PWTd + PWTs)$, corrected LV mass (g) as $0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6$ and LV work (mmhg.L/mt) as SV X HR X ESBP (SAP-systolic arterial pressure, EDD-end diastolic dimension, ESD-end systolic dimension, PWTd and PWTs-posterior wall thickness in diastole and systole respectively, IVS-interventricular septum, SV-stroke volume and ESBP-end systolic blood pressure).[13,14]

Transmitral flow velocities (peak early: E wave and late: A wave), their ratio (E/A); velocity time integral (EVTI and A VTI), their ratio (E/A VTI), E deceleration time and tissue Doppler indices (TDI E/e'septal and E/e' lateral) were also recorded in all patients. Tei index or Myocardial Performance Index (MPI), an echocardiographic Doppler load independent index of combined systolic and diastolic function, was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Global LV longitudinal strain was also assessed by TDI imaging. Apical 4 chamber view was used to record the cardiac cycle in TDI mode at a frame rate of more than 100 per second, following which 2 mm volume samples were placed at 6 different segments of LV in apical 4 chamber view for strain analysis. The average of these 6 segments resulted in the global longitudinal strain values expressed in '−%' representing the fractional contraction percentage of the reference segment. All patients underwent repeat echocardiographic assessment at 3 and 6 months of follow up.

2.6. Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) and categorical variables as percentages. Statistical analysis was performed using commercially available software (SPSS Version 17.0, Texas). Paired continuous variables were compared using paired *t*-test for normally distributed data. Independent continuous variables were compared using a two-sample *t*-test for normally distributed data. Categorical variables were compared with the use of the Pearson chi-square test. The Pearson correlation coefficient was obtained to examine the linear relationship between heart rate and other continuous variables. P value < 0.05 (2 tailed) was considered statistically significant. Binomial logistic regression analysis was done to derive the univariate and multivariate predictors for ejection fraction >30% at the end of follow up. The study conforms to ethical principles in the Declaration of Helsinki and the study has been approved by the local institutional ethics committee.

3. Results

A total of 187 patients were screened of which 62 were excluded (associated CAD in 18, significant valvular heart disease in 19, atrial fibrillation in 14 and poor echo window in 11). Hence 125 patients (mean age 47.2 ± 15 years, 56.9% males) were included of which 63 were in the control group and 62 in the Ivabradine group. The mean LVEF of the study population was 26.3 ± 3.6% (range 17.9%–35.2%), mean global LV strain was −10.02 ± 1.5% (−6.4 to −16.3%) while mean BNP was 750 ± 442 pg/dl (range 110–2000 pg/dl). Overall, 32.5% had hypertension while 34.1% had diabetes. All patients were on beta blockers and ACE inhibitors while 87%, 67% and 27% were on diuretics, digoxin and spironolactone respectively.

3.1. Comparison of baseline characteristics (Tables 1 and 2)

There was no significant difference between the two groups with respect to baseline demographic, clinical characteristics and medications. Mean LVEF (26.7 ± 3.6 vs 26 ± 3.6% (p = 0.3), global LV

Please cite this article in press as: D.C. Raja, et al., Heart rate manipulation in dilated cardiomyopathy: Assessing the role of Ivabradine, Indian Heart J (2017), http://dx.doi.org/10.1016/j.ihj.2017.08.009