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IVABRADINE VERSUS METOPROLOL IN PATIENTS WITH CORONARY ARTERY DISEASE - A PROSPECTIVE, OBSERVATIONAL STUDY

Cardiology

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ABSTRACT

Background: Coronary artery disease (CAD) is the leading cause of morbidity and mortality in developing countries with stable angina being the most common symptom. Heart rate is a key etiological factor in the pathophysiology of CAD as tachycardia induces myocardial ischemia by increasing oxygen demand and decreasing perfusion. So reduction in heart rate is the cornerstone of CAD management. Reducing heart rate with conventional drugs like ß-blocker is associated with drug interaction and adverse effects. Ivabradine is a novel heart rate lowering agent which is a selective inhibitor of the pacemaker I(f) current in the SA node.

Objectives: To compare the efficacy and safety of ivabradine versus metoprolol in patients with CAD.

Methods: A prospective, observational, comparative study was carried out in the Department of Cardiology of our hospital. A total no.of 60 patients diagnosed with CAD were included and divided in to 2 groups: Group 1:- received Ivabradine (5mg/day), Group 2:- received Metoprolol (50mg/day). Patients were assessed for HR, Ejection fraction (EF), Canadian cardiovascular society (CCS) class of angina. Two follow ups were done at 30, 60 days intervals. The results in both groups were analysed using paired t test.

Results: Ivabradine reduced mean heart rate from 89.07±1.99 at baseline to 75.17±0.40 bpm and in metoprolol group heart rate reduced from 90.47±1.75 to 77.53±0.86. Both groups showed improvement in EF and CCS class of angina. There was a decrease in episodes of angina attack and also the requirement of nitroglycerine tablets.

Conclusion: Ivabradine was found to be safer and more effective in preventing and treating angina attacks in patients with CAD.

KEYWORDS

Ivabradine, Metoprolol, CAD, CCS

INTRODUCTION

Coronary heart disease (CAD) is the leading cause of mortality and morbidity in developing countries with stable angina being the primary and debilitating symptom and also the first clinical manifestation in up to 50% of patients.[1] Angina pectoris is characterized by retro-sternal discomfort, heaviness, or a pressure-like feeling, which may radiate to the jaw, shoulder, back, or arm and which typically lasts several minutes.[2] Angina results when myocardial perfusion is insufficient to meet myocardial metabolic demand. The myocardial oxygen requirement is elevated by increase in heart rate and contractility. The myocardial perfusion is determined by coronary blood flow.

Heart rate is an important contributor in the pathophysiology of coronary artery disease and also heart failure.[3] A high heart rate induces myocardial ischemia and subsequent angina as it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole during which myocardial perfusion occurs.[4] So reduction in heart rate with drugs improves myocardial tissue perfusion.

Beta-blockers reduce myocardial ischemia and prevent angina pectoris largely by lowering heart rate and are recommended as an initial therapy for stable angina pectoris, unless contraindicated. Despite the demonstrated safety and effectiveness of beta-blockers, physician's use and patient compliance may be somewhat limited by the side effects of these agents which includes fatigue, sexual dysfunction, depression, cold extremities, light-headedness, gastrointestinal disturbances, bronchospasm, and atrioventricular (AV) block.[5]

Ivabradine is a specific and novel heart rate lowering agent which is If channel blocker and a selective inhibitor of the pacemaker If current in the SA node. Ivabradine reduces the slope of diastolic depolarization in these cells and lowers the heart rate at rest and during exercise.[6] It has been recently approved as an alternate drug 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.[3] Ivabradine is EMA approved for treating stable angina and heart failure in patients in whom β blockers are not tolerated or are insufficiently effective in reducing heart rate and FDA-approved only for the treatment of heart failure.[7]

However, significant data suggesting the superiority of ivabradine over β blockers are lacking in Indians. Hence, this study was undertaken to evaluate and compare the antianginal efficacy and safety of ivabradine versus metoprolol in patients with coronary artery disease prospectively in terms of heart rate reduction, improvement in ejection fraction, improvement in Canadian class of angina grading, reduction in consumption of nitroglycerine and decrease in number of angina attacks per week.

MATERIALS AND METHODS

This study was a prospective, observational and a comparative study conducted for a period of 3 months from July 2019 to September 2019. After obtaining permission from Institutional Ethics Committee (IEC), the study was carried out at Department of Cardiology (OPD & IPD) of our tertiary care teaching hospital. A written informed consent was obtained from the patients after explaining the nature and purpose of the study.

Selection Criteria

Patients of either gender aged between >18 to <70 years, diagnosed with coronary artery disease and heart rate ≥70 beats per minute in sinus rhythm were included in the study. Patients with history of hypotension, syncope, blood pressure <90/50 mmHg, recent or acute attack of myocardial infarction, evidence of heart block, marked anaemia (Hb<8g/dl), asymptomatic patients, pregnancy and lactation, known hypersensitivity to study drugs, taking drugs with enzyme inducing and inhibiting properties, history of revascularisation, end stage disease like liver disease, cancer, respiratory disease and renal disease and other major cardiac diseases like congenital heart disease, valvular heart disease, cardiomyopathies and peripheral vascular disease were excluded from the study.

Study Procedure

Patients who met the selection criteria were enrolled in the study. Patients were then grouped into two groups; Group 1: -received Ivabradine (5mg) and Group 2: - received Metoprolol (50mg). According to their clinical symptoms and signs, Canadian class of angina grading was assessed. Also, their baseline investigation parameters like BP, Hb, TLC, DC, ESR, FBS, serum urea, creatinine, lipid profile, serum electrolytes, LFT values was recorded in a case record form. ECG, ECHO was done to assess baseline heart rate and ejection fraction. The patients were then followed up for two consecutive visits at 1-month interval (30, 60 days) and specific investigations like BP, ECG, ECHO, Canadian class of angina grading,

no of angina attacks and no of nitroglycerine tablets used per week were repeated at every visit. Any adverse event reported by the subject or noted by the clinicians during each follow up visit was recorded.

Statistical Analysis:
Data were analysed using Graph pad prism version 6. Baseline characteristics of the study patients were tabulated by descriptive statistics (mean and standard deviation) and the quantitative data were analysed by ANOVA and Student t test. The adverse drug reactions were tabulated and expressed in percentage.

RESULTS:

Table 1: Baseline Characteristics

Baseline parameters		Tab Metoprolol (n=30)	Tab Ivabradine (n=30)
Age (years)		58.16±9.20	59.23±9.03
Gender (n)		M=26 F=4	M=21 F=9
BP (mmHg)	SBP	121.66±12.34	119.66±15.38
	DBP	81±8.03	78.33±9.33
HR (bpm)		90.47±9.46	89.07±10.9
Ejection fraction (%)		41.5±5.32	42.66±5.9
Canadian cardiovascular class (n)		1 2 3 4 0 10 11 9	1 2 3 4 1 10 13 6
Left ventricular hypertrophy (n)		16	13
Fasting blood sugar (gm%)		129.93±45.42	154.06±76.23
Serum Na+ (meq/L)		135.16±3.24	134.66±3.76
Serum K+ (meq/L)		3.74±0.53	3.55±0.34
Lipid profile (mg/dl)	HDL-C	44.03±10.81	39.93±9.01
	LDL-C	119.8±25.97	110.73±34.34
	Total Cholesterol	278.9±38.9	266.63±45.57
	VLDL-C	27.16±16.52	28.73±8.66
	TG	167.06±87.16	166.4±48.85

Data expressed as Mean±SD

Table 1 shows that the mean age of presentation was almost similar in both the drug groups and both groups showed male predominance in our study. The mean fasting blood glucose level was higher in ivabradine group compared to metoprolol. There was hypercholesterolemia in both the groups.

Table-2: Changes In Ejection Fraction And Heart Rate Among Patients Receiving Metoprolol And Ivabradine

PARAMETER	TIME POINT	METOPROLOL	IVABRADINE
Ejection Fraction	Baseline	41.50±0.97	42.67±1.09
	1 month	42.73±0.76	46.33±0.50***
	2 months	45.33±0.72##	52.37±0.33***###
Heart Rate	Baseline	90.47±1.75	89.07±1.99
	1 month	84.80±0.91	82.58±1.02
	2 months	77.53±0.86###	75.17±0.40*,###

(Data expressed as Mean±SEM, analysed by unpaired t test. * is p value <0.05,*** is p value<0.001, * is p value comparison between ivabradine and metoprolol. ##is p value <0.01,###is p value <0.001, # is p value comparison between baseline and 2nd follow up)

Table-2 shows changes in ejection fraction and heart rate among both groups. From the table, it was seen that there was significant increase in ejection fraction from baseline to 2nd follow up in both ivabradine and metoprolol group. Also, Ivabradine showed significant improvement in ejection fraction between 1st and 2nd month follow up visit. There was significant reduction in heart rate with ivabradine at 2nd follow up visit when compared to metoprolol. Also, the heart rate was significantly decreased from baseline to 2 months follow up period in both the groups.

Table 3 showed that at baseline, 9 patients in metoprolol group and 6 patients in ivabradine group were in class 4 of CCS angina class. But, at 2nd follow up, no patients were in class 4 from both the group. In the ivabradine group, 73.33% patients were in class 1 where as in metoprolol group 60% patients were in class 1 at the end of the study. This showed that, treatment with ivabradine has more improvement in CCS grading of angina than treatment with metoprolol.

Table 3: Improvement In Canadian Cardiovascular Society Grading Of Angina In Both The Groups

Drug	Time point	CCS Class Of Angina Grade			
		1	2	3	4
Metoprolol (n=30)	Baseline	0	10 (33.33%)	11 (36.66%)	9 (30%)
	1 month	15 (50%)	9 (30%)	3 (10%)	3 (10%)
	2 months	18 (60%)	11 (36.66%)	1 (3.33%)	0
Ivabradine (n=30)	Baseline	1 (3.33%)	10 (33.33%)	13 (43.33%)	6 (20%)
	1 month	8 (26.66%)	22 (73.33%)	0	0
	2 months	22 (73.33%)	8 (26.66%)	0	0

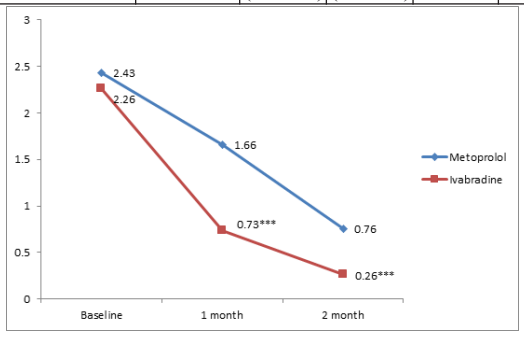

Figure 1: Reduction In No.of Angina Attacks/week In Both The Groups

The above figure showed that there was significant reduction in no.of angina attacks in both the groups at both the follow up visits but reduction is significantly higher with ivabradine than with metoprolol.

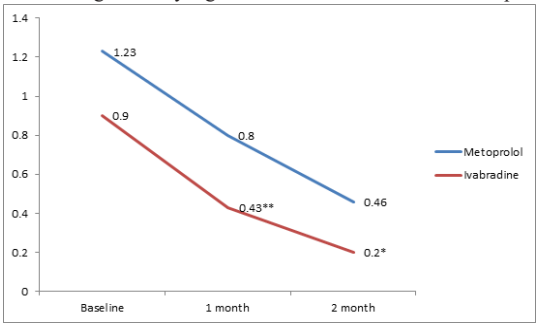

Figure 2 : Reduction In No.of Nitroglycerine Tablets Used /week In Both The Groups

The reduction of angina events leads to reduction in no.of nitroglycerine tablets consumed and the above figure showed that the no of nitroglycerine tablet used was significantly less with ivabradine than with metoprolol.

DISCUSSION:

Coronary artery disease is the leading cause of morbidity and mortality world wide.[8] Heart rate is a major determinant of cardiac output, myocardial oxygen demand and coronary blood flow. Increased resting heart rate is the most relevant risk factor for CAD and heart failure. Pharmacotherapy for IHD is to reduce the no.of angina attacks by reducing the resting heart rate. There are evidences that has suggested that many patients maintain a resting heart rate ≥ 70 beats/min despite treatment with beta blockers.[9]

Conventional anti angina drugs like CCBs and also K+ channel openers have undesirable negative inotropic activity. So, a better agent is needed which will reduce the heart rate without having negative inotropic effect. In recent years, a novel drug i.e. ivabradine has been introduced into clinical practice in CAD which selectively reduces the heart rate without producing negative inotropic effect.

The mean age of the subjects in our study in both the groups were 58.7 years. Similarly, a prospective study conducted by Jousilahti et al concluded that in both the gender groups, the CHD risk was highest in

the older age group (50-69 years).[10] It signifies that ageing is an important non modifiable risk factor for IHD. In the current study, the majority of the study subjects were males (78.3%) which is similar to study done by Elavarasi et al where the male prevalence was 76%. This showed that males are more prone for IHD compared to women.[11]

In our study, ivabradine reduced the mean heart rate from 89.07 bpm to 75.17 bpm whereas metoprolol reduced it from 90.47 bpm to 77.53 bpm over the same time period. The reduction in heart rate was significant in ivabradine compared to metoprolol at 2 months follow up. In a study done by Gurrala et al, it was found that ivabradine group had more reduction in HR compared to metoprolol but the decrease in HR was not statistically significant.[12] Similarly, in the BEAUTIFUL trial which evaluated ivabradine for improving cardiovascular outcomes in coronary patients , ivabradine reduced the mean heart rate (71.6bpm to 61bpm) in one month.[13] While comparing the heart rate in both the groups at different time points, it was found that the reduction in heart rate was significant in both the groups at 2 month follow up period when compared to baseline.

In the current study, we evaluated the increase in ejection fraction in both the groups and found that both the groups had significant increase in ejection fraction at 1month and 2 months follow up period but ivabradine showed better improvement in ejection fraction (52.37%) when compared to baseline (42.67%). In a previous study done by Fasullo et al where they compared ivabradine and metoprolol in patients with reperfused AMI, they found that in metoprolol group the EF was increased by 4.7% from baseline and in ivabradine group the EF was increased by 9.9% when compared to baseline.[14] This shows that ivabradine is also more effective in increasing the ejection fraction in CAD patients.

In our study, we found that the no.of angina attack/week was decreased significantly with ivabradine (2.26/week to 0.26/week) compared to metoprolol (2.43/week to 0.76/week) at both the follow periods. This finding is in line with study done by Tardif et al.[15] This was mainly related to reduction in heart rate, however ivabradine seems to have other properties also beyond heart rate decrease. In experimental model, the administration of ivabradine increases capillary density and improves cardiac angiogenesis in the myocardium after an infarction.[16] In addition, ivabradine seems to improve the coronary collateral circulation in patients with chronic stable CAD, an effect that influences ischemia to the same degree as HR reduction.[17]

In our study, the reduction of angina events led to reduction in no.of nitroglycerine tablets consumed by the patients and it was found that there was significant reduction in no.of nitroglycerine tablets consumption in ivabradine group compared to metoprolol group in both the follow up visits. This is mainly due to more reduction in no.of angina attacks with ivabradine than with metoprolol. This finding concurs with that of a study done by Tardif et al.[15]

In the current study, the morbidity was assessed in terms of CCS angina class status. At baseline, 9 patients in metoprolol group and 6 patients in ivabradine group were in class 4 of CCS angina class. But, at 2 months follow up, no patients were in class 4 from both the groups. In ivabradine group, 77.33% patients were in class 1 where as in metoprolol group 60% patients were in class 1 at 2 months follow up. This showed that, treatment with ivabradine has more improvement in CCS grading of angina than treatment with metoprolol. This finding is different from the finding of Gurrala et al where the percentage of patients in class 1 were same in both the groups (73.3%).[12]

Thus, it can be postulated that ivabradine leads to better heart rate reduction, better improvement in ejection fraction, improvement in CCC angina class and reduction in number of angina attacks/week and also reduction in number of nitroglycerine tablets used by the patients when compared to metoprolol.

This study has some limitation also like small sample size and short follow up.

CONCLUSION:

Based on the results, it may be concluded that ivabradine is as safe and more effective as compared to metoprolol in preventing and treating further angina attacks in patients with coronary artery disease by reducing heart rate and increasing the ejection fraction.

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