Research Article

An Observational Study on Long Term Safety and Efficacy of Ivabradine in Patients with Chronic Heart Failure

Dr. Nikhilesh Andhi*, P. Dhakshayani, K. Supriya, D. Aravind, M. Laharika

*Assistant Professor, Department of Clinical Pharmacy Practice, Samskruti College of Pharmacy, Kondapur, Ghatkesar, Medchal District, Telangana, India.

***Corresponding author's E-mail:** 2016marsn@gmail.com

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ABSTRACT

The chief objective of the study is to find out the safety and efficacy of ivabradine in patients with chronic heart failure. A prospective observational study has been guided in the cardiology department of tertiary care hospital. The data is collected from the out-patient and in- patient department after considering inclusion and exclusion principles for 6 months and a total of 220 patients were analyzed with data collection form by interviewing to the patients about the Socio-demographic questionnaire, MLHFQ (Minnesota Living and Heart Failure Questionnaire) for the evaluation of safety and efficacy of ivabradine and quality of life after Heart Failure. Statistical tools like the Chi-square test were applied to the data by using SPSS software. A total amount of 220 Heart Failure patients, males 148 (67.3%) patients were predominant over female patients of 72 (32.7%). The majority of the Heart Failure patients were under the peer group of >60 years (100%), symptoms were more in males (46%), past medical history i.e. Hypertension and Diabetes mellitus were more in number (128), Coronary Artery Disease (Anterior Wall Myocardial Infraction) (32), Non ST Elevated Myocardial Infraction (8). Most of the patients were treated with the dose of ivabradine i.e. 5mg rather than 2.5mg or 7.5mg. Among 5mg (90.9%), 2.5mg (5.5%) and 7.5mg (3.6%). The ivabradine is used for decreasing Heart Rate among all age groups i.e. >35 years are having more Heart Rate before ivabradine intake. After ivabradine intake, the normal Heart Rate is seen in age groups of 35- 40 years. Adverse effects of ivabradine are bradycardia (10%), Hypertension (8.9%), atrial fibrillation (8.3%), and luminous phenomenon (2.8%). Heart Failure is mostly seen in males and elderly people. The present study shows the safety and efficacy with respect to ivabradine in patient with congestive Heart Failure. After intake of ivabradine, the Heart Rate was bought to normal which shows the efficacy of the drug and the adverse effects are bradycardia, hypertension, atrial fibrillation, luminous phenomenon. But these adverse reactions were not seen in the sample size. This shows the safety of the drug.

Keywords: Heart failure, Ivabradine, Heart Rate, Hypertension, Bradycardia, Atrial fibrillation, luminous phenomenon.

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INTRODUCTION

The 'pure' heart rate lowering antianginal drug which has been introduced recently as an alternative to β-blocker is 'IVABRADINE'. Ivabradine (eye-VAB- a-deen) is the only authorized drug come under the category of HCN channel[1]. I_f current was first discovered in the 1970s in animal studies, which is found to be primarily mediated in humans by abundant SA node HCN_4[2]. This drug is also used by children who's suffering from heart failure as a consequence of an enlarged heart viz. dilated cardiomyopathy. Dosage in adults: Initial dose: 5mg BD, If heart rate> 70bpm the maximum dosage is 7.5mg. Pediatric Tablet: 5mg divided into equal halves to provide a dose of 2.5mg. The maximum dose for age 6 months to < 1 year the dose shouldn't increase equal to 0.2mg/kg BD, Maximum for age ≥ 1 year supposed to be 0.3mg /kg BID, and the dose shall not be increased up to 7.5mg BD. The patient who develops bradycardia. The recommended initial dose considers reducing the dose to 0.02mg/kg BID.

Mechanism of Action

The heart rate is persistent by the rate & thus the amount is explained by the rate of spontaneous diastolic depolarization in the SA node[3]The spontaneous diastolic depolarization is determined by a mixed Na^+ - K^+ current across I_f channels. It is directly and particularly restrained by ivabradine, which leads to reduced diastolic depolarization rate and declining of the heart rate[4, 5]. Ivabradine enters and blocks the f- channels from the protoplasm side of the plasma membrane and it does mostly when the channel is in the open state. Therefore, it prevents the rate of cardiac pacemaker movement of the heart[6].Ivabradine specified modes of action is to limit its usage to patients with sinus rhythm and prohibits in patients who are suffering from AF or AFL [7, 8].

Therapeutic use of Ivabradine is utilized in heart failure to improve symptoms in patients who are having sinus rhythm with a heart rate of above > 70/min and are optimized for heart failure treatment. Pharmacokinetic parameters include absorption. Taking ivabradine during meals minimizes intra-individual variableness in absorption time. Distribution The volume of distribution

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(~ 100L), under fasting conditions, it reaches peak plasma concentrations i.e. approximately 1hour. Metabolism It is metabolized by both liver and gut by oxidation tHeart rateough cytocHeart rateome $P_{450}3A_4$ ($CYP3A_4$). The active metabolite is N, desmethylated derivative. Ivabradine must not be co-prescribed with strong or moderate $CYP3A_4$ inhibitors such as diltiazem and verapamil[9]. Elimination Ivabradine's main ½ life is approximately 2 hours i.e. 70- 75% of AUC and its affective ½ - life is around 11 hours[10].Clearance is about 400ml per minute. About 4% is excreted and unchanged via urine. Pharmacodynamics effects include Ivabradine impetus a dose-dependent reduction in heart rate. At the recommended dosage, the heart rate declining is grossly 10bpm while asleep or exercising[11].In clinical practice and particularly in subjects with co-morbidities, ivabradine does not influence intra cardiac conduction, contractility, or ventricular repolarization nor it does not affect the central aortic pressure or LV after load[12].Ivabradine does not exert negative inotropic effects. It increases the uncorrected QT interval with heart- rate slowing but it does not prolong the QT interval[13]. Side effects and adverse effects include Headache: During the first month of treatment. Blurred vision, ventricular extra systole. The most basic adverse effects of ivabradine consist of bradycardia, atrial fibrillation, high blood pressure, and phosphenes. Luminous visual phenomenon and bradycardia two are dose-dependent and inter-connected to the pharmacological affect[14].The I_f channels are inhibited by the ivabradine which is present in the eyeball. Because of the current is inhibited by visual phenomena. It usually occurs mild-moderate. Generally, it occurs within 2 months of treatment initiation[15].The ivabradine medication is used to decrease the heart rate. But if the drug is used continuously used even later the heart rate is bought to normal. Then the heart rate is decreased[16, 17, 18, 19, 20]

Contraindications include Decompensated Heart Failure, BP lower than 90/50, Conduction abnormalities i.e. sick sinus syndrome, sinoatrial block, or third-degree AV block, unless a pacemaker determines the heart rate, Severe liver impairment, Patients taking cytochrome $P_{450}3A_4$ ($CYP3A_4$), Resting heart rate not exceeding 60bpm before therapy initiation. Ivabradine causes drug-drug interaction with CYP450 inhibitors. It may cause fetal toxicity when it is inclined to pregnant lady. Effective contraception in women is recommended while using ivabradine. BRAND NAMES**:** IVABRAD, BRADIA, IVABEAT 5mg, 7.5 mg tab[21].

MATERIALS AND METHODS

A prospective observational study conducted in cardiology department in a tertiary care hospital for duration of 6 months.

The data was gathered from the in-patient and out-patient department by interviewing the patients and reviewing their prescriptions. The data collection format was verified and authenticated by the hospital preceptors for the study. Study involved 220 patients

Subjects who were diagnosed with heart failure with treatment of ivabradine. Patients with pregnancy, lactating patients, renal patients and hepatic patients are excluded from the study.

Written informed consent was taken from patient or care provider to collect data. The data form includes Socio-demographic information like age, gender, weight, marital status, educational status, Past Medical History, social history, family history, and MLHFQ questionnaire was attached to it.

Statistical Analysis: Descriptive statistics was done by using SPSS software to determine mean and standard deviation of collected data. The statistical tool Chi square test was performed to determine P-value between the different variable with data collected (gender vs after heart rate, dosage vs after heart rate, past medical history hypertension vs before heart rate, past medical history vs before heart rate, before heart rate vs after heart rate). The P-value is used in determining the statistical significance within statistical hypothesis for drug related problem in heart failure patients to baseline visit. The P-value was set at <0.05 and confidence interval was 95%

RESULTS

In present study around 220 cases were included as per our criteria. **Table -1** indicates socio demographic details of the patient with the treatment of ivabradine. Male patients (67.3%) seems to be predominant than female patients (32.7%). **Fig 1** shows the gender wise distribution of the study population. **Fig 2** represents the age wise distribution of patients with respect to gender as shown in the **table 1** here it is represented that 60^{+}yrs were highest (100%) and < 35 and 35- 40yrs were least (12%) which is shown in the figure 2. In **Fig 3** represents the symptoms most of the patients have experienced symptoms of chest pain and irregular

heart beat (46%) and less number of patients experienced fatigue (19%) which is represented in the fig 3. **Fig 4** as shown in the **table 1** represents he past medical history of the patients here most of the patients have past medical history of Hypertension and Diabetes Mellitus which is represented in the fig 4.**Fig 5** as shown in the **table 1** represents dosage therapy and explains the average dose of patients who have taken 2.5mg were (12), 5mg were (200) and 7.5mg were (8). But maximum dosage of ivabradine is 5mg is taken by the most of the patients. **Fig 6** as shown in the **table 1** explains about the before and after heart rates of ivabradine in patients with different age groups i.e. <35yrs, 35- 40yrs, 40- 50yrs, 50- 60yrs and >60yrs were observed. Most common adverse effects were observed in patients i.e. bradycardia (10%), hypertension (8.9%), atrial fibrillation (8.3%) and luminous phenomenon (2.8%) are indicated in **Fig 7**. Here in fig 7 we can observe that most common adverse effect which is seen in the patients who are taking ivabradine is

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bradycardia. **Fig 8** represents deviation in heart rate in order to prove the efficacy of ivabradine on an average of 55 patients. Here in fig 8 the dark blue colour indicates heart rate before intake of ivabradine and red colour indicates heart rate after intake of ivabradine, thus through the figure8 we can clearly see the deviation in graph which is indicating the decrease in the heart rate providing the evidence of its efficacy. Chi square test was performed between variables like gender vs after heart rate (0.001), dosage vs after heart rate (0.001), past medical history hypertension vs before heart rate (0.074), past medical history vs before heart rate (0.004), before heart rate vs after heart rate (0.001), age vs cad (0.055) and P- value was clinically significant (<0.005).

Table 1: Mean, SD, P-value

Characteristics	N	Mean	Standard Deviation	P-value
Age	220	59.04	11.940	0.0001
Past Medical History I HTN	220	.62	.487	0.0001
Past Medical History II DM	220	.56	.487	0.0001
Past Medical History III CAD	220	.20	.401	0.0001
Ivabradine Dose	220	5.05	.402	0.0001
Before HR	220	103.89	11.294	0.0001
After HR	220	79.35	9.699	0.0001

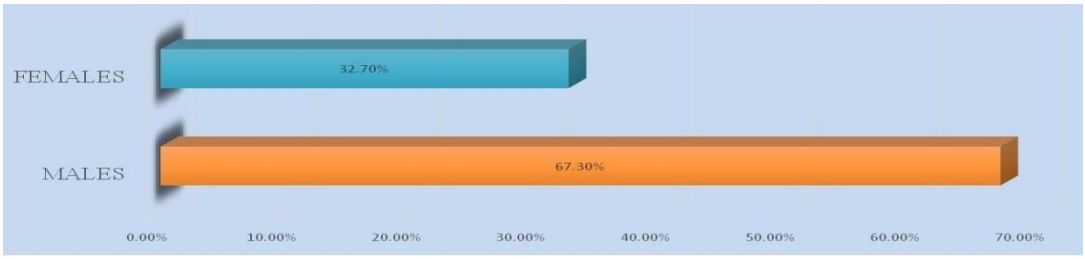

Figure 1: Gender Wise Distribution

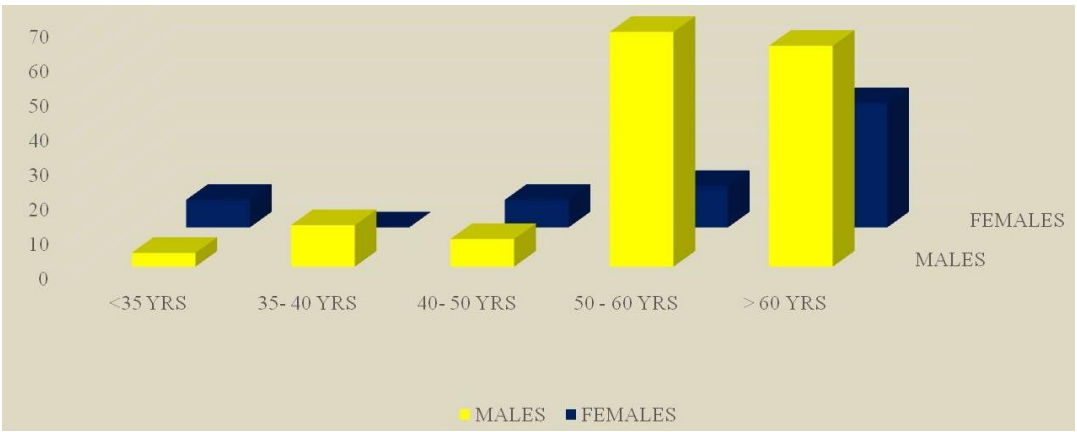

Figure 2: Age Wise Distribution Graph with Respect to Gender

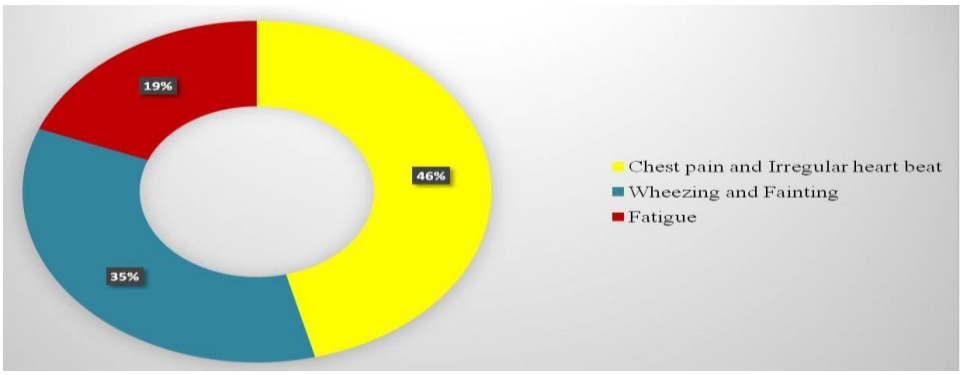

Figure 3: Percentage of Symptoms

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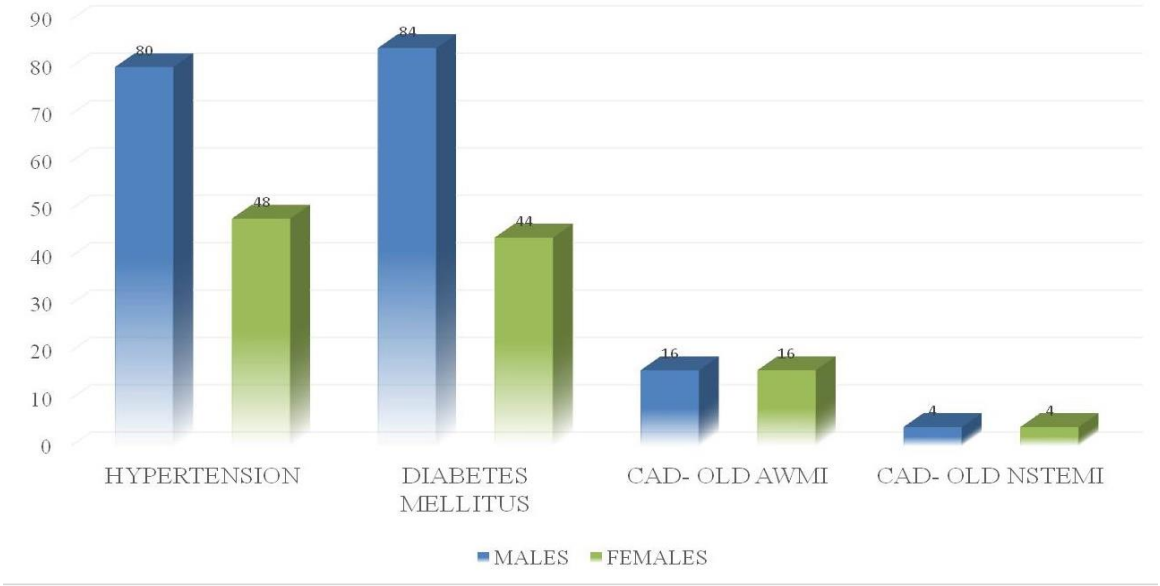

Figure 4: Past Medical History of Patients

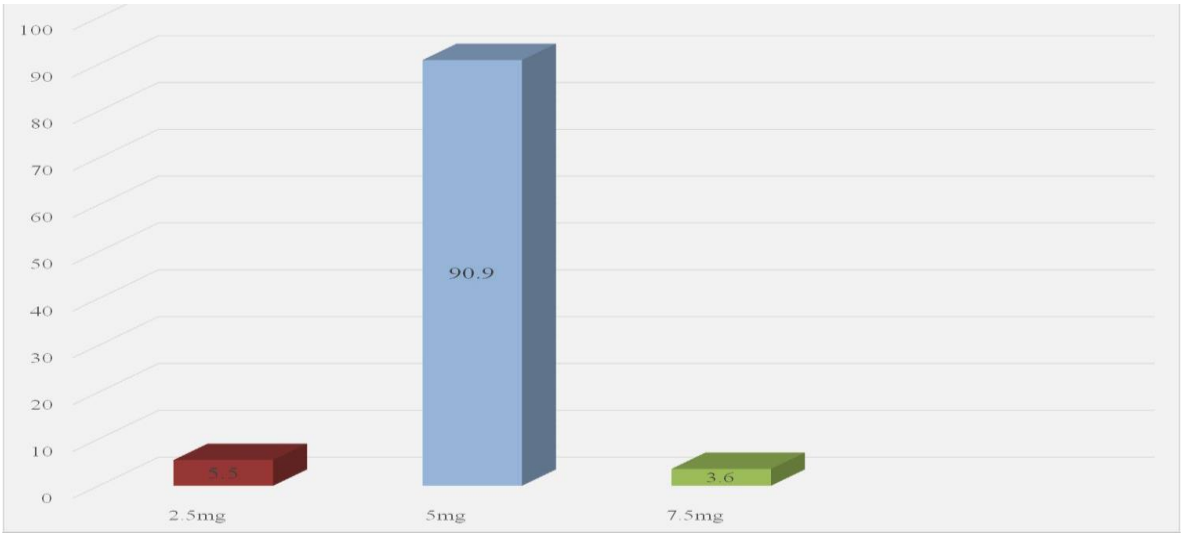

Figure 5: Dosage Therapy

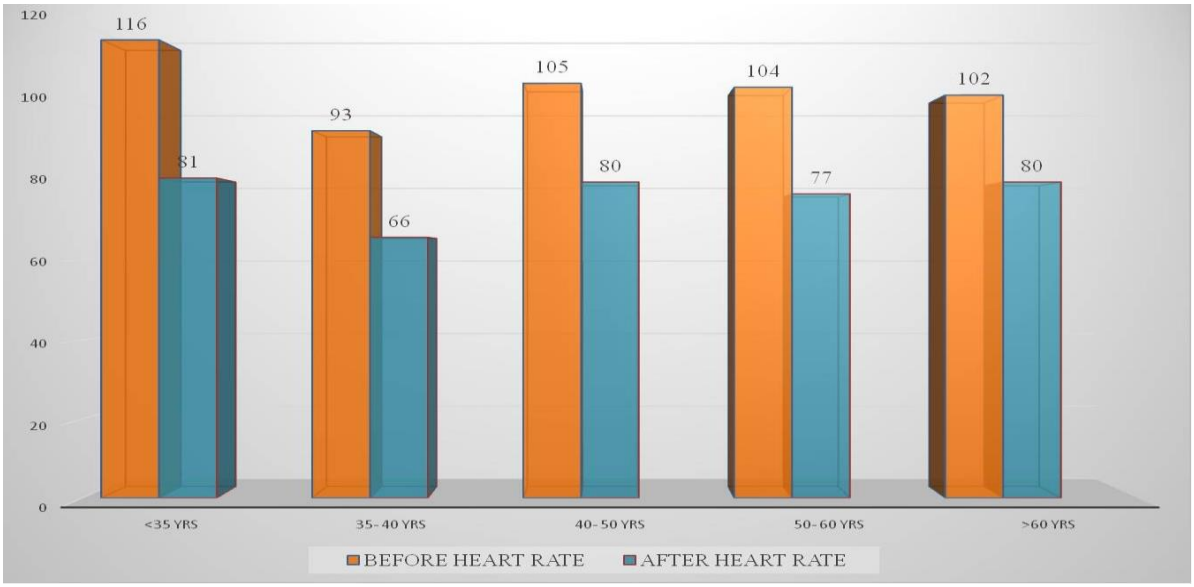

Figure 6: Before and After Heart Rates of Ivabradine Based on their Age Groups

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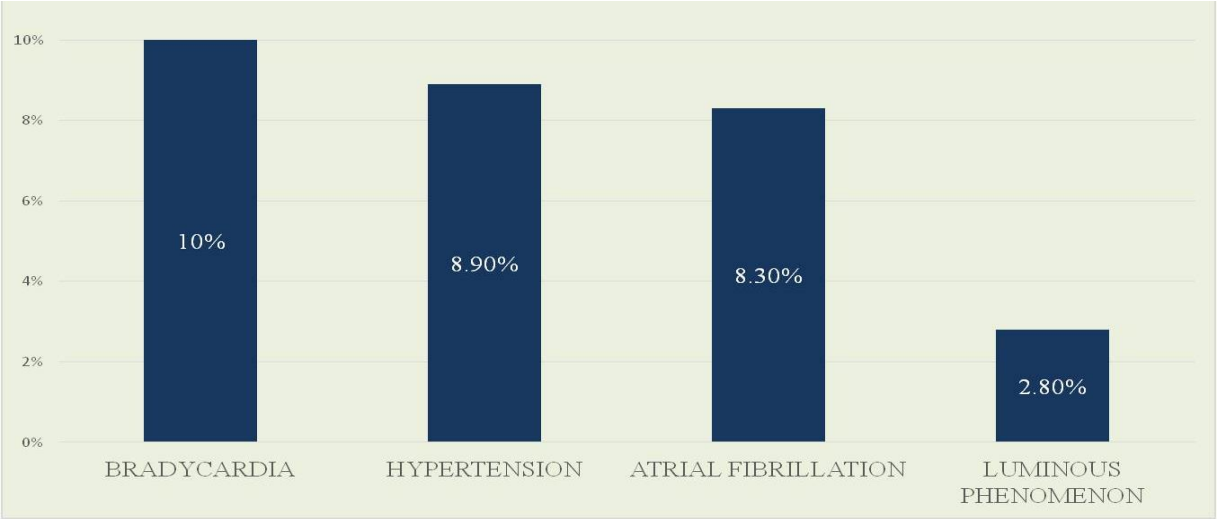

Figure 7: Adverse Effects of Ivabradine

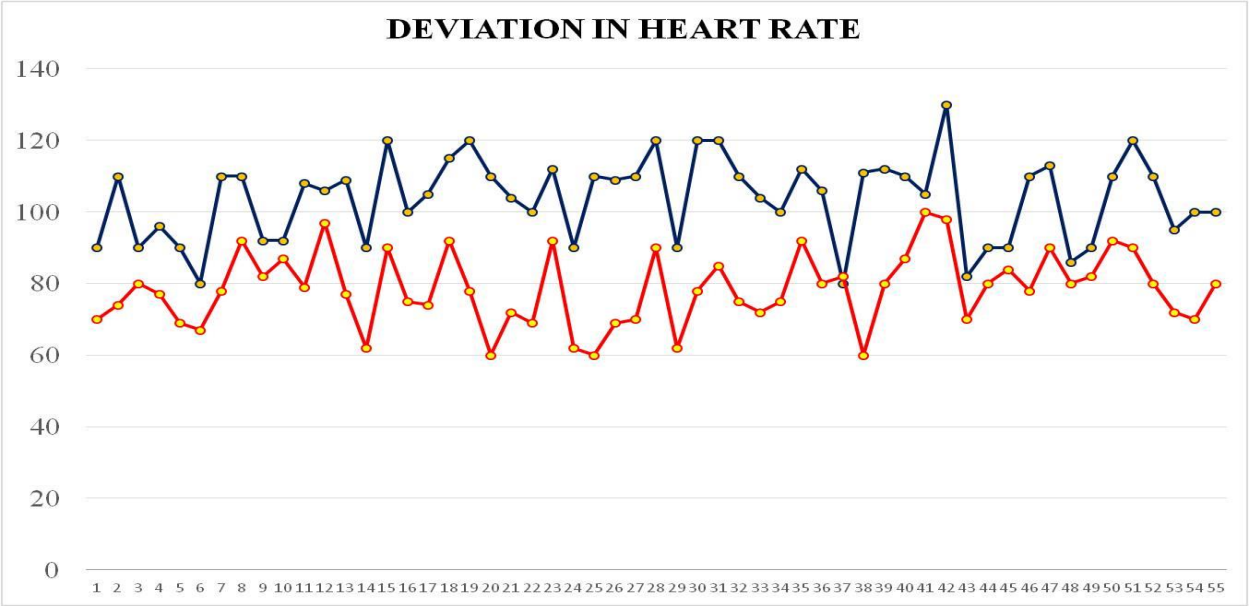

Figure 8: Deviation in Heart Rate

DISCUSSION

A prospective observational study, **"AN OBSERVATIONAL STUDY ON LONG TERM SAFETY & EFFICACY OF IVABRADINE IN PATIENTS WITH CHEART RATEONIC HEART FAILURE"** was conducted in secondary care hospital in outpatient and inpatient department. The data is collected for 220 patients using data collection forms.

According to our study among 220 patients, most of the heart failure patients were subordinate under the age group of >60 years (100%); males were (67.3%) and females were (32.7%). Similar nature of findings were reported by K K Adile, A Kapoor, S K Jain[22], A Gupta. In the current study, past medical history has more in number (128), viz. Hypertension and Diabetes Mellitus (128), Coronary Artery Disease (Anterior Wall Myocardial Infraction) (32), Non St Elevated Myocardial Infraction (8). Past medical history has reported by 60% of people. A study by Michel Komajda, Luigi Tavazzi[23] were showed nearly 80% of people were presented with similar PMHx. Chi square test was performed in our study showed that p-value was clinically significant, for all socio demographic details and therapy. In the present study among 220 patients 46% were with chest pain and irregular heartbeat, 35% were with wheezing and fainting and fatigue were 19% which is similar Lynn Elzir, Eileen O Meara[24, 25]. Ivabradine maintenance dose not exceed 7.5mg twice daily. So in this study 2.5mg dose were (5.5%), 5mg dose were treated in (90.9%) and 7.5mg dose were only (3.6%). Similarly findings reported by Yasar Sattar, Elham Neisani Samani and Nirav B Patel. According to this study the heart rate was high in age group <35 years rather than other groups. Before intake of ivabradine which is similarly see in in study by Ajit Mullasari[26]. The drug ivabradine has some adverse reactions viz. bradycardia (10.9%), hypertension (8.9%), atrial fibrillation (8.3%), luminous phenomenon

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(2.6%). A study was presented with similar symptoms. It was observed from our study that, ivabradine will help in lowering the heart rate and it also have some side effects like bradycardia, atrial fibrillation, hypertension, luminous phenomenon. No adverse reactions were reported in our study.

CONCLUSION

Heart Failure is mostly seen in males, elderly people viz. under >60 years of age group. Present study shows the safety and efficacy of ivabradine. In recent study ivabradine is preferred for heart failure. Among $Ca^{+}2$ channel blockers ivabradine is vital for clinical management in decreasing the heart rate in heart failure also it is accompanied by some sort of the side effects, but dose adjustments are done to avoid these effects. The research encourages that proper involvement of clinical pharmacist and their duty is to serve to identify and avoid to drug related problems as implicated. By doing so, mortality and further complication must be prevented. During the study it proves that the patients were treated with ivabradine. The drug interactions were moderately found which can overcome by alterations of frequencies. Ivabradine has shown greater effects in decreasing the heart rate which demonstrates the effectiveness of the drug & no adverse reactions were observed in our study that implies the safety of the drug.

REFERENCES

1. Roubille F, Tardif JC. New therapeutic targets in cardiology: heart failure and arrhythmia: HCN channels. Circulation. 2013 May 14;127(19):1986-96.
2. Milanesi R, Baruscotti M, Gnecchi-Ruscone T, DiFrancesco D. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. New England Journal of Medicine. 2006 Jan 12;354(2):151-7.
3. DiFrancesco D. Pacemaker mechanisms in cardiac tissue. Annual review of physiology. 1993 Mar;55(1):455-72.
4. Bois P, Bescond J, Renaudon B, Lenfant J. Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. British journal of pharmacology. 1996 Jun;118(4):1051.
5. Niccoli G, Borovac JA, Vetrugno V, Camici PG, Crea F. Ivabradine in acute coronary syndromes: Protection beyond heart rate lowering. International journal of cardiology. 2017 Jun 1;236:107-12.
6. Bucchi A, Baruscotti M, DiFrancesco D. Current-dependent block of rabbit sino-atrial node If channels by ivabradine. The Journal of general physiology. 2002 Jul;120(1):1-3.
7. Bucchi A, Tognati A, Milanesi R, Baruscotti M, DiFrancesco D. Properties of ivabradine-induced block of HCN1 and HCN4 pacemaker channels. The Journal of physiology. 2006 Apr;572(2):335-46.
8. Deedwania P. Selective and specific inhibition of I f with ivabradine for the treatment of coronary artery disease or heart failure. Drugs. 2013 Sep;73(14):1569-86
9. Dillinger JG, Maher V, Vitale C, Henry P, Logeart D, Manzo Silberman S, Allée G, Levy BI. Impact of ivabradine on central aortic blood pressure and myocardial perfusion in patients with stable coronary artery disease. Hypertension. 2015 Dec;66(6):1138-44.
10. Savelieva I, Camm AJ. If inhibition with ivabradine. Drug safety. 2008 Feb;31(2):95-107.
11. Medem AV, Seidling HM, Eichler HG, Kaltschmidt J, Metzner M, Hubert CM, Czock D, Haefeli WE. Definition of variables required for comprehensive description of drug dosage and clinical pharmacokinetics. European journal of clinical pharmacology. 2017 May;73(5):633-41.Tardif JC, Ponikowski P, Kahan T. Efficacy of the I f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. European heart journal. 2009 Mar 1;30(5):540-8.
12. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. SIGNIFY Investigators: Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014 Aug 31;371(12):1091-9.
13. Osmanska J, Jhund PS. Contemporary management of heart failure in the elderly. Drugs & aging. 2019 Feb;36(2):137-46.
14. Ennezat PV, Le Jemtel T, Cosgrove S, Hallas J, Hansen MR. Outcome postponement as a potential patient centred measure of therapeutic benefit: examples in cardiovascular medicine. Acta Cardiologica. 2020 Jan 2;75(1):10-9.
15. Badu-Boateng C, Jennings R, Hammersley D. The therapeutic role of ivabradine in heart failure. Therapeutic Advances in Chronic Disease. 2018 Nov;9(11):199-207.
16. Kharouf Q. Targeting HCN4 channels in epilepsy (Doctoral dissertation).
17. Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013 Sep 30.
18. Adile KK, Kapoor A, Jain SK, Gupta A, Kumar S, Tewari S, Garg N, Goel PK. Safety and efficacy of oral ivabradine as a heart rate-reducing agent in patients undergoing CT coronary angiography. The British journal of radiology. 2012 Aug;85(1016):e424-8.
19. Henri C, O'Meara E, De Denus S, Elzir L, Tardif JC. Ivabradine for the treatment of chronic heart failure. Expert Review of Cardiovascular Therapy. 2016 May 3;14(5):553-61.

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20. Sattar Y, Samani EN, Zafrullah FN, Latchana S, Patel NB. Ivabradine in congestive heart failure: patient selection and perspectives. Cureus. 2019 Apr 13;11(4):21-25.

21. Mullasari A. Efficacy and Safety of Ivabradine Once-Daily Prolonged-Release versus Twice-Daily Immediate-Release Formulation in Patients with Stable Chronic Heart Failure with Systolic Dysfunction: A Randomized, Double-Blind, Phase 3 Non-Inferiority (PROFICIENT) Study. Cardiology and Therapy. 2020 Dec;9(2):505-21.

22. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis–choosing a model and assessing its adequacy and fit. British journal of cancer. 2003 Aug;89(4):605-11.

23. L.Elzir, E.Omeara, S.D.Denus et al. Ivabradine for the treatment of heart failure clin Invest, 2014;4:555-565.

24. Servier. ProcorolanR, emc, summary of product characteristics, assessed 14 January 2018.

25. Michel Komajda, Luigi Tavazzi, Karl Swedberg, John Cleland, Helmut Drexler. Guidelines for the treatment of cHeart rateonic heart failure: executive summary: the task force for the diagnosis and treatment of cHeart rateonic heart failure of the European society of cardiology. (update 2005).

26. K K Adile, A Kapoor, S K Jain, A Gupta. Safety and efficacy of oral ivabradine as heart rate reducing agent in patients undergoing CT angiography. Published on 13th Feb 2014.

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