

Original Research Article

Therapeutic potential of a combination of recombinant human growth hormone (r-hGH) and vitamin D in children with idiopathic short stature

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Abstract

Purpose: To study the effectiveness and clinical significance of recombinant human growth hormone (r-hGH) in combination with vitamin D in the treatment of idiopathic short-stature children.

Methods: A total of 90 idiopathic short-stature children admitted at Children Health Care Center of Shiyuan Maternal and Child Health Care Hospital, Shiyuan between March 2017 and March 2020 were assigned to three groups: A, B and C, based on dose of r-hGH given. Group A received r-hGH at a dose of 0.26 mg/kg/week, while groups B and C received r-hGH at doses of 0.35 and 0.42 mg/kg/week, respectively. All the patients were given vitamin D along with the r-hGH doses administered. Height, growth rate, bone age, height standard deviation score, fasting blood glucose, thyroid function and treatment effectiveness were determined and compared among the three groups before treatment, and one year after treatment.

Results: Significantly higher height standard deviation score, growth rate, bone age, and height were observed in the three groups of patients after one year of treatment than before treatment, with group A < group B < group C ($p < 0.05$). Fasting blood glucose and thyroid function were not significantly different amongst the three groups after treatment ($p < 0.05$). Group C showed the highest treatment effectiveness, followed by group B, and then group A ($p < 0.05$).

Conclusion: The use of a combination of r-hGH and vitamin D produces a favorable treatment effectiveness in idiopathic short-stature children. However, further clinical trials are required to validate this treatment strategy.

Keywords: Recombinant human growth hormone, Vitamin D, Idiopathic short-stature children

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INTRODUCTION

Children with idiopathic short stature have heights and weights similar to those of normal babies at birth, but their growth rates, heights, and bone age become considerably lower than

those of their peers of the same gender in the course of growth and development [1-3]. Slow growth rate in children in the absence of congenital, endocrine, chromosomal and genetic factors, is considered idiopathic short stature.

However, some studies suggest that idiopathic short stature is related to the secretion of growth hormones [4-6]. Therefore, recombinant human growth hormone (r-hGH) remains the mainstay for idiopathic short-stature treatment, due to its similarity to human growth hormone, with respect to amino acid contents and protein structure. As a result, it is widely used in diseases triggered by insufficient secretion of growth hormone. Their growth rate increases after application of r-hGH and the patients may suffer from knee and joint pain. It is known that vitamin D promotes growth and development, protects the normal development of bones, and maintains balance in bone and muscle development [7-9]. The present research was designed to study the effectiveness of using different doses of r-hGH in combination with vitamin D for treating idiopathic short stature in children.

METHODS

General information on patients

A total of 90 idiopathic short stature children hospitalized between March 2017 and March 2020 were divided into groups A, B and C based on the doses of r-hGH administered. Group A consisted of 17 males and 13 females aged 3 - 12 years, with a mean age of 8.22 ± 1.38 years. Group B consisted of 15 males and 15 females, and aged 3 - 12 years, with a mean age of 8.31 ± 1.40 years. Group C comprised 16 males and 14 females, and aged 3 to 13 years old (mean age = 8.29 ± 1.35 years). The three groups of patients presented similar values in gender and age ($p > 0.05$).

Inclusion/exclusion criteria

Inclusion criteria

Patients as per the following were assessed as eligible: (1) those who met the diagnostic criteria for children with idiopathic short stature, with height and standard deviations lower than that of children of the same age and sex; (2) patients not older than 14 years; (3) patients whose heights and weights at birth were similar to those of healthy children of the same sex and age, and (4) those with no history of family or genetic disease.

Exclusion criteria

The following categories of patients were excluded: (1) those with chromosomal abnormalities and congenital malformations; (2) patients with abnormal thyroid function, and (3) those with abnormal liver and kidney functions.

This study was authorized by ethics committee of Children Health Care Center of Shiyuan Maternal and Child Health Care Hospital, and patients and their family members voluntarily signed informed consent form prior to the enrollment. Furthermore, the study followed international guidelines for human studies

Recombinant human growth hormone (r-hGH) administration

Patients in group A received r-hGH at a dose of 0.26 mg/kg/week in combination with vitamin D. Patients in group B were given r-hGH at a dose of 0.35 mg/kg/week in combination with vitamin D. In group C, the patients received r-hGH at a dose of 0.41 mg/kg/week, also in combination with vitamin D. The r-hGH (Changchun Jinsai Pharmaceutical Co. Ltd.; SFDA approval number: S20050024) was administered via subcutaneous injection. It was evenly drawn with a hypodermic syringe, and injected at 3 cm around the umbilical cord and the arm or thigh, every night before going to bed [10-12]. Vitamin D (Qingdao Shuangjing Pharmaceutical Co. Ltd.; SFDA approval number: H20113033) was given orally for 1 to 2 years, and a physical examination was performed every 3 months.

Evaluation of parameters

Changes in height as well as growth rate, bone age, height standard deviation score, fasting blood glucose index, thyroid function and treatment effectiveness were determined before and after treatment in the three groups.

Fasting blood glucose levels of 3.9 - 6.1 mmol/L were considered normal.

Thyroid function tests involved assays for thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3) and free tetraiodothyronine (FT4) [13-15].

Statistical analysis

Measurement data are presented as mean \pm standard deviation (SD), and were processed using Student's *t*-test. Enumeration data are expressed as numbers and percentages [n (%)], and were verified using chi squared (χ^2) test. All statistical analyses were done using SPSS version 20.0 software. GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to visualize graphics. The statistical differences were set at $p \leq 0.05$.

RESULTS

Height standard deviation score, growth rate, bone age, and height before and after treatment

Significantly increased height standard deviation score, growth rate, bone age, and height in the three groups of patients one year after treatment were observed than the corresponding values before treatment, with group A < group B < group C ($p < 0.05$). These results are presented in Figure 1, Figure 2, Figure 3 and Figure 4.

The mean height of patients in group A before treatment was 113.26 ± 10.70 cm, while the corresponding value after treatment for one year was 124.37 ± 11.06 cm. For group B, the mean height of patients before treatment was 112.96 ± 10.72 cm, and their mean height after treatment for one year was 132.51 ± 12.13 cm. The mean height of group C patients before treatment was 113.58 ± 10.69 cm, while their mean height after treatment for one year was 139.70 ± 12.25 cm. * $P = 0.009$, group A vs group B after one year of treatment; ** $p = 0.03$, group C vs group B after one year of treatment; ^a $p < 0.001$, group A before treatment vs group A after treatment; ^b $p < 0.001$, group B before and after treatment; ^c $p < 0.001$, group C before and after treatment.

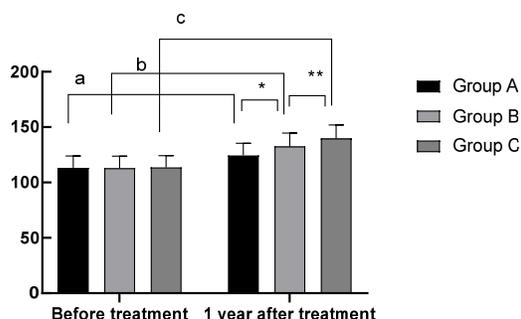


Figure 1: Mean heights of patients in the three groups before and after treatment

The growth rate of group A before treatment was 5.80 ± 0.19 cm/year, while the growth rate after treatment for one year was 7.43 ± 0.57 cm/year. The growth rate of group B before treatment was 5.86 ± 0.20 cm/year, while the growth rate after one year of treatment was 9.38 ± 0.84 cm/year. The growth rate of group C before treatment was 5.79 ± 0.22 cm/year, while the growth rate after one year of treatment was 13.36 ± 1.00 cm/year. * $P < 0.001$, group A vs group B after one year of treatment; ** $p = 0.001$, group C vs group B after one year of treatment; ^a $p < 0.001$, group A before and after treatment; ^b $p < 0.001$, group B before

and after treatment; ^c $p < 0.001$, group C before and after treatment.

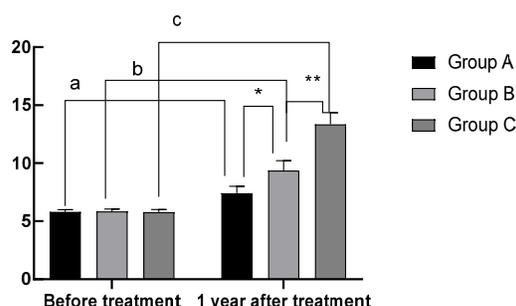


Figure 2: Comparison of the growth rate of the three groups before and after treatment

The bone age of group A was 7.21 ± 1.04 years before treatment, but after one year of treatment, the bone age was 9.12 ± 1.38 years. In group B, the bone age before treatment was 7.13 ± 1.02 years, but the bone age after one year of treatment was 10.89 ± 1.46 years. In group C, the bone age before treatment was 7.20 ± 1.03 years, but after one year of treatment, the bone age was 12.00 ± 1.58 years.

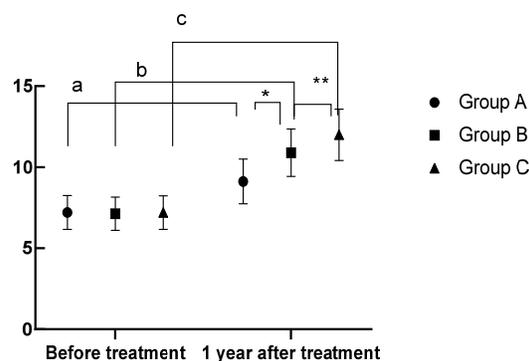


Figure 3: Comparison of bone age before and after treatment in the three groups. * $P < 0.001$, group A vs group B after one year of treatment; ** $p = 0.001$, group C vs group B after one year of treatment; ^a $p < 0.001$, group A before and after treatment; ^b $p < 0.001$, group B before and after treatment; ^c $p < 0.001$, group C before and after treatment.

The height standard deviation score before treatment in group A was 113.05 ± 9.33 cm, while the standard deviation of height after treatment for one year was 121.07 ± 10.00 cm. In group B, the height standard deviation score before treatment was 113.28 ± 9.86 cm, but after one year of treatment, the standard deviation of height was 126.39 ± 10.24 cm. The height standard deviation score before treatment in group C was 113.57 ± 9.55 cm, while the standard deviation of height after treatment for

one year was 135.51 ± 10.64 cm. $*P < 0.04$, group A vs group B after one year of treatment; $**p = 0.001$, group C vs group B after one year of treatment; $^ap < 0.002$, group A before and after treatment; $^bp < 0.001$, group B before and after treatment; $^cp < 0.001$, group C before and after treatment.

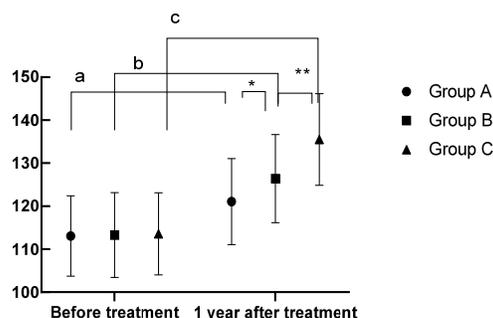


Figure 4: Comparison of height standard deviation score before and after treatment amongst the three groups

Fasting blood glucose and thyroid function

Post-treatment values of fasting blood glucose and thyroid function in the three groups were comparable, although the mean fasting blood glucose level of patients in group C was slightly higher than those of patients in groups A and B after one year of treatment ($p > 0.05$). These results are shown in Figure 5 and Table 1.

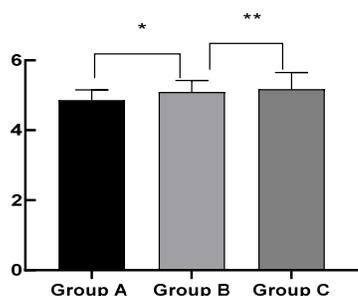


Figure 5: Comparison of fasting blood glucose levels amongst the three groups. The fasting blood glucose levels in groups A, B and C were 4.86 ± 1.11 , 5.09 ± 1.10 and 5.17 ± 1.12 mmol/L, respectively. $*P = 0.42$, group A vs group B; $**p = 0.78$, group B vs group C

Table 1: Comparison of thyroid function amongst the three groups

Group	TSH (μ IU/mL)	T3 (nmol/L)	T4 (nmol/L)	FT3 (pmol/L)	FT4 (pmol/L)
A	$2.59 \pm 0.48^*$	$2.27 \pm 0.55^*$	$100.37 \pm 10.34^*$	$5.74 \pm 0.88^*$	$18.66 \pm 1.20^*$
B	$2.58 \pm 0.51^\#$	$2.30 \pm 0.54^\#$	$101.28 \pm 10.55^\#$	$5.76 \pm 0.87^\#$	$18.84 \pm 1.19^\#$
C	$2.60 \pm 0.50^\#$	$2.31 \pm 0.55^\#$	$100.89 \pm 10.49^\#$	$5.75 \pm 0.85^\#$	$18.73 \pm 1.20^\#$
t	$0.08^*/0.15^\#$	$0.21^*/0.07^\#$	$0.34^*/0.14^\#$	$0.09^*/0.05^\#$	$0.58^*/0.36^\#$
P-value	$0.94^*/0.88^\#$	$0.83^*/0.94^\#$	$0.74^*/0.89^\#$	$0.93^*/0.96^\#$	$0.56^*/0.72^\#$

Therapeutic effectiveness

As shown in Figure 6, treatment effectiveness was highest in group C patients, followed by those in group B, and then group A ($p < 0.05$).

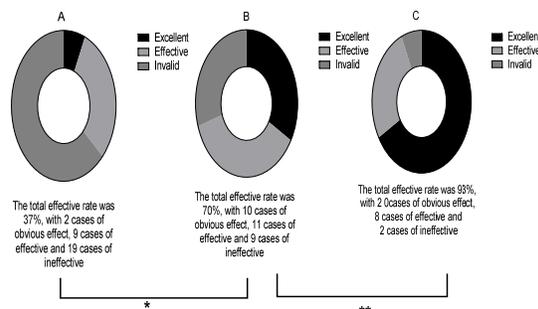


Figure 6: Comparison of treatment effectiveness amongst the three groups. A: treatment effectiveness in group A, in which there were 2 markedly effective cases, 9 effective cases, and 19 ineffective cases, resulting in total effectiveness of 37%. B: treatment effectiveness in group B, showing 10 markedly effective cases, 11 effective cases and 9 ineffective cases, giving a total effectiveness of 70%. C: Total effectiveness was 93%, arising from 20 markedly effective cases, 8 effective cases, and 2 ineffective cases. $*P = 0.01$, group A vs group B; $**p = 0.02$, group B vs group C

DISCUSSION

Idiopathic short stature, a relatively common disease in children, impairs the physique of the patient, and may give rise to unhealthy mentality such as inferiority complex and lack of self-confidence [16]. At present, the pathogenesis of idiopathic short stature is poorly understood, and the specific factors that influence it are not fully identified yet. However, several reports have suggested that the pathogenesis of idiopathic short stature is related to insufficient secretion of growth hormone in patients [19]. Growth hormone is essential for the normal growth and development of the human body, and it promotes the normal growth of bones and muscles.

Insufficient secretion of growth hormone leads to *atelirosis* and growth retardation. Therefore, in clinical practice, r-hGH is universally used as the main therapeutic drug for patients with idiopathic short stature. In addition, vitamin D plays a pivotal role in protecting the bones and reducing growth related pains in patients [22].

This study showed that changes in height, as well as bone age, height standard deviation score and growth rate of patients treated with r-hGH at a dose of 0.41 mg/kg/week were significantly superior to those of patients treated with r-hGH at doses of 0.26 and 0.35 mg/kg/week. The effects of r-hGH are identical to those of human growth hormone due to their similarities in protein structure and amino acid sequence.

Therefore, r-hGH promotes bone development and enhances stable growth. After treatment, the fasting blood glucose and thyroid function of the patients were homogenous among the three groups, but the fasting blood glucose level of group C treated with the largest dose of r-hGH was slightly higher than that of each of the other two groups.

Moreover, the fasting blood glucose of group B patients (given moderate dose of r-hGH) was slightly higher than that of group A, suggesting that r-hGH exerts an effect on blood glucose levels within a safe range. A study has shown that different doses of r-hGH produced different effects on patients with idiopathic short stature, with the largest doses of r-hGH generating the most promising effect [24].

CONCLUSION

This study demonstrates that the combination of r-hGH and vitamin D produces a good treatment effectiveness in idiopathic short-stature children. The most beneficial effect is obtained at r-hGH dose of 0.41 mg/kg/week in combination with vitamin D.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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