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Original Research Article

A Long-Term Study on Effectiveness and Safety of Ivabradine Versus Metoprolol on Heart Rate and LVEF in Post Myocardial Infarction Patients- A Tertiary Hospital Based Study

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Abstract

Background: Tachycardia and heart failure are a major concern in post myocardial infarction (PMI) patients and a therapeutic challenge. Beta blockers, the first-choice drugs used have certain disadvantages. Ivabradine known to reduce heart rate was compared with Metoprolol for their benefits and side effects.

Aim of the study: To analyze the effects of Ivabradine on heart rate and LVEF in comparison with Metoprolol at fixed doses over a period of 12 months from the time of discharge.

Materials: 278 MI patients were grouped and observed for 12 months for the effect of Ivabradine and Metoprolol drugs on their heart rate (HR) and LVEF values. Patients with acute inferior wall STEMI, HR above 70/minute were included. All patients were on treatment for 12 months. Patients likely to develop cardio-pulmonary complications excluded. MI was confirmed on ECG and serial CK-MB/ troponin T measurements and 2D ECHO. Patients were with Holter monitors.

Results: 278 patients were grouped as Ivabradine group wherein 138 patients (Ivabradine 5mg twice daily) and Metoprolol group 140 patients (Metoprolol 25 mg twice daily). All the risk factors were similar in both the groups. The mean HR and LVEF values were similar in both the groups. The range of HR was 64 to 86 beats per minute in all patients. The symptomatologies among the patients of both the groups were also similar. Reduction of HR was from 76.43±7.3 to 62.55±1.05 and in Metoprolol group from 77.51±4.50 to 61.45±2.35 beats per minute 13 (09.24%) patients from Ivabradine group and 19 (13.57%) patients from Metoprolol group showed a heart rate less than 60/bpm, others had heart beats > 60/mt.

Conclusions: Ivabradine was a competitive bradycardic drug in comparison to Metoprolol in early Post MI patients. It had similar action on LVEF as Metoprolol. It could be potentially used an alternative anti-tachycardia drug with no other cardiovascular side effects and wherever β-blockers are contraindicated.

Keywords: Cardiac Arrhythmia, Heart failure, angina, Atrial fibrillation, Bradycardia, coronary artery disease, funny current.

Introduction

Cardiac arrhythmias (VA) are known cause of mortality in post myocardial infarction (PMI) patients,[1] and remain as major therapeutic challenge. They include ventricular tachycardia and fibrillation with a re-entrant nature. Mechanism of action of Ivabradine is on the function of the Sino Atrial node (SA node) which is unique as its cells have an intrinsic property of generating cyclical changes in the resting membrane potential. This drives the cells to the threshold needed for spontaneous depolarization which causes repetitive, spontaneous action potentials resulting in its automaticity. The spontaneous depolarization occurs due to opening of specific ion channels allowing a slow, inward-depolarizing mixed sodium-potassium current which is called as the pacemaker or "funny" current (I_f)[2]. By inhibiting the cation movement across the transmembrane channel, Ivabradine with high degree of selectivity causes reduced slope of the diastolic depolarization of the pacemaker action potential, resulting in fall in heart rate. As Ivabradine blocks the open channel state creating a particularly favorable attribute; it was found to be use dependent (becoming more potent at faster heart rates). Reduction in heart rate with Ivabradine is dose dependent and as a result of its specific mechanism of action produces reduced heart rate without affecting the inotropy of the heart or change in vascular resistance[3,4]. Therapeutic dose of Ivabradine is between 2.5 and 7.5 mg given twice daily. Peak plasma concentration happens in 1 hour in fasting and delayed by 1 hour by intake of food. It undergoes first-pass hepatic metabolism using cytochrome P450 and CYP3A4 enzymes; which is relevant to the drug-drug interactions with it.[5] Among the cardiac adverse effects the commonest is bradycardia causing symptoms of dizziness or fatigue.[6] Contraindications to Ivabradine are the risk of worsening bradycardia, presence of sinus bradycardia at baseline (<60 beats/min) and significant sick sinus syndrome.[7] SIGNIFY (Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients With Coronary Artery Disease) trial pointed out the increased incidence of Atrial fibrillation (AF), (2.2%/year) when compared with placebo (1.5%/year),[8]. Beta blockers help in reduce the incidence of mortality and ventricular arrhythmias in post Myocardial infarction patients; even though its mechanism is not clear. Certainly, tachycardia is the risk factor of post-MI arrhythmias and mortality.[9] But beta blockers have hemodynamic effects unlike Ivabradine.[10] Beta blockers act by anti-ischemic effects and reduction in heart rate on cellular electrophysiology. Ivabradine has a propensity to produce Atrial Fibrillation by increasing the dispersion of atrial repolarization. But few clinical studies revealed that Ivabradine prevents rather than induces AF.[11] Ivabradine also produces QT interval prolongation and increased incidence of ventricular tachycardia especially when combined with Azithromycin and results in induction of torsade de pointes.[12] The present study compares the potential anti-arrhythmic effects of an established β-blocker Metoprolol and Ivabradine, at doses providing equal heart rate reduction. The present study was to understand the potential proarrhythmic signals and mechanisms of Ivabradine versus Metoprolol (that offered the same HR reduction but did not block hERG).

Materials:

278 patients with recent history of MI were included to evaluate in this single center prospective, cross sectional comparative study over a period of 12 months. An institutional ethical clearance was obtained, and committee approved consent form and Performa were used.

Inclusion criteria: Patients of all age groups and both the genders were included. Patients with the diagnosis of acute inferior wall STEMI were included. Patients with heart rate above 70/minute were included. Patients who were discharged (> 2 weeks) after initial treatment for myocardial infarction were included.

Exclusion criteria: Patients likely to develop pulmonary thrombo-embolism, earlier diagnosis of coronary artery disease, heart failure, second- and third-degree AV block, and patients with more than 90mm of Hg systolic blood pressure were excluded. Patients with sinus node dysfunction, acute left ventricular failure (LVF), COPD, CKD, peripheral vascular diseases were excluded. Patients with history of hypersensitivity to beta blockers or Ivabradine were excluded. Diagnosis of MI was confirmed by studying the ECG (persistent ST elevation in inferior leads) serial CK-MB/ troponin T measurements, 2D ECHO. Detecting ST elevation in the absence of LV hypertrophy or left bundle-branch block (LBBB) was considered as "new ST elevation" at the J point in at least two contiguous leads of ≥1 mm (0.1 mV) in inferior leads (II, III, a VF). Standard treatment for post MI patients was prescribed to all the subjects (thrombolytic therapy, heparin, nitrates, aspirin, clopidogrel, statins, angiotensin converting enzyme inhibitor. Drugs with known or suspected interactions with ivabradine (strong CYP3A4 inhibitors and QT-prolonging agents) were prohibited within five half-lives prior to inclusion and during the first 24 hours of the study. 278 patients were divided into, Group I patients received Ivabradine 5mg two times daily and Group M patients received Metaprolol 25 mgs twice daily, by way of randomization in 1:1 mode. Randomization was used at the point of entry of the patient to the study. The variables used were heart rate (assessed by using a 12- lead resting electrocardiography (ECG) with two measurements 10 minutes apart before treatment administration. Continuous ECG monitoring was done for 3 random days in a month for a period of one year using Holter ECG monitor to the patients. 2D Echo was done at the time of entry of the patient to the study, followed by once monthly for one year and left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF). Periodic blood pressures (systolic and diastolic) were recorded for all the patients on daily basis and communicated to the study center online.

Statistical analyses: Analyzing the data both the groups were compared as per the variables. Values were expressed as Mean, standard deviation; percentages were used to express the data. Chi square test and Student's t test were used for comparison. P value less than 0.05 was regarded as indicative of a significant difference.

Results:

Out of 278 patients, 138 were included in Group I, and 140 were included in Group M as per randomization. The incidences of risk factors like age, gender, smoking, BMI, COPD, and Diabetes Mellitus in both the groups were tabulated in **Table 1.** There was no statistically significant difference in the incidences of different variables in both the groups (p value was>0.05). The mean LVEF was 41.07±02.75 % in Group I and 40.82±5.1% in Group M; no significant difference (p=0.827). The mean baseline

heart rate was 76.439±7.43 beats per minute (bpm) in Group I and 77.51±4.50 bpm in Group M, and there was no significant difference (p-0.642). The heartbeat range among the patients was varying from 64 to 86 beats per minute with an overall mean value of 76.97±8.50. The baseline clinical parameters and demographic variables of the patient in both the groups are shown in **Table 1.**

Table 1: Showing the demographic data of the subjects (n-278).

Observation (Mean values)	Ivabradine (n=138)	Metoprolol (n=140)	P-value
Age (years)	54.6±35	56.10±10.12	0.061
Sex (male), % (n)	49.64% (n=138)	50.35% (n=140)	0.072
BMI (kg/m2)	29.45±03.71	28.90±7.02	0.082
Diabetes, % (n)	21.22% (n=59)	22.30% (n=62)	0.641
Hypertension, % (n)	36.33% (n=101)	40.28% (n=112)	0.735
Present smoker, % (n)	17.26% (n=48)	19.78% (n=55)	0.837
Dyslipidemia, % (n)	15.82% (n=44)	17.26% (n=18)	0.649
Baseline HR	76.43±7.3	77.51±4.50	0.642
LVEF (%)	41.07±2.75	40.82±5.1	0.827
Previous PCI, % (n)	29.13% (n=81)	30.57% (n=85)	0.901
Renal impairment, % (n)	12.23% (n=34)	13.66% (n=38)	0.712
COPD/asthma, % (n)	10.43% (n=29)	11.51% (n=32)	0.642
Systolic blood pressure (mmHg)	128.6±11.0	132.6±12.90	0.901
Diastolic blood pressure (mmHg)	82.32±8.23	80.51±2.1	0.847

The symptoms noted in the subjects were analyzed and tabulated in **Table 2.** The commonest presentation in both the groups was Difficulty exercising noted in 30.93% of group I and 33.45% of the M group followed in the order of frequent dizziness (21.94% and 26.61%), palpitations (20.86% and 23.74%), breathlessness (18.34% and 15.10%), pain in the chest (33.86% and 11.87%) and fainting in (04.31% and 04.67%), (Table 2). There was no statistically significant difference in the symptomatology of the patients of both groups (p>0.05)

Table 2: Showing the incidence of symptoms in the study groups (n-278)

Symptomatology	Group I-138 N (%)	Group M-140 N (%)	P value
Difficulty exercising	86 (30.93)	93 (33.45)	0.182
Dizziness	61 (21.94)	74 (26.61)	0.213
Palpitations	58 (20.86)	66 (23.74)	0.428
Breathlessness	51 (18.34)	42 (15.10)	0.601
Pain in the Chest	38 (13.86)	38 (11.87)	0.811
Fainting	12 (04.31)	13 (04.67)	0.734

Based on the Left Ventricular Ejection fraction using New York Heart Association (NYHA), (13) the patients were graded, and their data was tabulated in Table 3. 93/138 (33.45%) patients of the group I were having grade III and IV LVEF and 97/140 (34.89%) patients of group M has grade III and IV LVEF. There was no statistically significant difference in the LVEF grading by NYHA the patients of both groups (p>0.05), **(Table 3).**

Table 3: Showing the NHYA grading of patients based on LVEF (n-278).

NHYA (13) grading	Group I-138 N (%)	Group M-140 N (%)	P value
Class I	28 (10.07)	31 (11.15)	0.522
Class II	49 (17.62)	46 (16.54)	0.481
Class III	44 (15.82)	51 (18.34)	0.603
Class IV	17 (06.11)	12 (04.31)	0.142

Patients of Ivabradine group had a decrease in final mean heart rate from 76.43±7.3 to 62.55±1.05 and Metoprolol group from 77.51±4.50 to 61.45±2.35 beats per minute (Table 4). 13 (09.24%) patients from Ivabradine group and 19 (13.57%) patients from Metoprolol group showed a heart rate less than 60/bpm, others had heart beats > 60/mt. The mean LEDV and LESV values decreased in both the groups. Reduction in LEDV was more in metoprolol group (from 94.55±03.30 to 74.65±06.10) than in Ivabradine group (from 92.65±03.15 to 76.05±03.50) which was statistically significant (p value < 0.05). There was no difference in final mean LESV values of the two groups (from 54.10±01.15 to 42.20±02.50 in group AI and from 52.50±02.55 to 43.85±4.10 in group M respectively), (p value 0.061 and >0.05); hence was statistically not significant. The final mean LVEF values improved in the patients of both the groups in the range of 13.28 in group I and 14.28 in group M, but they were not statistically significant (p value was 0.143 and >0.05). The final mean systolic and diastolic blood pressure values improved in the patients of the both the groups, and they were statistically significant as the p value was 0.037 (Table 4).

Table 4: Showing the change in final mean Heart rate, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and leftventricular ejection fraction (LVEF) from baseline and p values (n-278).

Variables- Mean values	Group I	Group Mp value	P value
Heart Rate- bpm			
Basal	76.43±07.30	77.51±40.50	0.642
Final	62.55±01.05	61.45±02.35	**0.041**
2D Echo			
LVEDV			
Basal	92.65±03.15	94.55±03.30	0.235
Final	76.05±03.50	74.65±06.10	**0.021**
LVESV			
Basal	54.10±01.15	52.50±02.55	0.170
Final	42.20±02.50	43.85±4.10	0.061
LVEF			
Basal	41.07±02.75	40.82±05.21	0.827
Final	54.35±04.50	55.10±03.85	0.345
Improvement	13.28±1.20	14.28	0.143
Blood Pressure			
Systolic			
Basal	132.65±11.05	131.50±11.02	0.610
Final	116.50±08.15	114.85±5.15	0.037
Diastolic			
Basal	96.20±06.45	95.45±07.15	0.078
Final	83.65±04.25	80.15±5.75	**0.038**

Discussion:

Myocardial infarction is associated or followed by complications such as arrhythmias, mechanical (Mitral valve and chordae rupture/tear), inflammatory (early and late pericarditis and post-MI syndrome), left ventricular mural thrombus (LVMT), right ventricular (RV) infarction and cardiogenic shock.[14] Cardiac arrhythmias include Heart blocks, atrial and ventricular arrhythmias, supraventricular Tachyarrhythmia, atrial flutter, atrial fibrillation, Accelerated Junctional Rhythm, Bradyarrhythmias and Reperfusion Arrhythmias, Sinus tachycardia and inappropriate sinus rhythm (IAP).[15] Most of the cardiac arrhythmias occur between first and third day following myocardial infarction and must be diagnosed and treated appropriately to prevent further complications.[16] The strategies in MI treatment includes controlling pain adequately by medication, diuresis to prevent heart failure, oxygenation, volume replacement to prevent hypovolemia, administration of anti-inflammatory agents to treat pericarditis, and using beta-blockers and/or nitroglycerin to relieve ischemia; preventing and treating cardiac arrhythmias.[17] The present study included 278 patients grouped as Ivabradine group wherein 138 patients were given Ivabradine 5mg twice daily and Metoprolol group consisting of 140 patients who were treated with Tab Metoprolol 25 mg twice daily for the study period. In both the groups the risk factors like age, gender, smoking, BMI, COPD, and Diabetes Mellitus in both the groups were similar and there was no statistically significant difference in their incidences (p value was>0.05), (Table 1). The mean LVEF was 41.07±02.75 % in Group I and 40.82±5.1% in Group M; no significant difference (p=0.827). The mean baseline heart rate was 76.439±7.43 beats per minute (bpm) in Group I and 77.51±4.50 bpm in Group M, and there was no significant difference (p-0.642). The heart rate range among the patients was varying from 64 to 86 beats per minute with a overall mean value of 76.97±8.50. The symptomatology among the patients of both the groups were also similar and there was no statistical difference between them (p value was>0.05), (Table 2). There was no statistically significant difference in the LVEF grading by NYHA of the patients of both groups in the study (p>0.05), (Table 3). There was a fall in final heart rate of Ivabradine group from 76.43±7.3 to 62.55±1.05 and in Metoprolol group from 77.51±4.50 to 61.45±2.35 beats per minute (Table 4). 13 (09.24%) patients from Ivabradine group and 19 (13.57%) patients from Metoprolol group showed a heart rate less than 60/bpm, others had heart beats > 60/mt. Review of literature showed that β-Blockers were the first-line drugs used for prevention of secondary coronary catastrophe after MI; they were shown to minimize mortality markedly[18]. In a similar study by Gurral RR et al Ivabradine reduced mean heart rate (HR) from 85.6 bpm at baseline to 78.2 bpm. And metoprolol reduced HR from 81.9 bpm to 76.5 bpm over the same time period. Ivabradine reduced heart rate but did not cause any inotropic or lusitropic effect but maintained ventricular contractility.[19] In the “BEAUTIFUL” (morBidity-mortality Ev AlUaTion of the I(f) inhibitor Ivabradine in patients with coronary disease and left ventricULar dysfunction) study trial which evaluated Ivabradine used in MI patients with left ventricular systolic dysfunction to enhance the CVS outcomes in coronary patients, found it to reduce the mean heart rate by 11 bpm from the mean baseline heart rate (71.6 bpm) to 61 bpm at a mean dose of 12.36 mg/day used for one month.[20]. In the “SHIFT” trial which evaluated Ivabradine and its role in reducing the heart rate (HR) and cardiovascular outcomes, symptoms and quality of life in patients with systolic heart failure, Ivabradine was found to reduce the mean

HR of 79.9 bpm by 16 bpm versus 5 bpm for a placebo at one month and maintained throughout the course of the study.[21] Comparing the final mean values of LVEF in this study, it was observed that they improved in the range of 13.28 in group I and 14.28 in group M, but they were not statistically significant (p value was 0.143 and >0.05). The final mean systolic and diastolic blood pressure values improved in the patients of the both the groups, and they were statistically significant as the p value was 0.037 (Table 4). In the study by Gurram RR et al they observed that Metoprolol and Ivabradine showed significant improvement in the LVEF; Ivabradine showed much better improvement when compared to metoprolol. But the difference was not found to be statistically significant. In a previous study, Fasullo et al. [22] compared the roles of Ivabradine and metoprolol in patients with reperfused AMI with impaired left ventricular function and found HR reduced to 27 bpm and 25 bpm respectively and LVEF improved by 4.7% and 9.9% respectively at 60 days follow-up. There was one case of death in each group. The final mean LEDV and LESV values decreased in both the groups by 19.9±4.50 in metoprolol group and 16.6±3.10 in Ivabradine group, which was statistically significant (p value < 0.05). There was no difference in final mean LESV values of the two groups; they were 11.9± 1.20 in group I and 08.65± 1.15 in metoprolol group respectively (p value 0.061 and >0.05); hence was statistically not significant. Thus, it was concluded that Ivabradine leads to reduction in HR better and improved LVEF than metoprolol. In addition, Ivabradine possesses some other advantages like it is devoid of most of the adverse effects of beta-blockers (and of calcium channel blockers) and it can be suitably used as an alternative when the first line drugs cannot be adequately tolerated[23].

Conclusions:

Ivabradine was a competitive bradycardic drug in comparison to Metoprolol in early Post MI patients. It had similar action on LVEF as Metoprolol. It could be potentially used an alternative anti-tachycardia drug with no other cardiovascular side effects and wherever β-blockers are contraindicated.

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