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RESEARCH ARTICLE

A PROSPECTIVE AND RETROSPECTIVE STUDY ON THE CLINICAL EFFECTIVENESS AND ADVERSE REACTION RELATED TO THE USE OF IVABRADINE IN ISCHEMIC HEART DISEASES (IHD)

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ABSTRACT

The aim of the present study is to identify clinical indications for Ivabradine use in cardiovascular ischemic disorders in tertiary hospital, to identify the clinical benefits of Ivabradine using clinical parameter like echo and to observe any Adverse Drug Reaction during Ivabradine therapy in Ischemic Heart Disease treatment. Ischemic heart disease patients who are attending cardiology dept for their regular follow up were selected based on inclusion and exclusion criteria after obtaining informed consent. Ethical clearance got from human ethics committee institutional board. Quality of life with Ivabradine is assessed using preformed questionnaire both prospectively (6 months) and retrospectively(1 year) using Canadian Cardiovascular Society angina grading scale and New York Heart Association (NYHA) functional classification for heart failure with complete cardiac investigations during first clinical examination and 3,6 months later.. Quality of life is improved as per questionnaire. Ejection fraction is improved clinically and there is statistical significance ($p<0.05$). Left ventricular thickness and mass is reduced clinically but there is no statistical significance ($p>0.05$). Ivabradine is a safe anti anginal drug as it reduced post systolic wall thickening and prevented cardiac remodeling, without any adverse drug reaction of its own or drug interaction with polypharmacy and therefore can be prescribed for patients with various ischemic heart diseases.

Key words: Ivabradine, left ventricular thickness, left ventricular mass, Ejection fraction.

INTRODUCTION:

Even in the revascularization era, many stable angina patients suffer from persistent angina symptoms and / or silent ischemia[1]. Use of anti anginal medications was needed in a substantial number of patients even when they were symptom free. >60% of the patients were on beta blockers and roughly a third of the patients were taking anti anginal[2].

Current anti anginal agents almost all have frequent and sometimes severe side effects, most of which are related to their hemodynamic impact. Hypotension, leg oedema, negative inotropy and erectile dysfunction are the causes for treatment discontinuation.

As the treatment of stable angina implies use of pharmacological therapy to control ischemic cardiovascular events (e.g., statins, anti-platelet agents, and angiotensin converting enzyme inhibitors), most of the patients need to take four or more medications long term. In addition, proper control of risk factors such as diabetes or hypertension may require addition long term Pharmacological therapy. In this context, it is not unusual to see patients who need to take 7 or 8 different agents everyday. This is obviously associated with poor long term compliance[2].

There are limitations in patients with comorbidities for e.g, patients with angina pectoris and congestive heart failure. It is impossible to institute beta blockers or other negative inotropic anti anginal agents, and it is usually necessary to discontinue them if they were previously prescribed. Nitrates and nitrate like agents are often the only anti-ischemic therapy that can be used. Patients with angina and congestive heart failure remain undertreated with beta blockers[2].

Ivabradine is a specific inhibitor of the I_f (f is for “funny” so called because it had unusual properties compared with other current systems known at the time of its

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discovery) ion current that lowers heart rate without impacting contractility, conduction, or repolarization. Heart rate reduction decreases myocardial oxygen demand and increases perfusion by increasing diastolic filling time in the coronary circulation[3]

Heart rate reduction is an important component in the treatment of patients at increased risk of death from cardiac disease[4]. Contrary to beta blockers, I_f inhibition increases stroke volume and improve left ventricular function and ventricular remodelling[5,6]. It is safe and its most frequent side effects are mild, dose-related, transient, and reversible visual symptoms.

Ivabradine maintains the heart rate reduction over the year of follow up. The number of angina attacks reported by patients was reduced significantly by the addition of Ivabradine.

MATERIALS AND METHODS:

It was a hospital based clinical study done in cardiology Out Patient Department in a tertiary hospital. Patient with known history of IHD and newly diagnosed were selected according to inclusion and exclusion criteria. Patient information was collected in-person after informed

Consent in prospective cases and from case sheet (with permission from medical records department) in retrospective cases. Ivabradine was started as 5 mg per day. Complete cardiac investigations (ECG, ECHO, various lab tests) were taken on day of starting Ivabradine, then at 3rd & 6th months of follow-up.

Information was collected with the help of preformed questionnaire. Parameters seen in echo are: Ejection fraction, Interventricular septal thickness, Posterior wall thickness & Left ventricular internal diameter in diastole.[7] Left ventricle mass was calculated using 2 formula [8] based on the parameters seen in echo. Left ventricular hypertrophy cut off value was kept as 259(male)/166(female) [9]

Routine follow up was given by cardiologists and necessary intervention was made. No dose reduction or change of medicament was done nor surgical intervention required for the selected patients under study

Inclusion criteria:

- Presence of clinical heart failure for greater than or equal to 3 months before the screening visit. At the time of enrolment they should be in NYHA functional class 1-3 heart failure.
- Left ventricular ejection fraction (LVEF) of greater than or equal to 50% (by echo or ventriculography) within 3 months of screening and LVEF still greater than or equal to 50% on day of enrolment
- BNP (b-type natriuretic peptide) greater than or equal to 200 pg/ml at the time of heart failure diagnosis
- Patients must be euvolaemic on clinical examination and have been clinically stable for atleast 4 weeks with no medication changes
- Systolic blood pressure less than or equal to 150 mmHg but >85 mmHg and diastolic blood pressure less than or equal to 95 mmHg for 4 weeks prior to and at the time of enrolment
- Able to walk at least 50 meters at the time of enrolment

Exclusion criteria:

- Aged <18 or >85
- Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant
- Any planned revascularization i.e. CABG or stenting or performed within last 90 days
- Any myocardial infarct within last 90 days
- Significant chronic obstructive airway disease in the opinion of the investigator
- Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial construction
- Inability to sign informed consent
- Atrial fibrillation
- Heart transplant recipient
- Currently implanted left ventricular assist device
- Stroke in past 90 days
- Gastrointestinal disorder that could interfere with study drug absorption

Statistical analysis like Mean, Hotellings t square, F value and P value were calculated using SPSS software 17th version

RESULTS:

Ejection fraction is improved and clinical significance is there on both follow ups. Hotelling t square value is 65.115. statistically significant with p value <0.05 (p=0.00). Left ventricular internal diameter is reduced on both follow ups & has clinical significance. But there is no statistical significance, p value > 0.05(p=0.086). Hotellings t square value is 5.792. Left ventricular mass shows Devereaux regression (reduction in left ventricle mass which is used for calculating clinical improvement) calculated using 2 formulas and it is a positive factor for clinical improvement. No Adverse Drug Reaction reported with regular intake of Ivabradine, under prescription. Other possible indications for use of Ivabradine in Ischemic heart diseases are explored to be heart failure, left ventricuar dysfunction & cardiomyopathy.

IVABRADINE:

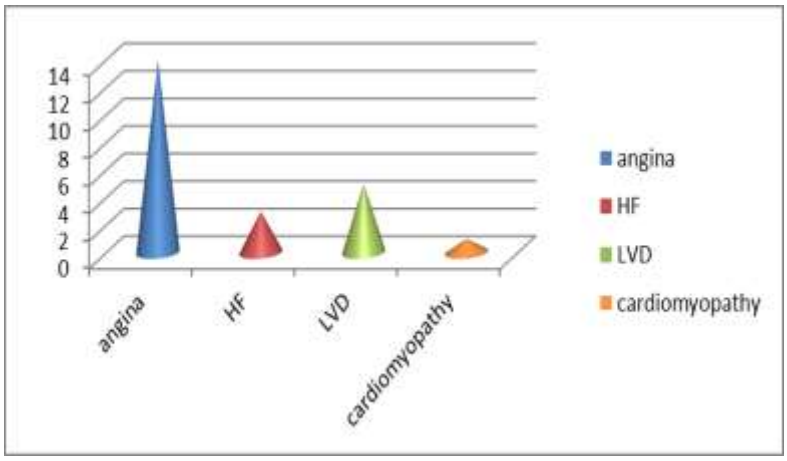

Figure 1: indications for ibvabradine observed in this study

Y axis- number of patients precribed Ivabradine for specific IHD

Before treatment:

CATEGORY	I	II	III	IV
NO. OF PTS	3	6	10	4

After treatment:

CATEGORY	I	II	III	IV
NO. OF PTS	6	12	3	2

Figure 2: NYHA categories before and after treatment with ivabradine

NYHA (New York Heart Association Classification For Angina):
Grade I : No symptoms with ordinary physical activity
Grade 2 : symptoms with ordinary physical activity
Grade 3 : symptoms with less than ordinary physical activity
Grade 4 : symptoms at rest

Table 1: improvement in the clinical parameters as by ECHO

FACTOR	TIME	MEAN ±SD	T SQUARE	F VALUE	P VALUE
EJECTION FRACTION	On start	40.8696 ± 17.00616	65.115	31.078	0.000
	After 3 months	47.1304 ± 16.31314			
	After 6 months	54.6087 ± 17.00465			
LEFT VENTRICUAR(LV) INTERNAL DIAMETER	On start	7.6583 ± 10.82240	5.792	2.765	0.086
	After 3 months	5.0709 ± 1.21833			
	After 6 months	5.3530 ± 1.38689			
LV MASS USING FIRST FORMULA	On start	271.4522± 86.84357	0.787	0.376	0.691
	After 3 months	263.5304± 78.67210			
	After 6 months	258.2739±104.50367			
LV MASS USING SECOND FORMULA	On start	229.1870± 69.96502	1.082	0.517	0.604
	After 3 months	218.5700± 68.64594			
	After 6 months	215.3652± 87.65552			

FIRST FORMULA[8]:

Left ventricular mass = $1.04[(IVS + PW + LVID_d)^3 - LVID_d] - 13.6$ g

IVS – interventricular septum

PW – posterior wall

$LVID_d$ – left ventricular internal dimension in diastole

SECOND FORMULA[8]:

Left ventricular mass= 1.04[(LVID+ PWT + IVST)-LVID]*0.8+0.6

LVID – Left ventricular internal dimension

PWT – Posterior wall thickness

IVST – inter ventricular septal thickness

DISCUSSION:

In the present study, the quality of life with ivabradine is studied. There is no intererence with cardiac, respiratory or sexual function. It shows clinical improvement. There was improvement in carrying out day-to-day activities as assessed by NYHA parameters also (FIG 2). No Adverse Drug Reaction is reported. The changes in heart rate got stabilized over time. No sinus bradycardia reported.Patient compliance is great. No drug-drug interactions with polypharmacy. Improved left ventricular remodelling.

Ivabradine is selective I_f inhibitor and does not has negative inotropic effects, it can be safely prescribed to all ischemic cardiovascular disorders apart from angina. This study thus revealed
the possible indications of ivabradine in ischemic heart diseases(FIG-1) and duration needed for its impact on the pathophysiology of ischemic heart diseases (TABLE-1)

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