ORIGINAL ARTICLES

EFFICACY OF IVABRADINE, METOPROLOL ALONE VS IVABRADINE PLUS METOPROLOL (COMBINATION) FOR HEART RATE REDUCTION AND HEART RATE VARIABILITY DURING COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY: A RANDOMIZED CONTROLLED TRIAL

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ABSRTACT

Objective: To establish the efficacy of Ivabradine, Metoprolol alone vs Ivabradine plus Metoprolol for the heart rate reduction in patients undergoing computed tomography coronary angiography.

Study Design: Randomized controlled trial.

Place and Duration of Study: Armed Forces Institute of Cardiology & National Institute of Heart Disease, Rawalpindi, from Oct 2017 to Jan 2018.

Material and Methods: Patients undergoing first CTCA angiography meeting inclusion criteria with heart rates more than 80 beats/min were included. Patients were randomized into three groups using computer generated random tables. Arm A was administered Ivabradibe plus placebo, Arm B was administered Metoprolol plus plecebo while Arm C was administered Ivabradine plus Metoprolol one hour before the scan. All the groups had scans under strictly similar conditions. Heart rate before and during scan along with heart rate variability were recorded.

Results: A total of 165 patients were included in the study, 55 patients in each group. Mean age of patients was 53.5 ± 0.5 years. One hundred and seven (64.8%) were males while patients 58 (35.2%) were females. Risk factor profile was almost similar in all the groups. Heart rate reduction in Arm A was 18.3 ± 3.8, in Arm B was 12.6 ± 5.8 and in Arm C was 24 ± 3.0 (p=0.02). Heart rate variability in Arm A was 3.2, in Arm B was 4.0 and in Arm C was 1.8 (p=0.001). Arm C had significantly lower heart rate and significantly less heart rate variability followed by Arm A then Arm B.

Conclusion: Ivabradine is an established safe and effective heart rate-reducing agent in patients undergoing CTCA, particularly in those patients, who cannot tolerate beta-blockers or calcium-channel blockers due to their side effects.

Keywords: Computed tomography coronary angiography, Heart rate, Heart rate variability, Ivabradine, Metoprolol.

INTRODUCTION

Stable heart rate is the foremost pre-requisite for the achievement of excellent image quality and the diagnostic accuracy with computed tomography coronary angiography (CTCA). Therefore, to reduce the coronary artery motion artifacts and enhance the image quality, an heart rate of 60-65 beats per minutes is essential, while an increase in heart rate is related with nearly linear deterioration of image quality and diagnostic accuracy[1]. β-Blockers and calcium channel blockers are the basic drugs which are utilize for the heart rate reduction, but their negative inotropic and dromotropic effects restrict their utilization in patients with hypotension, asthma, and peripheral vascular disease as some patients cannot bear the side effects[2]. The pacemaker current channel (If) is a hyperpolarization activated cyclic nucleotide gated channel, and Ivabradine is the first sinoatrial node If current inhibitor which is unusual from the conventional heart rate reducing agents. Ivabradine decreases the heart rate without influencing the cardiac contractility, ventricular repolarization, blood pressure, or

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atrioventricular conduction[3]. Ivabradine is undoubtedly a promising attractive substitute for inappropriate sinus tachycardia, stable angina, heart failure, and other cardiovascular diseases and it has beneficial implications for future clinical utilization[4].

Many studies[2,5,6] have shown that Ivabradine plays an significant part in the heart rate reduction in CTCA, specially with regard to the quantification of the efficacy of pre-treatment with Ivabradine before CTCA.

There is no contemporary data documenting the comparison of effect of Ivabradine and Metoprolol (in combination and alone) on heart rate reduction and heart rate variability in patients undergoing CT Angiography in AFIC & NIHD, Rawalpindi. Therefore we examined whether there was a significant difference between two drugs via randomized control trial.

MATERIAL AND METHODS

It was an allocation concealed triple blind (Patient-Investigator-Statistician) randomized control trial. Study was conducted at Cardiac Scan Department AFIC & NIHD, Rawalpindi. All the patients of both genders, with heart rates more than 80 beats/min while at rest and age between 25 to 65 years, undergoing first CTCA scan for the probable diagnosis of coronary artery disease were enrolled in the study. Data was collected using history & procedure details Performa. Patients with the previous history of CABG, PTCA/Stenting, with contraindications to beta blockers, patients with arrhythmia, allergy to iodinated contrast, already using beta blockers, anxiolytics, sedative and hypnotics, known cases of ischemic heart disease (IHD) and those patients who already had a CTCA scans were excluded. Patients who underwent scans in emergency were also excluded.

Patients were recruited into three groups using randomization technique. Randomization was done through computer generated random tables using list of the patients undergoing CTCA. Sample size was calculated using Harvard Sample size Calculator. Sample size was 165 patients (55 study participants in each group).

Arm A was administered tablet Ivabradine 5mg (tab Ivatab by Nabiqasim Industries®) plus a plecebo, Arm B was administered tablet metoprolol 100mg ½ tablet (tab Mepressor by Novartis®) plus a placebo and Arm C was administered tablet Mepressor 100 mg ½ tablet plus tablet Ivabradine 5mg one hour before the scan. All the patients were recruited after the written informed consent and confidentiality of the data was maintained.

The variables for this study included heart rate of the patients before the test and heart rate during the test and heart rate variability during the test. Heart rates were recorded by doctor for one complete minute just before the test while patients were still in the waiting room and during the test on the scanning table just after the Calcium scoring. All scans were performed on Somatom Definition DSCT scanner from Siemens using same scan protocols and nonionic iodinated contrast agent Iopromide (Ultravist-370 7 by Bayer schering pharma).

Patients were blinded to the medications; similarly doctor taking the history and recording the heart rate was also blinded to the identity of patient groups. Data of the sample study was of quantitative nature and sample size was enough to make distribution normal. To exclude other factors contributing to heart rate changes consenting doctor, paramedic administering the medication and doctors recording the heart rate were the same for all patients and similarly technicians carrying out the scans, rate auditory instructions and doctors supervising the scan were also the same. All the Patients waited for at least one hour (range 1-3 hours) in the waiting area of cardiac scan department. All the scans were carried out by appointment and done in the morning time before noon and as outdoor procedures. Heart rate variability (HRV) was defined as the standard deviation of the mean heart rate during CT coronary angiography.

Data entry and analysis was done by using SPSS (version 21.0). Chi-square test was used to the qualitative variables while ANOVA (Analysis of variance) was used for quantitative variables between three groups. A *p*-value<0.05 was taken as significant.

RESULTS

Total 165 patients were enrolled in the study. Table-I illustrates patient baseline characteristics.

Table-I: Patient baseline characteristics.

Characte-ristics	Total Patients (n=165)	Arm A (Ivabradine + Placebo) (n=55)	Arm B (Metoprolol + Placebo) (n=55)	Arm C Ivabradine + Metoprolol) (n=55)	*p*-value
Age Mean ± SD	53.5 ± 0.5 years	49.3 ± 2.8 years	51.7 ± 10.3 years	52.9 ± 6.6 years	0.671
Gender Male Female	107 (64.8%) 58 (35.2%)	21 (19.6%) 24 (41.4%)	35 (59.0%) 34 (58.6%)	35 (59.0%) 20 (18.0%)	0.025

Table-II: Association of Risk factor profile of three groups.

Risk Factor	Arm A n (%)	Arm B n (%)	Arm C n (%)	*p*-value
Hypertension	22 (60.0%)	47 (85.5%)	36 (65.5%)	0.006
Diabetes Mellitus	11 (20.0%)	8 (14.5%)	27 (49.1%)	0.001
Smoking History	20 (36.4%)	11 (83.6%)	46 (83.6%)	<0.001
Hyperlipidemia	13 (23.6%)	5 (9.1%)	19 (34.5%)	0.042
Family History of IHD	12 (22.8%)	11 (20.0%)	9 (16.4%)	<0.001

Table-III: Reduction in heart rate and heart rate variability by medication groups.

Variables	Arm A	Arm B	Arm C	*p*-value
Heart Rate Variability (mean)	3.2	4.0	1.8	0.002
Reduction in Heart Rate (Mean ± SD)	18.3 ± 3.8 Beats/min	12.6 ± 5.5 Beats/min	24.4 ± 3.0 Beats/min	<0.001

Table-II shows risk factor profile of the three groups. Hypertension was most prevalent among risk factors 105 (63.6%) followed by smoking history 77 (46.6%) and diabetes mellitus 46 (27.8%). Table-III shows that the use of two drugs (i.e. Ivabradine and metoprolol) in combination significantly lowered the heart rate variability 1.8 and significantly lowered the heart rate as well with reduction of 24.4 ± 3.0 beats/min.

DISCUSSION

Ivabradibe is a potential choice for patients undergoing CTCA, particularly for the patients who cannot tolerate beta blockers due to the side effects[7]. Ivabradine had no marked effect on either systolic or diastolic blood pressure[8]. The patient groups comprized of a well-defined patient population referred for their first diagnostic CTCA angiogram with the diagnosis of probable coronary artery disease. Risk factor profile was similar to reported earlier. Peak effect of both metoprolol and Ivabradine was achieved after an hour. All the treatment groups showed significant drop in the heart rate but the magnitude of was higher in Ivabradine alone group and was much bigger and statistically significant in case of Arm C. Ivabradine is an established safe and effective heart rate- reducing agent[9]. Ivabradine is a particular heart rate lowering agent that acts via selective and specific inhibition of the cardiac pacemaker If current, which controls the spontaneous diastolic depolarization in the sinus node and regulates the heart rate[10,11]. Its effects on the heart are particular to the sinus node, with no effect on intra atrial,

atrioventricular, or intraventricular conduction times, myocardial contractility, or ventricular repolarization[12-15]. Ma et al[16] reported that ivabradine enhance myocardial performance, left ventricular function and ventricular remodeling and even survival in rodent heart failure, including ventricular fibrillation, myocardial infarction, stable angina, and hypertension-induced cardiomyopathy[16]. Its side effects are uncommon and mainly limited to the dose related visual disturbances[10]. Hence, ivabradine is appropriate for large variety of patients, including those individuals for whom other heart rate lowering drugs might be contraindicated[1,13]. Beta-blockers are contrain-dicated in many conditions, despite the common use of beta-blockers before CTCA studies, it is quite common to have patients with heart rate continuously above the target range of 65 beats per minutes even though the use of oral as well as intravenous beta-blockers[13-15]. In this way, CTCA with oral ivabradine premedication is a practicable, safer, and better effective way to reduce the heart rate to generate images of diagnostically acceptable quality in nearly all coronary segments in comparison to beta-blockers.

CONCLUSION

Ivabradine is an established safe and effective heart rate reducing agent in patients undergoing CTCA, particularly in those patients, who cannot tolerate beta-blockers or calcium-blockers due to their side effects.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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