

ROLE OF HEART RATE REDUCTION WITH IVABRADINE IN LEFT VENTRICULAR FAILURE

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ABSTRACT

Objective: To compare mean heart rate reduction in Ivabradine and placebo group in left ventricular failure patients.

Study Design: Quasi experimental study.

Place and Duration of Study: Study was conducted at Combined Military Hospital, Kharian, from Jul 2018 to Dec 2018.

Methodology: Sixty four patients participated in the study. They were randomly divided into two groups of 32 each. One group was given Tab Ivabradine (10 mg twice a day) while second group received a placebo for a period of 4 weeks. After 4 weeks each patient was evaluated and heart rate, systolic and diastolic blood pressure were recorded. Mann-whitney U test selected to compare heart rate and ages of both groups t- test used to compare systolic and diastolic blood pressure among both groups. Chi-square test used to determine the association of heart rate between two groups. A p -value ≤ 0.05 was considered significant.

Results: Median (IQR) heart rate was significantly lower in Ivabradine group 58.3 (4) as compared to placebo 64.1(1) ($p < 0.01$). Systolic blood pressure (132.8 ± 3.6) was significantly lower in ivabradine group as compared to placebo group (137.1 ± 4.5) ($p < 0.01$). Difference in diastolic blood pressure was insignificant in both groups ($p = 0.55$). There was a significant association between heart rate of 55-60 beats per minute and ivabradine use ($p < 0.01$).

Conclusion: Ivabradine is safe and efficacious drug in reducing heart rate and systolic blood pressure for patients suffering from left ventricular failure. Early detection and management of left ventricular failure with ivabradine use leads to better prognosis of the disease.

Keywords: Heart rate, Ivabradine, Left ventricular failure.

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INTRODUCTION

Heart failure is worldwide public health issue with an estimated prevalence of 23 million worldwide¹. Prevalence of heart failure in United States is 5.8 million². American Heart Association defined heart failure as complex clinical syndrome as a result of functional and structural cardiac diseases leading towards failures of ventricle ability (filling and ejecting blood)³.

Left ventricular failure refers to left ventricle dysfunction leading towards insufficient blood delivery to vital body organs⁴. Left ventricular heart failure is classified into i) heart failure (HF)

with preserved ejection fraction (over 50%), ii) HF with reduced ejection fraction (<40%) and iii) HF with mid range ejection fraction (41-49%)⁵. Most common etiologies for left ventricular failure are ischemic heart diseases and hypertension. Prevalence of ischemic heart disease in Pakistan is 26.9% leading towards left ventricular failure⁶. Left ventricular hypertrophy also leads to left ventricular failure. Smoking, diabetes mellitus, obesity, life style and male gender are important risk factors for left ventricular failure⁷.

Pathophysiology of left ventricular failure includes multiple mechanisms. Poorly controlled hypertension is responsible for increased cardiac workload and after load resulting towards hypertrophy. In initial stage, hypertrophy act as compensatory mechanism and help in maintaining

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heart output. However, Long term hypertrophy-inhibits myocardium relaxation leading towards decreased left ventricular output and impaired cardiac filling⁸. Moreover, coronary arterial disease results in direct ischemic damage, arrhythmias leads to remodeling, cardiomyopathies are responsible for multiple mechanisms causing cardiac dysfunction and left ventricular failure⁹.

Ivabradine is a selective If channel inhibiting drug. Ivabradine helps in heart rate reduction by specifically and selectively inhibiting If channels¹⁰. Literature reported that ivabradine decrease heart rate without any effect on myocardial relaxation and contractility, blood pressure and ventricular repolarization/myocardial conduction¹¹.

Fox *et al* reported that mean heart rate in ivabradine group was 60.7 ± 9.0 beats per minute while in placebo group was 70.6 ± 10.1 beats per minute. Incidence of bradycardia was high in ivabradine group (18%) as compared to placebo (2.3%) $p < 0.001$ ¹². Pascual *et al* reported that ivabradine is well tolerated for heart rate reduction. Ivabradine represents as an attractive option for excessive catecholamine related tachycardia¹³. Limited data is available in Pakistan on role of ivabradine in heart rate reduction. Present study aims to compare mean heart rate reduction in Ivabradine and placebo group in left ventricular failure patients.

METHODOLOGY

This quasi experimental study was conducted at, Combined Military Hospital, Kharian. Study duration was 6 months (Jul 2018 to Dec 2018). A sample size of 64 patients calculated with $\mu_1 = 70.6$, $\mu_2 = 60.7$, $SD = 10.1$, 95% confidence interval, power of study 84% using WHO calculator¹². Non probability consecutive sampling used for patient's selection. Study approval was obtained from ethical review committee. Consent forms were taken from all participants. Patients with age >18 years, both gender, patients with heart rate (resting) 70 bpm on two consecutive electrocardiographic readings, patients diagnosed

with left ventricular failure were included in study. Patients with unstable cardiovascular condition, pulmonary diseases, poor liver function, severe psychological issues, pregnant and breast feeding mothers were excluded from study. History of previous ischemic event (myocardial infarction), revascularization and diabetes mellitus was recorded. Body mass index (BMI) was also calculated. Patients were randomly divided into ivabradine and placebo groups with 32 patients in each group using computer generated random numbers table. Ivabradine group was given Tab Ivabradine 10mg twice daily while placebo group patients received placebo twice daily for 4 weeks. After 4 weeks of drug use by each group, patients were evaluated for heart rate, systolic and diastolic blood pressure changes. Data was analyzed using SPSS version 16. Descriptive statistics and normality tests were computed for age, heart rate, systolic and diastolic BP while frequency and percentages were calculated for categorical data. Mann whitney U-test was selected to compare the heart rate as well as ages of both groups and t-test was used to compare the systolic and diastolic BP of both groups. To compare the association of heart beat between the two groups, chi-square test was computed. A p -value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 64 patients participated in the study. Median (IQR) age of the patients was 47.5 (9.5) years. There were 40 (62.5%) males and 24 (37.5%) females. Eight (12.5%) patients belonged to age group 18-40 years while 56 (87.5%) patients were from age group >40 years. Twenty Six (40.6%) patients were grouped with BMI ≤ 28 kg/m² while 38 (59.4%) were grouped with BMI > 28 kg/m². Previous revascularization was found in 34 (53.1%) patients while 30 (46.9%) did not show previous revascularization. History of myocardial infarction was reported in 34 (53.1%) while 30 (46.9%) did not have a history of myocardial infarction. Forty six (71.9%) patients were diabetic and remaining 18 (28.1%) patients were non diabetic.

Median (IQR) heart rate was significantly lower in ivabradine group as compared to placebo group (table-I). A statistically significant fall in systolic BP was detected in ivabradine group (table-I). There was no significant difference in diastolic BP among both groups (table-I).

There was a significant association between heart beat of 55-60 bpm and ivabradine use with majority of patients having a heart beat of 55-60

is also associated with reducing ischemia and reduce symptoms among stable angina pectoris patients¹⁶.

In the current study, total 64 patients participated. Median (IQR) heart rate was significantly lower in ivabradine group 58.3(4) as compared to placebo 64.1(1) ($p<0.01$). Lechat *et al* described that a significant heart rate reduction was observed with ivabradine without hemodynamic alte-

Table-I: Comparison of Heart rate, systolic BP and diastolic BP in Ivabradine and placebo group (n=64).

	Interventional Group		Central Tendency	p-value
			Median (IQR)	
Heart rate (bpm)	Ivabradine	32	58.3 (4)	<0.01
	Placebo	32	64.1 (1)	
			Mean \pm SD	
Systolic BP (mmHg)	Ivabradine	32	132.8 \pm 3.6	<0.01
	Placebo	32	137.1 \pm 4.5	
Diastolic BP (mmHg)	Ivabradine	32	80.2 \pm 2.6	0.55
	Placebo	32	79.9 \pm 1.34	

Table-II: Comparison of Heart beat with ivabradine and placebo groups (n=64).

	Interventional Groups		Total	p-value
	Ivabradine Group (n=32)	Placebo Group (n=32)		
Heart Beat (bpm)				
55-60	26 (40.6%)	4 (6.25%)	30 (46.8%)	<0.01
>60	6 (9.4%)	28 (43.8%)	34 (53.1%)	
Total	32 (50%)	32 (50%)	64 (100%)	

Table-III: Comparison of Age with ivabradine and placebo groups (n=64).

	Interventional Groups		Total	p-value
	Ivabradine Group (n=32)	Placebo Group (n=32)		
Age Categories				
18-40 yrs	6 (9.4%)	2 (3.1%)	8 (12.5%)	0.13
>40 yrs	26 (40.6%)	30 (46.8%)	56 (87.5%)	
Total	32 (50%)	32 (50%)	64 (100%)	

bpm in Ivabradine group (table-II). Both groups were age matched as there was no statistical difference in the median ages of two groups ($p=0.13$) as shown in table-III. No adverse effects were reported with Ivabradine in our study.

DISCUSSION

An increased heart rate is a significant marker of cardiovascular diseases risk in general population¹⁴. Ivabradine is associated with inhibition of If in sinoatrial node leading towards heart rate reduction without placing an effect on left ventricular systolic function¹⁵. Ivabradine

rations (100bpm \pm 25 baseline, 82bpm \pm 12, $p=0.000$)¹⁷. Flannery *et al* described that ivabradine is a well tolerated drug in left ventricular dysfunction patients¹⁸. Another similar study described that placebo had significantly high heart rate as compared to ivabradine (122 \pm 17.2SD & 88.4 \pm 12SD respectively, $p<0.001$)¹⁹.

In the current study, most of the patients in ivabradine group had heart beat 55-60bpm as compared to placebo (40.6% & 6.3% respectively, $p<0.01$). McAlister *et al* described that ivabradine is associated with heart rate reduction without

effecting left filling pressure in left ventricular failure patients²⁰. DiFrancesco *et al* described that 55% patients treated with ivabradine had ≤ 75 bpm as compared to placebo (>75 bpm) $p < 0.01$ ²¹.

In the current study, mean systolic blood pressure was significantly lower in 132.8 ± 3.6 SD as compared to placebo group 137.1 ± 4.5 SD ($p = 0.03$). Deedwania *et al* described that ivabradine had significant contribution in lowering systolic pressure as compared to matching placebo ($p < 0.01$)²². Another similar study described that ivabradine is associated with systolic blood pressure reduction without affecting diastolic pressure in acute heart failure²³.

In the current study, there were no adverse effects observed with ivabradine in our study. However, Tardif *et al* described that ivabradine patients showed symptomatic bradycardia and visual side effects as adverse events²⁴.

LIMITATION OF STUDY

Small sample size and conduction of study at single center limits generalisability of study.

CONCLUSION

Ivabradine is safe and highly effective drug in reducing heart rate among left ventricular failure patients. Early detection and management of left ventricular failure with ivabradine leads to better prognosis of the disease.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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