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Original Research Article

A comparative study on efficacy of metoprolol and ivabradine in acute ST elevation myocardial infarction patients

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ABSTRACT

Background: The ST-elevation myocardial infarction (STEMI), a fatal disease, is rapidly extending in patients, worldwide. Therefore, proper and timely diagnosis followed by appropriate management becomes necessary. The study aimed to compare the effectiveness of metoprolol and ivabradine in acute STEMI patients.
Methods: This was an observational, comparative, in-hospital study carried out in patients admitted in the in-patient cardiac department, intensive cardiac care unit of a tertiary care centre in India. Total 60 patients diagnosed with acute ST-elevation MI were included in the study and were equally divided into two groups. Group 1 involved patients who were given metoprolol for treatment and group 2 involved patients who were given ivabradine. The patients were assessed in terms of heart rate, NYHA class, and ejection fraction. Follow-up of 30 days was taken in all patients.
Results: Ivabradine reduced mean heart rate from 85.57 bpm at baseline to 78.23 bpm. Heart rate in the metoprolol group was reduced from 81.93 bpm to 76.47 bpm over the same time period. Metoprolol and ivabradine showed significant improvement in the ejection fraction volume during the in-hospitalization stay. Ivabradine showed a better improvement in ejection fraction when compared to metoprolol but the difference was not found to be statistically significant. Higher mortality was assessed in ivabradine group compared to metoprolol.
Conclusions: The study gives the gold standard efficacy and mortality benefit of metoprolol, although ivabradine on the other hand gave better responses in heart rate reduction and improvements in ejection fraction.

Keywords: Ejection fraction, Ivabradine, Metoprolol, ST-elevation myocardial infarction

INTRODUCTION

Acute myocardial infarction (AMI) is characterized by cellular death or necrosis of myocardial tissue occurring due to severe or prolonged ischemia. ST-elevation myocardial infarction (STEMI), a fatal form of AMI, is supposed to be the resultant of complete occlusion in a coronary artery. The extent and location of the infarction are influenced by degree of ischemic burden, availability of coronary collateral blood flow, rapidity of reperfusion and the location of the plaque in the coronary artery.[1]

Initially, AMI was treated symptomatically by controlling pain, arrhythmic condition, giving bed rest, nitrates and β-blockers. Then as the years passed, the AMI patients were being assessed angiographically, and treated using

thrombolytics and percutaneous coronary intervention (PCI) as first-line therapies. The other drugs were then been used for maintaining the conditions and improving prognosis.

Increased heart rate has been allied with an increase in cardiovascular mortality and increase in heart rate represent as a risk factor for hypertension, atherosclerosis leading to increased incidences of coronary artery disease, and myocardial infarction.[2,3] Therefore, heart rate control becomes a chief objective in treatment of patients with STEMI.

β-blockers lead to slowing of heart rate, reduction in myocardial contractility, and lowering of systemic blood pressure. Moreover, metoprolol reduces the oxygen requirements of the heart, thus making it useful in the long-term. The current guidelines for STEMI give the strong recommendation (class I) to oral β-blocker therapy in patients without a contraindication particularly with high HR or blood pressures.[4] Ivabradine, inhibitor of If current of cardiac pacemaker cells without affecting other cardiac ionic currents, reduces heart rate and has no effect on cardiac contractility, repolarisation, or atrioventricular conduction.[5,6] It has been recently approved as an alternate drug of choice for heart rate lowering in acute coronary syndrome especially in patients with clinical heart failure and in conditions where β-blockers are contraindicated, for example in patients of asthma or severe chronic obstructive airway disease.[2,3] Thus, this study aimed to compare the effectiveness of metoprolol and ivabradine in acute STEMI patients.

METHODS

This was an observational, comparative, in-hospitalization study carried out in patients admitted in the in-patient cardiac department, intensive cardiac care unit of a Tertiary care centre in India. Total 60 patients diagnosed with acute STEMI were included in the study and were equally divided into two groups. Group 1 involved patients who were given metaprolol for treatment and group 2 involved patients who were given ivabradine.

Patients, both males and females, of age >18 years, who got admitted within 24 hours of symptoms of myocardial infarction, with mean heart rate >80 beats/min, ST elevation of 1 mm in the peripheral leads / 2 mm in precordial leads were included in the study. Patients who were admitted to hospital 24 hours after onset of symptoms of STEMI; who previously underwent percutaneous coronary intervention and coronary artery bypass grafting; and those with persistent hypotension, cardiogenic shock were excluded from the study.

The patients after being diagnosed with ST elevation myocardial infarction were first given dual antiplatelet therapy followed by thrombolysis. Coronary Angiogram followed by revascularisation was done later as per the operators' discretion.

In group 1, twelve hours after thrombolysis patients received oral metoprolol: initially 25 mg bid, 24-48 hours later the dose was increased to 50 mg bid in patients with HR >70 beats/min if tolerated. In group 2, twelve hours after thrombolysis patients received 2.5 mg of ivabradine PO bid, increased to 5 mg twice per day 24 hours after, and 48 hours later the dose was increased to 7.5 mg twice in patients with HR >70 beats/min. Both drugs were titrated to obtain a HR target from 60 to 70 beats/min.

The heart rates and blood pressure were taken on admission, and thereafter every 6 hourly in hospitalisation stay and on follow-up; and ejection fraction values were noted on admission and on discharge. NYHA class was also assessed. Patients' follow-ups were taken after 30 days.

Statistical analysis

Results on continuous measurements are presented as mean and standard deviation. Results on categorical measurements are presented as counts and percentages. Student's t- test, Chi square test and paired t-test were used for analysis of the data. Data were analysed using SPSS software version 15.

RESULTS

A total of 60 patients were included in the study, with 30 patients in each group. Two patients were of age between 21-40 years, 29 patients were of age between 41-60 years, and 29 patients were of age between 61-80 years. 39 patients were male and 21 were female.

Diabetes (43.3% and 70.0%) and hypertension (43.3% and 70.0%) were most prevalent conditions in patients of both groups. Smoking was a co-morbid condition in 12 and 11 patients, respectively in both groups. The details about the prevalence of co-morbid conditions are presented in Table 1.

Table 1: Co-morbid conditions in patients of both groups.

	Metoprolol (N = 30 patients)	Ivabradine (N = 30 patients)
Asthma, n (%)	1 (3.3%)	3 (10.0%)
Cerebrovascular accident, n (%)	2 (6.7%)	6 (20.0%)
Alcoholic, n (%)	5 (16.7%)	1 (3.3%)
Diabetes mellitus, n (%)	13 (43.3%)	21 (70.0%)
Smoking, n (%)	12 (40.0%)	11 (36.7%)
Tobacco, n (%)	10 (33.3%)	11 (36.7%)
Hypertension, n (%)	13 (43.3%)	21 (70.0%)

Metoprolol and ivabradine individually showed significant improvement in ejection fraction during in-hospital stay. Ivabradine showed a better improvement in ejection fraction when compared to metoprolol but the difference was not found to be statistically significant (p = 0.148). Morbidity assessed in terms of functional status (NYHA) Class did not show major difference in both groups and was statistically insignificant (p = 0.065). More sick patients (class IV) were observed in ivabradine group (Table 2).

Table 2: Ejection fraction and NHYA class details.

Variable	Metoprolol (N = 30 patients)	Ivabradine (N = 30 patients)
Ejection fraction at admission (Mean±SD, %)	45.9±9.5	38.9±8.9
Ejection fraction at discharge (Mean±SD, %)	53.8±8.6	49.0±6.7
Improvement in ejection fraction (Mean ±SD, %)	7.9±5.2	10.1±6.2
NYHA class I, n (%)	22 (73.3%)	22 (73.3%)
NYHA class II, n (%)	2 (6.7%)	4 (13.3%)
NYHA class III, n (%)	6 (20.0%)	1 (3.3%)
NYHA class IV, n (%)	0 (0%)	3 (10.0%)

NYHA - New York Heart Association

Table 3: Heart rates of patients at different time points.

	Group	Mean	Std. Deviation	p value
HR1	Metoprolol	81.9	11.3	0.396
	Ivabradine	85.6	20.4	
HR2	Metoprolol	81.9	11.3	0.396
	Ivabradine	85.6	20.4	
HR3	Metoprolol	82.0	8.2	0.917
	Ivabradine	82.3	9.1	
HR4	Metoprolol	79.4	7.3	0.599
	Ivabradine	80.4	7.8	
HR5	Metoprolol	76.5	5.6	0.264
	Ivabradine	78.2	6.5	
FU	Metoprolol	74.6	3.1	0.899
	Ivabradine	74.5	2.9	

HR 1,2,3,4,5 = Heart rate of day 1,2,3,4,5 respectively; FU = Follow-up

The changes in heart rate over the treatment period and at follow-up are shown in Table 3. Ivabradine reduced mean heart rate from 85.6 bpm at baseline to 78.2 bpm. Heart rate in the metoprolol group was reduced from 81.9 bpm to 76.5 bpm over the same time period. No Significant difference was found in the mean heart rate reduction between the two groups in the prescribed duration of study.

In-hospital mortality was 6.7% and 10% in metoprolol group and ivabradine group respectively (p = 0.640). Higher mortality was seen in ivabradine group compared to metoprolol group as more number of sick patients (NYHA class-IV), diabetics and hypertensives were found in ivabradine group (Figure 1). However, none of the parameters reached statistical significance.

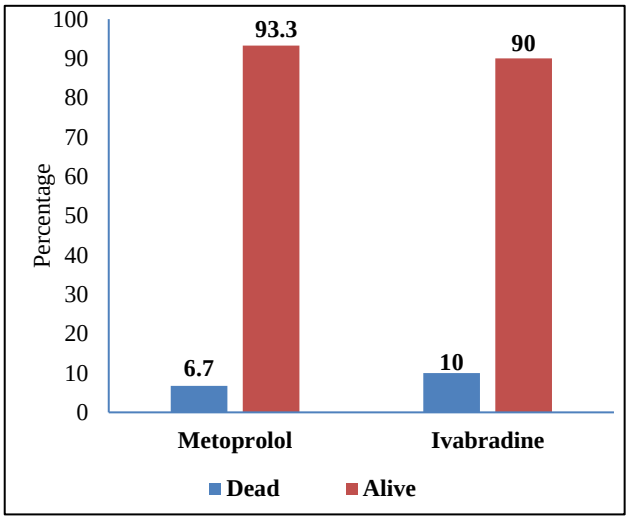

Figure 1: Mortality in both groups up to 30 days follow-up.

DISCUSSION

β-Blockers are a first-line treatment in secondary coronary prevention after acute myocardial infarction with a marked reduction in mortality.[7]

On the other hand, ivabradine reduces heart rate but does not pose any inotropic or lusitropic effect, thus maintaining ventricular contractility.[8] Ivabradine reduced mean heart rate from 85.6 bpm at baseline to 78.2 bpm. Heart rate in the metoprolol group was reduced from 81.9 bpm to 76.5 bpm over the same time period. Though the increment in heart rate was more in ivabradine group, no significant difference was found in the mean heart rate reduction between the two groups in the prescribed duration of study (7.1 and 5.4 bpm, respectively). Similarly, in the BEAUTIFUL trial which evaluated ivabradine for improving cardiovascular outcomes in coronary patients with left ventricular systolic dysfunction, ivabradine reduced the mean heart rate by 11 bpm from the baseline heart rate (71.6 bpm) to 61 bpm at a mean dose of 12.36 mg/day at one month.[9]

Moreover, the SHIFT trial evaluated the effect of pure heart rate reduction by ivabradine in addition to guideline based treatment on cardiovascular outcomes, symptoms and quality of life in patients with systolic heart failure, ivabradine reduced the mean heart rate (79.9 bpm) by 16 bpm versus 5 bpm for placebo at one month and maintained throughout the course of the study.[10]

Morbidity assessed in terms of functional status (NYHA class) did not show any major difference in both the groups and the values were not significant (p = 0.065) in the present study. In-hospital mortality was 6.7% and 10% in metoprolol group and ivabradine group, respectively (P = 0.640). Therefore, higher mortality was seen in ivabradine group compared to metoprolol group thereby suggesting that metoprolol as compared to ivabradine has mortality benefits. But on the other side, more number of patients with advanced heart failure and diabetics were in Ivabradine group. However, the percentage mortality difference between the two groups was not significant.

Metoprolol and ivabradine showed significant improvement in the ejection fraction during the in-hospital stay. Ivabradine showed a better improvement in ejection fraction when compared to metoprolol but the difference was not found to be statistically significant. In a previous study, Fasullo et al, compared ivabradine and metoprolol in patients with reperfused AMI with impaired left ventricular function. The heart rate reduction in metoprolol and ivabradine group was 27 bpm and 25 bpm, respectively; and the improvement in ejection fraction was 4.7% and 9.9% in metoprolol and ivabradine group, respectively at 60 days follow-up. There was one case of death in each group.[2]

Thus, it can be postulated that ivabradine leads to better heart rate reduction and better improvement in ejection fraction than metoprolol, though the difference was not statistically significant. 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.[11]

Additional studies now must assess other potential actions of ivabradine in patients with coronary disease. Moreover, studies can be performed to evaluate ivabradine's beneficial effects on post-myocardial infarction remodelling when HR is not reduced.[2] With increasing interest in effects of ivabradine, it is not only considered as drug of choice in case of contraindication of β-blocker, but it can effectively be used in combination with β-blockers for an optimal therapeutic effect.[12]

Study limitations

The study has some limitations of including small sample size, short follow up, and lack of randomization.

CONCLUSION

The study gives the gold standard efficacy and mortality benefit of metoprolol, although ivabradine on the other hand gave better responses in heart rate reduction and improvements in ejection fraction. Further advanced studies with greater sample size and extensive follow-ups are required to get considerable results about the efficacy, safety and tolerability of the drugs involved in this study.

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REFERENCES

1. Helms RA, Quan DJ. Textbook of therapeutics: drug and disease management: Lippincott Williams and Wilkins; 2006.
2. Fasullo S, Cannizzaro S, Maringhini G, Ganci F, Giambanco F, Vitale G, et al. Comparison of ivabradine versus metoprolol in early phases of reperfused anterior myocardial infarction with impaired left ventricular function: preliminary findings. J Cardiac Failure. 2009;15(10):856-63.
3. Liang M, Puri A, Devlin G. Heart rate and cardiovascular disease: an alternative to beta blockers. Cardiol Res Practice. 2009;2009.
4. O'gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):485-510.
5. Camm AJ, Lau C-P. Electrophysiological effects of a single intravenous administration of ivabradine (S 16257) in adult patients with normal baseline electrophysiology. Drugs R & D. 2003;4(2):83-9.
6. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I f current inhibition with ivabradine. Drugs. 2004;64(16):1757-65.
7. Maxwell S, Waring WS. Therapeutics Drugs used in secondary prevention after myocardial infarction: Case presentation. Br J Clin Pharmacol. 2000;50(5):405-17.
8. De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Failure. 2008;10(6):550-5.
9. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, Investigators B. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9641):807-16.
10. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.
11. Borer JS. Clinical Effect of 'Pure'Heart Rate Slowing with a Prototype I f Current Inhibitor:

Placebo-Controlled Experience with Ivabradine. Heart Rate Slowing by If Current Inhibition: Karger Publishers; 2006:54-64.
12. Berdeaux A. Ivabradine (Procoralan) alone or with b-blockers in myocardial ischemia. Heart Metab. 2010;47:30-3.

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