Comparison Study of Effect of Ivabradine versus Beta Blockers in Early Management of Acute Coronary Syndrome with Left Ventricular Systolic Dysfunction in a Tertiary Care Hospital of West Bengal

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ABSTRACT

BACKGROUND
Increased heart rate in ACS 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 ACS 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 has 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 early administration of ivabradine versus metoprolol in patients admitted in our hospital with acute coronary syndrome with LV systolic dysfunction. The clinical responses are evaluated and compared.

METHODS
In this study patients were mostly recruited from the critical care department of cardiology of R.G. KAR Medical College and Hospital, Kolkata, admitted due to acute coronary syndrome. After considering inclusion and exclusion criteria, patients were recruited in the study. Patients were divided into two groups. Group A patients received Metoprolol and group B patients received Ivabradine. Baseline and follow-up evaluation were done and necessary data were collected and analysed.

RESULTS
The present study reported significant reduction in heart rate in ivabradine group compared to other group. However, there was no significant difference in 30 days outcome between both groups. Despite the reduction in heart rate in this study, there was no significant improvement in secondary end points compared to other trials.

CONCLUSIONS
Administration of ivabradine in patients of ACS showed significant resting heart rate reduction as well as improved left ventricular ejection fraction though no improvement was seen in major cardiac adverse effects.

KEYWORDS
Ivabradine, ACS, LVEF, Thrombolysis
BACKGROUND

Patients with ischaemic heart disease fall into two large groups i.e. patients with chronic coronary artery disease who most commonly present with stable angina and patients with acute coronary syndrome. ACS is composed of patients with acute myocardial infarction with ST segment elevation on presenting electrocardiogram (STEMI) & those with unstable angina and non ST segment elevation MI.1 Elevated heart rate in ACS is an important pathophysiological variable that increases myocardial oxygen demand and also limits tissue perfusion by reducing the duration of diastole during which most myocardial perfusion occurs, elevated resting heart rate represents a significant predictor of all cause and cardiovascular mortality in population as it aids progression of atherosclerosis, plaque destabilization and arrhythmias.2

Beta blocker is one of the mainstay 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.3 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 ischaemia and improvement of ventricular arrhythmias particularly in STEMI patients with LV systolic dysfunction.4 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.2 More recently, the indications of ivabradine has been extended for use in association with beta blockers in patients of CAD. (Tendera et al 2011).5,6

In previous studies7,8 outside India, it was shown that the combined treatment with beta blockers and ivabradine have a favourable safety profile and same anti ischaemic activity compared with beta blockers alone in ACS patients. But in India studies relating to beta blocker alone versus ivabradine alone are lacking or less.

METHODS

Study Design

This is a prospective, controlled, observational, randomized study enrolled 40 patients with acute coronary syndrome. Patients were mostly recruited from the CCU of critical care department of cardiology of R.G.KAR Medical College and Hospital, Kolkata, admitted due to acute coronary syndrome in the period of April 2018 to May 2018, maintaining following criteria;

Inclusion Criteria

- Patients with ischaemic manifestations suspected to represent ACS.
- Moderate left ventricular systolic dysfunction (EF-30-45%).
- Sinus rhythm with heart rate greater than 60 beats per min on a resting standard 12 lead ECG.
- Others Standard treatment received for ACS.

Exclusion Criteria

- Patients with bradycardia, sick sinus syndrome, atrio ventricular block
- Patients with tachyarrhythmia like atrial fibrillation or flutter
- Patients of cardiogenic shock.
- Patients with NYHA score >3.
- Patients with acute MI requiring urgent coronary revascularization.
- Pregnant or breast feeding women or women of child bearing age.

All patients gave informed consent and the protocol was approved by the institutional ethics committee. Patients were assessed with ECG, Echocardiography and Doppler.

Baseline and Follow-Up Evaluation

All included patients were subjected to:

- Detailed history taking including demographic data, family history, risk factors of CAD, prior medical history, associated co morbidities, assessment of chest pain on admission, presence of any contra indications for fibrinolysis or beta blockers.
- Physical examinations including both general and systemic examinations with special attention to presence of basal crepitation with laboratory investigations (cardiac enzymes and troponin) which were withdrawn on admission.
12 lead ECG was recorded on admission and after thrombolysis if thrombolysis done.

- 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).
- Echocardiography was done on admission to notice the left ventricular ejection fraction after initial stabilisation. Ejection fraction was estimated by both Teichos and modified Simpson method.
- Coronary angiography done in this patients to notice the blocked coronary arteries.
- Reperfusion Therapy.
- Thrombolysis done in few patients (without giving antplatelet drug first) who fulfil the thrombolysis criteria and indications. The fibrinolytic drug used was streptokinase 1.500000 IU over 60 minutes and tenecteplase as per weight based dosage.
- Study Protocol.
- 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.

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.

Follow Up

After 30 days patients of both groups were again subjected to clinical examination including general and systemic examination and resting ECG and echocardiography to monitor the ejection fraction parameter.

Study End Point

1) Resting heart rate stabilisation and improvement of ejection fraction on 30 days follow up period.
2) 30 days mortality, reinfarction, arrhythmia, overt heart failure, need for revascularization or other major cardiac adverse events.

Statistical Methods

Data are presented as mean for continuous data and as number for categorical data. Between groups comparison was done by student t-test for continuous data and by chi-square test for qualitative data. Level of evidence was detected to be significant at P value <.05. All obtained data were analysed statistically by SPSS (Statistical package for social science) program.

RESULTS

The mean age of the study population was 54.93 years old. In our study, there were 24 male patients who represented 60% of study population and 16 female patients which represented 40% of study population. The demographic data included in table 1.

Table 1. Demographic Data of Study Groups

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>19</td>
<td>47.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>77.5%</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>25</td>
<td>62.5%</td>
</tr>
<tr>
<td>Family History of CAD</td>
<td>25</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

Table 2. Risk Factors

<table>
<thead>
<tr>
<th>Type of AMI</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Wall Infarction</td>
<td>20</td>
<td>50%</td>
</tr>
<tr>
<td>Antero Lateral Wall Infarction</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Inferior Wall Infarction</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>Non ST Elevated Infarction</td>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Lateral Wall Infarction</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Infero-Lateral Wall Infarction</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Table 3. Types of Acute Myocardial Infarction Detected on ECG

<table>
<thead>
<tr>
<th>Vessel Involved</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD Territory</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>RCA Territory</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>LCX Territory</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>LAD &amp; RCA Territory</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>LAD &amp; LCX Territory</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>RCA &amp; LCX Territory</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Triple Vessel Disease</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4. Vessels Involved

- Among them thrombolysis done in 23 patients i.e. 57.5% of study population and in rest 17 patients i.e. 42.5% were treated conservatively.
- There were significant differences between both groups in heart rate value on admission and on day 30 follow up (p value 0.0011)
- There were significant differences between both groups in left ventricular ejection fraction of admission day and day 30 follow up. (p value <.0001)
Reduced heart rate variability and increased resting heart rate are indicators of sympathovagal defect and has been found to be associated with cardiovascular mortality and morbidity in patients with acute coronary syndrome. It has been also shown to be a potent indicator of progression of coronary artery disease and it is associated with coronary plaque rupture with subclinical inflammation and plays a key role in pathogenesis of coronary atherosclerosis.

Ivabradine, a selective inhibitor of the funny channel, reduces resting and exercise induced heart rate without affecting cardiac contractility or blood pressure. It exerts antianginal and anti-ischaemic effects in patients with coronary artery disease. Improved exercise tolerance and reduced frequency of anginal attacks have been observed after funny current channel inhibition.

In this study, among the 40 patients all of them are associated with risk factors for coronary artery disease like hypertension and it is associated with coronary artery disease. Improved exercise tolerance and reduced frequency of anginal attacks have been observed after funny current channel inhibition.

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Administration of ivabradine in patients of ACS with left ventricular dysfunction showed significant resting heart rate reduction, angina frequency, rate of revascularisation as well as improved left ventricular ejection fraction though no improvement was seen in major cardiac adverse effects. So, ivabradine may be administered in cases of ACS specially where betablockers are contraindicated.

REFERENCES


