Original Article

Growth Hormone Therapy

Growth Hormone Therapy in Short Statured: a Study Among Children with Classic Growth Hormone Deficiency

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ABSTRACT

Objective: To determine the mean increase in height in response to growth hormone therapy in short statured children presenting with classic growth hormone deficiency.

Study Design: Quasi experimental study

Place and Duration of Study: This study was conducted at the pediatric endocrine OPD, National Institute of Child Health Karachi from 1st July 2013 to 31st Dec 2013.

Materials and Methods: All patients between 4-15 years of age of either gender presented with height SDS <2 plotted on CDC growth chart having peak serum growth hormone levels <10ng/ml and bone age more than 2 years behind chronological age were enrolled. Mid parental height was calculated and TCR (Target centile range) was plotted. Those patients with GH level <10ng/ml was given biosynthetic GH (Genotropin and Eutropin) in a dose of 15 IU/m^2 6 days a week s/c for 6 months. Bone age was noted at 0 and 6 months.

Results: Mean age of the patients was 9.73 ±2.66 years. There were 47 (52.2%) males and 43 (47.80%) females. Mean body surface area, bone age and chronological age of the patients was 0.76 ±0.18 m^2, 7.04 ±2.56 years and 9.73 ±2.66 years respectively. Mean post treatment increase in height from the baseline at 6 months was 8.79 ± 3.16 cm.

Conclusion: Significant increase in height in response to growth hormone therapy was noted in short statured children presenting with classic growth hormone deficiency.

Key Words: Short Statured Children, Classic Growth Hormone Deficiency, Height

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INTRODUCTION

Short stature is a common problem among children from different parts of the world. It has been a major concern of endocrinologists in developed as well in developing countries. [1] Short stature is defined as height or length more than 2SDS below the mean (<3rd percentile) for particular age and sex. The etiology of short stature is variable but the main cause include familial short stature, constitutional growth delay, growth hormone deficiency due to isolated or panhypopituitarism (classified on basis of hormonal axis involvement)[2], hypothyroidism, hypercortisolism, celiac disease, renal disease, cystic fibrosis various syndromes including classical Laron syndrome and idiopathic short stature (when all other organic and non-organic causes have been ruled out).[3] Growth hormone deficiency may be diagnosed or defined as, the presence of short stature i.e. (height SDS <2 for particular age and sex) and peak GH levels <10ng/ml following two standard provocative test (insulin induced hypoglycemia and clonidine /exercise).[4]

Since short stature is high magnitude problem globally irrespective of cause, primary or secondary. Whereas classic growth hormone deficiency, pituitary growth hormone deficiency if not treated on time can result in dwarfism. So, the establishment of definitive therapeutic response to growth hormone treatment would be beneficial for patients.

Although enormous studies have been done on this subject in neighboring and western countries but there is scarcity of data in Pakistan. Therefore, it is of paramount importance to conduct studies on this topic and to provide best available treatment to the needed patients. Furthermore, as evident from literature that early diagnosis and treatment leads to good prognosis therefore strategies could be made for prompt and early diagnosis and treatment of classic growth hormone deficiency to prevent dwarfism in our population.

MATERIALS AND METHODS

A Quasi experimental trial was conducted at pediatric endocrine OPD of National Institute of Child Health Karachi 1st July 2013 to 31st Dec 2013. All consecutive patients age between 4-15 years of either gender having height SDS <2 plotted on CDC (Centre of disease

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control) growth chart, peak serum growth hormone levels <10ng/ml, and bone age >2 years behind chronological age determined by Pyele's and Gruelich's standard were enrolled. Whereas short stature children with familial cause like short stature of parents, short stature children with constitutional cause of delay of growth and puberty, and short stature children with causes other than growth hormone deficiency (hypothyroidism, celiac disease, chronic kidney disease, Syndromic causes) were excluded.

The sample size was calculated by using WHO Sample Size Determination in Health Studies. Taking reported mean increase in height 9.8±2.9 cms[4], confidence level 95%, and margin of error 0.6 cms, the sample size came out to be 90 short statured children with growth hormone deficiency.

Short stature was defined as height or length more than 2SDS below the mean (<3rd percentile) with respect to age and sex. Growth hormone deficiency was labeled positive on the basis of presence of short stature i.e. (height SDS <2 for particular age and sex) and peak GH levels <10ng/ml following two standard provocative test (insulin induced hypoglycemia and clonidine /exercise). Growth hormone therapy was defined as recombinant (biosynthetic) growth hormone 15IU/m2 6 days in a week S/C for 6 months duration. Mean increase in height was measured at the end of 6 months by the following formula: Mean increase in height = Height at the end of 6 months− height at the baseline (cms).

All patients were evaluated for height (standing height measured with stadiometer), weight, upper to lower segment ratio, X-Ray of left hand/wrist for bone age, SGPT, serum creatinine, thyroid profile and celiac screening test (tTg IgA and IgG) those meeting the exclusion criteria was excluded. Growth parameters was first plotted on CDC growth charts (develop by American National Centre for Health Statistics in collaboration with the National Centre for chronic Disease Prevention and Health Promotion) and all those patients with height below < 2 SDS (3rd percentile was included in the study after satisfying inclusion criteria). Nine Centile United Kingdom charts was used to determine if the child height is below 0.4th centile. Mid parental height was calculated and TCR was plotted to identify the genetic growth potential and to exclude the familial and constitutional causes as well. After initial clinical haematological and endocrine screening, the selected patients were evaluated for growth hormone levels with the help of ITT (insulin tolerance test). Those patients with GH level <10ng/ml were given biosynthetic GH (Genotropin and Eutropin) in a dose of 15 IU/m^2 6 days a week s/c for 6 months. During treatment patients were called for follow up at 3 and 6 months. Follow up included height and weight measurements. Haematological tests including CBC, Serum creatinine, glucose, LFTs and thyroid profile (TSH, free T3 and T4). Bone age determined at 0 and 6 months, recording of side effects if any was measured at the end of 6 months.

Collected data was entered and analyzed using SPSS version 16. Frequencies and percentages were calculated for all qualitative variables like sex and educational status of the parents for which frequencies and percentages were presented. Mean ±SD was computed for numerical variables like age, weight, family monthly income, bone age, choronogical age, pre-treatment height, post treatment height and increase in height from the baseline. Effect modifiers like age, bone age, choronogical age, gender, educational status of the parents and family monthly income was addressed through stratification. Post stratification t test was applied and p value ≤0.05 was taken as significant.

RESULTS

Out of total 90 patients, majority of the patients 50 (55.6%) were presented with ≤10 years of age. The mean age of the patients was 9.73 ±2.66 years. There were 47 (52.2%) males and 43 (47.80%) females. Mean weight of the patients was 19.44 ±6.46 Kg.

Mean body surface area, bone age and chronological age of the patients was 0.76 ±0.18 m^2, 7.04 ±2.56 years and 9.73 ±2.66 years respectively. Majority of the patients 61 (67.80%) had ≤0.8m^2 body surface area while ≤7 years of bone age and ≤10 years of chronological age was found higher, i.e. 46 (51.10%) and 50 (55.60%) respectively.

Table No.1: Baseline characteristics of the patients (n=90)

Variables	Categories	n	%
Age, years	≤10	50	55.56
	>10	40	44.44
Gender	Male	47	52.22
	Female	43	47.78
Body surface area (in m2)	≤0.8	61	67.78
	>0.8	29	32.22
Bone Age	≤7	46	51.11
(in years)	>7	44	48.89
chronological Age (in years)	≤10	50	55.56
	>10	40	44.44
Family Income	≤35,000	42	46.67
(in rupees)	>35,000	48	53.33
Educational Status of Father	≤Matric	17	18.89
	≥Intermediate	73	81.11
Educational Status of Mother	≤Matric	67	74.44
	≥Intermediate	23	25.56
n: number,% Percentage			

Educational status of fathers was ≥intermediate in most of the patients 73 (81.10%) while majority of the mothers 67 (74.40%) had ≤matric educational status. Mean monthly family income was 35,566.67

±16,941.43 rupees. Majority of the patients had >35,000 rupees family income. (Table 1). Mean height SDS before growth hormone therapy was -4.22 ±1.46 while mean SDS after growth hormone therapy was -2.63 ±1.57 (p-value <0.001). Mean height before growth hormone therapy was 111.46 ±15.85 cm while mean height after growth hormone therapy was 120.25 ±15.10 cm (p-value 0.001). Mean post treatment increase in height from the baseline at 6 months was 8.79 ±3.16 cm. (Table 2)

The mean difference of increases in height from the baseline to 6 months after the treatment with respect to baseline characteristics are shown in table 2. Bone age was the only variable found significantly associated with post-treatment increase in height (p-value 0.005) whereas age (p-value 0.272), gender (p-value 0.244), body surface area (p-value 0.091), chronological age (p-value 0.272), family income (p-value 0270), educational status of father (p-value 0.940) and educational status of mother (p-value 0.770) were found to be insignificant.

Table No.2: Difference of post-treatment increases in height with respect to baseline characteristics of the children (n=90)

Variables	Categories	Post-treatment increases in height (cms) from the baseline to 6 months		
		Mean ±SD	p-value	95% CI
Age, years	≤10	9.12 ±2.98	0.272	-0.59 to 2.07
	>10	8.37 ±3.36		
Gender	Male	9.16 ±3.43	0.244	-0.54 to 2.10
	Female	8.38 ±2.82		
Body surface area (in m2)	≤0.8	9.18 ±2.39	0.091	-0.19 to 2.60
	>0.8	7.97 ±2.47		
Bone Age (in years)	≤7	9.70 ±3.23	0.005	0.58 to 3.13
	>7	7.84 ±2.81		
chronological Age (in years)	≤10	9.12 ±2.98	0.272	-0.59 to 2.07
	>10	8.37 ±3.36		
Family Income (in rupees)	≤35,000	8.39 ±1.84	0.27	-2.06 to 0.58
	>35,000	9.13 ±3.96		
Educational Status of Father	≤Matric	8.84 ±1.93	0.94	-1.64 to 1.76
	≥Intermediate	8.78 ±3.39		
Educational Status of Mother	≤Matric	8.73 ±3.13	0.77	-1.74 to 1.31
	≥Intermediate	8.95 ±3.31		

Independent t-test was applied, p-value <0.05 was taken as significant
CI: Confidence Interval, m: meter, SD: Standard Deviation

DISCUSSION

In this quasi experimental design, we have examined the increase in height after 6 months of growth hormone therapy. The findings of our study have showed significant difference in the mean height before and after the treatment. Mean post treatment increase in height from the baseline at 6 months was 8.79 ±3.16 cm. This finding matched with a study conducted in India which showed growth hormone deficiency in 16-23% cases of short stature and response to growth hormone therapy measured in terms of mean height gain was 9.8 ±2.9 cm among the patients with growth hormone deficiency in the first year of therapy.[4]

In our study, mean height SDS before growth hormone therapy -4.22 ±1.46 while mean height SDS after growth hormone therapy was -2.63 ±1.57 (p-value 0.001). In a meta-analysis, baseline pretreatment growth velocities of treatment and control groups were equivalent (pooled difference between treatment and control groups −0.05 ± 0.15 cm/y, with respective mean baseline growth rates of 4.22 ± 0.21 and 4.30 ± 0.25 cm/y. After 1 year, however, growth velocity was significantly greater in the GH-treated group than in controls; the pooled estimate for the difference in growth velocity between the 2 groups was 2.86 ± 0.37 cm/y.[6]

Short stature due to classic GH deficiency is universally accepted therapeutic indication for growth hormone treatment,[6] because dwarfism can occur due to deficiency of pituitary growth hormone.[7]

Human growth hormone prepared by recombinant DNA technique has been widely used for the treatment of GHD as well as its use in the list of FDA- approved indication in non GH deficient children has been implicated.[8]

Safety data from post marketing surveillance studies probably underestimate risks associated with higher doses of human growth hormone and changing risk factors (e.g., an increased prevalence of obesity, which carries a higher risk of diabetes) and do not inform post-treatment metabolic risks or the risk of cancer.[9-11]

A long term follow-up study from France involving persons who had growth hormone deficiency or idiopathic short stature or who were small-for gestational-age infants showed an increased standardized mortality rate of 1.33 after human growth hormone treatment, as compared with the general population in France;[12] assessment of cause-specific mortality identified increased risks of death attributable to bone cancer and circulatory system disorders among persons who received growth hormone and an increased risk of death with a dose of human growth hormone that was higher than 0.35 mg per kilogram per week. However, a similar surveillance study from Belgium, the Netherlands, and Sweden did not confirm this finding.[13] Higher-dose regimens and a longer duration of treatment increase costs and may also increase risks.[14]

CONCLUSION

Significant increase in height in response to growth hormone therapy was noted in short statured children presenting with classic growth hormone deficiency in tertiary care hospital.

Author's Contribution:

Concept & Design of Study:	Bader-n-Nisa
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Data Analysis:	Muhammad Ashfaq, Asifa Noor
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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