RESEARCH ARTICLE

Ivabradine effects on heart rate and quality of life among chronic heart failure patients

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Abstract

Objective: To determine the effect of Ivabradine in lowering heart rate and quality of life in chronic heart failure patients.

Methods: The observational study was conducted in the out-patient department of the National Institute of Cardiovascular Disease, Karachi, from December 2016 to June 2017, and comprised chronic heart failure patients aged 30-70 years who were on 5mg Ivabradine for 8-weeks. Heart rate was evaluated through electrocardiogram, and health-related quality of life was measured using the validated questionnaire. Baseline demographics and clinical characteristics were recorded, with follow-ups at week-4 and week-8. Safety and tolerability were assessed by adverse drug reactions monitoring. Data was analysed using SPSS 21.

Results: Of the 50 patients, 34(68%) were males. The overall mean age was 54.8±9.17 years. Baseline mean heart rate significantly reduced at first and second follow-up visit ($p< 0.001$). Mobility problems declined significantly as well ($p<0.05$). Health-related quality of life significantly improved on follow-up visits ($p<0.001$).

Conclusion: There was significant control of heart rate in chronic heart failure patients with improvement in all parameters of quality of life.

Keywords: Heart failure, Ivabradine, Heart rate, Health-related quality of life. (JPMA 71: 86; 2021)

DOI: https://doi.org/10.47391/JPMA.638

Introduction

Heart failure (HF) is one of the major health challenges which affects more than 26 million people around the globe.[1,2] The condition is highly prevalent in both western and eastern countries, and its associated co-morbidities may impair self-care behaviour, quality of life (QOL) and, thus, increase hospitalisation. The constant elevation of heart rate (HR) appears to be an independent predictor of morbidity and mortality in HF patients.[3]

According to the American Heart Association (AHA), the prevalence of HF in the United States is 2.2%[4] while it varies between 1.26 and 6.7% among Asian countries.[5] Considering the local population, the disease burden has precipitated due to limited resources in recent years. Based on the data shared by the World Health Organisation (WHO), 58% of the overall death burden in Pakistan is contributed by non-communicable diseases (NCDs) of which 29% is due to cardiovascular diseases (CVDs).[6]

Before Ivabradine approval, several classes of drugs, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitor, diuretic and digoxin, were prescribed for HF management.[7] Beta-blockers are known to regulate sympathetic activity, which, by lowering HR, improves QoL in HF patients, but the use is restricted due to poor tolerance among elderly patients.[7]

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Ivabradine, on the other hand, has shown better outcomes compared to beta-blockers.[8] It is administered as an add-on therapy for chronic HF patients with New York Heart Association (NHYA) Class II or III, left ventricular ejection fraction (LVEF) ≤35% and resting HR ≥70 beats per minute (bpm).[9] Ivabradine lowers HR by selectively binding to If channel at the sino-atrial node. Its use in HF patients has significantly reduced mortality, hospitalisation and healthcare cost.[9] According to the guidelines provided by the European Society of Cardiology (ESC), administration of 5-7.5mg Ivabradine decreases the cardiovascular death risk by 17%, HF-associated mortality by 39%, and up to 30% reduction in hospitalisation rate.[10]

As there is scarcity of local literature on the efficacy of Ivabradine in Pakistani population, the current study was planned to assess the effect of Ivabradine in reducing HR in local HF patients and to evaluate the safety and tolerability of Ivabradine by monitoring adverse drug reactions (ADRs).

Patients and Methods

The observational, single-arm, open-label study was conducted in the out-patient department (OPD) of the National Institute of Cardiovascular Disease (NICVD), Karachi, from December 2016 to June 2017, and comprised patients of either gender aged 30-70 years with a history of chronic HF diagnosed as per the Boston criteria[11] and the NYHA functional class II classification.[12]

After approval from the institutional ethics review

committee, the sample size was calculated using the WHO software[13] in the light of a study in which 28-day mean HR reduction was 15.4±10.7[14] and by keeping 95% confidence level with 5% margin of error. Additional patients were recruited due to high attrition rate.

Those excluded were patients suffering from acute myocardial infarction (AMI), cardiogenic shock severe hypotension <90/50mmHg, severe hepatic insufficiency, sick sinus syndrome, sino-atrial block, unstable or acute HF, pacemaker dependence, unstable angina, AV-block of 3rd degree, combination with strong cytochrome P450 3A4 (CYP3A4) inhibitors, and combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with HR-reducing properties. Moreover, patients presented with resting HR <70 bpm prior to treatment were also excluded as the primary aim of the study was to asses overall response rate of patients to Ivabradine in achieving HR <70 bpm. Pregnant, lactating women and women of child-bearing potential not using appropriate contraceptive measures were also excluded as their involvement would have led to increased risk.

After written informed consent from the patients, baseline demographic and clinical characteristics were recorded, and patients were followed up at week 4 (Visit 2) and week 8 (Visit 3). Demographic characteristics, like age, gender, body mass index (BMI), relevant medical history, risk factors, and concomitant medications, were recorded in the case report form (CRF). Ivabradine (SIVAB) 5mg was given to the patients according to their tolerability.

HR was measured through electrocardiogram (ECG) and health-related quality of life (HRQOL) was determined through EuroQoL 5-Dimensions 3-Level version (EQ-5D-3L), which is a validated questionnaire.[15]

The EQ-5D-3L consists of two parts. The first part is a descriptive questionnaire which assesses five dimensions of HRQOL, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension is measured at 1, 2 and 3 levels, where level 1 denotes 'no problem' and level 2 and 3 indicate 'problems'.[15] The second part includes EuroQoL Visual Analogue Scale (EQ-VAS) that registers the self-rated health status of the respondent on the vertical VAS from 0 to 100 where 100 indicates 'best imaginable health' and 0 means 'worst imaginable health state'.[15] ADR severity was evaluated on the basis of Hartwig's Severity Assessment Scale.[16] Data was analysed using SPSS 21. Continuous variables were expressed with descriptive statistics as mean, standard deviation (SD) and 95% confidence interval (CI) for quantitative variables and as frequencies and percentages for qualitative variables. Mean difference in HR from baseline to follow-up visits was analysed using paired sample t-test and one-way analysis of variance (ANOVA) as appropriate. Differences. Improvement in EQ-VAS score from baseline to last follow-up were presented through Box and Whisker plot, including mean, range and median values. The study was duly registered.[17]

Results

Of the 50 patients initially enrolled, 34(68%) were males. The overall mean age was 54.8±9.17 years. Of them, 37(%) completed the study (Figure 1). Baseline characteristics of all the patients were noted and each one of them was on at least three different medications other than Ivabradine (Table 1).

Baseline mean HR significantly reduced at first and second follow-up visits (p< 0.001) (Table 2).

The most frequent problem reported at the baseline was

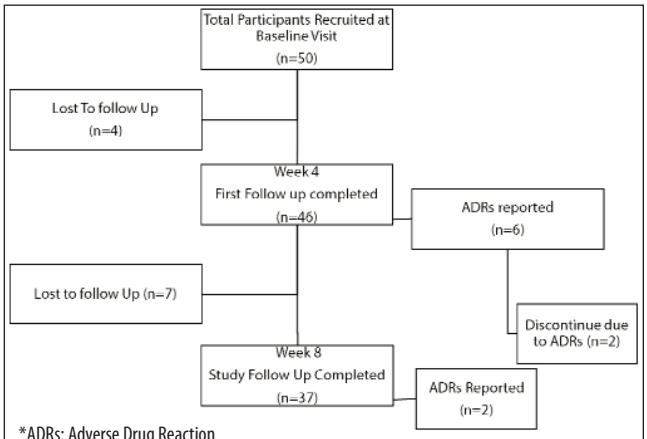

Figure-1: Flow chart of the study.

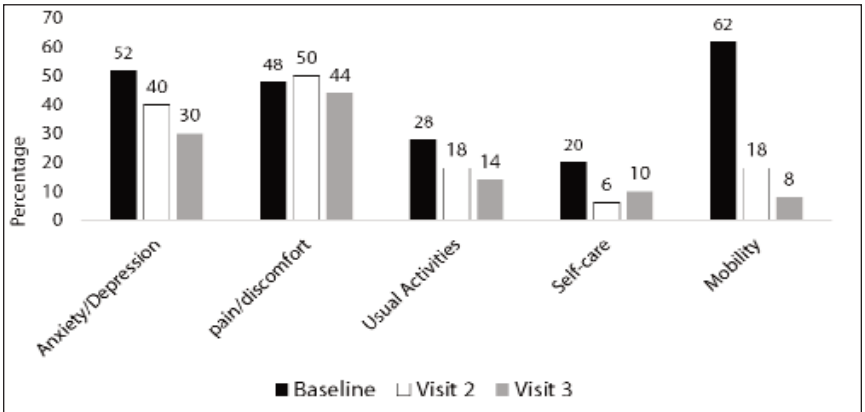

Figure-2: Problems reported on each visit evaluated through the EuroQol 5-dimension 3- Level (EQ-5D 3L) version.

Table-1: Baseline and Clinical characteristics (n=50).

Characteristics	
Age, years	54.8±9.17
Gender	
Male	34 (68)
Female	16 (32)
Body Mass Index, Kg/m^2	28.51±5.63
BMI <25 Kg/m^2	21.27±2.32
BMI >25 Kg/m^2	30.32±4.67
Heart Rate, bpm	93.98±15.29
Systolic Blood Pressure, mmHg	130.73±21.95
Diastolic Blood Pressure, mmHg	78.37±10.85
Respiration rate, breaths per minute	17.41±1.75
Medical History	
Diabetes	18 (36)
Ischaemic Cardiomyopathy	13 (26)
Dilated Cardiomyopathy	4 (8)
Hypertension	2 (4)
Alcohol user	5 (10)
Smoker	4 (8)
Others	4 (8)
Concomitant Medicine	
Anticlotting agents	49 (98)
β-Blocker	48 (96)
Statin therapy	47 (94)
Diuretic	44 (88)
ACE Inhibitor	25 (50)
ARBs	22 (44)
Anti-Anginal medication	10 (20)
Vasodilator	8 (16)

Values are given as mean ± SD or n (%); *37 patients completed the study, four loss to follow up at week 4; two discontinued due to ADR; seven loss to follow up by week 8; SD: Standard Deviation; Bpm: Beats per minute; BMI: Body Mass Index; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin II receptor blockers.

Table-2: Mean heart rate (HR) reduction from baseline to visit-3.

Heart Rate, Bpm	Mean±SD	95% CI	Mean difference	p-value
Baseline	93.98±15.29	89.58 - 98.37		
Baseline & visit 2	80.28±14.97	75.83 - 84.73	13.70*	<0.001**
Baseline & visit 3	78.81±14.25	73.98 - 83.62	15.17*	<0.001**

* Mean difference of HR is measured through Paired Sample T-test to evaluate the effect of Ivabradine; ** p<0.005 is considered significant; One-way ANOVA is applied to calculate p-value; S.D: Standard Deviation; Bpm: Beats per min; CI=Confidence interval.

issues with mobility, followed by anxiety/depression and pain/discomfort (Figure 2). While problems associated with mobility were significantly controlled (p<0.05), the other variables decreased but non-significantly (p>0.05). There was a significant variation in mean EQ-VAS values from baseline to visits 2 and 3 (p<0.05) (Figure 3).

There was no hospitalisation or life-threatening situation with Ivabradine. Only 2(1%) patients had to discontinue the drug due to bradycardia. Dose reduction was also done in 1(0,5%) patient with bradycardia. All ADRs were classified as of mild to moderate nature.

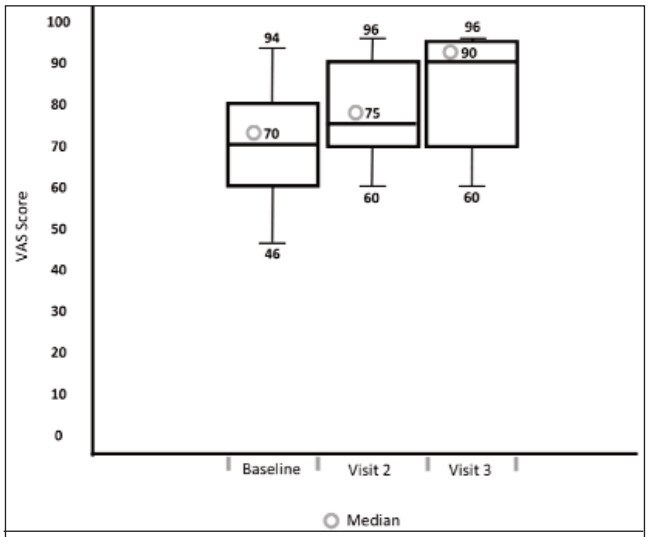

Figure-3: EuroQol-Visual Analogue Scale (EQ-VAS) score from baseline to visit-3.

Discussion

The findings showed that Ivabradine reduced HR over 8 weeks of therapy owing to HF management as well as QOL improvement. The safety and tolerability of the study drug was also proven with minimal ADRs.

The findings are consistent with studies showing an association between HR reduction and positive QOL outcome in HF patients.[14,18] The findings are also supported by a double-blind clinical trial involving Ivabradine which showed significant results on lowering hospitalisation rate of HF patients, reflecting on QOL and reduced healthcare costs.[19]

Another main QOL finding related to VAS-measured self-rated health status which improved significantly from baseline to visit 3, indicating a clear influence of Ivabradine on reducing the pathophysiologic alterations, like HR, improving mobility, and alleviating psycho-physiological constraints restricting routine activities in these patients, ultimately improving QOL.[20,21] Therefore, as per the European Medical Agency (EMA) and the United States Food and Drug Administration (FDA) recommendations, HR as a QOL parameter, has been included in the management of chronic HF patients.[22,23]

Ivabradine was well-tolerated with no hospitalisation or life-threatening situation. Dose titration phenomena and discontinuation of therapy were done as per the EMA recommendations with continuous monitoring of HR to minimise the occurrence of ADRs.[24] Although the majority of patients were taking β-blocker in combination with the study medication, it was noted during the observation period that a few patients experienced bradycardia and required dose de-escalation.[24]

To the best of our knowledge, this is the first local study conducted to assess the tolerability and safety of Ivabradine in HF patients. The current study has several limitations, including a small sample size and its single-centre nature. However, the study does provide evidence and basis to the clinicians and healthcare providers for further research on a large scale at multiples centres to target comparative analysis in Pakistan.

Conclusion

There was significant control of HR in HF patients with improvement in all QOL parameters. Ivabradine was found to be a well-tolerated drug with minimal and controllable side effects.

Acknowledgment: The authors are thankful to Ms. Mahwish Raza, Medical Affairs department of Getz Pharma for their assistance in the research and Advance Educational Institute & Research Center (AEIRC) & for their technical expertise in manuscript writing.

Disclaimer: The Abstract was presented at CardioCon in November, 2017.

Conflict of interest: None

Source of funding: Medical Affairs Department, Getz Pharma, Karachi.

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