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

Thesis submitted for partial fulfillment of Master's degree in Cardiology

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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 carvidolol.

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≤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.

٢.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.

٣.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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