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IS IT POSSIBLE TO DECREASE THE CONVENTIONAL GROWTH HORMONE DOSAGE IN GROWTH-DEFICIENT CHILDREN?
BÜYÜME HORMONU EKSİKLİĞİ OLAN ÇOCUKLARDA KLASİK BÜYÜME HORMONU TEDAVİSİ DOZUNU AZALTMAK MÜMKÜN MÜ?

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ABSTRACT

Objective: The prospect of financial savings by decreasing growth hormone dose, prompted us to study the effectiveness of lower dose treatment.

Subjects and methods: We studied 97 growth hormone deficient (GHD) children in two groups: 1) The study group (n=39) was treated with recombinant human GH (rhGH) at a low dose of 0.15 mg/kg/week 2) The control group (n=58) was treated with rhGH, at a conventional dose of 0.2 mg/kg/week. All patients were evaluated for auxology, Insulin like growth factor-1(IGF-1) and Insulin like growth factor binding protein-3-(IGFBP3) levels at baseline, 6 and 12 months after starting GH therapy.

Results: While there was no significant difference in IGF-1, IGFBP3, growth velocity (GV), and growth velocity SDS (GVSDS) levels after 6 months of therapy between the two groups, the GV and GVSDS levels were significantly higher in the control group after 12 months. This difference contributed to significant pubertal spurt in the control group. In both groups, no significant correlation was found among parental heights, target heights, IGF-1 and IGFBP3 levels with GV and GVSDS.

Conclusion: By decreasing the conventional GH treatment dose, we also decrease the cost of GH treatment approximately by 20% which may lead to an important cut in the treatment related cost.

Key words: Growth hormone replacement therapy, IGF-1, IGFBP3

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ÖZET

Amaç: Düşük doz büyüme hormon tedavisi ile sağlanabilecek maddi kazanç ihtimalini ortaya koymak için bu çalışma planlandı.

Olgular ve Metod: Büyüme hormonu eksikliği olan 97 çocuk 2 grupta incelendi. 1)Çalışma grubuna (n=39) rekombinant insan büyüme hormonu (rhGH) 0.15 mg/kg/ hafta dozunda verildi. 2)Kontrol grubuna (n=58), rhGH klasik doz olan 0.2 mg/kg / hafta dozunda verildi. Tüm olgular çalışma başlangıcında ve büyüme hormon tedavisinin 6. ve 12.aylarında değerlendirilip oksolojik kontrolleri yapıldı ve insülin benzeri büyüme faktörü (IGF-1) ile insülin benzeri büyüme faktörü bağlayıcı protein -3 (IGFBP-3) seviyeleri ölçüldü.

Bulgular: Kontrol grubu ile karşılaştırıldığında çalışma grubunda: Tedavinin 6.ayında IGF-1, IGFBP3, büyüme hızı (GV) ve büyüme hızı SDS (GVSDS) değerlerinde istatistiksel anlamlı fark bulunamazken, tedavinin 12.ayında kontrol grubunda GV ve GVSDS seviyeleri anlamlı yüksek bulundu. Bu fark kontrol grubunda bu dönemde gözlenen pubertal sıçramaya bağlandı. Her 2 grupta; GV ve GVSDS ile parental boy, hedef boy, IGF-1, IGFBP-3 değerleri arasında istatistiksel anlamlı fark bulunamadı.

Sonuç: Büyüme hormonu tedavisinde halen kullanılmakta olan konvansiyonel dozun azaltılması büyüme üzerinde anlamlı olumsuz etki yapmadığından daha düşük doz tedavi ile tedavi maliyetlerinde yaklaşık %20 civarında azalma sağlanabilir ki, bu tüm ülkeler için total tedavi harcamalarını azaltmada çok önemli bir kazanç olabilir.

Anahtar Sözcükler: Büyüme hormonu tedavisi, IGF1, IGFBP3

INTRODUCTION

Growth hormone (GH) has been used as a replacement therapy in GH-deficient (GHD) children for many years and refinements in the frequency and dosage of GH administration have improved adult height prognosis considerably. However, an optimal consensus is not yet achieved and GH dosing differs among physicians and between countries (1-6).

In GHD, serum IGF-1 and IGFBP3 concentrations were not routinely monitored during GH treatment; therefore, assessment of the growth response to GH remained the single most important parameter followed (6-8). Growth-promoting optimum dose differs between cases and therefore these markers are important in assessing GH compliance, efficacy and over- treatment.

The aim of our study was to monitor the changes in IGF-1 and IGFBP3 levels by two different GH doses (low dose; 0.15 mg/kg/week-in study group and conventional dose 0.2 mg/kg/week in control group) given for a year. We predicted that lower dose might be as effective as the standard dose resulting in substantial savings.

METHODS

We studied 97 children with GHD (age 2.4-19.4 years; 68 males, 29 females) including idiopathic growth hormone deficiency (n= 90) and GH-neurosecretary dysfunction (n= 7). GH deficiency was diagnosed by obtaining a peak GH concentration below 10 ng/ml in either levodopa or insulin stimulation. Levodopa is used 10 mg/kg/dose orally and blood samples for GH concentrations were taken in 0-45-90 minutes, whereas in insulin stimu-

lation, test samples were taken in 0-30-60 minutes after an IV insulin administration of 0.05-0.1 IU/kg. In 7 patients neurosecretary dysfunction of GH (NSD-GH) was diagnosed by obtaining insufficient peak and integrated GH concentrations during sleep. To diagnose NSD-GH; nine blood samples for GH levels were taken with 30 min.intervals during sleep. For normal response we were expecting to see at least 3 peaks (> 11.5 ng/ml) and the integral concentration of GH (ICGH) was expected to be more than 5-5.5 ng/ml. "Neurosecretary dysfunction of GH" was diagnosed by obtaining insufficient peak and integrated GH concentrations.

The patients were categorized in two groups:

1) The study group which consisted of 39 (28 males, 11 females) children were treated with recombinant human GH (rhGH) subcutaneously before bedtime, 6 days per week, at a low dose of 0.15 mg/kg/week (25µg/kg/day).

2) The control group consisted of 58 (40 males, 18 females) children and were treated with rhGH, subcutaneously before bedtime 6 days per week, at a conventional dose of 0.2 mg/kg/week (33µg/kg/day).

All patients' height, weight, pubertal status by Tanner standards and serum IGF-1 and IGFBP3 levels were evaluated at baseline, 6 and 12 months after starting GH therapy by using immunoradiometric assay (IRMA). Pubertal spurt is considered to be in stage II-III and stage III-IV for girls and boys respectively. All patients' cortisol levels and thyroid function test were in normal ranges at the time of study.

Results are reported as mean ±SD.

Informed written consent as well as written assent were obtained from the parents.

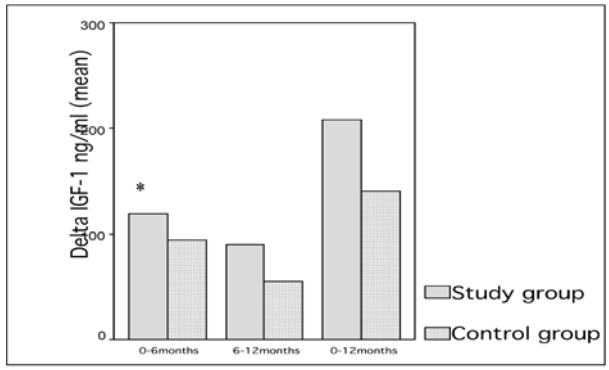
ANALYSIS

Statistical assessment of differences between the two groups was made by Chi-squared and t-test test. P values below 0.05 were considered statistically significant. The predictive value of baseline IGF-1 and IGFBP3 levels and relationships between variables were evaluated by multiple linear regression analysis (Pearson chi-square, Mann-Whitney U and Kendall's correlation). The SPSS (Statistical Package for Social Sciences) version 12.0 statistical package is used for the statistical analysis.

RESULTS

The control and study groups did not differ in descriptive characteristics and baseline values (Table 1). The results obtained are presented in Table 2.

Serum IGF-1 and IGFBP3 levels increased significantly during treatment (6th and 12 th months) in both groups compared with baseline values ($p<0.01$). At the 12th month of therapy; bone age (BA), height SDS, GV and GVSDS levels increased significantly in both groups. (Table 2, Figure 1)



* p>0.05 between study and control groups

Figure 1: ΔIGF-1 values in study and control groups before and after GH therapy

After 6 and 12 months of therapy ΔIGF-1 levels (difference of IGF-1 levels at 0-6 and 6-12 months) of the study group were not significantly different from the control group (Figure 1). On the other hand, after 6 months of therapy ΔIGFBP3 (difference of IGFBP3 levels at 0-6 months) levels were significantly higher in the study group ($p<0.05$) whereas at the end of the second 6 months, ΔIGFBP3 levels were significantly lower compared to the control group ($p<0.05$) (Figure 2). Molar ratio of IGF-1 to IGFBP3 was increased in both groups after 6 and 12 months of therapy ($p<0.01$) (Table 2).

When we compared the study group with control group, the most striking changes occurred at 12 months. While there was no significant difference in IGF-1, IGFBP3, GV, and GVSDS levels after 6 months of therapy, the GV and GVSDS levels were significantly higher

Table-1: The data of the study and the control groups before GH therapy

	STUDY (n=39)	CONTROL (n=58)
Gender		
Male	28 (71.8%)	40 (69%)
Female	11 (28.2%)	18 (31%)
Diagnosis		
GH Deficiency (n)	36 (92.3%)	54 (93.1%)
GH Neurosecretary Dysfunction (n)	3 (7.7%)	4 (6.9%)
Stimulations Tests (ng/ml)		
Peak GH after L-dopa stimulation	2.9±3.1	3.1±3.0
Peak GH after IUT stimulation	4.3±3.6	4.0±3.1
Peak GH during sleep	4.3±3.6	4.1±3.2
GH dose (mg/kg/week)	0.15	0.2
Mother height (cm)	154±6.9	155±6.7
Father height (cm)	166±7.2	165±6.4
Target height (TH)	163±9.0	163±7.6
Target height SDS (THSDS)	-0.97±0.97	-0.94±0.77
Puberty (Tanner)		
Prepubertal	27 (69.2%)	37(64.9%)
Pubertal	12 (30.8%)	20 (35.1%)

There was no difference between the groups for these parameters.($p>0.05$)

Table-2: The results of the study and control groups before therapy and after 6 and 12 months of therapy

	Before therapy		After therapy 6th month		After therapy 12th month	
	Study group	Control group	Study group	Control group	Study group	Control group
Mean Age (years)	11.68±2.74	11.16±3.24	12.33±2.73	11.71±3.35	12.80±2.7	12.40±3.35
Height SDS	-3.89±1.1	-3.8±1.26	-3.54±1.0	-3.41±1.05	-3.32±0.88	-3.14±1.05
GV	3.45±0.89 cm/year	3.44±0.98 cm/year	4.52±1.8 cm/6month	4.75±1.46 cm/6month	8.46±2.36 cm/year *	9.84±2.27 cm/year *
GVSDS	-2.46	-2.61	4.6±4.5	5.1±4.1	4.09*	5.92*
IGF-1/ IGFBP3 ratio	3.2±2.3	1.9±8.9	5.3±3.5	5±4.9	7.9±5.1**	6.9±5.0**
BMI (kg/m^2)	16.6±2.2	17.2±3	17.4±3.2	16.8±2.8	17.1±2.6	17.5±3.5
Bone age (year)	7.8±3.1	7.7±3.4	8.1±3.2	8.2±3.4	9.4±2.8	9.2±3.4
Puberty (Tanner) (n) Prepubertal / Pubertal	27/12	37/20	21/18	29/28	15/24	23/34
Number of patients at pubertal spurt stage ****	6 %15.4	6 %10.3	11 %28.2	15*** %25.9	11 %28.2	21*** %36.2

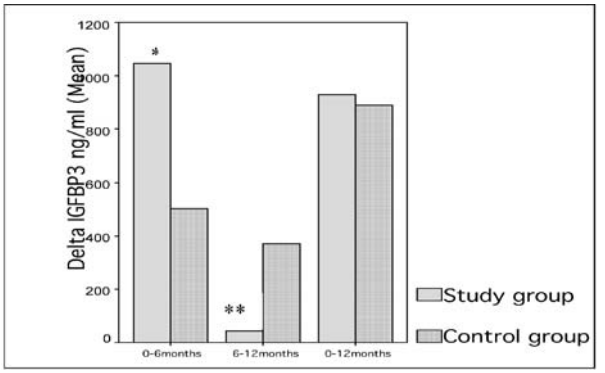
Values are mean ± SD

* The GV and GVSDS levels were significantly higher in control group after 12 months of therapy ($p<0.01$ and $p<0.01$ respectively).

** Molar ratio of IGF-1 to IGFBP3 was increased in both groups after 6 and 12 months of therapy ($p<0.01$)

*** Number of patients at pubertal spurt stage in control group was significantly higher compared with study group after 6 and 12 months of therapy ($p<0.01$ and $p<0.05$ respectively).

**** For males pubertal stage (P3-4), for females pubertal stage (P2-3)

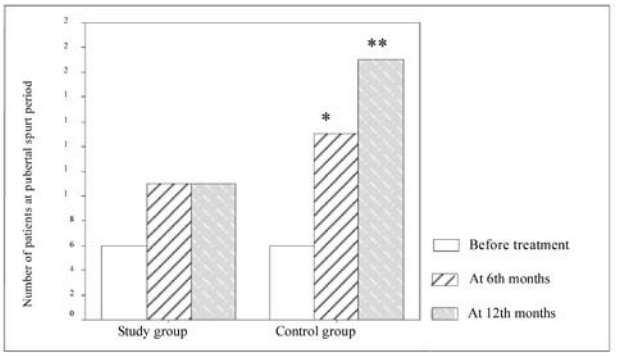


* p<0.05 between study and control groups (0-6 months)

** p<0.05 between study and control groups (6-12 months)

Figure 2: ΔIGFBP3 values in study and control groups before and after GH therapy

in the control group after 12 months of therapy (p<0.01 and p<0.01, respectively). We attributed this difference to significant pubertal spurt of the control group (p<0.05). Because, number of patients in the control group who had their pubertal spurt was significantly higher than the study group after 6 and 12 months of therapy (p<0.01 and p<0.05, respectively) (Table 2 and Figure 3).



* p<0.01 between control group after 6 months versus study group after 6 months

** p<0.05 between control group after 12 months versus study group after 12 months

Figure 3: Number of patients at pubertal spurt period before and after the treatment

No significant correlation was found between parental and target heights with GV and GVSDS, in neither group (p>0.05). Prior to the therapy and after 12 months of therapy, the IGF-1 and IGFBP3 levels were not correlated with GV and GVSDS (p>0.05).

Discussion

Optimal replacement dosages in GHD children and the specific relevance of IGF parameters to GH treatment in children have not been investigated in depth (9-10). The inability to show a clear relationship between GV, GH dose, and circulating IGF levels is probably a reflection of the lack of strong correlation between blood levels and the physiology of the GH/IGF system (10,11).

Little information is available on the relevance of parameters representing the IGF system in terms of GH treatment during childhood, but IGF-1 and IGFBP3 blood levels (basal and during GH therapy) are potential predictors of growth in GHD (10,12-14).

Patients with subnormal IGF-1 levels tended to grow less rapidly, suggesting that they might have benefited from higher IGF-1 levels. This could have been achieved via a higher GH dose (6,13,15). In the United States, daily doses between 0.025 and 0.05 mg/kg per day are commonly used. The accepted daily dose in Europe varies from 0.025 to 0.035 mg/kg per day, and in Japan the common daily dose is 0.025 mg/kg per day or less (10). Studies have led to higher doses of GH for improving height outcome, but the cost is also higher and the possible adverse effects of high IGF-1 levels are unknown. Three different authors; Ranke, Guilbaud and Blethen have shown that the dose and frequency of injections are important predictors of growth in children with GHD (10,16,17). Although both IGF-1 and IGBP3 were highly correlated, and both correlated with the growth response, IGF-1 was more informative in explaining the variation in growth response (6,18).

Radetti al reported that higher doses of GH in GHD children made no difference in height SDS [12]. Similar to that study, at the end of treatment we also observed no difference in height SDS (Table 2).

IGF-1 and IGFBP3 concentrations within normal ranges for age in GHD children could be valuable in assesing the GH dose, monitoring compliance, and avoiding

possible side effects related to high IGF-1 concentrations. As, the oncogenic potential is likely to be greatest in patients with high IGF-1 and low IGFBP3 concentrations, it seems prudent to monitor IGF-1 and IGFBP3 levels during GH treatment in children (3,5,8,10,19,20). Previous studies in GHD adults that used high-dose GH therapy led to side effects such as arthralgia; the association between high circulating IGF-1 levels and breast cancer in women and prostate cancer in men also raised concerns regarding the use of GH at high doses (7,10,19,21,22). Ahmad et al., by using low dose GH titrated according to circulating IGF-1 concentrations, were able to achieve IGF-1 SDS levels between the median and upper end of the age-related reference values in most of their adult patients, with no reports of patient withdrawal and side effects (23). On the other hand, Lanes et al reported that with a dose of 0.2 mg/kg/week, IGF-1 SDS increased significantly after the first 6 months, whereas no further increase was seen despite the use of higher GH dose (0.28 mg/kg/week) in the second 6 months (7). But, IGFBP3-SDS increased at both 6^{th} and 12^{th} months. There was no correlation between the GH dose used and IGF-1, IGFBP3 levels. Similar results have been reported by Tillmann et al who found significant increase in IGF-1 and IGFBP3 levels. The levels reached the highest levels after 6 weeks of GH treatment and remained relatively stable thereafter while receiving a constant mean GH dose of 0.5 IU/kg/week (8).

In our study, no significant difference in ΔIGF-1 levels was found between the groups at 0-6 and 6-12 months of therapy. But, ΔIGFBP3 levels were increased in the study group during the first 6 months whereas at the end of the second 6 months the increase was more significant in the control group (Figure 1-2).

Rikken et al found parameters such as IGF-1 and IGFBP3 to be unrelated to the response of long-term GH therapy (24). We also did not find any significant correlation of IGF-1 and IGFBP3 with GV and GVSDS, before and after 12 months of therapy in both groups.

Previous studies which showed the positive relationship between the dose of GH and serum IGF-1 but not serum IGFBP3 suggest that IGF-1 is more sensitive to GH than IGFBP3. The increase in IGF-1/IGFBP3 molar ratio with increasing dose of GH may reflect an increase in bioavailable IGF-1 (8,25,26). In our study, however, after 12 months of therapy there was no significant difference in ΔIGF-1 and ΔIGFBP3 levels compared to control group despite higher GH doses in the control group. IGF-1 / IGFBP3 molar ratio in both groups at 6^{th} and 12^{th} months were significantly higher compared with baseline molar ratio (Table 2).

Timing of onset and height at the start of puberty has been reported to influence final height in GHD children (1,27-30). Hibi et al. and Tanaka et al. showed that children with GHD in combination with gonadotropin deficiency, who underwent induction of puberty, had significantly higher mean final height than GHD children who had normal puberty (27,28). In our study, number of patients in the control group who had their pubertal spurt was significantly higher than the study group after 6 and 12 months of therapy ($p<0.01$ and $p<0.05$, respectively). The significant increase of GV and GVSDS at 12 months of therapy in our control group (who received higher dose of GH) might be due to the pubertal spurt of this group during 6-12 months (Table 2).

In conclusion, optimal replacement dosage which has the minimal negative influence on GV should be chosen in GHD children. We may decrease the cost of GH treatment approximately by 20 % and it may be a substantial saving for the countries.

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