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COMPARISON STUDY OF IVABRADINE WITH METOPROLOL IN MANAGEMENT OF ACUTE CORONARY SYNDROME

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Abstract

Introduction: Acute coronary syndrome remains as one of the most important causes for morbidity and mortality in developed countries. Therefore, evidence-based management strategy is required to offset the loss of health during an acute coronary syndrome. An effective approach includes both medical and surgical methods. This study was conducted to evaluate the medical method of management.

Objective: To study blood pressure and heart rate variability after administration of Ivabradine or metoprolol in cases with acute coronary syndrome.

Materials and methods: The study was a Prospective single center observational study conducted in patients attending Cardiology Intensive Care Unit in Nayyar Heart and Superspecialty Hospital, a tertiary care centre located in an urban area. All patients with Acute coronary syndrome admitted to the emergency or cardiac care unit were analysed with ECG as a preliminary diagnostic test and confirmed with troponin markers. They were either given Ivabradine or Metoprolol. Baseline evaluation and follow up was done and necessary data was collected and analysed.

Results: 100 patients were included in the study out of which 50 were given Metoprolol (Group A) and 50 were given Ivabradine (Group B). The mean age of studied cases was found to be 66.54 years in group A and 68.69 years in group B. It was observed that there was a fall in heart rate by 26.8 beats per minute with beta blocker and 24.4 beats per minute with Ivabradine. In case of blood pressure measurement, in patients with beta blocker administration, there was a fall of 25 mm Hg in systolic blood pressure and 17 mm Hg in diastolic blood pressure However, with Ivabradine there was only a fall of 8mm Hg in systolic Blood pressure and 6 mm Hg in diastolic blood pressure.

Conclusion: Although Metoprolol is the drug of choice to decrease heart rate and blood pressure in acute coronary syndrome, Ivabradine is being increasingly used in cases where beta blockers are contraindicated as it has similar efficacy in lowering heart rate without compromising contractility of cardiac muscle, thereby maintaining LVEF and blood pressure.

Keywords: Acute coronary syndrome, Beta Blockers, Metoprolol, Ivabradine.

Introduction

Coronary artery disease includes stable angina and acute coronary syndromes. It occurs due to atherosclerotic plaque deposition in the arterial walls leading to ischemia and myocardial cell death.It is a chronic process spanning over decades but an acute attack may occur in most cases due to the rupture of an unstable plaque, leading to thrombus formation. Consequently,occluding the blood vessel completely and leading to acute myocardial injury. Acute coronary syndromes encompass a spectrum of conditions,namely, unstable angina, NSTEMI and STEMI.[1] Due to myocardial tissue injury, hypoperfusion of organs occurs as contractility of cardiac musculature is affected. This leads to sympathetic nervous system activation leading to catecholamine(epinephrine, norepinephrine) release in order to increase end organ perfusion by increasing heart rate and stroke volume (β1-AR), and therefore cardiac output. But on the contrary, it further worsens myocardial ischemia by increasing the myocardial workload and systemic vascular resistance.[2]

Since decades, Beta Blockers have been used following MI and have proven effective in increasing survival. Beta blockers, especially selective Beta 1 receptor blockers, suppress reflex sympathetic response and decrease heart rate and blood pressure. Therefore, myocardial oxygen demand is reduced and diastole duration is increased leading to adequate perfusion. Beta blockers also decrease risk of ventricular arrhythmias which are the leading cause of sudden cardiac death in the hours following an acute attack of MI.[3]

But beta blockers are notorious for their effect on Atrioventricular nodal conduction, precipitating Atrioventricular nodal blocks especially in inferior wall MI. Therefore, they are contraindicated in conditions like PR interval more than 240 msec, second/third degree AV block, obstructive airway diseases, SBP less than 120 mm of Hg, HR more than 110 per minute.[4]

Ivabradine works by altering the pacemaker activity of sinoatrial node by inhibiting I(f) current in a dose dependent manner, thereby reducing resting heart rate and improving myocardial oxygenation in MI.[5] Unlike beta blockers, ivabradine does not affect cardiac contractility,blood pressure and helps preserve LVEF. It has no effect on cardiac inotropy, repolarization or atrioventricular conduction and also improves cardiac perfusion by prolonging diastole.In addition to this, Ivabradine also prevents cardiac necrosis by inhibiting proteolysis of the extracellular matrix during myocardial infarction by inhibiting Extracellular Matrix Metalloproteinases inducer (EMMPRIN) [6]

Materials and Methods

The study was a prospective single center study conducted in patients attending the cardiology unit between April 2020 to July 2020 in Nayyar Heart and Superspecialty Hospital. A total of 100 patients were randomized into two groups of 50 each. Group A received metoprolol and Group B received Ivabradine. The 2 groups were similar to each other.

On Admission-

1. A detailed history was taken which included symptoms on presentation like chest pain, palpitation, difficulty in breathing on exertion or at rest, demographic data, personal history, family history, past medical history and presence of any comorbidity like dyslipidemia, hypertension and diabetes mellitus.
2. Physical examination included general physical examination and systemic examination with special focus on cardiopulmonary auscultation. 12 lead ECG was recorded for every patient and lab investigations like cardiac enzymes and troponins were done.
3. Coronary loading which included nitrates, aspirin 300 mg, clopidogrel 150 mg, atorvastatin 40mg was given. Echocardiography was performed to analyse left ventricular ejection fraction
4. Coronary angiography was done to visualise coronary artery perfusion and accordingly thrombolysis or coronary angioplasty was recommended.
5. Eventually patients were randomly prescribed ivabradine or metoprolol. After that, heart rate and blood pressure monitoring was done at 6 hours, 12 hours and 24 hours.

Inclusion Criteria –

1) All patients with Acute Coronary Syndrome.
2) Patients with sinus rhythm with heart rate greater than 60 beats per minute on a resting 12 lead ecg.

Exclusion Criteria –

1. Patients with coexisting bradyarrhythmia, Atrioventricular block, tachyarrhythmia like atrial fibrillation or atrial flutter.
2. Pregnant or breastfeeding women.
3. COPD, asthmatics
4. Patients with heart failure grading NYHA > 3

Ethical consideration: all patients were explained the management protocol and informed written consent was taken. The protocol was approved by the institutional ethics committee.

Results

The mean age of patients in group A was found to be 66.54 years and in group B was 68.69 years.

Table1: Demographic data of study groups

	Group A	Group A	Group B	Group B
	Frequency	percentage	Frequency	percentage
Female	23	46%	29	58%
Male	27	54%	21	42%
Family history of coronary artery disease	32	64%	28	56%

Table 2: risk factors for acute coronary syndrome

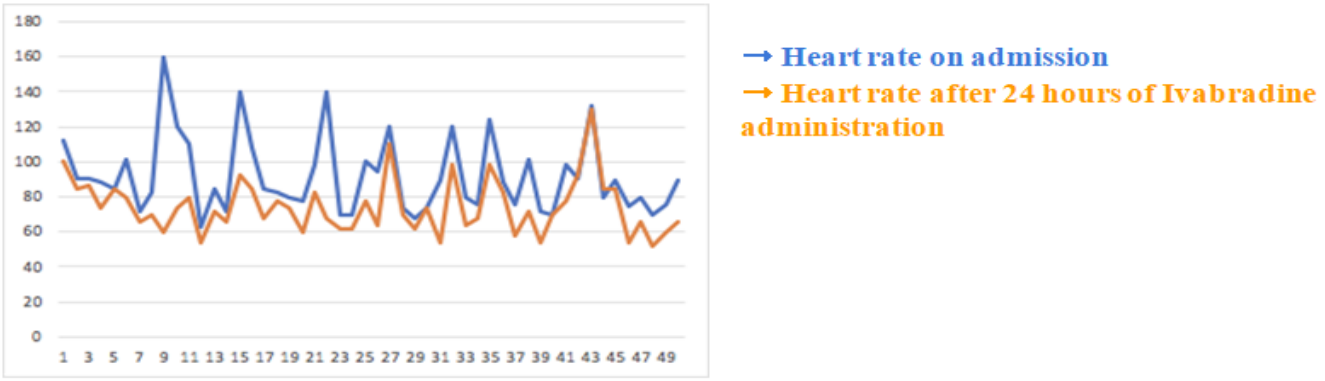
risk factors	**frequency**
hypertension	78
smoking	43
dyslipidemia	59
diabetes mellitus	61

Major risk factors for Coronary artery disease are hypertension, smoking, dyslipidemia and diabetes mellitus with Hypertension being the most common cause.

Table 3: types of acute myocardial infarction detected on ECG

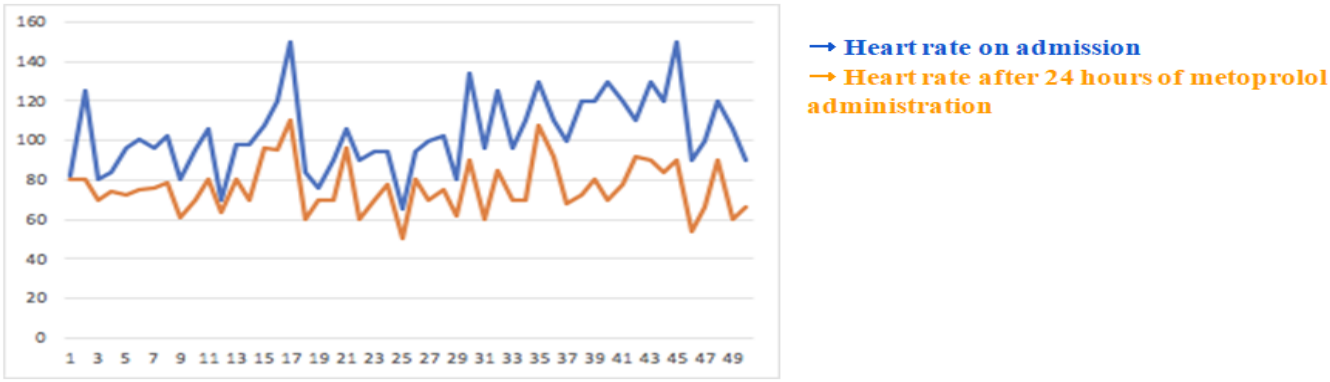
Types of AMI	Frequency
Anterior wall MI	49
Anterolateral wall MI	6
Inferior Wall MI	23
Non ST elevation MI	11
Unstable angina	4
lateral wall infarction	5
Infero-lateral wall infarction	2

GRAPH 1: Heart rate variation with Ivabradine administration after 24 hours



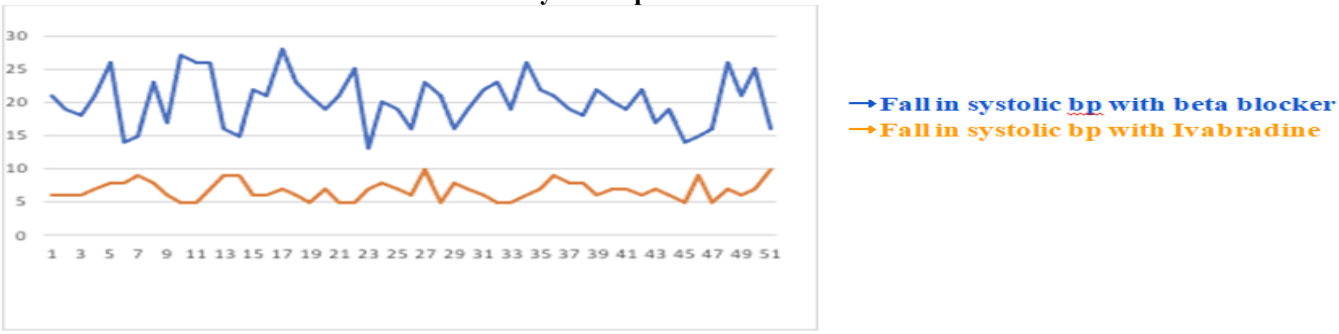
Patients receiving Ivabradine showed a fall of 24.4 beats per minute 24 hours after administration.

GRAPH 2: Heart Rate variation variation with Metoprolol administration after 24 hours



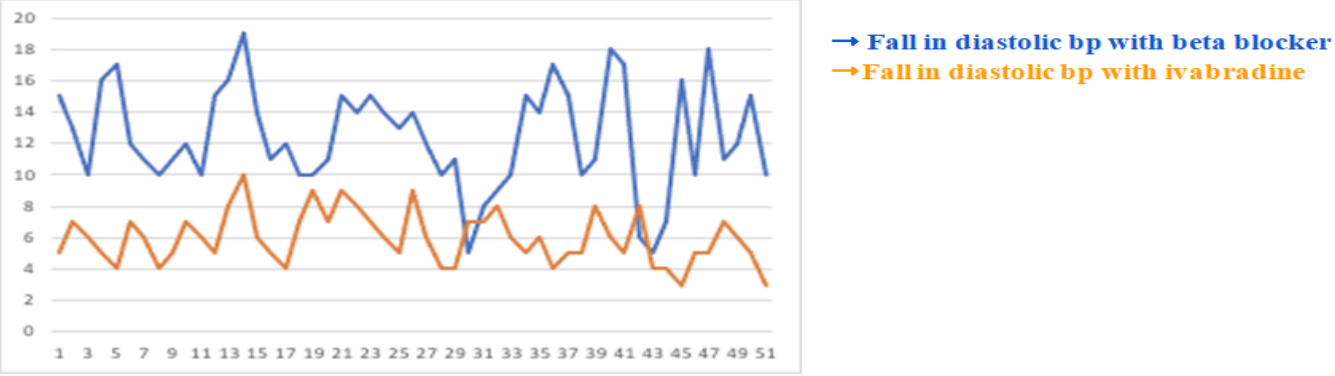
In patients receiving metoprolol average fall in the heart rate was 26.8 beats per minute after 24 hours of administration.

GRAPH 3: Fall in systolic bp with beta blocker vs ivabradine



At 24 hours after administration, patients receiving beta blocker experienced an average fall of 25 mm Hg in systolic blood pressure whereas with Ivabradine, fall in systolic blood pressure was only 8mm Hg.

GRAPH 4: Fall in diastolic Bp with beta blocker vs Ivabradine



In patients receiving beta blocker, fall in diastolic blood pressure was noted to be 17 mm Hg whereas with Ivabradine, fall in diastolic blood pressure was only 6 mm Hg after 24 hours of administration of respective drugs.

Discussion

In this study, average fall in the heart rate with beta blockers was 26.8 beats per minute whereas with Ivabradine was 24.4 beats per minute after 24 hours of administration of respective drugs. There is not much variation in the average fall in the heart rate in either of the two hence equating the efficacy of either of the drugs. Ivabradine mainly acts to reduce the heart rate through its inhibition of the funny channel exerting good antianginal effects and anti ischaemic effects in patients with Coronary artery disease. [7]

Through comparison with the two study groups where Group A received Metoprolol and Group B received Ivabradine, the fall in the systolic and diastolic BP of patients receiving the latter was very less. In clinical scenarios where interference in systemic blood pressure is not required, Ivabradine has increasingly become the drug of choice.

Beta blockers have a tendency to reduce the systemic blood pressure as seen by the study where the average fall in the systolic BP was 25 mm Hg and diastolic BP was 17 mm Hg after 24 hours in group A patients receiving metoprolol , through their effect on the sympathetic system.

The sympathetic nervous system stimulates the body's response to stress. The main mediators of sympathetic activation, adrenaline and noradrenaline act on the beta adrenergic receptors predominantly present in the heart, kidneys, eyes (B1) resulting in positive inotropic, chronotropic, renin release and aqueous humour production. Beta 2 receptors are more commonly located in peripheral vascular smooth muscles causing vasodilatation and relaxation of other smooth muscles. During such periods of low blood supply to the heart, a systemically stressful response is created which is associated with increasing circulating catecholamines. If beta blocker is added to such a state in the body, the detrimental effects on the heart are reduced by reducing the heart rate which is the main pathophysiological component in a patient with ACS along with blood pressure and myocardial contractility.

With these receptors being present in various cells of the body, their side effects often include, low blood pressure, low cardiac output, low heart rate and atrioventricular block, lung diseases such as bronchial asthma and chronic obstructive pneumonopathy. [8]

When such conditions are coexisting in patients with coronary artery diseases, we sought for alternative options such as Ivabradine which through its sinoatrial node activity controls only the heart rate.

As can be proven by this study, the average fall in the systolic BP was 8 mm Hg and diastolic BP was 6 mm Hg after 24 hours in group B patients receiving ivabradine in consequence of the fact that the latter drug does not act on the sympathetic nervous system.

The BEAUTIFUL trial which was conducted to prove the efficacy of ivabradine in coronary artery disease patients well documented that this drug on account of it's antianginal properties is safe to use in symptomatic coronary patients with left ventricular dysfunction and an elevated heart rate where beta blockers were not effective or is contraindicated. [9]

In a similar study conducted by De M, Ghosh AK, Das US, et al. where administration of Ivabradine proved to be equally effective in lowering the heart rate and did not cause any cardiac adverse events on a 30 day follow up period. [10]

Conclusion

In acute coronary syndrome, both ivabradine and metoprolol have comparative effects on decreasing the heart rate, but ivabradine does not affect contractility of cardiac musculature. Hence, LVEF and blood pressure remains unaffected and can be used as a drug of choice in cases where beta blockers are contraindicated.

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