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The Efficacy of Ivabradine Alone, Metoprolol Alone and Combination of Ivabradine and Metoprolol in Reducing Heart Rate Among Patients Undergoing Computed Tomography Coronary Angiography

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Abstract
Objectives: to determine the efficacy of Ivabradine alone, Metoprolol alone and Combination of Ivabradine and Metoprolol in reducing heart rate among patients undergoing Computed Tomography Coronary Angiography (CTCA). **Methodology**: it was a randomized controlled trial comprised of 200 patients. Patients undergoing CTCA having heart rates greater than 80 bpm were divided into three groups. Group A was given Ivabradine and a placebo, Group B received Metoprolol and placebo while Group C was administered with Ivabradine and Metoprolol an hour prior to the scan. The scan was carried under similar situations. Heart rate and variability was recorded before and during the scan. **Results**: The mean heart rate variability and mean reduction in heart rate of Group A was 3.13±1.01 and 19.02±2.05 respectively. The mean heart rate variability and mean reduction in heart rate of Group B was 4.27±1.08 and 12.11±2.45 respectively. While, the mean heart rate variability and mean reduction in heart rate of Group C was 1.88±0.42 and 25.03±2.74 respectively. **Conclusion**: Ivabradine is an effective and safe drug for reducing heart rate in patients having CTCA, especially among patients who are unable to tolerate calcium channel blockers and beta blockers owing to their side effects.
Keywords: Ivabradine, Metoprolol, Computed tomography coronary angiography, heart rate reduction, heart rate variability.

Introduction

In order to obtain desirable image quality and accurate diagnosis through CTCA (Computed Tomography Coronary Angiography), the first and foremost requirement is stable heart rate [1]. A heart rate of 60-65 bpm is required to decrease the artifacts which result from coronary artery motion and to increase the quality of image as well [2]. Calcium channel blockers and B-blocker are the widely used drugs to reduce the heart rate [3]. Nevertheless, the negative ionotropic and dromotropic effects produced by these drugs restrain their usage among patients suffering from asthma, hypotension, and peripheral vascular disease [4].

A hyperpolarization cycle nucleotide gate channel is known as Pacemaker current channel. Ivabradine is a drug that inhibits this current channel, being unique from the rest of the heart rate decreasing agents [5]. Ivabradine has the ability to reduce the heart rate without producing any fluctuation in the ventricular repolarization, AV conduction, cardiac contractility, or blood pressure [6]. The drug seems to be a reliable alternative for cases like stable angina, sinus tachycardia, heart failure or similar diseases [7,8].

It has been established by various studies that Ivabradine has a substantial role in reducing the heart rate during CTCA especially in terms of determining the efficacy of before doing the CTCA[9,10]. There is no recent data available that compares the efficacy of Ivabradine with Metoprolol either alone or in combination, on reducing the heart rate and variability in heart rate among patients undergoing CTCA. Hence, the following study is composed to determine the difference between two drugs through a randomized controlled trial.

Methodology

The mode of study was triple blinded randomized controlled trial. The study took place at Bahawal Victoria Hospital,Bahawalpur. The participants of this study belonged to both genders, having heart rate greater than 80bpm at rest, age from 25 to 65 years, having their first CTCA for the diagnosis of coronary artery disease. Data collection was done with the help of history taking, examination and a detailed Performa.

Patients having prior history of PTCA/Stenting, CABG, contraindications to beta blockers, having arrythmia, allergic to iodine contrast media, already on beta blockers, sedative, anxiolytics or hypnotics, being known cases of IHD, and the ones already having CTCA scan were not included in the study. The process of randomization was done by a computer-generated program. Sample size was determined with the help of Harvard Sample size calculator. There were 68 patients in group A, 66 in group B and 66 in group C.

Group A was given tab Ivabradine 5mg with a placebo. Group B received tab Metoprolol 100mg half tablet

and a placebo. Group C was administered with Metoprolol 100mg and Ivabradine 5mg an hour before the CTCA was performed. Written informed consent was taken from each patient before the start of procedure. Heart rate of the patients before and during the test and heart rate variability during the test were considered the variables of the study. The calculation of heart rate was done by a doctor for one whole minute before the test and during the test just after the scoring for Calcium was done.

The procedure of scanning was done on "Somatom Definition DSCT scanner from Siemens". The same protocols were followed for each patient. Nonionic iodinated contrast agent Loperamide was used for each patient. Patients were unaware of the medications given to them (blinded), likewise the recording staff such as doctors and nurses were also blinded. Data was quantitative in nature and satisfactory sample size was present to make a normal distribution. In order to remove any other factor causing change in heart rate, the doctors (consenting and recording heart rate), paramedics giving the medications, technicians performing the scan, were same for all patients. The scans were performed in order of appointment and in the morning as outdoor procedures. Heart rate variability (HRV) was defined as "the standard deviation of the mean heart rate during CT coronary angiography".

Data analysis and entry was done with the help of SPSS (version 21.0). for qualitative data, Chi-square test was used while for quantitative data ANOVA test was applied. A p-value<0.05 was considered significant.

Results

Two hundred patients were included in this study, both genders. These patients were analyzed into three groups i.e. n=68 (Ivabradine +Placebo) Arm A, n=66 (Metoprolol +Placebo) Arm B and n=66 (Ivabradine + Metoprolol). The mean age of the Arm A, B and C patients was 48.26±2.35 years, 49.69±3.52 years and 51.45±2.73 respectively. Gender distribution of three groups were shown in table I. Age difference was statistically significant (p=0.000).

Hypertension, diabetes mellitus, smoking history, hyperlipidemia and family history of IHD of Group A was observed as n=46 (67.6%), n=17 (25%), n=27 (39.7%), n=17 (25%) and n=16 (23.5%) respectively. Hypertension, diabetes mellitus, smoking History, hyperlipidemia and family history of IHD of Group B was observed as n=55 (83.3%), n=11 (16.7%), n=51 (77.3%), n=7 (10.6%) and n=12 (18.2%) respectively. While, Hypertension, diabetes mellitus, smoking History, hyperlipidemia and family history of IHD of Group C was observed as n=50 (75.8%), n=33 (50%), n=55 (83.3%), n=29 (43.9%) and n=11 (16.7%) respectively. The differences were statistically significant for diabetes mellitus (p=0.000), smoking status (p=0.000), hyperlipidemia (p=0.000). (Table II).

The mean heart rate variability and mean reduction in heart rate of Group A was 3.13±1.01 and 19.02±2.05 respectively. The mean heart rate variability and mean reduction in heart rate of Group B was 4.27±1.08 and 12.11±2.45 respectively. While, the mean heart rate variability and mean reduction in heart rate of Group C was 1.88±0.42 and 25.03±2.74 respectively. The differences were statistically significant. P-value ≤0.05 is considered significant. (Table III).

Table. I

Demographic Characteristics among the groups

Variable	Arm A n=68	Arm B n=66	Arm C n=66	P-value
Age (years)	48.26±2.35	49.69±3.52	51.45±2.73	0.000
Gender				
Male	n=39 (57.4%)	n=46 (69.7%)	n=42 (63.6%)	0.332
Female	n=29 (42.6%)	n=20 (30.3%)	n=24 (36.4%)	

Table. II
Association of risk factors among the groups

Variable	Arm A n=68	Arm B n=66	Arm C n=66	P-value
Hypertension	n=46 (67.6%)	n=55 (83.3%)	n=50 (75.8%)	0.108
Diabetes mellitus	n=17 (25%)	n=11 (16.7%)	n=33 (50%)	0.000
Smoking History	n=27 (39.7%)	n=51 (77.3%)	n=55 (83.3%)	0.000
Hyperlipidemia	n=17 (25%)	n=7 (10.6%)	n=29 (43.9%)	0.000
Family history of IHD	n=16 (23.5%)	n=12 (18.2%)	n=11 (16.7%)	0.573

Table. III
Reduction in heart rate and heart rate variability

Variable	Arm A n=68	Arm B n=66	Arm C n=66	P-value
Heart rate variability	3.13±1.01	4.27±1.08	1.88±0.42	0.000
Reduction in heart rate	19.02±2.05	12.11±2.45	25.03±2.74	0.000

Discussion

Maffei E et al [11] evaluated the effect of various pharmacological intervention on CT-CA upon 560 patients having coronary artery disease. Six groups were made and group 1 being the one receiving no treatment, group 2 oral metoprolol, group 3 other drugs, group 4 IV atenolol while group 5 received IV atenolol along with nitrates. Heart rate, adverse effects of drugs and timing were recorded. All the drugs significantly reduced the heart rate. Group 4 drug, IV atenolol proved to be the best in terms of lowering the heart rate. Nitrates had no effect on heart rate. Time required for preparation of patient was most efficacious with group 4 and 5. It is believed that the use of pharmacologic interventions in patients having CT-CA is efficacious and safe. Better results can be achieved with IV beta blockers for reducing the heart rate and preparing the patients.

An attractive alternative for reduction of heart rate in order to prepare for CT-CA is Ivabradine in place of beta blockers, says Guaricci AI et al [12]. they conducted a study upon 123 patients, dividing them into two groups. One of them were given oral ivabradine for 5 days while the other received beta blockers. Heart rate and blood pressure were recorded before and during the CT-CA. and the target heart rate to be achieved was <65bpm. Target heart rate was achieved in 97% of patients using ivabradine. It was concluded that Ivabradine is "safe and effective" in achieving the target heart rate in more and more patients and in decreasing the requirement of additional administration of IV beta blocker for preparation of CT-CA.

"Ivabradine is the first specific heart rate-lowering agent" that has completed its clinical development for angina pectoris of stable nature [13]. Ivabradine is known for its selective current inhibition and reduction for heart rate at such concentrations that don't alter the other ionic currents. With the use of this drug, there is no negative ionotropic or lusitropic effect which preserves the ventricular contraction. The drug reduces the heart rate without altering any basic electrophysiological properties that are not related to heart rate. Patients that are suffering from left ventricular dysfunction, the drug decreases the resting heart rate without any change in contractility of myocardium. Hence pure reduction in heart rate can be obtained in clinical setting with the help of selective and specific I_f current inhibition.

Similar views are shared by Sulfi S et al [14]. Ivabradine is also the drug of choice that is being adapted widely for stable angina pectoris. It is the first drug to be specific for heart rate reduction. being selective for i(f) current, it reduces the heart rate at concentrations that does not affect other electrical activities of the heart. It has no ionotropic effects; hence it preserves the ventricular contractility. It exclusively lowers the heart rate and hence proves to be effective alternative to customary treatment for patients have stable angina.

Ivabradine was tested against metoprolol in patients with heart transplantation on left ventricular mass, heart rate and survival of patients by Rivinus R et al [15]. Out of 84, 44 patients received metoprolol while 40 patients were administered with ivabradine. Immediately after transplant, so significant difference was observed. However, significant results were shown by ivabradine two years after the transplant in the follow up. It was

seen that patients using ivabradine had markedly reduced heart rate i.e. 76.7 bpm and left ventricular mass was also reduced in these patients. Survival rate of these patients increased as well. Whereas metoprolol did reduce heart at 82 bpm but not more than ivabradine. It was observed that treating heart transplant patients with ivabradine not only reduces heart rate and left ventricular mass, but it also provided better survival in comparison to metoprolol succinate.

The comparison of ivabradine with metoprolol was also made in patients with acute inferior wall MI with regards to tolerability feasibility, and efficacy [16]. Group A comprising of 232 patients received ivabradine and the heart rate reduction was seen as 62.22±2.95 and group B also composed of 232 patients, received metoprolol and the rate of heart rate reduction was 62.53±3.59. In both these groups, the ejection fraction was seen to ameliorate. In terms of primary end points, no significant difference was seen among the two groups with regards to death, reinfarction and heart failure. It was established that Ivabradine is "equally effective and well tolerated"as metoprolol, in patients with acute inferior wall STEMI in order to reduce heart rate.

When Ivabradine was assessed for its single dose in patients being prepared for CTCA on long term calcium channel blockers already versus IV metoprolol, the obtained results were similar to the ones described above. Out of 120 patients, the 63 patients that received one single dose of ivabradine oral, the heart rate reduction was significantly higher than those 62 patients receiving IV Metoprolol. The side effects with ivabradine were lower as compared to metoprolol and the systolic and diastolic was not altered by Ivabradine. Hence single dose of ivabradine was declared safe and more effective than IV metoprolol for reduction of heart rate in patients using calcium channel blockers.

A randomized double blinded placebo-controlled trial was carried out by et al for testing the efficacy of IV bolus of Ivabradine in order to reduce heart rate before CTCA. 55% of the patients were able to achieve the target heart rate of <65 bpm. Mean heart rate at the time of CTCA was found to be 67 ± 10 beats/min with ivabradine. The procedural convenience score evaluated Ivabradine as "very good" in 79% of the patients. The radiation dose was also decreased in patients on ivabradine i.e. 13 ± 7 mSv. It was determined that IV bolus of ivabradine is helpful in obtaining earlier, safer and well sustained heart rate reduction during CTCA. It has better procedural convenience and less radiation exposure.

Similarly, when Pitchler P et al [19] and Tayyub F et al [20] compared ivabradine with metoprolol they found that they both produced the same results in terms of reducing heart rate but ivabradine offers better results with fewer adverse effects, hence It is more safe and effective in preparing the patients for CTCA.

Conclusion

Ivabradine is an effective and safe drug for reducing heart rate in patients having CTCA, especially among patients who are unable to tolerate calcium channel blockers and beta blockers owing to their side effects.

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