

A PROSPECTIVE STUDY ON COMPARATIVE EFFICACY BETWEEN IVABRADINE AND BETA-BLOCKERS IN INDIAN ACUTE CORONARY SYNDROME PATIENTS

PRADEEP BATTULA^{1*}, PRATHIMA REDDY B², POONAM L², HEMANTH KUMAR L², DIMPU SRI N²

¹Department of Pharmacy Practice, Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh, India. ²Department of Pharmacy Practice, Creative Educational Society's College of Pharmacy, Kurnool, Andhra Pradesh, India. Email: doctorbattulapradeep@gmail.com

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ABSTRACT

Objective: The main objective of this study was to assess the tolerability and efficacy between ivabradine and beta-blockers in acute coronary syndrome (ACS) patients with reduced ejection fraction and also assess the contraindications for beta-blockers.

Methods: A prospective observational study was conducted for duration of 6 months. The study population includes 100 patients in which Group-A – 50 and Group-B – 50. The subjects were selected according to inclusion and exclusion criteria. The patients were classified based on their symptoms in regards to normal breathing and varying degrees in shortness of breath using the New York Heart Association classification.

Results: The majority of the patients were highly affected in the age group between 55 and 64 (32%) years of age. The prevalence of ACS was high in rural (56%). Both drugs showed a decrease in the mean heart rate from 112.98±23.90 to 89.97±10.27 beats/min in Group-A and 99.6±20.44 to 86.76±13.14 beats/min in Group-B (p=0.24). The results obtained were clinically and statistically significant with standard p-value (p>0.05).

Conclusion: Ivabradine was equally effective as beta-blockers but it clinically was shown that it lowers heart rate with no negative inotropism.

Keywords: Acute coronary syndrome, Beta-blockers, Ivabradine, Heart rate, New York Heart Association.

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INTRODUCTION

A variety of clinical conditions from unstable angina to ST-elevation myocardial infarction (STEMI) consequent to myocardial ischemia called as acute coronary syndrome (ACS). Clinically severe chest pain is a hallmark symptom of ACS, which lasts for more than 15 min. Electrocardiogram and cardiac biomarkers such as troponins T/I or creatine phosphokinase-myocardial band are useful to decide about the type of ACS. The chance of rising coronary artery disease (CAD) in Indians is higher than Caucasian Americans, Chinese, and Japanese. It is also one of the highest reasons for death and burden causing disease in India and also all over the globe [1]. Heart rate is one of the principal determinants of myocardial oxygen consumption, and elevated heart rate is a condition where energy requirements and myocardial oxygen demands are increased and also causes shorten the length of each cardiac cycle, thereby reducing diastolic perfusion time and oxygen supply [2-4]. Epidemiological data have shown that a heart rate >85 beats/min is associated with a greater risk of cardiovascular events and higher mortality [5,6]. We are conducting this study to assess the tolerability and efficacy between ivabradine and beta-blockers in ACS patients with reduced ejection fraction (EF) and also assess the contraindications for beta-blockers. Beta-blockers are the most frequently used first-line therapy [7,8]. Ivabradine is a selective inhibitor of the funny current (I_f). Inhibition of I_f are associated with reduction in sinus rate and a prolong sinus recovery time and reduced infarct size [9-17]. Ivabradine should be administered in symptomatic patients (New York Heart Association [NYHA] II-IV) with left ventricular (LV) EF ≤35% [18]. Ivabradine exerts some of its favorable effects by declining cardiac pro-inflammatory cytokines and also inhibits peroxidants and collagen buildup in atherosclerosis or congestive heart failure [19-23].

METHODS

A prospective observational study was conducted in MyCure Hospitals, Kurnool, Andhra Pradesh, inpatient of cardiology ward for duration of

6 months. The study populace includes 100 patients, in which Group-A was 50 patients and Group-B was 50 patients. Group-A and Group-B were treated with ivabradine (some patients received in combination with beta-blockers, some were shifted from beta-blockers and remaining treated with ivabradine alone) and β-blockers respectively. These research inclusion criteria include patients who were diagnosed with ACS, age >18 years, EF ≤50% and blood pressure (BP) ≥120/80. Exclusion criteria include those having active myocarditis, bradycardia (heart rate <50 beats/min) or conditions associated with increased risk for bradycardia, stroke within previous 4 weeks, hypotension (systolic BP <90), severe primary valvular disease, patients with functional (or) orthopedic limitations that could impair performance during cardiovascular functional tests, pregnant women, third-degree atrioventricular (AV) block, known hypersensitivity to beta-blockers or ivabradine. The patients were classified into four categories based on their symptoms of normal breathing and varying degrees in shortness of breath using the NYHA classification. All the data were entered and analyzed in Microsoft Excel 2010 version and data were presented as mean±standard deviation. To analyze the difference between the treatment groups, unpaired two-tailed t-test selected for continuous variables. We accept the null hypothesis if p>0.05 and reject if p<0.05.

- Null hypothesis (H₀): No difference between ivabradine and beta-blockers in terms of efficacy in reducing heart rate
- Alternative hypothesis (H₁): There is a difference between ivabradine and beta-blockers in terms of efficacy in reducing heart rate.

RESULTS

Our study sample size was 100 patients, in that Group-A was 50 patients and Group-B was 50 patients. These groups were treated with ivabradine and beta-blockers respectively. In the Group-A (50) patients, treatment with daily doses of ivabradine was 2.5 mg in 11 (22%) patients, 5 mg in 37 (74%) patients, and 7.5 mg in 2 (4%) patients. In Group-B (50) patients, the metoprolol daily doses were 12.5 mg in 2 (4%) patients, 25 mg in 40 (80%) patients, and 50 mg in 2 (4%)

patients and carvedilol daily doses were 3.125 mg in 3 (6%) patients, 6.25 mg in 1 (2%) patient, 10 mg in 1 (2%) patient, and 20 mg in 1 (2%) patients. Among Group-A patients who underwent combination therapy (ivabradine + beta-blockers) were 4 and who shifted from beta-blocker to ivabradine were 8. Among 100 patients, males were 71%, females were 29%. Age categorization of total study population was done in 100 patients, aged between 35 and 44 years was 13 (13%), aged between 45 and 54 years was 30 (30%), aged between 55 and 64 years was 32 (32%), aged between 65 and 74 years was 21 (21%), and >75 years was 4 (4%) were found. The maximum number of patients 32 (32%) was present in the age group between 55 and 64 and the minimum number of patients 4 (4%) was present in the age group >75 years. The majority of the patients were in the age group between 55 and 64 (32%) years of age, which are highly affected by ACS. The prevalence of ACS was high in rural (56%). Diabetic mellitus (53%) and hypertension (51%) were found to be the leading risk factor for the development of ACS followed by smoking (15%) and alcohol consumption (8%). Among the 100 patients, surgical procedure was performed in 58 patients, coronary artery bypass grafting (CABG) (29%), and percutaneous transluminal coronary angioplasty (PTCA) (28%). Coronary angiography showed single vessel disease is 30% in Group-A and 21% in Group-B, double vessel is 14% in Group-A and 11% in Group-B, and triple vessel is 23% in Group-A and 18% in Group-B. In Group-A, patients with severe EF was 14 (14%) and with moderate 36 (36%) and in Group-B, patients with severe EF was 4 (4%) and with moderate 46 (46%). Contraindications for beta-blockers to select ivabradine include pulmonary edema 22 (44%) patients, persistent tachycardia 21 (42%) patients, cardiogenic shock 4 (8%) patients, lower respiratory tract infection 2 (4%) patients, and severe airway obstruction 5 (10%) patients. Predisposing factors in ivabradine were done in 50 patients. Pulmonary edema was 22 (44%), persistent tachycardia was 21 (42%), cardiogenic shock was 4 (8%), lower respiratory tract infection was 2 (4%), and severe airway obstruction was 5 (10%). Pulmonary edema was more when compared with other factors. According to NYHA classification, in our study Class-I (no limitation of physical activity; according to physical activity does not cause undue fatigue, palpitation, dyspnea) was 6 patients. Class-II (Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea) was 14 patients. Class-III (Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea) was 15 patients and Class-IV (unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases) was 15 patients. The NYHA classification was seen in 50 patients treated with ivabradine and in Grade I 6 (12%), Grade II 14 (28%), Grade III 15 (30%), and Grade IV 15 (30%) were found. Hence, maximum patients were found in Grades III and IV. Minimum patients were in Grade I, which are given in Table 1. Ivabradine decreased the mean heart rate from 112.98 ± 23.90 to 89.97 ± 10.27 (Group-A) beats/min and beta-blockers decreased the mean heart rate from 99.6 ± 20.44 to 86.76 ± 13.14 (Group-B) beats/min. p-value is analyzed by unpaired two-tailed t-test ($p=0.24$) (Table 2). Both drugs decreased the mean heart rate to 89.97 ± 10.27 (Group-A) versus 86.76 ± 13.14 (Group-B) beats/min. After performing statistical tests, ivabradine is equally effective as beta-blockers. $p>0.05$ says that the study accepts the null hypothesis. This analysis suggests that ivabradine is equally effective as beta-blockers (Table 2).

DISCUSSION

The study was on considerations and comparative efficacy between ivabradine and beta-blocker in patients with the ACS. CAD is affecting Indians 5–10 years earlier than other communities. In some studies, below 4–5 years suffering from acute myocardial infarction is reported to be high in 25–40% [1]. Therefore, existing guidelines for STEMI have given Class-I recommendation to oral beta-blockers therapy administration promptly to patients without contraindications. Beta-blockers have the propensity to cause AV block and there is a 19% incidence of high degree heart block complicating acute inferior

infarction [16]. However, the use of beta-blockers is restricted in some patient's subgroups with severe LV dysfunction and acute bronchospasm or having cardiac conduction abnormalities. In this case, ivabradine can be a best possible alternative. Ivabradine is a pure heart rate lowering agent in patients with sinus rhythm [15]. The greater part of studies stated that beta-blockers were equally effective with ivabradine in reducing the heart rate. In our study, we have found that in non-surgical patients both drugs showed equal effects but during the surgical intervention in the patients who underwent surgery with CABG and PTCA, there was post-operative persistent tachycardia with heart rate (>120 bpm). Ivabradine is a safe alternative to lessen heart rate in post-cardiac surgery patients; it allows to reduce the heart rate, which is the target in the immediate post-operative phase and that cannot be obtained in all patients by increasing the beta-blockers dose. Ivabradine particularly inhibits the I_f of cardiac pacemakers without disturbing other cardiac ionic currents and has no effect on cardiac contractility, repolarization, (or) AV conduction [15]. Beta-blockers are the most regularly used first-line therapy. The use of β -blockers is complex and controversial in patients with conduction abnormalities, severe LV dysfunction and active bronchospasm, severe airway obstruction, chronic fatigue, cardiogenic shock, hypersensitive to β -blockers, severe hypertension, peripheral vascular disease, patient on ventilator, persistent tachycardia, and post-operative persistent tachycardia [16]. Ivabradine quite the reverse to beta-blockers has been shown better myocardial perfusion. Ivabradine showed improvement in clinical outcomes in treating heart rate in ACS patients [15]. Both drugs decreased the mean heart rate to 89.97 ± 10.27 (Group-A) versus 86.76 ± 13.14 (Group-B) beats/min ($p=0.24$). We found that beta-blockers were equally effective as ivabradine in ACS patients for lowering the heart rate. The result obtained was clinically significant and statistically not significant at $p>0.05$. Hence, this research proved that ivabradine and beta-blockers both were effective in view of efficacy. Clinically, ivabradine showed a significant reduction in heart rate than beta-blockers. Studies in patients with ischemic heart disease have revealed that a combination of ivabradine and beta-blockers is more effective than beta-blockers alone in improving exercise tolerance [8]. In our study, we were unable to reach the equal number of gender distribution in both groups and untimidated discharge of a few

Table 1: Patients basic information

Patient information	Number of patients (%)
Age distribution in total study	
35–44	13 (13)
45–54	30 (30)
55–64	32 (32)
65–74	21 (21)
>75	4 (4)
Total	100 (100)
Predisposing factors percentage in ivabradine	
Pulmonary edema	22 (44)
Persistent tachycardia	21 (42)
Cardiogenic shock	4 (8)
Lower respiratory tract infection	2 (4)
Severe airway obstruction	5 (10)
New York Heart Association classification in ivabradine	
Grade I	6 (12)
Grade II	14 (28)
Grade III	15 (30)
Grade IV	15 (30)

Table 2: Mean heart rate before and after treatment in ivabradine and beta-blockers

Ivabradine mean heart rate		Beta-blockers mean heart rate	
Before	After	Before	After
112.98 ± 23.90	89.97 ± 10.27	99.6 ± 20.44	86.76 ± 13.14

$p=0.243783962$

patients. Follow-up was only up to the hospital stay. The sample size was limited only up to 100 patients. The study period of 6 months was short to evaluate the complete health status after the treatment. We were unable to assess the serious adverse drug reactions on drug administration during a hospital stay. However, rational drug prescribing and patient safety are important things; polypharmacy and misuse of drugs are also the most important things; physicians and clinical pharmacists must focus to avoid all, which cause non-adherence to patients [23-25].

CONCLUSION

Our study highlights the predisposing factors for selecting ivabradine, also tolerability, and efficacy between ivabradine and beta-blockers. The final conclusion suggests that ivabradine is equally effective as beta-blockers.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to make this research to be successful.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest regarding the content of this article.

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