The Effect of Growth Hormone on Idiopathic Dilated Cardiomyopathy

K. A. Mohseni, MD, V. Mokhberi, MD and S. Abdi, MD

Abstract

Objective- Idiopathic dilated cardiomyopathy (IDCM) is currently an important cause of mortality and morbidity due to chronic heart failure. The aim of our study was to assess whether there could be any clinical and /or echocardiographic improvement in patients with IDCM who had undergone treatment of recombinant human growth hormone (GH).

Methods- Fourteen patients with IDCM and moderate heart failure (e.g. New York Heart Association functional class II-III) were studied at base line, immediately and 3-months after treatment with GH. The study was a double-blind clinical trial. Traditional treatment (e.g. digoxin, ACEI, B-blocker and diuretics) was continued during the study. Cardiac performance was evaluated with clinical and echocardiographic examinations.

Results- In spite of statistical improvements in the left ventricular ejection fraction (LVEF)(mean ±SD from 35.6±5.9% at the base line of this study to 39.6%±6.7% immediately and 39.3%±7.9% three months after treatment, *p* value <0.05), other data of the clinical and echocardiographic findings were not significantly different between base line and post-treatment.

Conclusion- We conclude that 3-months of GH therapy in patients with idiop thic dilated cardiomyopathy had little beneficial effects on cardiac mass and performance ***(Iranian Heart Journal 2003; 4 (4):68-71).***

Key words: Idiopathic cardiomyopathy ■ Growth hormone ■ Cardiac performance

Idiopathic dilated cardiomyopathy (IDCM) is a major factor of cardiac dysfunction.[1,2] It is characterized by progressive dilatation of the ventricles. This process accounts for the marked elevation of left ventricular systolic wall tension, which is a function of both wall thickness and chamber size.[3]

There is no specific therapy for IDCM. Medical management is aimed at the alleviation of the symptoms. Only cardiac transplantation offers final treatment for this condition.

Evidence is accumulating that GH is a physiologic regulator of myocardial growth and performance.[4-6]

Administering GH to patients with congenital deficiency increases wall thickness and normalizes cardiac performance.[7,8] On the other hand, a long–term excess of GH causes cardiac hypertrophy and a hyperkinetic syndrome, with increased cardiac output and reduced vascular resistance.[9,10]

More recently, GH itself has been shown to improve cardiac function in experimental heart failure,[12] and GH activated cardiac cell growth.[11-13] On the other hand, there are data against this finding which indicate no beneficial effect on cardiac performance by GH therapy. [15]

These observations provide a rationale for testing the effect of GH in patients with heart failure due to IDCM.

This study has been conducted in our cardiac center since Autumn 1998, with 14 consecutive patients having undergone

From the Department of Cardiology , Imam Khomeini Hospital , Sari , Iran
Correspondence to: K. A. Mohseni, MD, Imam Khomeini Hospital, Sari, Iran

treatment with recombinant human growth hormone in a case-control study.

Methods

The study involved 14 patients with IDCM. The patients were divided into two groups and were studied with randomized double-blind clinical trial. The case group consisted of 7 patients (4 men, 3 women) and their mean age was 55±7 years (ranging from 45 to 65 years). The mean clinical duration was 8 ±2 years. Four patients were NYHA functional class II and 3 patients were NYHA functional class III. The control group comprised 7 patients (5 men, 2 women) with a mean age of 49±10 years (ranging from 35to 65years). The mean (±SD) clinical duration was 7 ±3 years. Four patients were NYHA FCII and 3 patients were NYHA FC III.

The criteria for enrollment in this study were clinical evidence of heart failure despite traditional therapy and LVEF below 45% as assessed with echocardiography. The exclusion criteria were the presence of coronary artery disease, valvular heart disease, systemic hypertension, hypertrophic cardiomyopathy and active myocarditis. The patients were treated with traditional drugs (such as digoxin, ACEI, B-blockers and diuretics). Written informed consent was obtained from each patient.

Study–Protocol

All the patients were studied at three times: base line, immediately and 3-months after treatment. GH was administered subcutaneously at a dose of 0.15 u/kg/week divided every other day, which is a low replacement dose for patients with GH deficeincy for 3-months.

Procedures

Doppler echocardiography measurements were performed with a Vingmed 750 system; parameters were calculated with echocardiography, including left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), left ventricuar ejection fraction (LVEF), E-point septal separation (EPSS), interventricular septal thickness (IVSTh) and left posterior wall thickness (LPWTh) in both groups.

All data are presented as means ±SD. The effects of GH on hemodynamic measurements were compared by means of the Student T-test.

Results

All the patients completed the three-month course of GH treatment with no reported side effects. Echocardiographic data of case and control groups are shown in Table I and II, respectively. GH therapy induced no significant increase in LV mass and wall thickness and neither LVEDD nor LVESD was changed by GH therapy. GH improved the LVEF both immediately and 3-months after treatmeant (35.6±5.9 to 39.6±6.7 and 39.3±7.9, respectively, *p* value <0.05).

Table I. Echocardiographic data before, immediately and 3-months after GH therapy in the case group.

Indices	At base line	Immediately treatment after	3-months after treatment	P-Value
LVEF(%)	35.6±5.9	39.6±6.7	39.3±7.9	<0.05
EPSS(mm)	21.1±7.5	20.7±6.8	20.6±8.3	NS
LVEDD(mm)	62.8±9	62.7±10.3	64.4±9.4	NS
LVESD(mm)	54±10.5	53± 11.1	52.6± 12.8	NS
IVSTh(mm)	11±1	11.1±1.6	10.7±1.4	NS
LVPWTh(mm)	10.3±1.1	10.4±1.5	10.1±1.2	NS

LVEF=Left ventricular ejection fraction
EPSS = E-point septal separation
LVEDD=Left ventricular end diastolic dimension
LVESD = Left ventricular end systolic dimension
IVSTh = Interventricular septal thickness
LVPWTh=Left ventricular posterior wall thickness
NS=not significant

Table II: Echocardiographic data before, immediately and 3-months after GH therapy in the control group.

Indices	At base line	Immediately after treatment	3-months after treatment	P-Value
LVEF(%)	32.7±8.6	30.3±8	28.3±12	NS
EPSS(mm)	23.7±9.5	23±8.6	23.3±9.6	NS
LVEDD(mm)	69.8±12.4	69.9±13.3	69.5±12.5	NS
LVESD(mm)	61±14.5	62± 16.9	60.7± 15.7	NS
IVSTh(mm)	10±2.6	10.1±2.6	9.7±2	NS
LVPWTh(mm)	10± 3	9.7±2.2	9±2.6	NS

LVEF=Left ventricular ejection fraction
EPSS = E-point septal separation
LVEDD=Left ventricular end diastolic dimension
LVESD = Left ventricular end systolic dimension
IVSTh = Interventricular septal thickness
LVPWTh=Left ventricular posterior wall thickness
NS=not significant

Discussion

In this study, we attempted to induce an improvement of cardiac performance by GH therapy, but the result of our investigation revealed few beneficial effects of recombinant human growth hormone therapy on left ventricular mass, dimension and ultimately cardiac performance.

Beneficial effects of GH on cardiac function have been reported in humans with GH-deficiency and idiopathic dilated cardiomyopathy.[11-14]

On the other hand, there are data that indicate GH therapy shows no effects on the left ventricular performance.[15]

The exact mechanism of action of GH on the heart is unclear. Evidence for direct and indirect effects of GH on cardiac function is based on the observation of GH and IGF-I receptors on the heart and the increment in cardiac IGF-I mRNA in response to GH administration. Furthermore, the development of ventricular hypertrophy in experimental models of hypertension in rats is associated with increased expression of IGF-I mRNA.[16] This pattern of hypertrophy appears to be more physiological than that due to mechanical overload.[17] *In vitro* studies of the direct effects of IGF-I on cardiac myocytes demonstrate an enhancement of contractility and an increase in the size of cultured cardiac myocytes.[18]

Such changes are not seen with an *in vitro* administration of GH. The lack of acute effects of GH has been comfirmed by others.[19] Conversely, the *in vivo* administration of GH (and IGF-I) produces an increase in left ventricular mass by echocardiography.[20] This suggests that the *in vivo* mechanism of action of GH on the heart is mediated at least in part by IGF-1, as observed in other organs and tissues. These findings are consistent with an important role for the GH/IGF–1 axis in determining cardiac morphology and function. The mechanism of action of the GH/IGF-1 axis on the heart is poorly defined but may include a combination of protein anabolic effects. and In animal models of long–term GH–excess, a paradoxical alteration in myosin heavy chain isoform in favor of the V3(β-β) isoform is seen. This isoform is associated with a lower shortening velocity and ATPase activity, and may therefore improve energy economy.[9]

Cardiac hypertrophy is an important physiologic adaptation to an excess hemodynamic load on the heart, GH via an increased myocardial mass, and decreasing chamber size, systolic wall stress and peripheral vascular resistance causes improvement of ventricular mechanics.

Indeed, wall stress is a major determinant of myocardial O_2–consumption and energy demand in patients with dilated cardiomyopathy and heart failure.

There are data indicating that patients with congestive heart failure who had low baseline insulin–like growth factor I (IGF-I) are likely to have fewer beneficial effects from GH administration.[14] Whether or not patients have a low level of IGF–I in our

study is not clear, nor is the sufficiency of the course and/or dose of GH administration. These are subjects that require further studies.

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