INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

A STUDY ON EFFECTS OF IVABRADINE IN ST-ELEVATED MYOCARDIAL INFARCTION AFTER INTRAVENOUS THROMBOLYTIC THERAPY

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Article Received on: 11/12/18 Approved for publication: 19/01/19

DOI: 10.7897/2230-8407.100396

ABSTRACT

Background: Myocardial infarction occurs when blood flow to the heart muscle stops or is suddenly decreased long enough to cause cell death. Elevated heart rate occurs with an increase in myocardial oxygen demand and is known to induce myocardial ischemia in patients with Coronary artery disease. Ivabradine inhibits I_f current in the hyper polarization activated Cyclic Nucleotide Channel (HCN) of the SA node and thereby reduce heart rate through controlling spontaneous diastolic depolarization. The present study was undertaken to evaluate the clinical effects of Ivabradine on heart rate, blood pressure, ejection fraction from 2Dimensional echocardiography (2DECHO), QT and QTc patterns from Echocardiogram (ECG). Materials and methods: 17 Patients male and female of 25-85years age group were included in the study. Results: 17 Patients diagnosed with ST elevated myocardial infarction and undergone thrombolytic treatments with Streptokinase or Tenecteplase were included in the study and Ivabradine was added to their treatment regimen. We found a reduction in heart rate, prolongation of QT interval, shortening of QTc interval, improvement in ejection fraction when compared to their baseline values. Conclusion: Our study demonstrates that addition of oral Ivabradine to the treatment regimen in ST elevated myocardial infarction (STEMI) patients after thrombolytic therapy is valuable therefore, we suggest Ivabradine as a safe and effective agent in the treatment of STEMI and is not a direct agent in provoking Torsade de pointes.

Keywords: Myocardial infarction, Ivabradine, Heart rate, I_f current, HCN channel, thrombolytics.

INTRODUCTION

Acute Coronary Syndrome (ACS) describes a condition when there is an insufficiency or excessive oxygen and nutrient requirement to the heart muscle but which is not accomplished due to atherosclerotic plaque rupture or thrombus formation in the arteries supplying blood to the heart. Plaque rupture leads to the exposure of contents i.e. collagen, inflammatory cells, lipid material to the blood stream, leading to the aggregation of platelets, which on activation releases ThromboxaneA2, causing vasoconstriction. Fibrinogen molecules appear to bind with Glycoprotein IIb/IIIa receptor and fibrin is formed and a clot is produced. The event of thrombus formation leads to a complete or partial closure of coronary arteries, leading to an impaired blood supply which results in a decreased supply of oxygen to the myocardium[1]. Increase in heart rate is a compensatory mechanism during myocardial infarction[2, 3] thereby specific heart-rates lowering with Ivabradine reduces myocardial oxygen demand,[3] simultaneously improving oxygen supply. Ivabradine is a first specific heart rate lowering agent which is selective for I_f (funny current) inhibition, and activated on hyperpolarisation in diastolic range of voltages. this is described in sinoatrial node myocytes, which is mixed sodium potassium inward current[4]. Funny channels are activated by intracellular cyclic adenosine monophosphate (c AMP) concentrations[4]. Structural subunits of these channels are Hyperpolarisation activated Cyclic Nucleotide gated Channels(HCN)[5]. These channels have four isoforms. HCN 4 channel is most predominantly present isoform in SA nodal cells. Previously beta blockers were used to control heartrate[2,3] in this condition but early use of intravenous (IV) beta-blockers was associated with hazard of an early mortality, particularly in patients with acute heart failure, with an increased risk of cardiogenic shock.[2] This hazard appears to be related to the negative inotropic effect of beta-blockers. Ivabradine do not weaken the force of myocardial contractility or rate of myocardial relaxation, preserving ventricular contractility. Currently oral doses of this drug are available with 5mg, 7.5mg doses[5,6]. Absorption of this drug is rapid with a peak plasma level within 1hr under fasting condition,70%plasma protein bound, metabolised by oxidation process in liver mostly by CYP 3A4 enzyme, Ndesmethylated derivative is active metabolite and followed by renal route of excretion[6].Use of Ivabradine is contraindicated in hepatic ,renal impairment conditions in people with resting heart rate less than 60 beats per minute ,sick sinus syndrome, combination with CYP3A4 inhibitors, pregnancy, lactating female[6,5]. The most common adverse effects related to use of this drug are bradycardia and 1st degree AV block related to cardiovascular, nausea, vomiting abdominal pain related to gastrointestinal system, Phosphene formation (luminous phenomenon), blurred vision related to Eye, headache, dizziness related to nervous system[6]. QTc interval prolongation increases the risk of torsade de pointes, particularly when QTc interval exceeds 500ms. So agents having effect on heart rate will have an effect on QT pattern. The duration of repolarisation is dependent on heart rate; QT interval is shorter with tachycardia and longer with bradycardia[7].

MATERIALS AND METHODS

It is a prospective interventional study conducted in patients from Cardiology department in ''Mahatma Gandhi Memorial Hospital" located in Warangal, Telangana, India. The participants in the study were 40 in number who were admitted due to STEMI and received an intravenous thrombolytic after their admission. Of these patients 7 were Hypertensive and 3 patients were Diabetic and were on their respective drug therapies.

Out of these patients 17 patients were included in the study and were on regular drug therapy without any renal or hepatic impairment and available for their regular follow up purpose for a month. 23 patients were excluded from the study of which 8 patients were referred to higher centres due to their critical condition. 10 patients were on irregular drug therapy and remaining 5 patients were not available for their follow up. Prior to the study approval was obtained from Institutional Ethics Committee and the approval number is MGM/VCOP/PHARMD/V/10/2018, informed consent is obtained from the included patients in the study.

In this study, we calculated heart rate by using Fingertip pulse oximeter and blood pressure by using Sphygmomanometer and calculated QT interval manually from ECG by counting the number of boxes from the beginning of QRS complex to the end of T wave, QTc interval is calculated using Bazett's formula. All the parameters were expressed as Mean ± Standard deviation (SD). Data analysis was done by using paired t test in MS EXCEL2007.

Inclusion criteria
Patients with STEMI, normal sinus rhythm, heart rate >70bpm, ejection fraction<35% [6].

Exclusion criteria
Patients with resting heart rate below 70 beats per minute; cardiogenic shock; severe hypotension (< 90/50 mmHg), severe hepatic insufficiency, sinoatrial block, atrial fibrillation and flutter. Unstable or acute heart failure, Pacemaker dependent unstable angina, AV-block, concurrent use of CYP3A4inhibitors, Concurrent use of CYP3A4 inducers, Pregnancy, lactation. [6].

RESULTS

Age and gender
At study entry, the mean age and standard deviation of the study population (n=17) was 55.17±15.04 years. Numbers of male were 12 (70.5%) and female were 5 (29.4%). This is presented in fig 1,2.

Past history and social history of the subjects
Out of 17 patients enrolled in the study, 7 were hypertensive patients (41.1%) and 3 were diabetic (17.6%) and 1 patient was both hypertensive and diabetic (5.88%). 6 patients had no past medical history (35.2%). The figure is presented in fig 3.
The social history was collected and 8 patients were smokers (47%) and 9 patients were alcoholic (52.9%) and 5 patients had a social history of both smoking and alcohol consumption (29.4%). Presented in fig 4.

Effect on blood pressure
Compared to baseline and follow up after a month, the changes in systolic blood pressure (SBP) was from 137.64±17.51 to 131.76±16.29 respectively with a p value 0.156 and the pattern of change in diastolic blood pressure (DBP) was from 84.70±8.74 to 80±6.14 and p value 0.179. Presented in fig 5.

Effect on heart rate
There was a significant decrease in mean heart rate before the treatment from 85.23±8.42 to 78±11.1 after follow up for one month and p value was 0.039 which is illustrated in fig 7. Individual changes in heart rate is described in fig 6.

Comparison of ejection fraction
We found that 11 patients had an improved ejection fraction (64.7%), 2 patients had no change in ejection fraction (11.7%), 4 patients had a decreased ejection fraction (23.5%) compared to their first visit which is presented in fig 8. We also found a mean increase in ejection fraction compared to baseline from 41.11±8.99 to 45.64±13.2 after Ivabradine treatment with a p value of 0.248. Illustrated in fig 9.

Effect on QT interval
We found that 11 patients had a QT prolongation (64.7%) and 6 patients had a decreased QT interval (35.2%) compared to their first visit and the pattern of changes was presented in fig 10.
The mean changes in QT prolongation changes before and after Ivabradine treatment was found to be 414.23±84.35to 419.11±56.88 and p value was found to be 0.84. Illustrated in fig 11.

Effects on QTc pattern
We observed that 7 patients (41.1%) had a prolongation of QTc interval and 10 patients (58.8%) had a QTc shortening and when compared to baseline value473.70±67.7 QTc interval was shortened after Ivabradine treatment 452.23±57.68 with a p value of 0.32 illustrated in fig 13. The changes of QTc pattern was presented in fig 12.

DISCUSSION

In the present study, use of Ivabradine 5mg in STEMI patients decreased heart rate from 85.23±8.42 to 77.88±11.36 without any significant change in blood pressure. This decrease in heart rate is supported by a similar study conducted by PGSteg which concludes that due to tachycardia in acute myocardial infarction an increase in imbalance between myocardial oxygen and supply occurs so Ivabradine intravenously decreased heart rate.[2]

According to study conducted by Deep Chandh Raja et al; in Dilated Cardiomyopathy patients, ejection fraction was improved after 3 months of treatment with Ivabradine in 63 patients[8]. Similarly we found an improvement in ejection fraction in 11 (64.7%) subjects by 4.53% after one month of treatment.

Ivabradine inhibits hERG (the human Ether-a-go-go-Related Gene) channels and prolong QT interval without changes in QTc pattern in a study conducted by Jules C et al; and suggested that Ivabradine was not a direct agent for the cause of Torsade de pointes[7], in the present study we found, QT interval prolongation is seen in 12 patients within borderline range (up to 450ms in men and 470ms in women[9]) and QTc interval was reduced compared to baseline values.

LIMITATION OF STUDY

This study has some limitation as the sample size is low and it lacks the power to demonstrate a significant improvement in ejection fraction, changes in Qtc pattern and blood pressure. Further larger trial is required to determine its safety and effectiveness as a treatment regimen in STEMI patients.

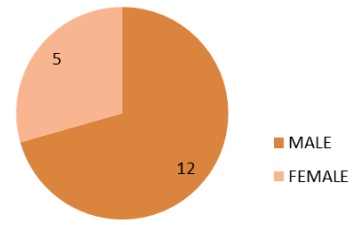

Figure1:Gender distribution of the patients

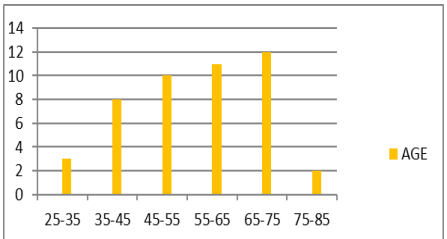

Figure 2:Age distribution of the patients

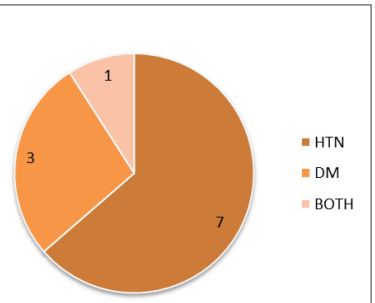

Figure 3:Pasthistory of the patients

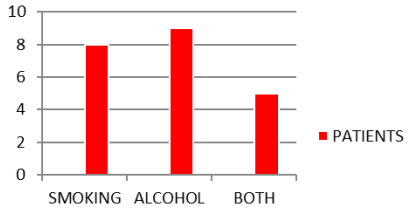

Figure 4:Social history of the patients

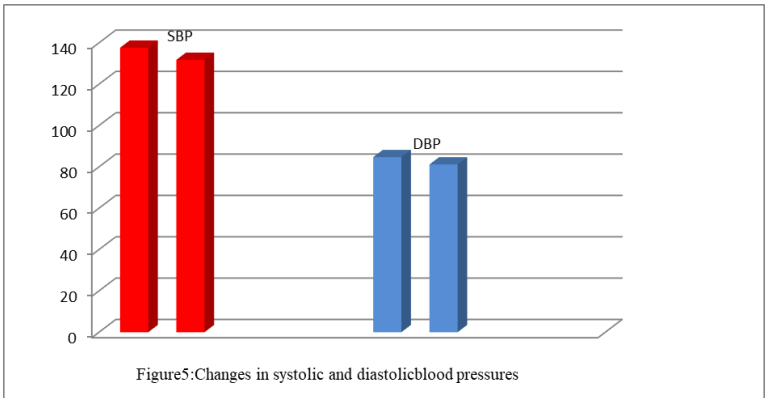

Figure5:Changes in systolic and diastolicblood pressures

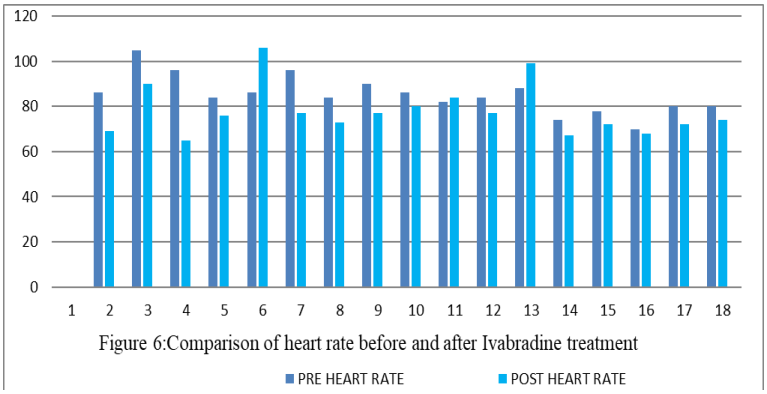

Figure 6:Comparison of heart rate before and after Ivabradine treatment

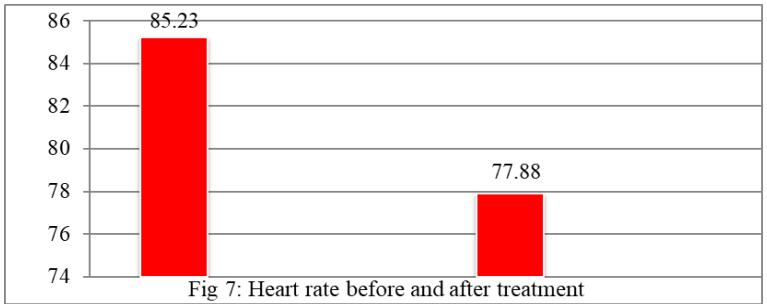

Fig 7: Heart rate before and after treatment

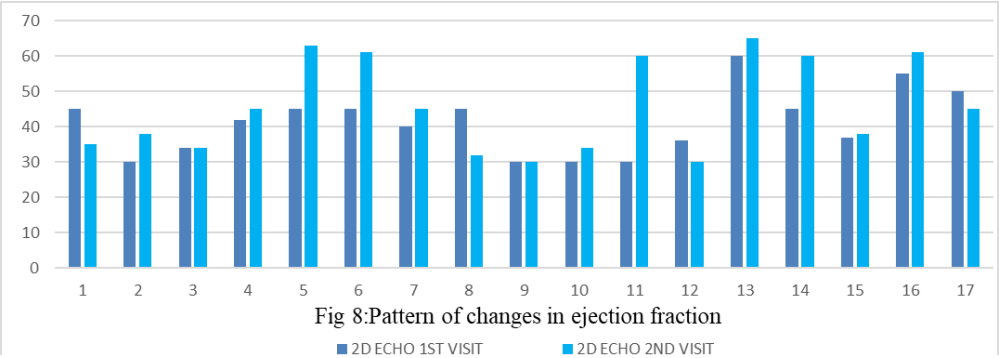

Fig 8:Pattern of changes in ejection fraction

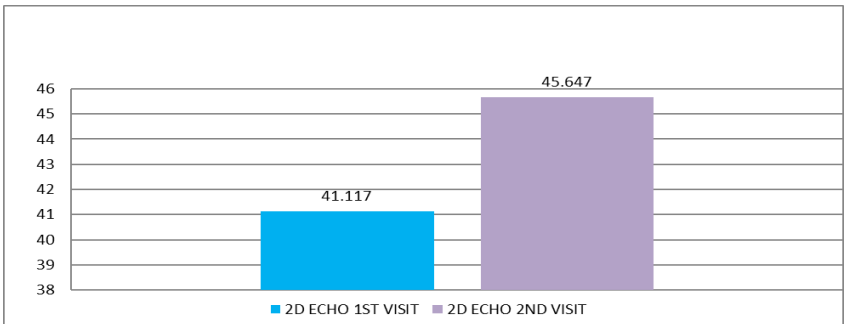

Figure 9: Mean changes in ejectionfraction before and after treatment

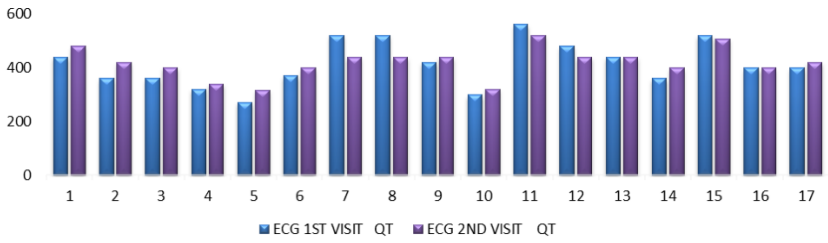

Fig 10:Pattern of changes in QT interval

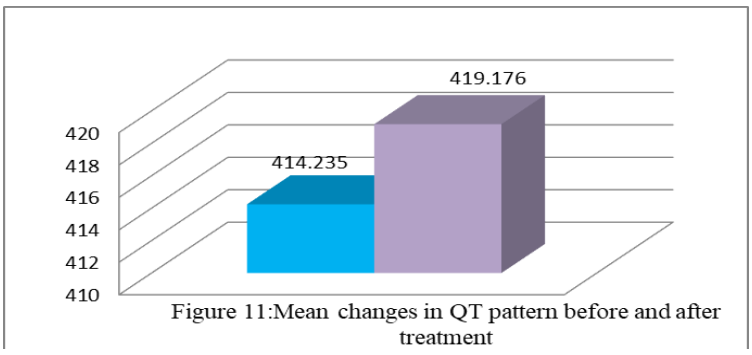

Figure 11:Mean changes in QT pattern before and after treatment

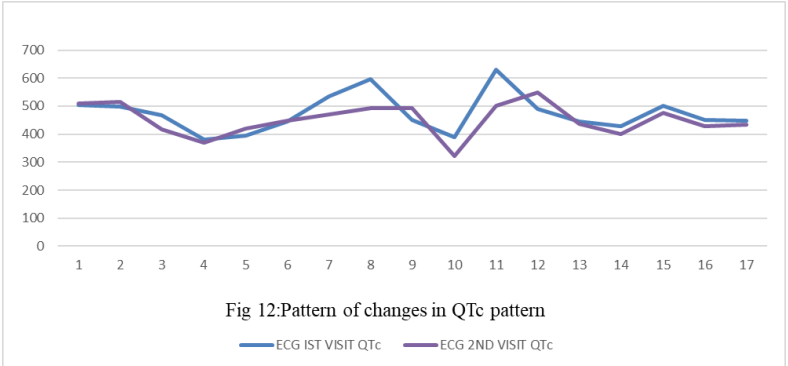

Fig 12:Pattern of changes in QTc pattern

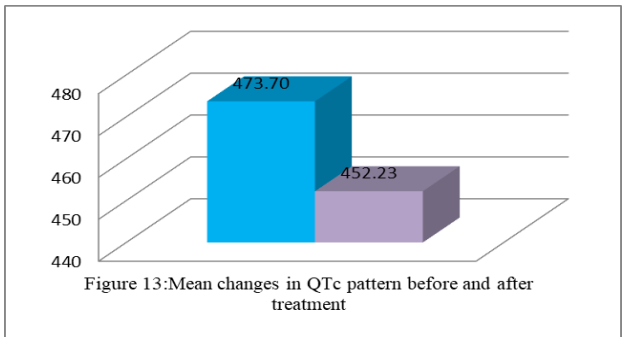

Figure 13:Mean changes in QTc pattern before and after treatment

Table 1: Comparison of baseline values with values after treatment with Ivabradine

S.NO	Parameter	Baseline	Post Ivabradine	P value
I	Systolic BP(mm Hg)	137.64±17.51	131.17±14.95	0.15
II	Diastolic BP(mm Hg)	84.7±8.74	81.17±6.96	0.17
III	Heart rate(beats per minute)	85.23±8.42	77.88±11.36	0.03
IV	Ejection fraction (%)	41.11±8.92	45.64±13.08	0.24
V	QT interval (milli seconds)	414.23±84.35	419.11±56.88	0.84
VI	QTc interval(milli seconds)	473.70±67.7	452.23±57.68	0.32

CONCLUSION

Our study concludes that addition of oral Ivabradine to the standard treatment regimen in STEMI patients reduced heart rate, with no significant changes in blood pressure, improved ejection fraction, prolonged QT interval with shortening of QTc.

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Cite this article as:

Nithisha Reddy Katkuri *et al*. A study on effects of ivabradine in ST-elevated myocardial infarction after intravenous thrombolytic therapy. Int. Res. J. Pharm. 2019;10(3):158-162 http://dx.doi.org/10.7897/2230-8407.100396

Source of support: Nil, Conflict of interest: None Declared

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