EFFICACY AND SAFETY OF IVABRADINE IN PATIENTS WITH CHRONIC STABLE HEART FAILURE

Elavarasi P. *,1, Ezhil Ramya J.2 and Vasanth S.3

1,3 Assistant Professor, Department of Pharmacology, Govt. Tiruvarur Medical College.
2 Associate Professor, Department of Pharmacology, Govt. Tirunelveli Medical College.

ABSTRACT

INTRODUCTION: Chronic heart failure is associated with increasing incidence of mortality and morbidity. Unlike western countries where heart failure is a disease of elderly, in India it affects younger age group. The lifetime risk of developing HF at the age of 40 yr is 11.4 % for men and 15.4 % for women. Ivabradine is a novel specific and selective heart rate lowering agent that acts in sino-atrial node cells by selectively inhibiting the cardiac pacemaker in a dose dependant manner. OBJECTIVE: To evaluate the efficacy and safety of Ivabradine in patients with chronic stable heart failure prospectively.

MATERIALS AND METHODS: Interventional, open label, prospective, single centered study conducted in the Out patient Department of Cardiology, Tirunelveli Medical College Hospital and 50 patients attending cardiology OPD receiving chronic heart failure therapy. End points noted were improvement in ejection fraction and improvement in left ventricular function. RESULTS: After treatment with Ivabradine, there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline. After treatment with study drug patients with moderate LV dysfunction was reduced to 20 at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline. After treatment with study drug the improvement in ejection fraction% was (45.48±5.03) (p<0.001) at the end of 1 month and (49.08±4.17) (p<0.001) 3 months compared with the baseline (41.36±6.23). CONCLUSION: We conclude that Ivabradine is safe and effective in treating patients with chronic stable ischemic heart disease.
KEYWORDS: Chronic stable heart failure, Ivabradine, left ventricular function, Ejection fraction.

INTRODUCTION
Chronic heart failure is associated with increasing incidence of mortality and morbidity.\textsuperscript{[1]} Heart failure is the inability of the heart to pump blood and/or reduced blood supply to various organs which is inadequate as per the requirement. Heart rate is being recognised as a modifiable risk factor in patients with cardiovascular disease.\textsuperscript{[2]} Unlike western countries where heart failure is predominantly a disease of elderly, in India it affects younger age group. The important risk factors for heart failure include coronary artery disease, hypertension, diabetes mellitus, cardiotoxic drugs, valvular heart disease and obesity.\textsuperscript{[3]}

The lifetime risk of developing heart failure is estimated at about 20 per cent both in men and women. The lifetime risk of developing HF at the age of 40 yr is 11.4 per cent for men and 15.4 per cent for women. More than 500,000 new cases are diagnosed each year.\textsuperscript{[4]} To achieve maximum benefit from medical therapy for heart failure, it is necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.\textsuperscript{[5]} In current clinical practice, however many patients with chronic heart failure require treatment with more than one group of drug in addition to diuretics, ACE inhibitors or beta-blockers.\textsuperscript{[6]}

Ivabradine is a novel specific and selective heart rate lowering agent that acts in sino-atrial node(SA) cells by selectively inhibiting the cardiac pacemaker in a dose dependant manner.\textsuperscript{[7]} If current has atypical or funny properties compared to other current systems such as a mixed Na\textsuperscript{+}-K\textsuperscript{+} inward movement activated on hyperpolarization and modulated by autonomic nervous system. It is one of the most important ionic current for regulating the pacemaker activity in the SA node. Ivabradine reduces the slope of diastolic depolarization in these cells and lowers the heart rate at rest and during exercise.\textsuperscript{[2,8]}

Diuretics are the main stay of therapy to relieve congestive symptoms. Three classes of drugs are available: loop diuretics, thiazide group and potassium sparing diuretics. Loop diuretics include furosemide, torsemide and bumetanide. These are most potent diuretics that act on the ascending loop of Henle. Recent data suggest that torsemide and bumetanide are more effective than furosemide in the treatment of advanced heart failure.\textsuperscript{[9]}
The drugs that produce both venous and arterial dilatation are the preferred agents in heart failure as most forms of heart failure have elevated preload and after load. The ACEI acts on both the arterial and venous capacitance vessels. They act by inhibiting the production of angiotensin II as a consequence preventing the deleterious effects of angiotensin II through its action predominantly on the type 1 receptors. The levels of bradykinin are raised which result in the production of nitric oxide and other important endogenous vasodilators.[10]

Beta blockers, unlike ivabradine, reduce $I_f$ activation by decreasing the sympathetic activity and cAMP formation, resulting in a lower HR. Left ventricular function and ventricular remodeling may be improved with $I_f$ inhibition with beta blockers like atenolol. $I_f$ inhibition with ivabradine does not alter myocardial inotropy or left ventricular function and reduces the remodeling process thus supporting cardiac output and coronary outflow during exercise. Beta blockers have been used only in a limited manner because of hemodynamic or pulmonary intolerance. Beta blockers should be avoided in patients with reactive airway disease (asthma) or with SA or AV nodal dysfunction or in combination with other drugs that inhibit AV conduction like verapamil.[11]

There is still limited clinical trials related to Ivabradine, which show its efficacy and safety in chronic heart failure. Thus the present study is aimed to evaluate the efficacy and safety of the selective $I_f$ current inhibitor ivabradine in patients with chronic heart failure.

**AIM OF THE STUDY**
To evaluate the efficacy and safety of Ivabradine in patients with chronic stable heart failure prospectively.

**MATERIALS AND METHODS**
Interventional, open label, prospective clinical study started from April 2014 to May 2015, single centered study conducted in the Out patient Department of Cardiology, Tirunelveli Medical College Hospital, Tirunelveli and 50 patients attending cardiology OPD receiving chronic heart failure therapy. **INCLUSION CRITERIA:** Patients with age of $\geq$18 to $\leq$80 years, both sexes, history of chronic heart failure, heart rate in sinus rhythm of atleast $\geq$80 beats per minute, reduced ejection fraction and left ventricular dysfunction. **EXCLUSION CRITERIA:** Patients with age group of below 18 yrs to more than 80 yrs, heart rate of $< 80$ beats per minute, H/O of hypotension, BP $< 90/50$ mmhg (in both the upper limbs either in the sitting or standing posture), normal ejection fraction and left ventricular function, recent
or acute attack of myocardial infarction, signs and symptoms of acute decompensated heart failure, evidence of moderate to severe heart block, signs of congestive cardiac failure, symptomatic liver dysfunction or renal impairment, H/O pregnancy and lactation, known hypersensitivity to study drugs, not on sinus rhythm/other types of arrhythmia, taking anti-arrhythmic drugs and taking drugs with enzyme inducing and inhibiting properties.

**WITHDRAWAL CRITERIA:** Non compliance with protocol, protocol deviation, request for withdrawal by the patients, heart rate <80 bpm while on medication and adverse effects (decision about withdrawal from the study made either by patients or investigator).

**ETHICAL CONSIDERATIONS:** Approval from Institutional Ethical Committee of Tirunelveli Medical College Hospital was obtained, before starting the clinical study. Written informed consent was obtained in local vernacular language from every patient before enrollment.

**SCHEDULE OF STUDY VISIT**

a) Screening and recruitment: The subjects were enrolled based on the inclusion criteria after screening. During enrollment clinical assessment and the following baseline investigations were done.

- **Blood investigations:** Hemoglobin, differential WBC count, ESR, bleeding time and clotting time were done in a blood sample using biochemical automated analyser.
- **Blood sugar, urea and creatinine and serum electrolytes** were measured in a blood sample using automated analyser.
- **Liver function tests including ALT, AST, total bilirubin, direct and indirect bilirubin** were measured in a blood sample.
- **Baseline heart rate** was measured by taking 12 lead electrocardiography.
- **Baseline left ventricular ejection fraction (LVEF) (%)** was assessed by echocardiogram.

\[
LVEF = \frac{\text{Diastolic - systolic volume}}{\text{Diastolic volume}}
\]

Normal ▶ 60% male &
▶ 55% female.

- **Baseline left ventricular systolic function** was assessed by echocardiogram.

Grading of left ventricular (LV) systolic dysfunction based on LVEF as follows: \(^{[12]}\)

- No dysfunction = LVEF > 45%
- Mild dysfunction = LVEF 45-54%
Moderate dysfunction = LVEF 44-30%
Severe dysfunction = LVEF < 30%

- Baseline blood pressure was measured manually after 5 minutes of rest twice at least 2 minutes apart in right arm in sitting posture with the cuff at heart level using sphygmomanometer.

b) Treatment protocol

Patients received the drug as follows
Tab. Ivabradine 5-7.5 mg OD for 3 months.

After screening, ivabradine 5 mg once daily was prescribed to all patients who were included in this clinical study. Patient’s evaluation at baseline was used as the control. The study patients were reviewed every 2 weeks. Dose of ivabradine was titrated up to 7.5 mg once daily according to the heart rate (if still >100bpm) after 4 weeks of the study. Ivabradine was given orally once daily for a duration of 3 months for each patient. Also the patients were given a diary to note down the adverse events. The tablets were provided for 15 days only. Then the patients were instructed to report to the out patient department after 2 weeks along with the diary and empty strips to collect the drugs. During each visit heart rate was monitored by taking ECG. At the end of 1st and 3rd month, left ventricular function and ejection fraction were measured by using echocardiogram. Ivabradine tablets (ivanode) 5mg and 7.5 mg provided by pinnacle pharmaceuticals.

c) Follow up

Follow up was done after 15, 30, 45, 60, 75 and 90 days, clinical examinations including vital signs such as blood pressure, heart rate were measured. At the end of 1st and 3rd month, laboratory investigations such as blood Hb gm%, total count, ESR, serum electrolytes, LFT, blood sugar, urea and creatinine were performed. Also echocardiogram and ECG was done.

Efficacy Parameters
- Improvement in ejection fraction (EF) using echocardiography.
- Improvement in left ventricular function (LVF) using echocardiography.
SAFETY ASSESSMENTS
Any adverse events reported by the subject or noted by the clinician during each follow up visit was recorded. If continuation of the drug was considered harmful, the subject could be withdrawn from the study. Any adverse event was considered as serious if it was fatal, life threatening, disabling or if it prolonged hospitalization of the subject.

STATISTICAL ANALYSIS
Statistical analysis was performed with the help of statistical package SPSS (Statistical package analysis package for the social sciences) version 11.
➢ Baseline characteristics of the study patients were tabulated by descriptive statistics (mean and standard deviation) and frequency table.
➢ The analysis of efficacy parameters like left ventricular function and ejection fraction improvement were done by using “Student paired t test” at the end of 1 and 3 months before and after giving Ivabradine
➢ The adverse drug reactions were tabulated and expressed in percentage.

RESULTS
In the period of 1 year from April 2014 to May 2015, 60 cases of chronic heart failure, attending the outpatient Department of Cardiology were screened for their eligibility based on the inclusion and exclusion criteria. Among the 60 patients, 55 patients were enrolled for the study and given tab. Ivabradine once daily orally and 5 patients were withdrawn from the study due to non compliance and reduction in heart rate below 70 bpm. At the end of 1 month, those 50 patients continued the study and completed the study.

The demographic data concerning the patient’s age, sex, weight, vitals, hemodynamic and laboratory parameters were statistically assessed at the baseline.

TABLE 1: BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>BASELINE PARAMETERS</th>
<th>TAB.IVABRADINE (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (mean/SD)</td>
<td>56.06 ± 11.21</td>
</tr>
<tr>
<td>Gender (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
</tr>
<tr>
<td>Heart Rate (bpm) (mean/SD)</td>
<td>93.08± 11.67</td>
</tr>
<tr>
<td>Ejection Fraction (%) (mean/SD)</td>
<td>41.36±6.23</td>
</tr>
<tr>
<td>Canadian cardiovascular class (n)</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>
Table 1 shows the baseline characteristics of the study population (mean/SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>80</th>
<th>14</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular dysfunction (n)</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Hb (%) (mean/SD)</td>
<td>20</td>
<td>70</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>WBC (cells/cumm)</td>
<td>13.47±1.95</td>
<td>8873±1311.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr) (mean/SD)</td>
<td>15.17±1.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar (gms%) (mean/SD)</td>
<td>168.6±64.5303</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (%) (mean/SD)</td>
<td>20</td>
<td>70</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>WBC (cells/cumm)</td>
<td>139.18±3.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr) (mean/SD)</td>
<td>4.2±0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar (gms%) (mean/SD)</td>
<td>74.24+30.81</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE: 1 AGE DISTRIBUTION OF THE PATIENTS IN THE STUDY

- Figure 1 shows that the age distribution of chronic heart failure patients involved in this study.
- Maximum number of patients (19 patients) were in the age group of 51-60 yrs.
Figure 2 is a pictorial representation of sex distribution of study patients. 76% patients were male and 24% patients were female.

**EFFICACY PARAMETERS**

**TABLE 2: IMPROVEMENT IN LEFT VENTRICULAR FUNCTION**

<table>
<thead>
<tr>
<th>Left ventricular function</th>
<th>No dysfunction</th>
<th>Mild dysfunction</th>
<th>Moderate dysfunction</th>
<th>Severe dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Baseline</td>
<td>0</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>1 Month</td>
<td>0</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>3 Months</td>
<td>3</td>
<td>41</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2 shows, study drug improved the left ventricular (LV) function at the end of 1 and 3 months of treatment when compared with baseline.

At the baseline there were 5 patients with severe LV dysfunction, 35 patients with moderate LV dysfunction and 10 patients with mild LV dysfunction.

After treatment with Ivabradine, there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline. After treatment with study drug patients with moderate LV dysfunction was reduced to 20 at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline.
FIGURE 3: IMPROVEMENT IN LEFT VENTRICULAR FUNCTION AT THE END OF 1&3 MONTHS COMPARED WITH BASELINE

- Graphical representation of improvement in left ventricular function at the baseline, at the end of 1 and 3 months.
- Blue dotted line in the graph shows logarithmic trend line of left ventricular function at the baseline.
- Red and green dotted lines show logarithmic trend line of left ventricular function at the end of 1 and 3 months respectively.

FIGURE 4: Improvement in ejection fraction % (mean/SD) at the end of 1 & 3 months of treatment compared with baseline
Figure 4 shows ejection fraction % (mean and SD) at the end of 1&3 months compared with baseline.

After treatment with study drug the improvement in ejection fraction % was (45.48±5.03) (p<0.001) at the end of one month and (49.08±4.17) (p<0.001) three months compared with the baseline (41.36±6.23).

**TABLE 3: LABORATORY PARAMETERS OF THE STUDY POPULATION**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hemodynamic Parameters</th>
<th>RBS (mg%)</th>
<th>Liver Function Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb%</td>
<td>Total bilirubin (U/L)</td>
<td>AST (U/L)</td>
</tr>
<tr>
<td>At the baseline (Mean/SD)</td>
<td>13.47 ±1.95</td>
<td>168.6±64.5</td>
<td>0.81±0.28</td>
</tr>
<tr>
<td>At the end of 1 month (Mean/SD)</td>
<td>13.72±2.35</td>
<td>168.74±53.9</td>
<td>0.82±0.11</td>
</tr>
<tr>
<td>P value</td>
<td>0.318</td>
<td>0.967</td>
<td>0.719</td>
</tr>
<tr>
<td>At the end of 3 months(Mean/SD)</td>
<td>13.76±1.88</td>
<td>169.62±57.7</td>
<td>0.84±0.11</td>
</tr>
<tr>
<td>P value</td>
<td>0.196</td>
<td>0.766</td>
<td>0.419</td>
</tr>
</tbody>
</table>

The above table shows the laboratory parameters of study patients at the baseline, at the end of 1 month and at the end of 3 months. No significant changes were seen in hemodynamic parameters. No significant elevation in liver enzymes were found during the treatment period and follow up.

**ADVERSE DRUG REACTIONS**

No patients were withdrawn from the study due to adverse drug reactions during the study period. No serious adverse events were reported in study patients. The most common adverse drug reactions reported were tabulated.

**TABLE 4**

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>No. of patients n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradyarrhythmia</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Blurring of vision</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Photopsia</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Coronary artery disease is the leading cause of morbidity and mortality in world wide.[1]

Heart rate is a major determinant of cardiac output, myocardial oxygen demand and coronary blood flow. High resting heart rate has emerged as a simple but relevant risk factor for
coronary artery disease and heart failure. Pharmacotherapy for heart failure is to improve the left ventricular function and ejection fraction.\cite{13}

In recent years, a new drug to reduce HR, Ivabradine has been introduced for clinical practice by Euro Society of Cardiology. According to the results of the INITIATIVE trial which compared Ivabradine with atenolol over 4 months in 939 patients with stable angina pectoris and documented coronary artery disease, Ivabradine showed non-inferiority in reducing the total exercise duration and exercise performance and improved performance.\cite{14} According to our study, the majority of the study subjects were male patients 76% (figure 1) and males in the community were more prone for ischemic heart disease than females. In our study, heart rate reported in patients with chronic heart failure at baseline 93.08±11.67.

In this study, Ivabradine improved the left ventricular function based on LVEF compared with baseline. After treatment with Ivabradine, there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline. After treatment, moderate LV dysfunction was reduced to 20 patients at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline (table 2&figure 3).

Like wise, after giving Ivabradine showed there was significant improvement (p<0.001) in ejection fraction%. It was 45.48±5.03 at the end of one month and 49.08±4.17 at the end of three months compared with the baseline (41.36±6.23). (figure 4). A SHIFT echocardiography substudy was conducted by Montreal Heart Institute which showed that LVEF was increased by (2.4 ± 7.7%) in the Ivabradine group but LVEF was unchanged in the placebo group (−0.1 ± 8.0%). More than a third (36%) of the patients in the ivabradine group had ≥5% increase in LVEF vs. less than a quarter (23%) of the placebo group (P=0.003).\cite{15}

In our study, Ivabradine did not influence the blood pressure. The routine hematological and biochemical evaluations did not show any significant difference in the pre–post values (p>0.05). A study conducted by Aditi Chaturvedi, Yogendra Singh et al. showed that Hb, LFTs, RFTs, serum electrolytes and RBS done at baseline and after 8 weeks of use of the Ivabradine did not show any significant difference p>0.05 (using the paired “t” test).\cite{16}
In our study, Ivabradine related adverse drug reactions reported were bradyarrythmia, QT prolongation and visual disturbances like blurring of vision and photopsia. Study conducted by Borer et al.\textsuperscript{[17]}, Tardif et al.\textsuperscript{[18]} and Ruzyllo et al.\textsuperscript{[19]} showed similar adverse drug reactions. These reactions were considered to be mild and abated on its own after treatment period. But no patients were withdrawn from the study due to adverse drug reactions and no patients experienced serious adverse drug reactions.

Efficacy of Ivabradine by assessing the left ventricular function and ejection fraction improvement in chronic heart failure patients were the strength of this study. Small sample size and lack of long term follow up were the limitations of this study. Thus the present study showed that Ivabradine causes improvement in left ventricular dysfunction, ejection fraction. Therefore the study drug, Ivabradine is safe and effective in treating chronic heart failure. Further studies are needed with larger sample size and long term follow up.

**CONCLUSION**

Based on the results of our study, we conclude that Ivabradine is safe and effective in patients with chronic heart failure already on therapy.

**ACKNOWLEDGEMENT**

Authors would like to thank Dr. J.Ezhil Ramya M.D, Associate professor of Pharmacology, Tirunelveli Medical College for allowing us to do the study and for their guidance and support to complete the study.

**Funding source:** Nil

**Conflict of interest:** Nil

**REFERENCES**

2. Prakash Deedwania, Selective and Specific Inhibition of If with Ivabradine for the Treatment of Coronary Artery Disease or Heart Failure, Drugs, springer, 2013; 73: 1569–1586. DOI 10.1007/s40265-013-0117-0


