Original Article

Effects of Early Initiation of Growth Hormone Therapy on Different Auxological Parameters in Growth Hormone Deficient Children: Experience from an Indian Tertiary Care Center

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Abstract

Objectives: The aim of the study was to evaluate the efficacy of early initiation versus late growth hormone in improving the predicted adult height in growth hormone deficiency (GHD) children. **Methods:** A retrospective study of 550 GHD children with short stature, who had taken rGH for duration of minimum 12 months were included. They were divided into groups of less than 8 years and more than 8 years of age based on the initiation of growth hormone therapy. Their pretreatment and post-treatment auxological parameters were evaluated. **Results:** There were 148 children in less than 8 years group and 402 children in more than 8 years old group. In 8 years or younger age group, the pre-treatment mean height of –2.015 SDS improved to –0.7753 SDS after one year of treatment. There was an improvement in the mean height from –2.0447 SDS to –1.2658 SDS post-treatment in more than 8 years group. The pre- and post-treatment difference between the Z score of height, weight, and BMI were statistically significant (<0.001). **Conclusion:** A significant height improvement occurred in both the groups' children after 1 year of GH treatment but the gain in final adult height was better when initiated less than 8 years of age. No significant side effects were noted during this period.

Keywords: Indian children, growth hormone deficiency, short stature

Introduction

Short stature in children is one of the most common causes of visit to an endocrinologist.[1] It is defined as height 2 standard deviation (SD) less than the mean for age and gender. The etiology for short stature can be multifactorial and recombinant growth hormone (rGH) is used worldwide for the treatment of short stature for both GH-deficient and GH-resistant conditions.[2,3]

The prevalence of growth hormone deficiency (GHD) among children with short stature is estimated to vary between 2.8% and 69%, and is predicted to be much higher in children post neurosurgical interventions.[4]

However, the data from India is limited with the largest study being from Bajpai *et al*.[5] that included 96 children. Studies have reported better final height outcomes in children with GHD when started on rGH at younger age groups in comparison to older children,[6-9] however the mean age of initiation of rGH in Indian studies are between 9 and 12 years,[9,11-16] despite there being an additional support from the gonadal hormones in peripubertal children. This has been attributed mainly to the fact that during early diagnosis the growth compromise is lesser, and allows for better outcomes and also longer duration of treatment. Also children who gain adequate height on therapy in early years turns out have better pubertal height spurts as against the children who get growth hormone closer to puberty.

We report the largest study from an Indian tertiary center of 550 prepubertal children with GHD treated with rGH to evaluate the influence of age at treatment initiation on final height outcome.

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Table 1: *Z* score of pre and post treatment auxological data in <8 yrs

	Auxological data *Z* score (SD)		
	Pre-treatment	Post-treatment	*P*
Height *Z* score	-2.42 (0.63)	-1.12 (0.60)	<0.001
Weight *Z* score	-1.23 (1.28)	- 0.14 (0.90)	<0.001
BMI *Z* score	0.26 (1.32)	0.57 (1.10)	0.02

Table 2: *Z* score of pre and post treatment auxological data in >8yrs

	Auxological data *Z* score (SD)		
	Pre-treatment	Post-treatment	*P*
Height Z score	-2.37 (0.54)	-1.55 (0.68)	<0.001
Weight Z score	-0.89 (1.24)	- 0.39 (1.02)	<0.001
BMI Z score	0.38 (1.37)	0.42 (1.18)	0.65

Table 3: Univariate analyses of different variables with final height

	SD final height	SD height gain	*P*
Age at onset	-0.25	0.61	NS
Duration of therapy	0.21	0.19	NS
BA-CA	0.09	0.07	NS

Methods

A retrospective study was conducted from 2010 to 2017 in Indraprastha Apollo Hospital. Data were collected from the patient records of children being treated with rGH. The children were divided into two groups based on the age at which growth hormone therapy was initiated as follows:

- Less than 8 years of age
- More than 8 years of age.

Diagnostic criteria

GHD: GHD was diagnosed with auxological criteria (height SDS <2) and peak growth hormone levels less than 10 ng/mL following two standard provocative tests (clonidine and insulin).

Inclusion criteria

- Children with a confirmed diagnosis of GHD and
- Children who received growth hormone therapy for at least 12 months.

Exclusion criteria

- Children with short stature due to
- Non-growth hormone-deficient causes
- Syndromic causes (such as Prader Willi, Noonan etc.)
- Patients with other pituitary hormone deficiencies were treated accordingly with hormone replacement to attain normal levels of the respective hormones before growth hormone therapy was started.

Study variables

Data were recorded at the start of the treatment and at the end of the treatment. Auxological parameters included height measured to the nearest 0.1 cm (Harpenden stadiometer), weight to the nearest 0.1 kg (Electro W-No-45) and body mass index (BMI) (weight/height^2 in kilograms/square meter) were recorded. Bone age was calculated using RUS score of Tanner Whitehouse 2 method. At the end of the treatment, pubertal development was also assessed by Tanner stage. CDC growth charts were used for monitoring the height and weight. Adult height predictions were done using Bone expert.

Growth hormone treatment

All patients received treatment with recombinant synthetic human GH for at least 12 months. GH was administered by daily subcutaneous injections at a dose of 30-35 µg/kg/day.

Statistical analysis

Z scores were calculated using Microsoft Excel with macros. Height, weight, BMI, predicted adults height (PAH) were all expressed as SD scores. Stepwise linear regression analysis was performed to evaluate factors influencing end height SDS and increase in height SDS. Regression coefficients were calculated on multivariate analysis to assess the impact of individual factors on the dependent variable. Independent *t* test and paired *t* test were used to compare the various pre-treatment and post-treatment data.

Paired *t*-test was used to compare the data between two groups (<8 years at initiation and >8 years at initiation) at the end of the study.

Written informed consent for participation in the study was given by one of the parents of the children and assent was also obtained whenever required. The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Results

The study included data of a total 550 pre-pubertal children with short stature being treated with 1 year of rGH and was divided into two groups based on the age on initiation of growth hormone treatment – one group being children less than 8 years and the other more than 8 years of age. There were 148 children in less than 8 years of age and 402 children in 8 years and above. 300 were females and 250 males. The mean age of growth hormone initiation in the age group above 8 years was 9.7 years while in below 8 years was 6.1 years.

As shown in Table 1, in the 8 years or younger age group, the pre- and post-treatment height Z scores were –2.42 ± 0.63 and –1.12 ± 0.60, respectively. Pre-treatment weight Z score was –1.23 ± 1.28 and post-treatment was –0.14 ± 0.90 kg, whereas the Z score of BMI pre- and post-treatment was –0.26 ± 1.32 and

Table 4: Indian studies evaluating growth hormone

Study	No.	Mean age (yrs)	Height velocity (cm/yr)	Dose GH
Raghupathy (1991)	8	13.8		30ug/kg/d
Menon (1991)	20	9.4	8+2	0.5IU/kg/wk
Kannan (1991)	30	2-14	10.9+2.2	6IU/wk
Bajapai (2006)	96	9.9+3.7	10.3±2.9	0.07-0.1 IU/kg/day
Khadilkar (2007)	15	12	12.1	0.23mg/kg/wk
Garg (2010)	71	10.07±3.26	8.7+2.7	0.035 mg/kg/day
Kota (2011)	25	8.6±2.9	5.8	0.3 mg/kg/week
Ekbote (2011)	28	8.6	12.6	10 mg/m2/week
Kochar (2018)	550	<8=6.1	11.5	35ug/kg/day
		>8=9.7	10.2	

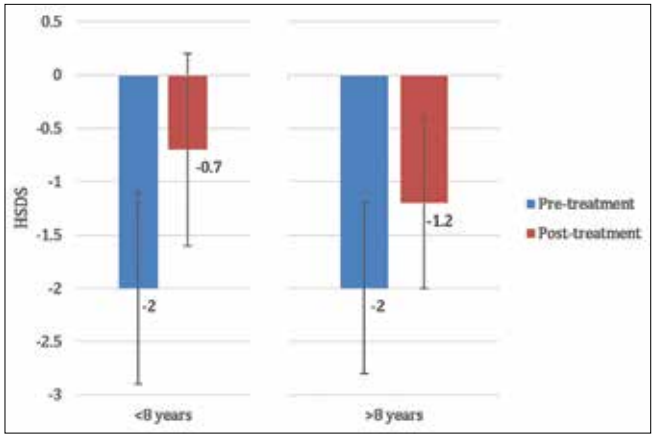

Figure 1: HSDS at baseline and after treatment in each group

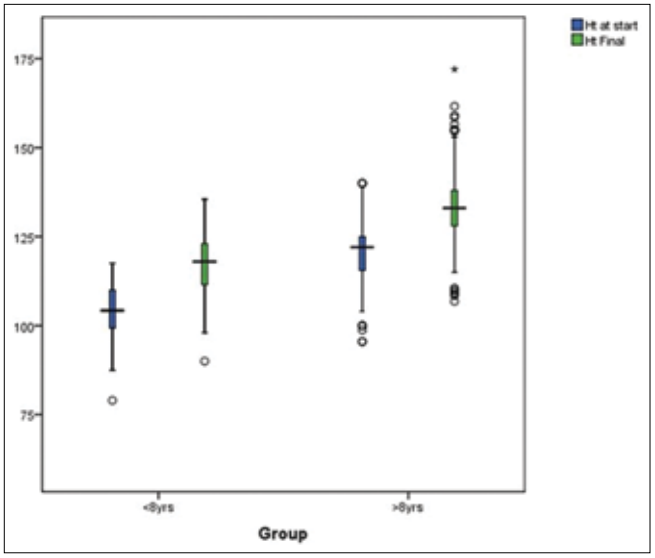

Figure 2: Comparison of post GH treatment height gain outcomes

0.57 ± 1.10, respectively. All the parameters were statistically significant (<0.05).

As shown in Table 2, in children above 8 years, pretreatment height Z score was –2.37 ± 0.54 and post-treatment was –1.55 ± 0.68. The Z score of pre- and post-treatment outcomes for height and weight were statistically significant (<0.001).

As seen in Table 3, it was seen that increased duration of treatment and BA-CA had a positive correlation with final height outcomes but the difference was not statistically significant. Age at initiation (<8 years) of treatment had an inverse correlation with the final height achieved.

As shown in Figure 1, an increase in HSDS towards the normal range was observed in both the groups. The height velocity was 11.5 cm/year in the <8 years group and 10.2 cm/year in the ≥8 years group [Figure 2].

There were 8 cases of panhypopituitarism secondary to craniopharyngioma (3 cases), medulloblastoma (1 case), neurofibroma (1 case), empty sella syndrome (2 cases), and corpus callosum agenesis (1 case).

Seventeen patients who received growth hormone therapy had some adverse events. Two children complained of headache, ten children complained of local site reaction whereas five cases of early morning facial puffiness were reported. There were no dropouts due to side effects.

Discussion

The most common ailments which receive the focus of the parents and pediatricians in early childhood tend to be failure to gain weight and recurrent symptomatic infections. Short stature comes to light only in the adolescent and preadolescent children in India. Much of the time required to attain maximum benefits with growth hormone therapy has already elapsed.[10]

There are several studies on the effects of growth hormone on short stature from India,[5,9,11-16] but none have compared the outcomes among different age groups to ascertain the maximum benefits [Table 4].

Unlike our study, the mean age of initiation of growth hormone in the Indian studies range from 8 to 13 yrs.[9,11-16] Early initiation resulted in better height outcomes and also proved to be financially better for the Indian parents as the cost is lesser in younger children due to lower doses.

In a study by Josefsberg, *et al*.,[17] they documented best results when rGH was started in children below 5 years of age and continued up to 5 years. It has been shown in some studies that if started below about 8 years of age at a height of − 3SDS and at a dose of about 33 μg/kg/day, adult height can be achieved in most cases,[18] while other studies have advocated long term treatment up to 5-9 years for achieving final height.[19] But we were not able take the same age group of <5 years, as the age of referral to endocrinologist was higher in our population, which needs to be looked into.

All these studies emphasize the need to start growth hormone therapy early to help attain better height velocity before puberty and in turn better pubertal height spurts, all of which contribute to maximum adult height. Even in our study children <8 years had better height outcomes and may be a contributing factor to better pubertal height spurts.

In a French prospective study, they divided the children less than 3 years of age into two groups according to their height SDS for chronological height at the start of GH treatment: group A consisted of children with an initial height within the −2 SDS, and group B of children with initial growth retardation (> −2 SDS). Both group A (the mean height significantly improved by −2.1 ± 0.6 at the start of GH treatment to 0.5 ± 0.8 after 5 years) and B (from –3.6 ± 1.0 at the start of the GH treatment to 0.9 ± 1.2 after 5 years) showed a significant change in annual mean height SDS for chronological age during treatment. Their evaluation reported that the height SDS at the initiation of treatment was the single most important variable affecting the final outcomes in smaller children and hence achieving better catch up growth. Thus, reiterating the benefits of starting growth hormone therapy early in GHD.[20]

There is sufficient data from western studies advocating the early initiation of growth hormone in younger children vs older, but such comparative data is insufficient from India to ascertain similar benefits.

The Indian studies have reported the height velocity ranging from 5.8 to 12.6 cm in the first year of treatment, the results of which were similar to our study. But we report higher height velocity in children less than 8 years group in comparison to the older children. The duration of treatment ranged from 1 to 3 year in the Indian studies and in our study, there were children with treatment continuing up to 3.7 years, but the numbers of these were very few.

Treatment with rGH is tolerated quite well in the Indian population with only very few isolated reports of urticaria, headache, one case of vitiligo, transient hyperglycemia in the Indian studies.[12,14] The numbers of adverse events in our study were similar to these studies. These adverse events being mild did not result in dropouts from the therapy.

One of the biggest challenges in India for continued rGH treatment is the financial burden thrust upon families, which results in early discontinuation and poor adherence to therapy. Evidently, the final height achieved is suboptimal and much lesser than the predicted adult height.

It is thus of utmost importance to diagnose and treat GHD early not only to attain the best results but also to provide a cost-effective strategy for optimal height outcomes to the patients and their families.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

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Conflicts of interest

There are no conflicts of interest.

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