Original Article

Ivabradine Induced Safety and Efficacy in Patients with Chronic Heart Failure: A Retrospective Study

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ABSTRACT

Background: Heart failure is a disabling condition affecting 26 million people worldwide. Progress in understanding of the pathogenesis of HF has led to new treatments, which include I_f channel inhibitor ivabradine, which acts selectively and specifically by inhibiting the cardiac pacemaker current I_f. The purpose of the study is to evaluate the safety and efficacy of ivabradine in HF patients. **Materials and Methods:** It was a retrospective, observational single-center study done in the Kottayam district of Kerala with a sample size of 391 patients with Chronic Heart Failure, and the data was collected from 2016-2020 using a structured data collection form. Various statistical tests were conducted using SPSS-version 16. **Results:** Among 391 patients with chronic heart failure 65.22% were males and the remaining were females. A significant reduction in heart rate was observed in patients taking Ivabradine compared to patients not taking Ivabradine. It also reduced the number of hospitalizations among patients. ADR was reported in 27 patients. A greater proportion of patients (188 patients) has been administered with Ivabradine 5mg BD. 128 patients were given 2.5mg BD,49 patients were prescribed with 5mg TID and only 26 patients were given 5 mg OD tablets. **Conclusion:** Ivabradine is the only agent shown to clinically lower the heart rate without negative inotropism on conduction and contractility. Increased heart rate produces an adverse impact on the myocardium. Ivabradine is an attractive, effective, and safe choice in patients with heart failure.

Key words: Heart failure, Heart rate, Ivabradine, Standard therapy, Treatment outcome, Efficacy.

INTRODUCTION

Heart failure is both common and disabling. The prevalence of heart failure continues to increase as a result of both an aging population and improvements in survival after large myocardial infarctions. The most common reason for admission to hospital in people aged over 65 years is chronic heart failure. The number of readmission to hospitals is also higher for heart failure than for any other condition. Ischaemic heart disease, hypertension, and idiopathic dilated cardiomyopathy are the most common underlying causes of heart failure. Identification and correction of potentially reversible precipitants, target-dose titration of medical therapy, and management of hospitalizations for decompensation are the optimal therapy for CHF.[1] Standard therapy for patients with CHF includes beta-blockers, diuretics, ACE inhibitors, ARBs, digoxin, statins, and vasodilators. Ivabradine was found to be more effective in reducing the heart rate and also for those who are unable to tolerate β-blocker therapy, in combination with other prognostic HF medication.[2] By reducing the I_f current-regulated diastolic depolarisation in the SA node, ivabradine slows HR and thereby increases the diastolic duration without altering the action potential duration or causing negative inotropy. Ivabradine is a specific I_f channel blocker and a selective inhibitor of the pacemaker I_f current in the

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SA node.[3] The Systolic Heart Failure Treatment with Ivabradine Trial provides evidence for the reduction in hospitalizations with ivabradine.[4] It is a useful agent for elderly patients and those with diabetes or asthma for whom beta-blockers are contraindicated.[5] Bradycardia, atrial fibrillation, phosphenes, and hypertension are the most common adverse events associated with ivabradine. Ivabradine should not be given during pregnancy because it causes reproductive toxicity in animal studies.[6] The purpose of the study is to analyze the safety and efficacy of ivabradine in chronic heart failure and to determine the reduction in hospitalizations.

MATERIALS AND METHODS

A retrospective observational study was carried out in the out-patients and in-patients of the concerned department at Caritas Hospital, Thellakom, Kerala. About 391 patients were selected for the study based on the inclusion and exclusion criteria. The sample size was calculated using the Cochran's formula and the required samples were 385. The patient data was collected using a data collection form which include the demographic details, diagnosis, laboratory data and the treatment given.

Cochran's formula:

$$n0 = z2\ pq/\ e2$$

where, n0 is the sample size

z is the selected critical value of desired confidence level

p is the estimated proportion of an attribute that is present in the population

$$q = 1 - p$$

e is the desired level of precision

Study Site

The study was conducted at the Cardiology department, Caritas Hospital, Thellakom,Kerala.It is a 655 bedded multi-speciality hospital.

Study Design

This is a single-center, Retrospective, Observational study

Study period

Six months in Caritas Hospital, Kerala.The retrospective data from January 2016-December 2020 was collected.

Study Criteria

The key inclusion criteria included eligible patients of ≥ 20 years of age, patients with systolic heart failure, cardiac inpatients with specifications like resting heart rate ≥ 75 bpm, LVEF ≤35%, beta blockers, or other standard therapies which are contraindicated or not tolerated. And those patients on Ivabradine.

Study participants: Below 20 years of age, population not on any cardiac drug, recent (30 days) MI, congenital heart disease and patients admitted for cardiac transplantation were excluded from the study.

Ethical Approval: The study was approved by Caritas Ethics Committee

Approval date: 05/09/2021

Data collecting method

The data was collected using the data collection form and the data collection includes the details like age, sex, weight, height, history, diagnosis, vitals and the treatment given.

Statistical Analysis

The whole data collected were entered into an MS spreadsheet and statistical analysis was done in SPSS version 16 and Microsoft Excel 2019. The graphical data were also generated using both excel and SPSS. Many of the variables were expressed in the form of a percentage. The relation between variables was found by testing *p*-value <0.05 and by Z test for proportion. Paired t-test was used to estimate the variation in heart rate in both the ivabradine group and in a standard therapy group. Mean and standard deviation was calculated for the analysis. Bar charts, Pie charts were used for visualizing these findings.

RESULTS

A total of 391 patients with chronic heart failure according to the methodology were enrolled in the study, among them 255 (65.22%) were male and the remaining were females (34.78%). In this study a large proportion of patients were from the rural area, followed by 122 patients from the urban area and comparatively a least proportion i.e, 115 patients were from the semi-urban areas. A large proportion of patients were within the age group of 60-69 and the least proportion of patients were among 20-29, 30-39, and 90-99 age groups. The study evaluated the reasons behind the past admissions. For that 81.82% of patients were having cardiac-related admissions and only 18.18% of patients were having non-cardiac admissions.

Table 1: Number of past admissions and days of hospitalization.

		Mean	SD
No. of past admissions	With Ivabradine	1.44	1.04
	Without Ivabradine	1.41	0.69
No. of Days of hospitalization	With Ivabradine	5.92	4.23
	Without Ivabradine	7.16	4.65

Table 2: Cardiac Drugs.

Drugs	Number of Patients	Percentage (%)
Ivabradine 2.5mg Bd	128	32.73
Ivabradine 5mg Od	26	6.64
Ivabradine 5mg Bd	188	48.08
Ivabradine 5mg Tid	49	12.53

Table 3: Comparison of means of HR in the past between Ivabradine alone or in combination with standard therapy and standard therapy alone.

Group		N	Mean of HR	SD	Standard error mean	
1		13	74.44	4.54	1.26	
2		13	84.48	6.21	1.72	
	t-test for equality of means (HR)					
	t	d_f	Significance levels	Mean difference	Std error difference	95%confidence interval of the difference (95% CI)
						lower upper
Equal variances assumed	-4.71	24	0.000	-10.04	2.13	-14.44 -5.64
Equal variances not assumed	-4.71	21.98	0.000	-10.04	2.13	-14.46 -5.62

N- number of days of hospital stay, Mean- Average of the HR for 13 days.
Group1- ivabradine group
Group 2 – non- ivabradine group

The mean and standard deviation of the number of past admissions and number of days of hospitalizations are shown in Table 1. The mean past number of days is less for patients on treatment with Ivabradine (5.92) than patients not on treatment with Ivabradine (7.16).

Chest discomfort (190,35.12%) and dyspnea (149, 27.54%) are the major reasons for the recent admission among the patients.

Table 2 shows different doses of ivabradine given to the patients include 5 mg bd(48.08%), 2.5 mg bd(32.73%), 5 mg tid (12.53%) and 5 mg od (6.64%).

Among 391 patients, 76 had selective β-blockers and 29 had non-selective. The other drugs were statins (35.77%), ACE inhibitors (1.27%), Diuretics (33.86%), ARBs (2.70%), Vasodilators (7.47%), Digoxin (18.92%).

Bradycardia (3.32%) and AF (3.32%) were the most common ADRs. Only 1 patient developed phosphenes (0.26%).

Table 3. shows the comparison of means of HR in the past between Ivabradine alone or in combination with standard therapy and standard therapy alone.

From a total of 391 patients enrolled in the study, for Group 1, we have 123number of favorable cases in patients treated with Ivabradine alone or Ivabradine in combination with standard therapy and 105 patients represent standard therapy alone group. The study showed a significant change in the heart rate of both the groups (H_0: μ1= μ2, H1: μ1≠μ2, p=0.000, 95%CI) for Ivabradine alone or in combination with standard therapy (M=74.44, SD=4.54) and standard therapy alone (M=84.48, SD=6.21). The null hypothesis assumes that the variances are equal in both groups (H0:μ1= μ2, H1:μ1≠μ2) and the -value is < 0.05 which is statistically significant. It indicates strong evidence against the null p hypothesis. Therefore, we reject the null hypothesis.

μ1 – mean of HR for ivabradine group and non-ivabradine group are equal

μ2 - mean of HR for ivabradine group and non-ivabradine group are not equal

For sample1 we have the sample size N_1 = 391, the number of favorable cases X_1=123 so then the sample proportion is 0.9795.

For sample 2 we have the sample size N_2 = 391, the number of favorable cases X_2 =105 and the sample proportion is 0.2685.

The following null and alternate hypotheses for the population proportion needs to be tested:

$$H_0: P_1 < P_2$$

$$H\alpha: P_1 > P_2$$

Where, P1 – a population with ivabradine

P2-population without ivabradine

This corresponds to a right-tailed test and a Z test for two population proportions will be used.

Figure 1 show a significant reduction in heart rate in patients taking Ivabradine with standard therapy (n=55) when compared to standard therapy alone.[2,3] The mean heart rate in the Ivabradine group on day 1 is 85.44 and it keeps decreasing and reaches a near to normal heart rate. In patients taking standard therapy alone, the mean heart rate is initially high (100.26) compared to patients taking Ivabradine.

Group 1- Ivabradine alone / in combination with standard therapy.

Group 2-Standard therapy alone

For Group 1, we have n=391 recently admitted patients treated with Ivabradine alone or in combination with standard therapy and n=120 patients in the past admission standard alone group. The study showed a significant change in the heart rate of both the groups (H0: μ1= μ2, H1: μ1≠μ2,p=0.009, 95% CI) for ivabradine alone or combination with standard therapy

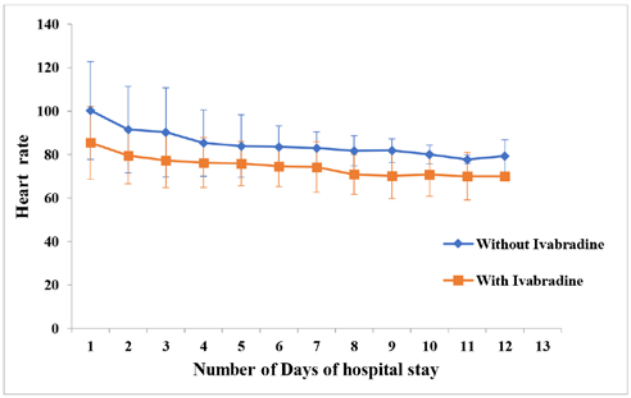

Figure 1: Time-dependent change in the resting heart rate during the treatment. Data are shown as mean ± S.D.

Table 4: Comparison of the mean HR of recent admission in patients administering Ivabradine alone or with standard therapy to that of the past admission's HR of patients taking standard therapy alone.

Group	N	Mean (HR)	Standard Deviation	Standard Error Mean
1	11	74.32	4.14	1.25
2	12	81.37	7.14	2.06

	t-test for equality of means						
	t	d_f	Significance level	Mean Difference	Std. Error Difference	95% Confidence Interval of the difference (95% CI)	
						Lower	Upper
Equal variances assumed	-2.86	21	0.009	-7.05	2.47	-12.18	-1.92
Equal variances not assumed	-2.92	17.91	0.009	-7.05	2.41	-12.12	-1.98

N-Number of days of hospital stay

Table 5: The comparison of means of a number of admissions with Ivabradine alone or in combination with standard therapy to that of standard therapy.

Group	Number of Patients	Mean	Standard Deviation	Standard Error Mean
1	123	1.31	0.80	0.09
2	175	1.42	0.72	0.07

	t-test for equality of means						
	t (Days)	d_f	Significance level	Mean Difference	Standard Error Mean	95% Confidence Interval of the Difference (95% CI)	
						Lower	Upper
Equal Variances Assumed	-0.999	189	0.319	-0.111	0.111	-0.33	0.11
Equal Variances not assumed	-0.981	158.59	0.328	-0.111	0.113	-0.33	0.11

Group 1- ivabradine group (123 patients)
Group 2- non-ivabradine group (175 patients)

Table 6: Comparison of means of number of days of hospitalization with and without Ivabradine.

Groups	Number of patients		Mean		SD	Standard error mean
1	225		5.83		3.85	0.42
2	167		7.21		4.83	0.46
	t-test for equality of means(days)					
	t	d_f	Significance level	Mean difference	Std error difference	95%confidence interval of the difference (95% CI)
						lower upper
Equal variances assumed	-2.14	191	0.034	-1.38	0.64	-2.65 -0.11
Equal variances not assumed	-2.21	190.39	0.029	-1.38	0.62	-2.61 -0.15

Group 1- ivabradine group (225 patients)
Group 2- non-ivabradine group (167 patients)

(M=74.32, SD=4.14) and standard therapy alone(M=81.37, SD=7.14). We can see that patients on the study drug, on average had slightly fewer days of hospital stay as compared to standard therapy which is shown in Table 4.

μ1- mean of HR for ivabradine group and non-ivabradine group are equal

μ2 - mean of HR for ivabradine group and non-ivabradine group are not equal.

The study showed an insignificant change in the number of admissions with both the groups (H0:μ1= μ2, H1:μ1≠μ2,*p*=0.32) for Ivabradine alone or in combination with standard therapy (M=1.31, SD=0.80) and standard therapy alone(M=1.42, SD=0.72) (Table 5).

The mean number of days of hospitalization for Group 1 patients is 5.83 and their standard deviation is 3.85 and for group 2 patients, the mean is 7.21 and the standard deviation is 4.83. Therefore, Group 1 has the least number of days when compared to Group 2. The study showed a significant change in the number of days of hospitalization with both the groups (H0:μ1= μ2, H1:μ1≠μ2, p value=0.34, 95% CI) which is indicated in Table 6.

From Figure 2, it is clear that 241 patients showed an improvement, 148 patients showed a good response with the therapy, and 2 of the patients had no improvement since they discontinued the therapy and requested for discharge.

Figure 3 (a)Visit 1 shows HR of patients started with standard therapy alone which indicates an unstable reduction in HR in patients, (b) Visit 2 shows HR of Ivabradine alone or in combination with standard therapy and standard therapy alone. Here it is clear that patients with Ivabradine group showed a stable HR response to the therapy, (c) Visit 3 shows HR of Ivabradine alone or in

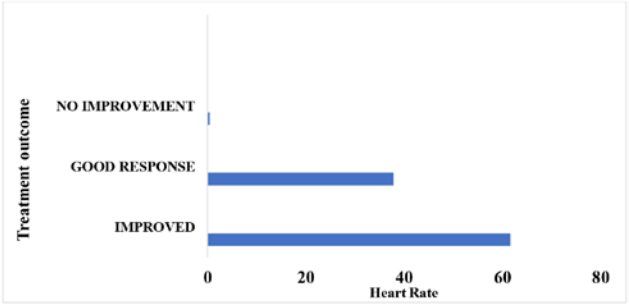

Figure 2: Treatment outcome and number of patients based on reduction in symptoms.

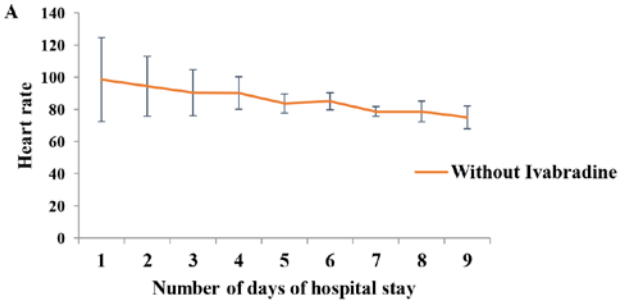

Figure 3 (a): Visit 1- HR of patients with standard therapy alone (*N*=200) group.

combination with standard therapy and standard therapy alone. Here it is clear that patients with Ivabradine group showed a good response to the therapy and compared to standard therapy the length of hospital stay was decreased in patients with Ivabradine therapy, (d) Visit 4 shows HR of patients with Ivabradine alone or in combination with standard therapy. Here it is clear that patients with Ivabradine therapy showed a decrease in HR.

In the recent admission 391 patients were administering Ivabradine (the sample proportion is $p\hat{}_1$=0.9795) and in the past admission 123 patients were administering Ivabradine (the sample proportion is $p\hat{}_2$ = 0.2352). This data can be summarized as follows: The null and alternate hypotheses for the population proportion needs

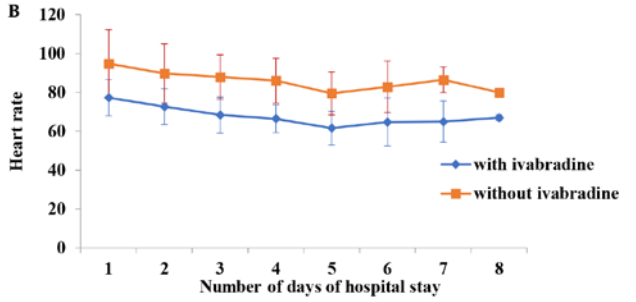

Figure 3 (b): Visit 2-HR of patients with Ivabradine alone or in combination with standard therapy (*n*=123) and standard therapy alone (*n*=175).

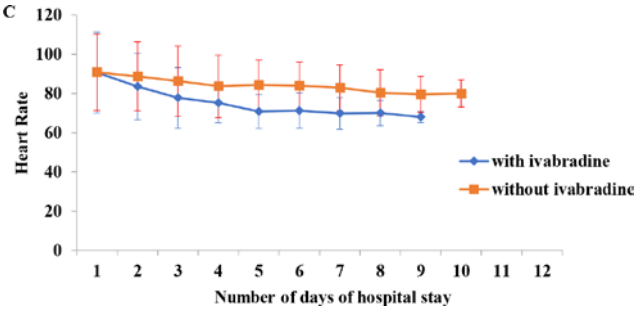

Figure 3 (c): Visit 3- HR of patients with Ivabradine alone or in combination with standard therapy (*n*=225) and standard therapy alone (*n*=167).

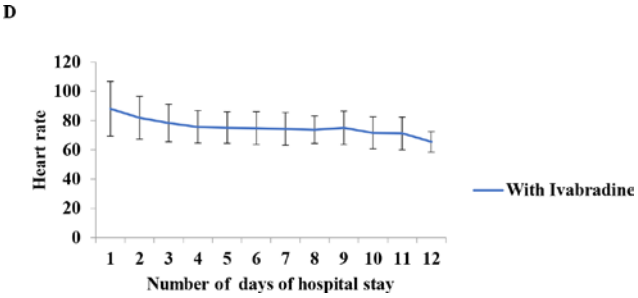

Figure 3 (d): Visit 4- HR of patients with Ivabradine alone or in combination with standard therapy (*n*=391)

to be tested:

$$H_0: P_1 \leq P_2$$

$$H_\alpha: P_1 > P_2$$

P1-population without ivabradine

P2-population with ivabradine

This corresponds to a right-tailed test and a Z test for two population proportions will be used.

Here in this study, some patients have taken the medicine for a long time of 7 years and none of the patients stopped their medication (Figure 4).

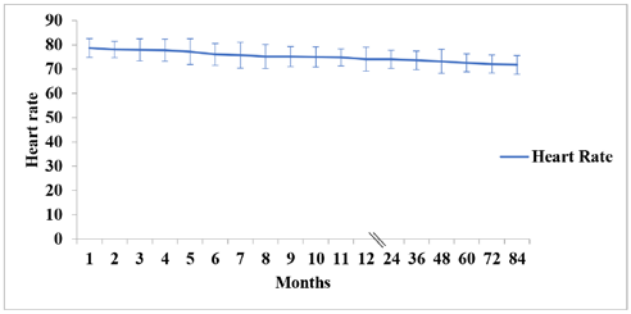

Figure 4: The graph shows the HR of patients treated with ivabradine in different months.

DISCUSSION

A total of 391 patients with chronic heart failure according to the methodology were enrolled in the study, among them 255 (65.22%) were male and the remaining were females(34.78%). According to a study conducted among heart failure patients, it was observed that the incidence of heart failure is significantly higher in males than that of females,[7,8] and in this study, a similar type of result is acquired. However, women tend to develop heart failure at an older age compared to men and that might be the reason for the under-representation of women in clinical trials for heart failure.[9] A large proportion of patients were within the age group 60-69 and the least proportion of patients were among 20-29, 30-39, and 90-99 age groups. Most of the HF burden occurs in individuals aged ≥65 years.[8]

In this study, a large proportion of patients were from the rural area, followed by 122 patients from the urban area and comparatively the least proportion of 115 patients were from the semi-urban areas. This might be due to living in a rural setting has been associated with poorer health and decreased consumption of health care resources. Organizational elements, such as a decreased supply of health care providers, a long way to reach health care centers, and decreased accessibility of physicians, may contribute to adverse outcomes of CHF in rural communities. Lower literacy levels of rural patients with CHF are slower to adopt healthy behaviors when compared with urban patients with CHF.[10]

On observing the social habits, it was noted that 30.43% of patients were alcoholics and 29.99% were smokers. The potential relationship between alcohol use and smoking on cardiovascular disease is of great health concern, as both have important effects on the cardiovascular risk factors.[11] Among 391 patients about 176 patients had a past admission due to cardiac (*n*=144, 81.82%) and non-cardiac (*n*=32, 18.18%) causes.This was assessed to analyze whether the all-cause hospital

admission was reduced in ivabradine patients.When the mean and standard deviation of the number of days of hospitalizations was evaluated it was found that the mean past number of days is less for patients on ivabradine (5.92) than patients on standard therapy (7.16). On the other hand, when the mean and standard deviation of the number of past admissions was evaluated it was found that the mean number of admission is higher for patients on ivabradine (1.44) than patients on standard therapy(1.41) (Table 1). Among systolic HF patients, the beta blocker dose titration is dependent on patient comorbidities and other demographics. But in some patients who cannot tolerate beta-blockade and in those heart rate that exceeds the baseline by adding ivabradine the additional heart rate reduction is beneficial. Pharmacological treatments of HF include ACE, ARBs, beta-blockers, diuretics, statins, nitrates/hydralazine, and digoxin.[12] The standard therapy given to the patients in the study includes β-blockers, ACE inhibitors, ARBs, diuretics, digoxin, and statins. 5 mg twice per day is the recommended starting dose of ivabradine. The maximum dose is 7.5 mg twice daily. An initial dose of 2.5 mg is to be considered in elderly patients.[13] Here the dose adjustment was done at each visit in the range of 2.5–5 mg TID according to dose adjustment criteria; the dose was increased if the resting HR was higher than 75 beats/min, maintained if between 50 and 75 beats/min, decreased if lower than 50 beats/min or patients had signs or symptoms related to bradycardia, and discontinued if lower than 50 beats/min or the patient had signs or symptoms related to bradycardia at the lowest dose (Table 2). The study showed a significant change in the heart rate of both the groups (H0: $\mu1 = \mu2$, H1: $\mu1 \neq \mu2$, p=0.009, 95% CI) for ivabradine alone or combination with standard therapy(M=74.32, SD=4.14) and standard therapy alone(M=81.37, SD=7.14)(Table 4). The study showed an insignificant change in the number of admissions with both the groups (H0:$\mu1 = \mu2$, H1:$\mu1 \neq \mu2$,p=0.32) for Ivabradine alone or in combination with standard therapy (M=1.31, SD=0.80) and standard therapy alone(M=1.42, SD=0.72) (Table 5). But, in accordance with the SHIFT and J-SHIFT study, it was consistent that there was a reduction in rehospitalization in patients with heart failure.[12,14] It is demonstrated that treatment with ivabradine was directly linked to improvement in symptoms and self-reported global assessment which eventually helps to reduce the rehospitalisation.[15,16] When the time-dependent change in the resting heart rate was assessed it shows a significant reduction in heart rate in patients taking ivabradine with standard therapy (n=55) when compared to standard therapy alone (n=23), as the effectiveness of Ivabradine in reduction of heart rate was fixed as a baseline heart rate of 75 bpm.[13] Here, the mean heart rate in the Ivabradine group on day 1 is 85.44 and it keeps decreasing and reaches a near to normal heart rate. In patients taking standard therapy alone, the mean heart rate is initially high (100.26) compared to patients taking Ivabradine. It shows a significant reduction in heart rate in patients taking Ivabradine with standard therapy (n=55) when compared to standard therapy alone (Figure 1). It is very crucial to study the efficacy of ivabradine in long-term treatment. So, when it is evaluated there were patients who had taken the medicine for a long time of 7 years and none of the patients stopped their medication. Ivabradine was effective and well-tolerated in CHF patients seen in clinical practice throughout one year of treatment.[17] Furthermore, in the SHIFT trial, it was observed an outcome of HR reduction when using ivabradine as an adjunct to standard HFrEF therapy, with a median follow-up of 22.9 months. The trials demonstrated that ivabradine use was associated with a reduction in the primary endpoint of the composite of cardiovascular death or hospitalization for worsening HF symptoms.[14] The treatment outcome was assessed based on the physician's global assessment and classified patients as improved, good response, and no improvement. The majority of patients had an improvement and good response with the Ivabradine therapy which crucially reveals its effectiveness. Physician global assessment was based on a scoring system inquires changes in functional status which classify the patients into: 'markedly improved', 'moderately improved', 'slightly improved', 'no change', 'slightly worsened', 'moderately worsened', or 'markedly worsened'. The study also included patient self-assessment which was based on a separate questionnaire evaluating changes in health status.[13] Adverse events associated with ivabradine use includes symptomatic and asymptomatic bradycardia, phosphenes, atrial fibrillation, third-degree AV block and hypotension.[18] Here in this there is an incidence of bradycardia(3.32%), atrial fibrillation (3.32%) and phosphenes(0.26%) occurred with ivabradine.

CONCLUSION

The current study was aimed to assess the efficacy of ivabradine in reducing the heart rate in patients with chronic heart failure. From the study, it is evident that ivabradine significantly reduces the heart rate. The patients effectively respond when ivabradine was given with standard therapy than that when standard therapy was given alone. Increased heart rate produces an adverse impact on the myocardium. Ivabradine is an attractive, effective, and safe choice in patients with heart failure. Social habits like alcohol use and smoking increase the risk of cardiovascular diseases. Ivabradine is the only agent

shown to clinically lower the heart rate without negative inotropism on conduction and contractility. Ivabradine was found to be associated with cost savings and better clinical outcomes when it is correlated with length of hospitalization and rehospitalization. So this opens up a door for future study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reaction; **HR:** Heart rate; **HF:** Heart failure; **BD:** Twice daily; **OD:** Once daily; **TID:** Three times a day; **CHF:** Cronic heart failure; **ACE:** Angiotensin converting enzyme; **ARBs:** Angiotensin receptor blockers; **SA node:** Sinoatrial node.

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