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Original Research Article

Ivabradine in Patients with Ischemic Heart Disease - A Prospective, Longitudinal, Comparative Study to Metoprolol

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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 to metoprolol in patients with CAD.

Methods: A prospective, longitudinal, comparative study was carried out in the Department of Cardiology of our hospital. 60 patients diagnosed with CAD were divided in to 2 treatment groups: Group 1 and 2 received Ivabradine(5mg/day) and Metoprolol(50mg/day) respectively. Patients were assessed for HR, Ejection fraction (EF), Canadian cardiovascular society (CCS) class of angina, QOL scores. Two follow ups were done at 90, 180 days. Long term QOL (EQVAS) evaluated compared statistically.

Results: Ivabradine reduced HR from 89.07±1.99 to 75.17±0.40 bpm and metoprolol from 90.47±1.75 to 77.53±0.86bpm, EF from 42.67± 1.09% to 52.37± 0.33%. Both groups showed significant but comparable improvement in CCS class of angina and EQ-5D-3L dimensions at 6 months. Over longer term (18 months) statistically superior significance in Ivabradine group in EQVAS (p.02). Also there was significant 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

Ischemic heart disease 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] Ischemia has major negative

impact on health-related quality of life (QoL) because of pain, limited exercise tolerance, and poor general health status. [2,3] Angina 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. [4] Angina typically 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 that is again compromised with increase in heart rate. Heart rate is an important contributor to the pathophysiology of coronary artery disease and also heart failure. [5,6] A high heart rate induces myocardial ischemia as it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole during which myocardial perfusion occurs. [6] So reduction in heart rate with drugs comes with observable outcome in myocardial ischemia and QOL.

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. [7]

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. It reduces the slope of diastolic depolarization in these cells and lowers the heart rate at rest and during exercise with no interference to cardiac contractility and intracardiac conductance. [8] 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. [5] 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. [9]

However, significant data suggesting the superiority of ivabradine over β blockers are lacking in Indians. Moreover, long term safely outcome of ivabradine in patients with CAD without clinical HF was debated. [10] Hence, this study was undertaken to evaluate and compare the antianginal efficacy and safety of ivabradine to 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. We have also evaluated the quality of life (QOL) of ischemic patients with heart rate reduction by the drugs on a longer time frame.

Materials and Methods

This study was a prospective longitudinal comparative study conducted for a period of 6 months from July 2019 to December 2019 with a longer quality of life follow up of 18 months. 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 randomized into two groups; Group 1: -received ivabradine (5mg once daily) and Group 2: -received metoprolol (50mg daily). Both the groups were initially evaluated according to their clinical symptoms and signs, Canadian class of angina grading. Baseline investigations like hematologic and biochemical parameters (Hb, TLC, DC, ESR, FBS, serum urea, creatinine, lipid profile, serum electrolytes, LFT) were recorded in a case record form. Baseline hemodynamic parameters and ECG, ECHO was done to assess baseline heart rate and ejection fraction. The patients were then followed up for two consecutive visits at 3-month interval (90, 180 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. QOL was assessed using EQ-3D-5L questionnaire [11] at baseline and at end of 6 months of treatment for each group. In addition, patients were followed up for a mean period of 18 months for long term subjective and objective outcomes.

Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows version 26 (published in 2019). [12] Qualitative data were expressed in percentage and continuous data were expressed in mean, standard deviation (SD) and standard error of mean (SEM). Data were analysed using paired, unpaired t tests, ANOVA for parametric data. For non-parametric data like scores and non-normally distributed data were analysed using tests like Wilcoxon signed rank test for related data and Mann Whitney's test for paired data. Graphs charts and tables were constructed with SPSS and Microsoft excel and word. Level of significance declared if p-value was <0.05 (p<.005= high significance).

Results

Among 60 patients, 78.3% (n=57) were male and 21.7% (n=13) were female. Minimum age recorded as 42 years with maximum of 62 years. Mean age was 58.69±1.47 years. Table 1 shows baseline characteristics of both the groups. The mean age of presentation was almost similar in both the drug groups and both groups showed statistical comparability with no significance (p>.05).

Table 1: Baseline characteristics of both treatment groups

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)		I II III IV 10 7 10 3	I II III IV 12 3 6 9

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, both the group showed statistical comparability (p>.05)			

Table 2 shows changes in ejection fraction and heart rate among both groups. From the table, it was seen that there was significant improvement in ejection fraction and HR from baseline to 6 months in both treatment group (p<.001). Also, Ivabradine showed significant increase in ejection fraction at the end of 3rd and 6th months (p<.05). There was significant reduction in heart rate with ivabradine at 6 months when compared to metoprolol (*p=.04*).

Table 2: Changes in ejection fraction and heart rate among patients of both treatment groups

PARAMETER	TIME POINT	METOPROLOL	IVABRADINE
Ejection Fraction	Baseline	41.50±0.97	42.67±1.09
	3 months	42.73±0.76	46.33±0.50*
	6 months	45.33±0.72##	52.37±0.33*,###
Heart Rate	Baseline	90.47±1.75	89.07±1.99
	3 months	84.80±0.91	82.58±1.02
	6 months	77.53±0.86###	75.17±0.40*,###
Ejection fraction expressed in percentages and HR in beats per minutes. data expressed as Mean±SEM, analysed by unpaired t test. * is significance (intergroup comparison) p value <0.05; # is p value (baseline vs treatment) <0.05 ## is p value <0.01, ### is p value <0.001			

Fig-1 marked improvement in CCS classification (p=.008 for iv a and 0.022 for beta group; Wilcoxon signed Rank Test), but on intergroup comparison (Mann Whitney U test) both the groups were comparable (*p=.08*). Increased frequency of class I and II (56.6 to 83.3% and 50% to 66.7%) with decrease in class III and class IV participants (43.4 to 16.7% and 50% to 33.3%) was evident in group 1 and group 2 respectively.

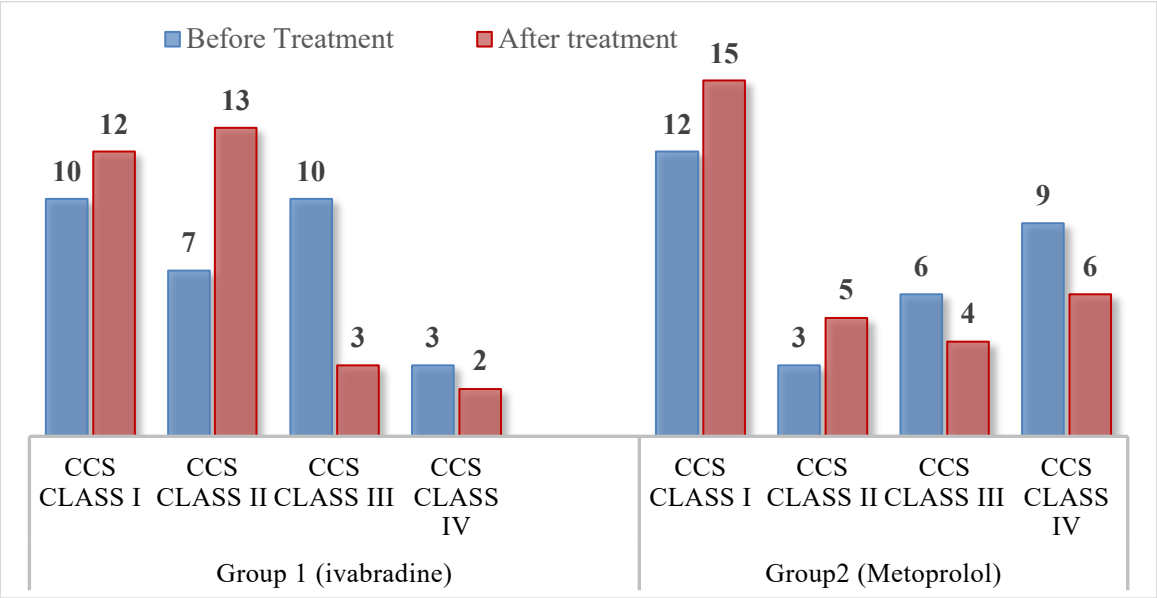

Figure 1: Improvement in Canadian cardiovascular society grading of angina in both the groups

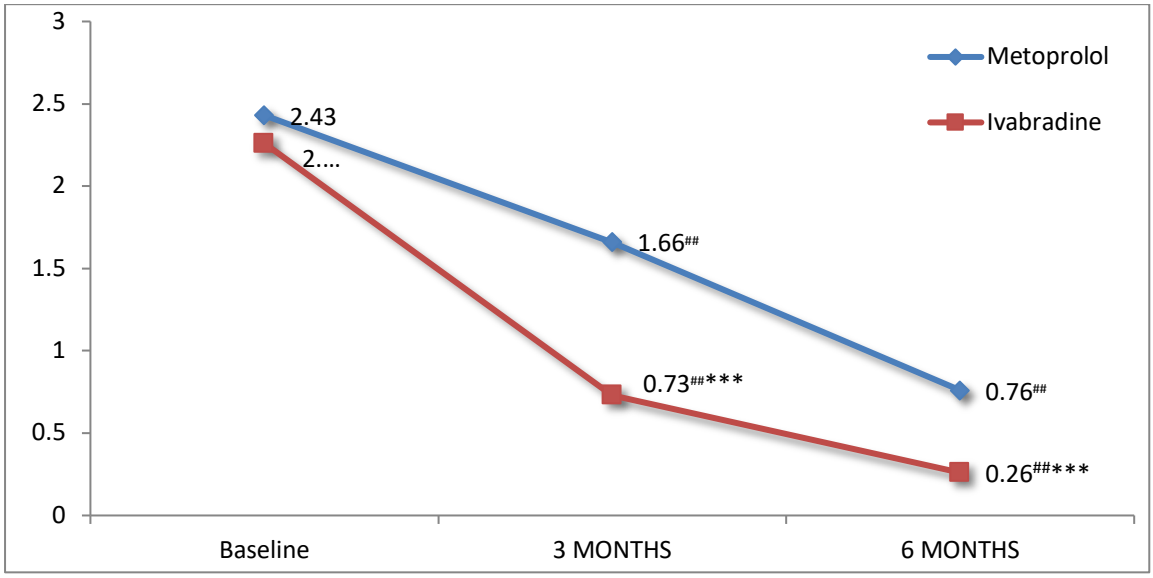

Figure 2: Reduction in number of angina attacks/week in both the groups
*** significance (intergroup comparison) p<0.05, *** very high significance p value<0.001;# p value (baseline vs treatment) <0.05 ## is p value <0.01;### is p value <0.001**

Figure 2 showed that there was significant reduction in episodes of angina attacks in both the groups at both the follow up visits but reduction was significantly highly significant with ivabradine than with metoprolol (p<.001).The reduction of angina events leads to reduction in nitroglycerine tablets consumed. Figure 3 showed that the no of nitroglycerine tablet used was significantly less with ivabradine than with metoprolol (*p<.05).

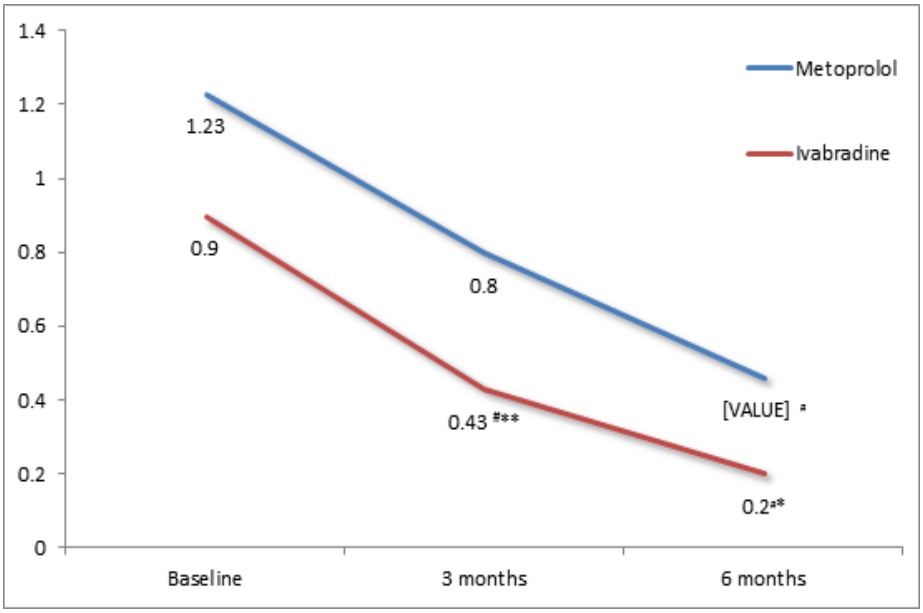

Figure 3 : Reduction in numbers of nitroglycerine tablets used /week in both the groups * significance (intergroup comparison) p<0.05, * very high significance p value<0.001; # p value (baseline vs treatment) <0.05 ## is p value <0.01,### is p value <0.001**

QOL profile:

According to the EQ-5D-3Lquestionnaire, from baseline to 6 months changes in scores were highly significant (*p<.001*, Wilcoxon Signed Rank Test) for all 5 dimensions for both the groups as depicted in table 6. However, across 2 groups (I vs B) there was no significant differences (p<.05) after treatment for 6 months.

Table 3: Difference from intergroup and intragroup scoring in EQ-5D-3L questionnaire from baseline to after drug treatment

5D	Mobility	Self-care	Usual activities	Pain discomfort	Anxiety depression
Ivabradine Group (p)	0.008##	<.001###	<.001###	<.001###	<.001###
Metoprolol group (p)	0.005##	.004##	.001##	<0.001###	0.001##
Intergroup (p)	0.79	0.09	0.301	0.854	0.94
# intragroup significance @ p<.05, ##high significance p<.01, ###very high significance @p<.001 intra group significance Wilcoxon signed rank test; intergroup significance Mann-Whitney U Test					

Self-estimated health status score (EQVAS) at baseline had a mean score of 61.57 (SEM 1.52)and 66.07 (1.49) for Metoprolol and Ivabradine group respectively. After 6 months' treatment, EQVAS mean was 73.43 (SEM 1.71)and 76.43 (1.68) for metoprolol and Ivabradine treated groups respectively. Over 6 months, improvement for both the groups were statistically highly significant (*p<.001*). but comparable intergroup (*p=0.236).*

After a median interval of 18 months (18.3±1.2 months) EQVAS scores were re-evaluated for both the groups. Improvement of EQVAS score for both the groups were highly significant (*P<.001*). Ivabradine group showed statistically significant improvement (*p=.02)* compared to metoprolol. Figure 4 depicts the changes in EQVAS scores over time.

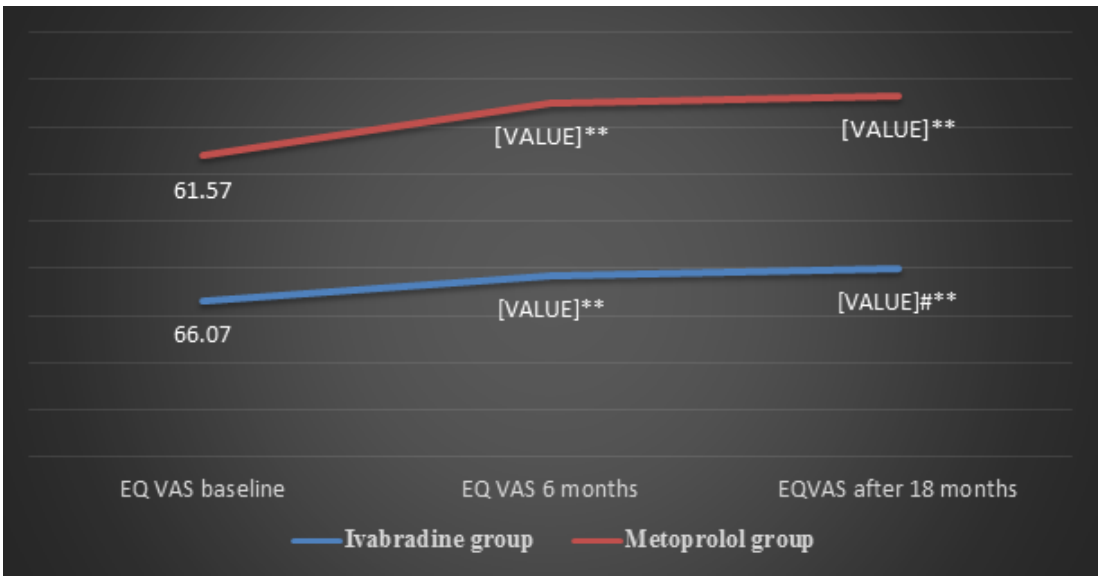

Figure 4: Groupwise distribution of Mean EQVAS scores at different time frames. intragroup significance from baseline (p<.001), intergroup significance# (p<.05), here p=.02**

Safety:

8 patients of metoprolol group complained of weakness and 5 of them had sinus bradycardia and 4 had headache. 2 patients of Ivabradine group complained of bright light in visual field and responded with temporary stoppage of Ivabradine. Headache and weakness was also seen in Ivabradine group with 2 patients each. No change in QT or other ECG changes noted in Ivabradine group.

Discussion

Coronary artery disease is the leading cause of morbidity and mortality worldwide. [1] Heart rate is a major determinant and independent risk factor of ischemic heart disease and heart failure. [3] reducing HR is logical and practicable with conventional beta blockers. But, there are evidences that has suggested that many patients maintain a resting heart rate ≥ 70 beats/min despite treatment with beta blockers. [13] Conventional anti angina drugs like CCBs and also K+ channel openers have undesirable negative inotropic activity. [8] So, 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.

In the present study, the mean age of the subjects in our study in both the groups were 58.69±1.47 years. Similarly, to a prospective study conducted by Jousilahti et althat concluded CHD risk was highest in the older age group (50-69 years). [14] 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%) similar to study by Elavarasi et al with male prevalence was 76%. [15] Males are more prone for IHD compared to women.

In our study, both Ivabradine and Metoprolol reduced the mean heart rate significantly from 89.07±1.99 to 75.17±0.40bpm and 90.47±1.75 to 77.53±0.86 bpm respectively over the 6 months' time period. Reduction of HR in the former group was statistically superior to metoprolol group (*p=0.04).* 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. [16] 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 12 months. [17]

In the current study, the increase in ejection fraction(EF) in both the groups were highly significant from baseline to 6 months (p<.001) and ivabradine showed statistical superiority in EF 52.37± 0.33% from 42.67± 1.09% at baseline (p=.02). 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. [5] This shows that ivabradine is also more effective in increasing the ejection fraction in CAD patients.

In our study, we found that the episodes of angina attack/week were decreased significantly with ivabradine (2.26 to 0.26/week) compared to metoprolol (2.43 to 0.76/week) at both the follow periods (p<.001). This finding is in line with study done by Tardif et al. [18] 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. [19] 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. [20] The reduction of angina events led to significant reduction in nitroglycerine tablet consumption in ivabradine group compared to metoprolol group in both the follow up visits (p<.05). This finding concurs with that of study done by Tardif et al. [18]

Marked improvement were seen in CCS angina classification from baseline for both the groups (p=.008 for iva and 0.022 for beta group), but on intergroup comparison both the groups were comparable (*p=.08*). Increased frequency of class I and II (56.6 to 83.3% and 50% to 66.7%) with decrease in class III and class IV participants (43.4 to 16.7% and 50% to 33.3%) was evident in ivabradine and metoprolol groups respectively. That reflects subjective improvement with heart rate reduction with drug treatment. Gurrala et al documented comparable results in both the groups. [16]

Quality of life study adds a new dimension to the study. QOL studies are limited globally. EQ-5D-3L questionnaire developed by EuroQoL group valid and widely in use due to its simplicity to administer, score and interpret. Index based scores determine 5 dimensions like mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression, each with three levels of response or severity (no problems, some problems, or extreme problems). [11] In addition, the visual analogue scale (VAS) component of the EQ-5D enables the patient to place their current health state on a range from 0 (worst imaginable health state) to 100 (best imaginable health state). In our study, changes in scores were highly significant (*p<.001*) for all 5 dimensions for both the groups from baseline to 6 months. However, on intergroup comparison there was no significant differences (p<.05) after treatment for 6 months.

In terms of self-estimated health status score (EQVAS), over 6 months, improvement for both the groups were statistically highly significant (*p<0.001*), but comparable intergroup (*p=0.236).* But after a median interval of 18 months (18.3±1.2 months) EQVAS scores for both the groups were highly significant (mean 75.68 median 80 SEM 1.16). Ivabradine group showed statistically significant improvement (*p=.02)* compared to metoprolol at median interval of 18 months of treatment. Similar conclusions that treatment with ivabradine seems to be associated with improvements in self-reported QoL related to angina pectoris, notably in terms of angina frequency and disease perception inferred by Tendera et al [21] (sub study of SIGNIFY trial [10] using SAQ questionnaire [22]).

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. [23] Long term improvement in QOL with Ivabradine superior to metoprolol is a promising finding. Moreover, safety data showed no atrial fibrillation or other ECG alteration other than bradycardia contrary to the findings of SIGNIFY trial. [10] Limitations like small sample size and short follow up were noted in present.

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. Long term QOL benefit adds to consider ivabradine a better choice at least in place of beta blockers in selected cases.

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