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Ivabradine, A Heart Rate Lowering Drug: A Clinical Investigation

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Abstract: Resting heart rate is the main determinant of cardiovascular outcomes. Heart rate > 70 bpm is alarming, it leads to heart failure. Ivabradine is a specific drug of I*f* channels to stabilize heart rate. It is the only drug with no side effects and specific mode of action. Aim of this study is to evaluate the efficacy of Ivabradine on patients. The extent of recovery is measured and checked clinically that Ivabradine is better choice for heart rate or not. A total of 146 patients were examined using Ivabradine, their medical history and the condition at the time of visit is correlated and a conclusion is made that Ivabradine is better than B-blockers both in its efficacy and cost-effectiveness. Ivabradine was proved to be a good and precise drug in reducing heart rate. Both literature and clinical investigations indicated that Ivabradine is emerging, new and best choice for heart rate stability in HF patients.

Key words: Ivabradine · Heart Rate · Heart Failure · Efficacy · Biological Effects

INTRODUCTION

Resting heart rate characterizes cardiovascular morbidity and mortality. The faster heart rate is a predictor of cardiovascular events. So lowering the heart rate improves cardiovascular outcomes on HF patients [1]. Chronic heart failure is most common disorder now a day. The heart rate alarms its adverse effects. Due to its high emergence in human population, novel treatment should be used, with fewer side effects. Patients with coronary artery disease (CAD) and HF, heart rate greater than 70 bpm is associated with 34% risk of cardiovascular death. Increased heart rate not only leads to ischaemic episodes but also has a major role in coronary artery disease (CAD). It increases the myocardial oxygen consumption and reduces the diastolic time of myocardial perfusion and act as a predictor of mortality [2].

Ivabradine is a new medicine in the treatment of HF, lowers heart rate. Ivabradine a new, specific, attractive putative therapeutic agent and use-dependent I*f* inhibitor; lowers heart rate by exerting anti-ischaemic activity. The main channel involved in the regulation of HR in sino-artial node (SAN) is I*f* ionic current [3]. Ivabradine act on heart rate by reducing it. Some animal studies indicate that Ivabradine does not show any vasodilatory effect on inotropic properties. It also lowers the risk of cardiovascular events, better than B-blockers [4]. The routine analysis and stability of Ivabradine in dosage form can be achieved by very precise and accurate methods, RP HPLC and spectrophotometer [5]. An economical evaluation of drugs in UK reveals that Ivabradine is cost-effective in eligible patients with HF. And it is expected to have 95% chance to be cost-effective [3]. A 5mg dose of Ivabradine is quite effective for the HF patients but a study about the efficacy of doses of Ivabradine is conducted on patients of chronic stable angina pectoris, a conclusion is made that 7.5 mg dose is also helpful and good choice for patients' recovery with no untoward effects [6]. It has no negative effect on intra-cardial conduction, contractility or ventricular repolarization. European society of cardiology guidelines recommend that Ivabradine should not be given to asymptomatic patients as NYHA class-I and should be recommended to patients falling in NYHA class II-IV, with heart rate > 70 bpm [7]. First line therapy for heart failure patients is beta-blockers, recommended by International guidelines. But these drugs have contra-indications and are very difficult to manage in real-life. Much contemporary surveys show a continuous elevated heart rate in patients on this therapy. Ivabradine is indicated in place of beta-blockers. It not only reduces heart rate, lowers hospitalization, mortality but also have no or very mild side effects and reversible after reduction in doses [8].

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The Biological Effects of Ivabradine: Ivabradine is a specific drug for I*f* channel to close them. It directly acts on the I*f* ionic channel, with no adverse effects on other cardiac channels. Ivabaradine blocks cardiac pace-maker cell *f* channels specifically; it enters the channel and binds intracellular to a site, to close the pore. This action causes heart rate reduction, hence myocardial oxygen demand reduces and oxygen supply increases. As a result diastole prolongs allowing increased coronary flow. Ivabradine lowers heart rate very specifically without disturbing inotropic and iusitropic effect [8].

Endothelial dysfunction associated with variability of heart rate in patients provide new basis as a correlation between cardiovascular outcomes and endothelial dysfunction [10]. It promotes cardiovascular effects by acting as pro-atherosclerotic and pro-thrombotic agent [11]. Ivabrdaine is proved to be a potent mediator for the treatment of endothelial dysfunction. Ivabradine has strong anti-oxidative effect on vasculature. Monocyte chemotactic protein-I (MCP-I) expression is also down regulated by Ivabradine. MCP-I induces leukocyte arrest and trans-endothelial migration which make a link between atherosclerotic lesion formation and endothelial dysfunction [12]. At an immune level, chemokine induced migration of CD-4 positive lymphocytes is inhibited by Ivabradine. This inhibition of T-lymphocytes migration in vascular system lowers the pro-inflammatory cytokine formation hence low chances of atherosclerotic lesion formation [13]. Activation of rennin-angiotensin-aldosterone system (RAAS) characterizes heart-failure. In HF, angiotensin-II elevation promotes structural and electrical remodeling associated with atrial fibrosis [14]. Cardiac ACE is promoter of activation of RAAS. Ivabradine diminishes the mRNA regulation and expression of cardiac ACE, hence, maintains cardiac function in HF [15].

MATERIALS AND METHODS

A small study is conducted at Tahir Heart Institute, to evaluate the efficacy of Ivabradine for HF patients. Those patients were choosen for this study which were already on Ivabradine medication. Medical history of patients was noted down at the time of visit. Evaluation was made at the basis of these parameters height, weight, sex, age, BMI, BP and heart rate. 146 patients were involved in this two months study with a diagnosis of IHD. After proper check-up the patients were put on Ivabradine along with other medicines related to their HF complications, as standard therapy. Patients treated with Ivabradine, fall in NYHA class I-IV having HR > 70 bpm. After 2-months their recovery is evaluated. As literature and research reveal that Ivabradine is a best choice for a doctor to comfort his patients from elevated heart rate. The aim of study was to evaluate the efficacy of Ivabradine, that how much extent this drug benefits the patients.

RESULTS AND DISCUSSION

The percentage of its efficacy was calculated keeping in mind all the parameters. 6 catagories were made according to the betterment of patients. 0 grade means no improvement, 1= very mild, 2= mild, 3= moderate, 4= good, 5= excellent improvement.

All patients before receiving the Ivabradine treatment were suffering from elevated HRs and difficulty in breathing and walking. According to this grading, the percentages were calculated. 0 grade patients are those patients who show no betterment. 1 grade patients showed very little improvement in HR, 2 grade patients showed mild improvement while 3 and 4 grades showed good improvement. 5 grades is that condition of patient where all adverse effects are wiped out. While taking the history of grade 3, 4 and 5 patients, their symptoms were quite same with high recovery so while making final decision these three categories will be assumed as same. The mean heart rate of the patients before taking Ivabradine was 83 bpm, while after Ivabradine treatment their heart rate lowered to about 70 bpm. This infers a marked difference between heart rates before and after Ivabradine intake properly.

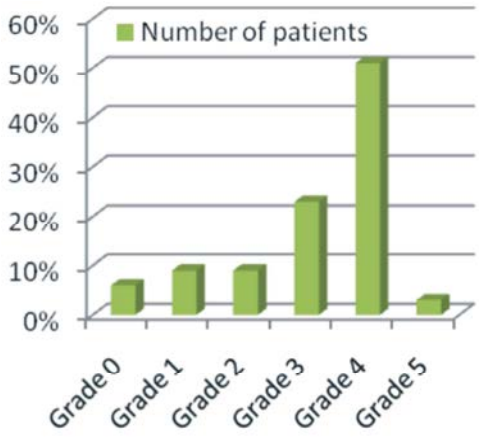

Fig. 1: Number of patients

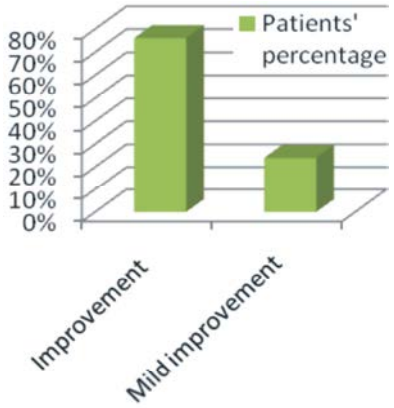

Fig. 2: Patients' percentages

Ibavradine showed 76% efficacy in this study with 24% very mild improvement. Very mild improvement in patients may be due to poor hygiene or smoking.

Ivabradine is the first innovative drug for elevated heart rate, with no other side effect on heart, specific for heart rate. It decreases the probability of heart failure by balancing the heart rate. In addition Ivabradine has many other biological effects related to HF as anti-oxidant function; reduce heart rate by inactivating RAAS, improving endothelial dysfunction. This study reveals that Ivabradine is best choice for heart rate reduction as compared to B-blockers, with a better percentage of effectiveness. Cost-effectiveness and as a new innovative drug, it has replaced B-blockers, due to its specific action [16-17].

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