

Efficacy of “Ivabradine” in Patients with Idiopathic Dilated Cardiomyopathy as assessed by Echocardiography

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Introduction

Contemporary with the recent understanding of the pathophysiology of heart failure as a neurohormonal syndrome, Beta-adrenoreceptor blockers (BBs) represented a breakthrough in the pharmacologic treatment of patients with heart failure through quelling of the deleterious effects of sustained activation of the nervous system. The benefits of BBs in myopathic ventricles are multifactorial and are partly attributable to gradual reduction in the heart rate.

However, a considerable percentage of patients does not receive BBs due to several reasons, such as absolute contraindications and intolerance to the recommended doses[1].

Ivabradine is a novel drug that acts through blockade of I_f channel (cardiac pacemaker f-current) and leads to selective reduction of the heart rate without influencing the conduction system nor contractility. It selectively inhibits the I_f current in the sinus node by binding to the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels from the intracellular side of the membrane of the pacemaker cells with higher affinity (and its main metabolite, S 18982) to the HCN4 isoform, the main isoform in the heart [2].

Normally, the expression of HCN4 channels is low in Purkinje fibers and the ventricles, however in failing hearts, the

density of HCN channels and I_f current are increased as a part of complex ionic remodelling which may have important implications regarding ventricular arrhythmogenesis, particularly related to enhanced automaticity [3-5].

Changes in autonomic regulation with a shift towards a higher sympathetic tone associated with end-stage heart failure may also influence the I_f expression in ventricular myocardium. Consequently, inhibition of the I_f current in these circumstances may have an anti-arrhythmic effect or might suppress idioventricular rhythm [6].

Experimental studies using a chronic heart failure model in rats demonstrated that ivabradine effectively reduced heart rate, increased stroke volume, decreased left ventricular systolic diameter and improved myocardial function, probably due to its ability to shift the ventricular systolic pressure-volume curve leftwards and reduce collagen accumulation [7,8].

Aim of the work

To prospectively assess the efficacy of I_f channel blocker as an add on therapy in patients with idiopathic dilated cardiomyopathy using echocardiography.

Patients and Methods

Patient selection:

Thirty patients with idiopathic dilated cardiomyopathy will constitute the population of the study. All will be receiving the optimal medical therapy according to the international guidelines which include:

- 1. Maximally tolerated dose of ACEI.*
- 2. Maximally tolerated dose of carvedilol.*
- 3. Aldosterone antagonist.*

In addition to loop diuretics and other medications as the clinical status of the patient dictates.

Inclusion criteria:

Patients admitted to Ain Shams University hospitals presenting with idiopathic dilated cardiomyopathy; NYHA III-IV; LVEF $\leq$ 40%.

Exclusion criteria:

Patients who have one or more of the following will be excluded from the study:

- 1. Patients who are less than 18 years old.*
- 2. Pregnant females.*

3. *Patient with previous history or currently suffering from ischaemic heart disease.*
4. *Patients suffering from atrial flutter or atrial fibrillation.*
5. *Patients suffering from Rheumatic heart disease.*
6. *Patients suffering from advanced liver cell failure.*
7. *Patients suffering from advanced renal failure.*
8. *Patients suffering from congenital heart disease.*
9. *Patients suffering from hypertrophic, restrictive cardiomyopathy or types of cardiomyopathy other than dilated cardiomyopathy.*
10. *Patients with idiopathic dilated cardiomyopathy with HR below 60 bpm prior to randomization.*
11. *Patients with diseases that cause sinus tachycardia such as moderate to severe anemia.*

Methods:

- **The suitable patients will be subjected to:**

1. Thorough history taking and clinical examination assessing

- a. NYHA class
- b. signs of systemic and pulmonary congestion.

2. Baseline lab assessment including

- a. CBC (HB %),
- b. serum creatinine level
- c. serum sodium and potassium level
- d. liver function tests (ALT and AST)

with follow up after 3 months.

3. Echocardiographic (ECHO) examination done at the start of the study and 3 months after (according to the recommendations of the American society of Echocardiography) assessing

- a. Left ventricular end diastolic and endsystolic diameters (LVEDD, LVESD) using short axis parasternal window at the level of papillary muscles.
- b. Left ventricular end diastolic and endsystolic volumes (LVEDV, LVESV).
- c. Ejection fraction and fractional shortening (by M-mode and 2D).

- d. Left atrial diameter.
- e. Mitral regurgitation; its presence and severity as measured by area in cm^2 ; using apical 4 chamber and parasternal long axis views.
- f. systolic pulmonary artery pressure using TR.

➤ **The patients will be randomized into two main groups:**

- a. Study group: who will receive Ivabradine (Procoralan) as an add on therapy in an increasing titrated dose till reaching a resting heart rate of 60 bpm or the patient reaches 7.5 mg twice daily.

The starting dose will be half a 5mg tablet (i.e. 2.5mg) every 12 hours for 2 weeks, then one tablet 5mg every 12 hours for 2 weeks, then 7.5mg tablet every 12 hours.

- b. Placebo group: who will receive a placebo (control group).

➤ **Then all the patients will be followed up for at least three months for NYHA class and echocardiographic parameters, then data analysis will be conducted by comparing the results of pre and post treatment examination.**

Statistics

Data will be subjected to adequate statistical analysis including mean +/- standard deviations and the results will be thoroughly discussed.

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LIST OF CONTENTS

• Introduction	1
• Aim of the work	3
• Review of literature	4
Chapter 1: Dilated Cardiomyopathy	4
• Definitions and classifications of “cardiomyopathy	4
• Dilated Cardiomyopathy (DCM)	8
➤ Definition	8
➤ Diagnostic criteria	8
➤ Etiology	9
➤ Pathophysiology of HF in patients with DCM	15
➤ Clinical Evaluation of patients with DCM	23
➤ Investigations	26
➤ Management of patients with DCM	30
I) General measures	30
II) Pharmacological treatment	30
III) Device Therapies and Surgical Management	42
IV)Emerging specific therapies	47
Chapter 2: Heart Rate Reduction by “Ivabradine” as a New Therapeutic Approach in Heart Failure	48
➤ Rationale for the benefits of HR reduction in HF	48
➤ HR reduction by Ivabradine	53
➤ Ivabradine and left ventricular remodeling	57

• Patients and methods	62
• Results	73
• Discussion	91
• Conclusion	99
• Recommendations	100
• Summary	101
• References	104
• Master table	124
• Arabic Summary	127

List of Tables

Table No	Title	Page
1	WHO classification of cardiomyopathies	5
2	The Criteria for the Diagnosis of Heart Failure in the Framingham Heart Study.	25
3	ACC/AHA stages of heart failure and NYHA classification	26
4	Investigations that are indicated in the management of a case of heart failure.	27
5	Common echocardiographic abnormalities in heart failure .	29
6	Diuretics used for treating fluid retention in chronic HF.	41
7	Indications for Cardiac Transplantation	45
8	Demographic characteristics of both groups at randomization	75
9	Risk factor distribution within both groups	76
10	Baseline characteristics of the clinical parameters of both groups at randomization	77
11	Baseline characteristics of the population study at randomization as regards various echocardiographic parameters	78
12	Distribution of patients according to their NYHA functional classes in each group after 3 months	79
13	Blood pressure (systolic and diastolic) and resting heart rate readings at baseline and after 3 months of randomization in both groups and the percent change(from baseline) in each group and the p-value regarding the percent change.	81
14	Echocardiographic parameters of group (A) at baseline(pre-randomization) and at 3 months	84
15	Echocardiographic parameters of group (B) at baseline and at 3 months	85
16	Mean percent change (at 3 months from baseline) in both groups as regards various echocardiographic parameters.	85
17	Mean resting heart rate achieved after 3 months in each NYHA functional class at 3 month within the study population	87

List of Figures

Fig. No.	Title	Page
1	Primary cardiomyopathies that primarily manifest with cardiac involvement according to AHA expert panel 2006 classification	6
2	Classification of cardiomyopathies. : A position statement from the ESC working group on myocardial and pericardial diseases	7
3	Vicious cycle in systolic dysfunction. Different remodelling stimuli induce complex cellular changes, ultimately resulting in systolic and/or diastolic dysfunction and increased wall stress, thereby promoting pathological remodeling	23
4	Sites of action of diuretics on the kidney	41
5	1 year mortality with SD (Kaplan-Meier estimate) according to baseline heart rate and study treatment group in CIBISII trial. Patients were divided into tertiles of distribution of heart rate change over entire population.	50
6	Distribution of patients according to heart rate after 2 months in CIBIS II trial. Patients were divided into tertiles of distribution of heart.	50
7	Pure heart rate reduction achieved with the I _f current inhibitor, Ivabradine (Procoralan)	54
8	Cardiac output, stroke volume, and left ventricular diastolic as well as systolic cavity diameters determined in anesthetized rats with chronic heart failure, either untreated, or treated per os with ivabradine at the dose of 10 mg/kg/day during the last 4 days of the 90 day observation period	58
9	Heart rate, cardiac output, stroke volume, and left ventricular diastolic as well as systolic diameters determined in anesthetized rats with chronic heart failure, either untreated or treated per os for 90 days with ivabradine at the dose of 10 mg/kg/day	58
10	Distribution of gender, risk factors and NYHA class among the whole study population.	74
11	Comparison between group (A) and (B) as regards gender distribution.	75

12	Risk factors distribution among the study groups.	76
13	Baseline distribution of NYHA functional classes of patients in both groups.	77
14	Distribution of the NYHA functional classes of patients 3 months post- randomization in both groups.	79
15	Pie charts showing distribution of patients with NYHA functional class change after 3 months of randomization in both groups	80
16	Changes in clinical parameters A(SBP), B(DBP) and C(resting heart rate) in both groups at day 0 and day 90.	82
17	Illustration of the mean percent change in the echocardiographic parameters at baseline assessment and at 3 months post-randomization in both ivabradine and placebo groups. (A) LVEDD, LVESD, LVEF(M-mode), FS , (B)LVEDV, LVESV, EF (2D) and (C) LAD, MR area, PASP	86
18	Mean resting heart rate achieved after 3 months in each NYHA functional class at 3 months within the study population	87
19	Correlation between the mean percent change in heart rate from the baseline and mean percent change in LVEDV	88
20	Correlation between the mean percent change in heart rate from the baseline and mean percent change in LVESV	88
21	LV systolic function measured by M-mode(left) and 2D(right) at randomization of patient no.(3) who was randomized in the ivabradine group (group”A”)	89
22	LV function measured by M-mode(left) and 2D(right) after 3 months of regular anti-failure treatment and ivabradine of patient no.(3).	89
23	LV function measured by M-mode(left) and 2D(right) at randomization of patient no.(24) who was randomized in the control group (group”B”).	90
24	LV function measured by M-mode(left) and 2D(right) after 3 months of regular anti-failure treatment and ivabradine of patient no. (24)	90