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To Study The "Comparative Effect of Beta Blockers and Combination of Ivabradine with Beta Blockers on Heart Rate in Patients with Coronary Artery Disease Admitted to Cardiac Unit in a Tertiary Care Hospital"

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ABSTRACT:

BACKGROUND: Increased heart rate is an important pathophysiological variable of mortality as it aids progression of atherosclerosis, plaque destabilization and arrhythmias. Conventionally, Beta blockers are the main drug treatment in CAD as it decreases mortality by decreasing heart rate and cardiac arrhythmias. Ivabradine, a selective inhibitor of funny current channel, reduces resting and exercise induced heart rate and thus reduces myocardial oxygen demand without affecting cardiac contractility, conduction, relaxation and repolarization. Now, the indications of Ivabradine have been extended for use alone or in association with Beta blockers in patients of CAD. This present study was carried out to analyse the effect of administration of Ivabradine with Metoprolol on heart rate in patients with Coronary Artery Disease. The clinical responses are evaluated and compared.

METHODS: A Prospective study was carried out with a sample size of 50. In this study patients were taken from Cardiology Unit in Apollo Hospitals, admitted due to coronary artery disease. After considering inclusion and exclusion criteria patients were evaluated for their demographic details, risk factors, comorbidities. Patients were divided into two groups. Group A patients received Metoprolol 25mg, 50mg and Group B patients received Metoprolol 25mg, 50mg + Ivabradine 5mg, 7.5mg. Baseline and follow-up of heart rate were evaluated and necessary data were collected and analysed.

RESULTS: The mean age of the study population was 64 years old. In our study, there were 27 male patients who represented 54% of study population and 23 female patients who represented 46% of study population. Our study revealed that the 44% of the patients had normal BMI followed by patients who were obese (30%). All the patients were having comorbidities, the most common ones were HTN & DM (15). There was significant difference in % reduction of heart rate between both the groups i.e; Group A (Metoprolol 25mg,50mg) – 10 %, Group B (Metoprolol 25mg,50mg + Ivabradine 5mg,7.5mg) – 34 %. Administration of Ivabradine + Metoprolol showed reduction in mean heart rate by 18 bpm, while Metoprolol showed reduction in mean heart rate by 6 bpm. In this study, despite of the reduction in heart rate there was not much effect on blood pressure after administration of Ivabradine + Metoprolol when compared to the Metoprolol alone.

CONCLUSION: Administration of Ivabradine + Metoprolol in patients with CAD showed significant reduction in heart rate when compared to Metoprolol alone though there was no much difference in blood pressure after administration of Ivabradine.

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KEYWORDS: Coronary Artery Disease, Hypertension, Atherosclerosis, Beta Blockers, Cholesterol, AVN conduction.

I.INTRODUCTION

Coronary artery disease is the narrowing or blockage of the coronary arteries. This condition is usually caused by atherosclerosis. Atherosclerosis is the build-up of cholesterol and fatty deposits (called plaques) inside the arteries. These plaques can clog the arteries or damage the arteries, which limits or stops blood flow to the heart muscle.[1] If the heart does not get enough blood, it cannot get the oxygen and nutrients it needs to work properly. This can cause chest pain (angina) or a heart attack. Coronary artery disease starts at very young. The blood vessel walls start to show streaks of fat. As we get older, the fat builds up, causing minor damage to our blood vessel walls. The other substances that move through the blood stream, such as inflammatory cells, cellular waste products, proteins and calcium, stick to the vessel walls. These things combine with the fat and form plaque. Coronary heart disease occurs when the flow of oxygen rich blood to the heart muscle is blocked or reduced. This puts an increased strain on the heart muscle and can lead to:

•Angina- Chest pain caused by restricted blood flow to the heart muscle

• Heart Attacks- Where the blood flow to the heart muscle is suddenly blocked

• Heart Failure- where the heart is unable to pump blood around the body properly

Ivabradine is an oral medication that directly and selectively inhibits the hyperpolarization activated cyclic-nucleotide gated funny (If) current in the sinoatrial node resulting in heart rate reduction. It has a plasma elimination half-life of 6 hours and is administered twice daily. Ivabradine is extensively metabolized by cytochrome P450 3A4, and its metabolism is affected by inducers and inhibitors of the 3A4 enzyme.[2] Ivabradine showed improved exercise tolerance, Beta-blockers have rather been associated with worsening diastolic dysfunction. Ivabradine decreases the heart rate by selectively inhibiting the sino-atrial node's funny current channels. Ivabradine has been associated with a reduction in all-cause mortality, cardiovascular mortality, and heart failure hospitalizations in patients with heart failure. Beta blockers are a group of drugs that inhibit the sympathetic activation of β-adrenergic receptors.

Cardio-selective blockers (e.g., atenolol, bisoprolol) primarily block β1 receptors in the heart, causing decreased heart rate, cardiac contractility, cardiac workload, and AVNconduction. Nonselective beta blockers (e.g.pindolol,proponalol) inhibit all β receptors and may cause bronchoconstriction, peripheral vasoconstriction and metabolic imbalances (e.g.Hypoglycaemia and Hyperglycaemia, hypertriglyceridemia) in addition to cardiac effects.

Cardio-selective beta blockers have a lower side-effect profile and are preferred in the management of coronary heart disease, compensated heart failure, acute coronary syndrome, and certain types of arrhythmias. Propranolol, a nonselective beta blocker, is the first-line drug in the management of essential tremor, portal hypertension, migraine prophylaxis, and thyroid storm. Beta blockers are contraindicated in patients with symptomatic bradycardia, AV block, decompensated heart failure, and asthma.Initiation and cessation of beta-blocker therapy should always be gradual to avoid side effects or symptoms of withdrawal (e.g., rebound tachycardia, hypertension, acute cardiac death).

1.Coronary Artery Disease patients often present with Tachycardia are treated with beta blockers like Metoprolol. [3,4]

2.It is also noted from different publications that adding Ivabradine produces a synergistic effect and results in controlled heart rate and reduces morbidity and mortality.[5,6]

II.METHODOLOGY

This is a prospective, controlled, observational, randomized study that enrolled 50 patients with the coronary artery disease. Patients were mostly recruited from the critical care department of Cardiology of Apollo Hospitals, Hyderabad, admitted due to coronary artery disease during the period Jan 2021 to June 2021, maintaining following criteria;

INCLUSION CRITERIA:

1. All in-patients who are above 18 years of age and are taking beta blockers alone and Ivabradine in combination with beta blockers for the treatment of coronary artery disease admitted in cardiology unit.
2. Sinus rhythm with increased heart rate requiring medical attention.

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EXCLUSION CRITERIA:

1.Patients with bradyarrhythmia, sick sinus syndrome, atrioventricular block.
2.Patients with tachyarrhythmia like atrial fibrillation or flutter.
3. Patients of cardiogenic shock.
4.Patients with Acute Myocardial Infarction requiring urgent Coronary Revascularisation.
5. Paediatric patients.
6. Pregnant women.
7. Out patients with Coronary Artery Disease

Baseline and Follow-Up Evaluation

All included patients were subjected to-
Detailed history taking including demographic data, family history, risk factors of Coronary Artery Disease, past medical history, assessment of chest pain on admission, presence of any contra indications for beta blockers, and their heart rate.
Patients received the conventional cardiovascular treatment which included nitrates, anti-platelets (aspirin 300 mg loading then 150 mg/day, clopidogrel 300 mg loading then 75 mg/day), statins (atorvastatin 40mg/day).

Eventually patients were prescribed randomly by the attending cardiologist as per his choice either metoprolol or ivabradine and we divided them to the following groups
1.Group A included 20 patients who received metoprolol.
2.Group B included 20 patients received ivabradine along with beta blocker.
Patients of both groups were received the same conventional cardiovascular treatment which included nitrates, antiplatelet (aspirin 150 mg/day), statins (atorvastatin 40mg/day).

- Ivabradine administration protocol for group B patients included:
- Within 48 hours of hospital administration the starting dose was 5 mg daily (2.5 mg twice daily).
- After one week patients with resting heart rate greater than 60 beats per minute received doses of 10 mg daily for follow up of 30 days (5 mg twice daily).
- If during treatment, heart rate reduced below 50 beats per minute at rest or the patient experienced symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose was titrated downward.

III. RESULTS

Table 1.1: Distribution of Patients Based on Comorbidities

CATEGORY	NO. OF PATIENTS
HTN	5
DM	2
HTN, DM	**15**
HTN, hypothyroidism	2
HTN, DM, hypothyroidism	7
HTN, CAD	3
HTN, COPD	1
HTN, DM, CVA	2
HTN, LV dysfunction	2
DM, CAD, ACS	3
DM, CKD, LV dysfunction	1
HTN, DM, COPD, PVD	1
NONE	6

In this study, among 50 patients all of them are associated with risk factors for Coronary Artery Disease like 15 patients are associated with Hypertension and Diabetes mellitus, 7 patients are suffering from hypothyroidism, 3 patients with a family history of Coronary artery disease, 6 patients were having no comorbidities, 9 patients were suffering from COPD and CKD. Among which the most common ones were HTN and DM.

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Figure 1.2: % Reduction of Heart Rate

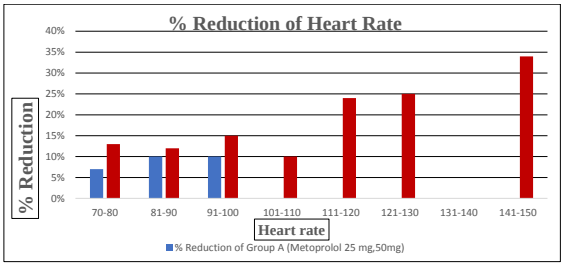


Figure 1.3: Mean Heart Rate of Group A (Metoprolol)

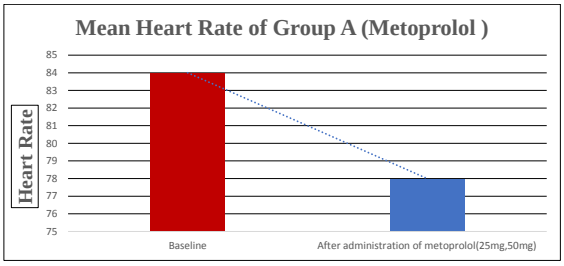
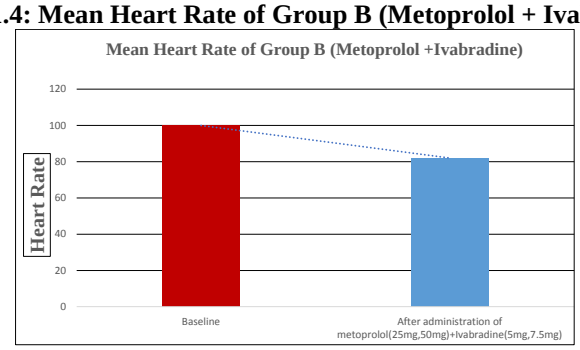


Figure 1.4: Mean Heart Rate of Group B (Metoprolol + Ivabradine)



IV.DISCUSSION:

Cardiovascular diseases (CVD) are a leading cause of death and disability as well as major public health burden worldwide. CVD covers a wide range of illnesses related to the circulatory system including coronary artery disease (CAD), heart failure (HF), and stroke. HF is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or ejection of blood. HF is a growing health concern worldwide with over 37.7 million people being affected by it.

Increased heart rate (HR) is associated with deleterious effects on several disease conditions. Chronic heart failure (CHF) is one of the cardiovascular diseases with recurrent hospitalization burden and an on-going drain on health care expenditure.

Beta blocker is one of the main stays of therapy in heart failure with reduced ejection fraction. When given in concert with ACE inhibitors, beta blockers reverse the process of LV remodelling, ameliorate patients' symptoms, prevent recurrent hospitalisation, prolong life and reduces mortality. Since beta blockers reduce heart rate, beta blockers are the main drug treatment used for patients with ACS. AHA guidelines provide a class 1 recommendation for oral beta blockers within first 24 hours of symptom onset.

In Acute coronary syndrome beta blocker reduces myocardial oxygen consumption by reducing heart rate and cardiac index resulting in reduction of chest pain. It also prevents re infarction and development of ventricular arrhythmias particularly in STEMI patients with LV systolic dysfunction.

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But there are some clinical scenarios where beta blockers cannot be used 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 in the early management of patients with acute coronary syndrome.

In these conditions Ivabradine is a good choice of drug. It reduces heart rate without interfering systemic blood pressure. Therefore, it reduces angina, recurrent hospitalisation and recurrent coronary events.

Ivabradine, a selective inhibitor of funny current channel, reduces resting and exercise heart rate and thus reduces myocardial oxygen demand without affecting cardiac contractility, conduction, relaxation, repolarization and blood pressure. It exerts anti anginal and anti-ischaemic effects in patients with ACS resulting longer diastolic perfusion time & reduced myocardial O2 consumption.

More recently, the indications of ivabradine have been extended for use in association with beta blockers in patients of CAD. (Tendera et al 2011).

When the distribution of patients was done based on gender in our study with a sample size of 50, majority of our sample size were found to be males (27) followed by females (23). This was found to be similar with the results of the study "Sex differences in Coronary Artery Disease" et al Kazuyuki Yahagi, Harry R Davis.

In our study, when the distribution of patients was done based on age groups, we had found that the greater number of patients with Coronary Artery Disease fall in the age group of 61-70 years old followed by the age group of 41-50. These results are similar with the study "Combination of Ivabradine and Metoprolol in a wide range of Stable Angina patients" et al Dimitar Divchev, Georg Stocki.

Our study revealed that 44% of the patients had normal BMI (18.5-24.9) followed by the obese patients accounting 30% and overweight patients accounting 26%. There were no patients in morbidly obese category (BMI >40). In a similar study conducted by Rosario Rossi, Daniele laccarino, et al found that 43% of patients had normal BMI, 36% had obesity and 26% were overweight.

In this study, among 50 patients all of them are associated with risk factors for Coronary Artery Disease like 15 patients are associated with Hypertension and Diabetes mellitus, 7 patients are suffering from hypothyroidism, 3 patients with a family history of Coronary artery disease, 6 patients were having no comorbidities, 9 patients were suffering from COPD and CKD. Among which the most common ones were HTN and DM.

Other Cardiac drugs which were prescribed to the patients included statins such as Rosuvastatin 40 mg and Atorvastatin 20 mg, antiplatelet drugs such as Aspirin 75 mg and Clopidogrel 75 mg.

In this study, Ivabradine was prescribed at a dose of 5 mg and 7.5 mg BD and dose of Metoprolol was 25 mg BD and 50 mg OD.

The present study reported significant % reduction of heart rate between both the groups i.e.,

Group A (Metoprolol 25mg,50mg) – 10%

Group B (Metoprolol 25mg,50mg + Ivabradine 5mg,7.5mg) – 34%

Addition of Ivabradine to Metoprolol showed reduction in mean heart rate by 18 bpm, while in Group A Metoprolol showed reduction in mean heart rate by 6 bpm.

The better results observed in the Group B receiving Ivabradine and Metoprolol indicate that Ivabradine might be more beneficial in patients with higher grades of heart failure. In this study, the dose of the Metoprolol was 25 mg BD and 50 mg OD. The dose of Metoprolol could not be up-titrated in patients to the target dose (200mg/day) due to intolerance to the Beta blocker. Hypotension and dizziness were the reasons for intake of lower dose than recommended dose of Metoprolol. This inability to administer the target dose of the Beta blocker could be one of the reasons for higher incidence of CAD and rehospitalization in the Group A.

The results of this study established that the addition of Ivabradine to Metoprolol significantly reduced the heart rate and improved the clinical status of the patients. The study also shows that Ivabradine can be considered as an alternative to Beta blocker when it is contraindicated or intolerated.

In situations where up-titration of Beta blocker dose is not possible due to in tolerance or contraindications, the addition of Ivabradine can be considered to reduce the risk of Cardiovascular events.

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V.CONCLUSION

Increased heart rate produces adverse impact on myocardium. Beta blockers are effective agents for reducing heart rate but in some patients, Beta- blockers may not be used due to contraindication or intolerance. Several studies suggest that Ivabradine is an attractive, effective, and safe choice in patients with HF. Ivabradine provides additional benefits when used in combination with the other antianginal drugs such as Beta- blockers (except diltiazem and verapamil).
Based on the results of our study we conclude that:

Group B (Metoprolol + Ivabradine) is more effective in reducing the heart rate when compared to Group A (Metoprolol) in the patients with coronary artery disease. So, Combination therapy of Metoprolol and Ivabradine may be administered in patients with CAD specially where Beta blockers are contraindicated.
Future studies with newer indications can support the clinicians to increase their confidence in the use of Ivabradine.

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