Impact of growth hormone treatment on children's height

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Submission date: 15-Mar-2023 01:19PM (UTC+0800)
Submission ID: 2037581412
File name: 3c_-_Impact_of_growth_hormone_treatment_on_children_s_height.pdf (93.69K)
Word count: 3209
Character count: 17098

Paediatrica Indonesiana

VOLUME 54 November • 2014 NUMBER 6

Original Article

Impact of growth hormone treatment on children's height

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Abstract

Background The use of growth hormone (GH) is a routine treatment for growth hormone deficiency (GHD), small for gestational age (SGA), and Turner syndrome (TS). During the treatment, height measurement at regular intervals is a vital step to assess success. To date, there have been no previous studies on GH treatment in Dr. Soetomo Hospital, Surabaya, the referral hospital in East Indonesia.

Objective To compare body height between pre- and post-growth hormone treatment in pediatric patients.

Method This study was a non-randomized, pre-post clinical trial performed at Dr. Soetomo Hospital, Surabaya. The prospective cohort was accessed during January 2008-June 2013. The inclusion criteria was GH treatment for more than 3 months. Clinical data on GH treatment, including diagnosis, age, height pre-and post-treatment, height gain, duration of treatment, and parental satisfaction were collected. Two-tailed, paired T-test and Pearson's test were used for statistical analyses.

Result Nineteen patients underwent GH treatment during the study period, but only twelve patients had complete data and were included in the study. Eight subjects were female. Subjects' mean age was 11 (range 8-15) years. Nine patients had GHD, 2 had TS, and 1 had SGA. Mean pre-treatment height was 121.05 cm, while mean post-treatment height was 130.5 cm. Mean duration of treatment was 10.5 (range 3-30) months. Mean height gain was 0.8 cm/month in GHD and SGA cases, and 0.78 cm/month for the TS cases. Eleven parents reported satisfaction with the results of GH treatment in their children. There is significant diffrent between pre- and post-treatment (P=0.001). Pearson's correlation test (r=0.90) revealed a strong correlation between growth hormone treatment and height gain.

Conclusion Growth hormone treatment has impact on heights in GH defficiency, Turner syndrome, and small for gestational age.

[Paediatr Indones. 2014;54:318-23.]

Keywords: *GH treatment, height gain*

Short stature is common chief complaint in pediatric endocrinology outpatient clinics. Short stature may due to several etiologies, including GH deficiency, small for gestational age, or Turner syndrome. Growth hormone treatment in growing children has been approved by the *Food and Drug Administration* (FDA),[1] the *European Agency for the Evaluation of Medicinal Products* (EMEA),[2] and local regulatory agencies. Pediatric GH is currently licensed for six different conditions: growth hormone deficiency (GHD), Turner syndrome (TS), small for gestational age (SGA), Prader-Willi syndrome (PWS), chronic renal insufficiency (CRI), and short stature due to short stature homeobox (SHOX) deficiency. All of these were ratified by the most recent (2010) *National Institute of Health and Clinical Excellence* (NICE) review. Whilst the primary purpose of pediatric GH therapy is mostly indicated to improve short- and long-term growth, in other conditions (e.g., PWS) its role is to improve body composition. Recent UK national audits indicate that approximately 4,700 children received GH therapy, with approximately 760 new patients per year.[3]

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In addition to GHD, in which the basis of therapy is physiologic replacement, GH is now being used in non-GH deficient states associated with short stature, with the purpose of normalizing growth, height, and height velocity (HV), both in the short- and long-term (i.e., final height). In these situations GH is started either once the condition is first diagnosed, or once the height velocity falls below acceptable levels. Growth hormone treatment improves height in children with GHD, TS, and SGA.[1,4] Early intervention with growth hormone treatment improves adult stature, with some patients reaching their final target height. In 2003, *The Lawson Wilkins Pediatric Endocrine Society of Endocrinology* published a consensus recommendation for GH therapy monitoring and dose adjustment.[1] This study aimed to compare body heights between pre- and post-growth hormone treatment in pediatric patients at Dr. Soetomo Hospital, Surabaya.

Methods

This study was a non-randomized, pre- and post clinical trial performed at Dr. Soetomo Hospital, Surabaya. A prospective cohort was collected from January 2008 to June 2013. Clinical data on GH treatment, including diagnosis, age, height pre-and post-treatment, height gain, duration of treatment, and parental satisfaction were collected. The inclusion criterion was GH treatment for more than 3 months. A comparison of pre- and post-treatment data was analyzed by two-tailed, paired T-test, and correlation was analyzed by Pearson's test.

Growth hormone deficiency was defined to be present in short children who failed the GH stimulation test (within peak GH of less than 10 ng/dL) by using insulin or clonidine. Tests were performed in Dr. Soetomo Hospital and processed by the same laboratory during the study. Small for gestational age data was recalled from anamnesis and defined a weight and/or length less than -2 SD for the length of pregnancy.[5] The diagnosis of Turner syndrome requires the presence of charcteristic physical findings in addition to a complete or partial absence of the second sex chromosome, with or without cell line mosaicism.[6] Growth hormone treatment was given subcutaneously once daily, at dosages appropiate for patient diagnosis, age, and body weight.

Results

There were 19 patients on GH treatment during the study period, but only 12 patients had complete data and were included in the study. Among them, 9 had GH deficiency (GHD), 2 had TS, and 1 was SGA. Subjects' mean age at the start of GH treatment was 11 (range 8-15) years. Eight patients were female. Nine GH deficiency patients were treated with GH. Their ages at the time of diagnosis ranged from 8 to 15 years. Their height gain ranged from 2.4 cm in patient #8 to 24 cm in patient #2 (**Table 1**). The height gain in each patients can be seen in **Figure 1**.

The two patients with TS, both aged 11 years, had height gains of 12 cm and 5 cm, respectively, in one year of treatment. The SGA patient, aged 11 years, had a height gain of 2.5 cm in 3 months of treatment (**Table 2**).

Figure 2 shows pre- and post-GH treatment data. In the first patient diagnosed with Turner

Table 1. Height gain during GH treatment in GH defficiency subjects

Patient #	Age at treatment start, years	Dosage, mg	Height gain, cm/month	Duration of treatment, months
1	8	0.5	0.67	18
2	15	0.9	0.8	30
3	14	0.7	0.88	24
4	8	0.7	0.73	11
5	13	0.7	1.3	9
6	14	0.8	1.2	5
7	14	0.7	1.3	3
8	11	0.6	0.8	3
9	11	0.6	1	7

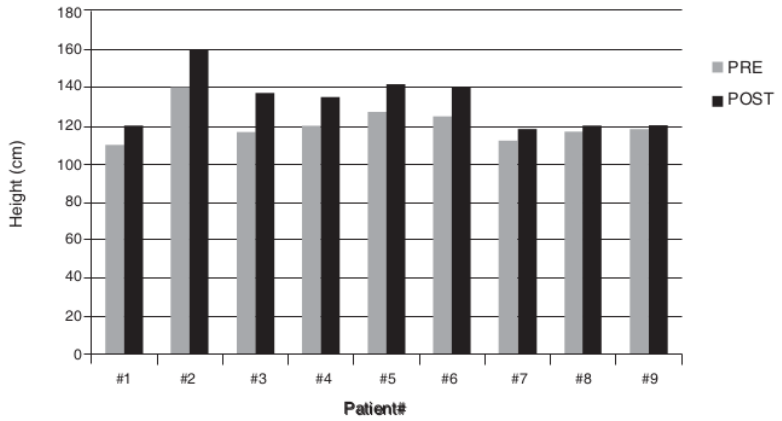

Figure 1. Height gain in GH defficiency patients: pre- and post-treatment

Table 2. Height gain during GH treatment in TS and SGA patients

Patient #	Age at treatment start, years	Diagnosis	Pre- treatment height, cm	Post- treatment height, cm	Dosage, mg	Height gain, cm/month	Duration of treatment, months
1	11	TS	120	132	2	1.2	10
2	11	TS	128	133	2	0.4	12
3	11	SGA	122	124.5	0.5	0.8	3

TS: Turner syndrome, SGA: small for gestational age

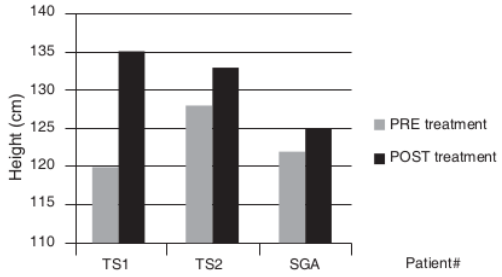

Figure 2. Height gain in the TS and SGA patients: pre- and post-treatment

TS: Turner syndrome, SGA: small for gestational age

syndrome (TS1) heights were 120 cm pre-treatment and 132 cm post-treatment. In the second Turner syndrome (TS2) patient, heights were 128 cm pre-treatment and 133 cm post-treatment. For the SGA patient, heights were 122 cm pre-treatment and 124.5 cm post-treatment. **Table 3** shows mean duration of treatment ranged from 3 to 30 months.

Eleven parents reported satisfaction with the results of GH treatment. Pre- and post-treatment heights were significantly different (P=0.001). There was a correlation between pre- and post-GH treatment revealed by Pearson's correlation test (r=0.90).

Table 3. Height gain in all subjects during the study (n=12)

Parameters	
Mean height (SD), cm	
Pre-treatment	121.05 (9.19)
Post-treatment	130.5 (12.2)
Mean duration of GH treatment (SD), months	10.5 (8.67)
Mean (average of) height gain, cm/month	
GHD	0.8
TS	0.78
SGA	0.8

Discussion

In Dr. Soetomo Hospital, GHD was found in 9/12 short stature patients. A UK study reported that GH is licensed within the UK for the following indications, with the current percentage of GH-treated patients being: GHD 57.4%, TS 18.7%, SGA 5.2%, Prader-Willi syndrome 4.6%, and chronic renal insufficiency 2.5%.[3]

Stimulation tests were performed once with clonidine or insulin to establish diagnoses. The Growth Hormone Research Society considered a cut off point less than 10 ng/mL to indicate GH deficiency.

Growth hormone stimulation tests were performed only once before treatment. The National Cooperative Growth Study in the United States, 1987 to 2000, showed that 70% of GHD diagnoses were done with at least one GH stimulation test (with GH measurements pre- and post-stimulus).[7,8] The growth hormone doses are as follows: GHD 0.024-0.034 mg/kg/day; SGA up to 0.48 mg/kg/week; and TS up to 0.067 mg/kg/day.[9] Children treated with GH in the USA receive, on average, a 40% higher dose than those in Europe.[10]

The mean height gain in our study was 0.8cm/month for GHD patients. Kirk *et al.* reported that growth hormone treatment in GHD cases grew 2.7cm/year faster compared to untreated GHD cases, with significantly higher height standard deviation scores (SDS).[3] Wacharasindhu reported that growth response was satisfactory even at lower than suggested doses.[11]

An approximate comparison of first-year response standards for GH starting at age 6 years, showed a height velocity of 10.5 cm/year. NCGS data on prepubertal children with idiopathic growth hormone deficiency showed a mean gain of 0.77 SDS during the first year of GH treatment,[8] which was close to the 0.74 SDS reported in the Park study (2005).[12] In general, children using GH therapy are taller in the USA.[1] These negative predictors of height gain may theoretically be outweighed by concomitant use of higher GH doses in the USA.[12]

Solimen *et al.* reported that children with GHD in the treatment group grew an average of 2.7 cm/year faster than those who received no treatment in the 12 months of the study, with a statistically significant difference between the groups ($P < 0.05$). Similarly, children in the treatment group had a significantly higher height SDS: -2.3 ± 0.45 vs. -2.8 ± 0.45 in the untreated group ($P < 0.05$).[13]

Data in Dr. Soetomo Hospital during 2002-June 2013 stated that there were 8 Turner syndrome patients. All patients suffered from short stature and about 80% had pubertal delay and karyotyping study showed 45X. In our study, two TS patients, both 11 years old, agreed to GH treatment. Their mean height gain was 0.78cm/month. There was one SGA patient who joined the study whose height gain was 0.8 cm/month.

Bang *et al*. reported that children born SGA, with TS or skeletal dysplasia, respond less well to GH compared to those with GHD. In SGA, TS and skeletal dysplasia, approximately half or more of patients had a change in height SDS of 0.5 and a similar or even higher percentage of patients had a change in height velocity of 3 cm/year.[14]

In July 2001, the Food and Drug Administration approved recombinant human GH for the long-term treatment of growth failure in children who were born SGA and failed to manifest catch-up growth by age 2 years. The basis for treatment after 2 years of age is the evidence that height is not likely to normalize spontaneously after this age. Thus, SGA children > 2 years should be considered for therapy if they do not have evidence of ongoing catch-up growth, and if greater height for age would be expected on the basis of family heights. Dosing is approved up to 0.48 mg/kg body weight/week. The primary rationale for GH therapy is primarily to increase linear growth rate in short children born SGA and have persistent short stature, so that they may attain a height within the normal range for gender and age, and ideally within the target height percentile range. Therapy may prevent lifelong, detrimental, quality of life issues associated with short stature. Long term outcome data are needed to determine the effects of GH treatment on metabolic and neurodevelopmental outcomes, as well as to document adult heights.[3]

Growth hormone improves height in short, SGA children without accelerating pubertal progression. In a previous study, after 2 years of GH therapy, the height-for-age Z-score increased from -2.8 to -1.6 in group I (treatment), compared 2.2 to -1.7 in group II (control) ($P<0.05$). The percentage of pubertal children rose from 55% to 65% of the cases versus 60% to 75% in the controls ($P>0.05$). GH treatment resulted in increased

growth velocity Z-score during the first year [4.3±0.5 in group I vs. -0.5±0.6 in group-II; (P<0.05)] and second year of treatment [1.7±0.4 in cases vs. -0.6±0.7 in controls; (P<0.05)].[15]

Growth hormone stimulated linear growth in nearly all patients. Similarly, Chernausek *et al*. reported improvement in growth velocity after GH treatment. The mean of their subjects' pretreatment growth velocity was 3.96± 1.0 cm/year. However, the mean first year growth rate of patients who received daily GH was 8.16± 1.6 cm/year compared to 6.76±1.5 cm/year for those treated with GH three times per week (P=0.001 between dosing frequencies).[16]

Insulin like growth factor-1 (IGF-1) measurements are useful for monitoring compliance, but a lack of increase in IGF-I on treatment does not allow for discrimination between GH insensitivity and poor compliance. Careful follow-up during GH treatment should be performed. With regard to laboratory assessments, it is recommended that blood glucose, thyroid function, HbA1c, and IGF-1 be monitored regularly to ensure these parameters are within normal levels. Current guidelines suggest that IGF-1 monitoring be performed at least annually, as it is the basis for adjusting GH dose.[17-19]

Since the first use of human GH in 1958 and after the development of recombinant GH in 1985, a large number of short, GH-deficient children have been treated, with a remarkably good safety record.[19] Adherence to treatment has a large impact on overall treatment outcome. Desrosiers *et al*. reported that growth rates in poorly compliant patients were significantly lower compared to patients who missed fewer doses. Height velocity in patients missing >15 injections per month (equivalent to >3-4 per week) was 6.3 cm/year compared with 9.4 cm/year in those missing 11-15 doses per month (P<0.03). Growth velocity suffers a significant decline if >2 injections per week are missed.[18,]

A limitation of our study was the small sample size. Growth hormone treatment is not supported by government insurance, hence, the cost may prohibit some children from receiving treatment. Further study with a larger sample size is needed to better assess the effects of GH on children with short stature.

In conclusion, growth hormone treatment has impact on heights in GH defficiency, Tuner syndrome, and small for gestational age.

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