CARVEDILOL THERAPY IN CHILDREN WITH DILATED CARDIOMYOPATHY

A prospective randomized blind trial among Egyptian children

Thesis

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BY

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Abstract

Dilated cardiomyopathy (DCM) is the most common type of heart muscle disease in children. Because the cause of DCM is unknown, specific therapy is not possible and so the treatment of DCM is essentially that of congestive heart failure. This study shows that the use of carvedilol as adjunct therapy in pediatric patients with dilated cardiomyopathy improves the clinical status of the patients and both systolic and diastolic functions of the heart. 53 pediatric patients were examined and followed up for four months after being divided into two groups; study group (27 cases who received carvedilol beside the anti-failure drugs) and control group (26 cases who received placebo and anti- failure drugs i.e. digitalis, furosemide, captopril and aspirin). The end results showed that there is a significant improvement in NYHA class, FS%, LVESD and LVEDD in the patients of the study group which was not obtained in the control group.

Key words: Carvedilol, DCM

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List of abbreviations

ACE: Angiotensin Converting Enzyme.

COMET: Carvedilol or Metoprolol European Trial.

CHF: Congestive Heart Failure.

DCM: Dilated Cardiomyopathy.

EF: Ejection Fraction.

FS: Fraction Shortening.

HCM: Hypertrophic Cardiomyopathy.

HF: Heart Failure.

HLA: Human Leukocyte Antigen.

IDC: Idiopathic Dilated Cardiomyopathy.

LVEDD: Left Ventricular End Diastolic Dimension.

LVESD: Left Ventricular End Systolic Dimension.

MR: Mitral Regurgitation.

NYHA functional class: New York Heart Association functional class.

PG: Prostaglandin.

RCM: Restrictive Cardiomyopathy.

TNF: Tumor Necrosis Factor.

Introduction and Aim of the Work

INTRODUCTION

Heart failure (HF) can be defined as a clinical syndrome in which the heart is unable to adequately fulfill its pumping function and cannot supply enough oxygenated blood to meet demand necessary for normal tissue metabolism, including that necessary for growth and development. Standing out among the principal etiologies of childhood heart failure are congenital heart diseases, rheumatic disease, arrhythmia, myocarditis and dilated cardiomyopathy (DCM) ***[Vitor M. P. Azevedo, et al., 2005]***.

According to the World Health Organization, DCM is characterized by dilatation and inadequate contraction of the left ventricle or of both ventricles. It can be idiopathic, familial or genetic, associated or not with an innate error of metabolism, viral and/or immunological, alcoholic/toxic or associated with recognized cardiovascular diseases in which the degree of myocardial dysfunction cannot be explained by the abnormal load conditions or by ischemic damage. Histology is non-specific. Presentation is generally by heart failure, which is normally progressive. Arrhythmia, thromboembolism and sudden death are common and may occur at any stage of the disease ***[Vitor M. P. Azevedo, et al., 2005]***.

Because the cause of dilated cardiomyopathy (DCM) is unknown, specific therapy is not possible and so the treatment of

DCM is essentially that of congestive heart failure ***[Bruns et al., 2001].***

It was thought that Carvedilol, in addition to standard therapy for dilated cardiomyopathy in children improves cardiac function and symptoms; it is well tolerated, with minimal adverse effects, but close monitoring is necessary as it might worsen congestive heart failure and precipitate asthma. Control studies are necessary to assess the effect of carvedilol on mortality and hospitalization rates ***[Rusconi et al., 2004].***

Objective and Aim of the work

This study aims to assess the role of Carvedilol, which is a beta-blocker in the treatment of children with dilated cardiomyopathy, and to demonstrate its effects and tolerability.

Review of Literature

Cardiomyopathies

Definition:

Cardiomyopathies are heart muscle disorders that affect all chambers of the heart. The ventricular systolic function, diastolic function, or both functions are disrupted leading to an inadequate blood flow to organs and tissues of the body ***[Towbin,et al., 2006].***

Classification:

Cardiomyopathy was classified from a functional standpoint into:

1- Dilated cardiomyopathy [DCM], most common form, characterized by ventricular dilatation, hypocontractile to variable degrees and systolic dysfunction as the main clinical feature producing signs and symptoms of congestive heart failure. Most forms of secondary cardiomyopathy are of this type.

2- Hypertrophic cardiomyopathy [HCM], formerly known as idiopathic hypertrophic sub-aortic stenosis, characterized by left ventricular hypertrophy that may be asymetric leading to symptoms of left ventricular outflow tract obstruction, systolic function is usually preserved however, there is a diastolic dysfunction or arrhythmias which result in sudden death.

3- Restrictive cardiomyopathy [RCM], with impaired diastolic filling, markedly dilated atria with generally normal ventricular dimensions and systolic function. Symptoms result from pulmonary and right-

sided systemic venous congestion. Syncope may also be a presenting feature.

4- Arrhythmogenic right ventricular cardiomyopathy (ARVC) arises from an electrical disturbance of the heart in which heart muscle is replaced by fibrous scar tissue. The right ventricle is generally most affected.

5- unclassified if it had features of more than one functional type.

[Friedberg et al., 2008].

Although the World Health Organization classifies acute viral myocarditis as an inflammatory cardiomyopathy distinct from DCM, both groups were classified here as DCM because of their similar echocardiographic appearances. ***[Gerald Cox, et al., 2006]***.

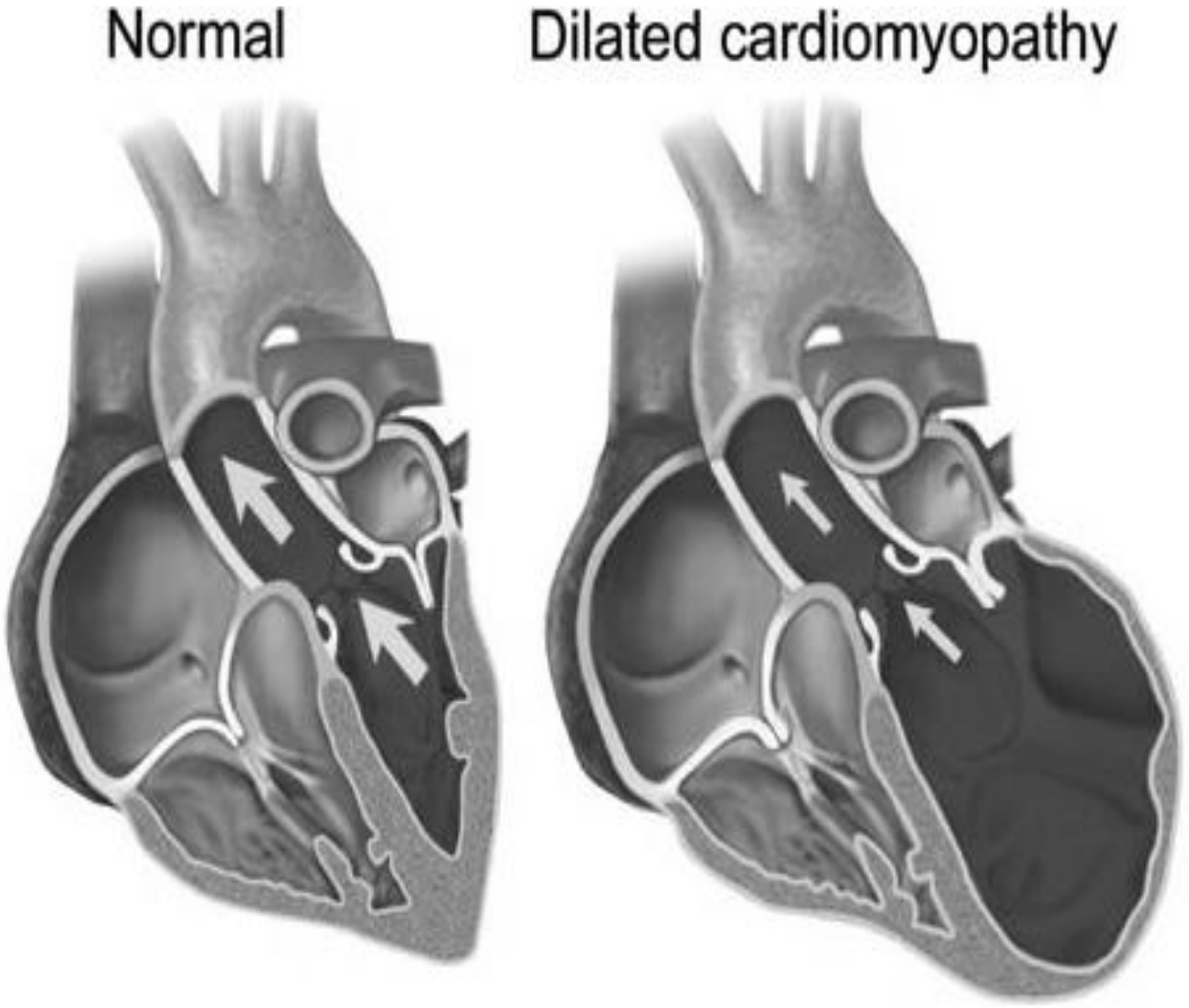
Aetiology:

The following table lists the known causes of cardiomyopathies in childhood ***[Towbin et al., 2006], [Denfield et al., 1998].***

Infection *Viral:* Coxsackievirus B and A Echovirus Adenovirus Mumps Rubella, Rubeola *Bacterial:* Diphtheria Meningococcal Gonococcal *Fungal:* Candidiasis Aspergillosis *Protozoal:* American trypanosomiasis (Chigas disease) Toxoplasmosis *Rickettsial:* Rocky mountain spotted fever *Spirochetal:* Lyme disease **Metabolic conditions** *Endocrine* Thyrotoxicosis Hypothyroidism Diabetes mellitus Infant of diabetic mother Diabetic cardiomyopathy Hypoglycemia Pheochromocytoma Neuroblastoma Catecholamine	**Nutritional deficiency:** Protein: Kwashiorkor Thiamine: Beriberi Vitamin E and selenium (Keshan disease) Phosphate Others Carnitine deficiency b-ketothiolase deficiency Hypertaurinuria **General system disease:** *Connective tissue disorder:* Systemic lupus Juvenile rheumatoid Polyarteritis nodosa Kawaaki disease Pseudoxanthoma elasticum *Infilterations and granulomas:* Leukemia Sarcoidosis Others Hemolytic uremic syndrome Mitochondrial cytopathy Reye syndrome Peripartumcardiomyopathy Osteogenesis imperficta Noonan's syndrome **Heredofamilial conditions:** *Muscular dystrophies and myopathies:* Juvenile progressive (Duchenne) Myotonic dystrophy (Steinert) Limb-girdle (Erb)

cardiomyopathy Congenital adrenal hyperplasia **Familial storage disease:** *Glycogen storage disease:* Pompe disease (Type II) Cori disease (Type III) Andersen disease (Type IV) McArdle disease (TypeV) Hers disease (Type VI) *Mucopolyaccaridosis:* Hurter syndrome Hunter syndrome Sanfilippo syndrome Morquio syndrome Scheie syndrome Maroteaux-Lamy syndrome *Sphingolipidosis:* Nieman- Pick disease Farber disease Fabry disease Gaucher disease Tay-Sachs disease Sandhoff disease Gm1 gangliosidosis Refsum disease	Cardioskeletal myopathy (Barth syndrome) X-linked cardiomyopathy Juvenile progresive spinal muscular atrophy (Kugelberg-Welander) Nemaline myopathy Myotubular myopathy *Neuromuscular disorders:* Friedreich's ataxia Multiple lintiginosis **Ischemic:** Congenital coronary artery malformation Familial hypercholesterolemia Post vasculitis (Kawasaki) **Sensitivity and toxic reactions:** sulphonamides penicillin anthracyclines iron (hemachromatosis) chloramphenicol **Tachyarrhythmias:** Supraventricular tachycardia Atrial flutter Ventricular tachycardia

Dilated cardiomyopathy (DCM)



A normal heart is shown on the left compared to a heart with dilated cardiomyopathy on the right. Note the increased dimensions of the left ventricle.

[Franklin, et al, 2000]

Definition:

Idiopathic dilated cardiomyopathy (ICM) refers to congestive cardiac failure secondary to dilatation and systolic dysfunction (with or without diastolic dysfunction) of the ventricles (predominantly left) in the absence of congenital, valvular, or coronary artery disease or any systemic disease known to cause myocardial dysfunction. DCM is the most common type of heart muscle disease in children ***[Michels, et al., 2008].***

All 4 cardiac chambers are dilated and are sometimes hypertrophied. Dilation is more pronounced than hypertrophy, and the left ventricle is affected more often than the right ventricle. The cardiac valves are intrinsically normal, although the mitral and tricuspid valve rings are dilated, and the valve leaflets do not appose each other in systole, giving rise to varying degrees of mitral regurgitation, tricuspid regurgitation, or both. Persistent mitral regurgitation leads to thickening of the mitral valve leaflets, and, at times, distinguishing this thickening from other causes of mitral regurgitation is difficult. Thrombus formation (secondary to the low-flow cardiac output state) is often seen in the left ventricular apex and, at times, is seen in the atria. Occasionally, the right ventricle is preferentially involved in the cardiomyopathic process; this often indicates a familial basis ***[Michels,et al., 2003].***

Incidence:

The **incidence** of DCM is about 5-8 cases per 100,000 population per year. ***[Andrews, et al., 2008].***