

Effect of different doses of recombinant human growth hormone therapy on children with growth hormone deficiency: a retrospective observational study

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Abstract. – OBJECTIVE: The aim of this study was to explore the effects of different doses of recombinant human growth hormone (rhGH) treatment on children with growth hormone deficiency (GHD).

PATIENTS AND METHODS: Medical records of 174 GHD patients admitted to our hospital from June 2019 to January 2022 were retrospectively evaluated. A total of 136 patients met the inclusion criteria, of which 70 received 0.1 U/(kg·d) (low-dose group) and 66 received 0.2 U/(kg·d) dose of rhGH treatment (high-dose group). Growth and development status [height, weight, height standard deviation (HtSDS), growth rate], bone age, bone density, speed of sound (SOS) as distal radius bone mass, biochemical indicators of growth and development [insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3)], growth hormone (GH) levels and incidence of adverse reactions were collected and compared between the two groups before and after one year of the treatment.

RESULTS: After the treatment, height, weight, HtSDS, and growth rate of the two groups increased compared to before the treatment and were significantly higher in the high-dose group than in the low-dose group ($p < 0.05$). After one year of treatment, the following observations were made: the bone age of the two groups increased compared to the baseline values and was higher in the high-dose group compared to the low-dose group ($p < 0.05$). The SOS of the two groups decreased but was significantly higher in the high-dose group compared to the low-dose group ($p < 0.05$). Serum levels of IGF-1, IGFBP-3, and GH in both groups increased compared to the baseline values and were higher in the high-dose group than in the low-dose group ($p < 0.05$). There was no significant difference in the incidence of adverse reactions between the high-

dose group (8.6%) and the low-dose group (6.1%) ($p > 0.05$).

CONCLUSIONS: High-dose rhGH treatment for GHD is safe and can more effectively upregulate IGF-1, IGFBP-3, and GH, and promote the growth and development of children.

Key Words:

Recombinant human growth hormone, Different doses, Growth hormone deficiency.

Introduction

Growth hormone deficiency (GHD) is a common type of dwarfism that is caused by the impaired body insensitivity to growth hormone. It adversely impacts children's growth and development, resulting in lower body height compared to the same age group^{1,2}. GHD is associated with a varying degree of impact on the physical and mental health of the affected children³. Therefore, providing timely, safe and effective treatment for GHD is of great significance.

Insulin-like growth factor-1 (IGF-1) is the crucial mediator of growth hormone (GH)⁴ and the IGF-1/GH axis is the main endocrine system regulating linear growth in children⁵. Hormone replacement with the recombinant human growth hormone (rhGH) is the most commonly used method of the clinical treatment of GHD since its initial licensing in 1985⁶. It simulates the function of pituitary growth hormone to a certain extent, regulates multiple metabolic pathways, and promotes growth and development⁷. Studies^{8,9} show

that rhGH is a potent stimulator of IGF-1 secretion, promotes chondrocyte generation in the epiphyseal region of the long shaft, accelerates bone development, and regulates cell metabolism. However, there is still no consensus on the optimal dosage of rhGH in clinical practice. The aim of this study was to use different doses of rhGH to treat children diagnosed with GHD in our hospital, in order to clarify its application value and provide practical references for a safe and effective treatment.

Patients and Methods

Patients

Clinical data of 174 GHD patients that were admitted to our hospital from June 2019 to Ja-

nuary 2022 were retrospectively assessed. A total of 136 patients (71 males and 65 females) met the conditions of this study. Patients were aged 6-12 years, with an average age of 8.89 ± 1.54 years. The body mass index (BMI) was 16.5-21.1 kg/m^2 , with an average BMI of $18.63 \pm 1.00 \text{ kg/m}^2$. Seventy patients that received 0.1 U/(kg·d) dose of rhGH and were retrospectively assigned to the low-dose group, and 66 patients that received 0.2 U/(kg·d) dose of rhGH and were assigned to the high-dose group (Figure 1). This study was approved by the Hospital Medical Ethics Committee (No. EYLL-2022-018, Date: 2022-03-13) and was conducted according to the Helsinki Declaration (revised in 2013). Due to the retrospective nature of the study, informed consent from patients was waived.

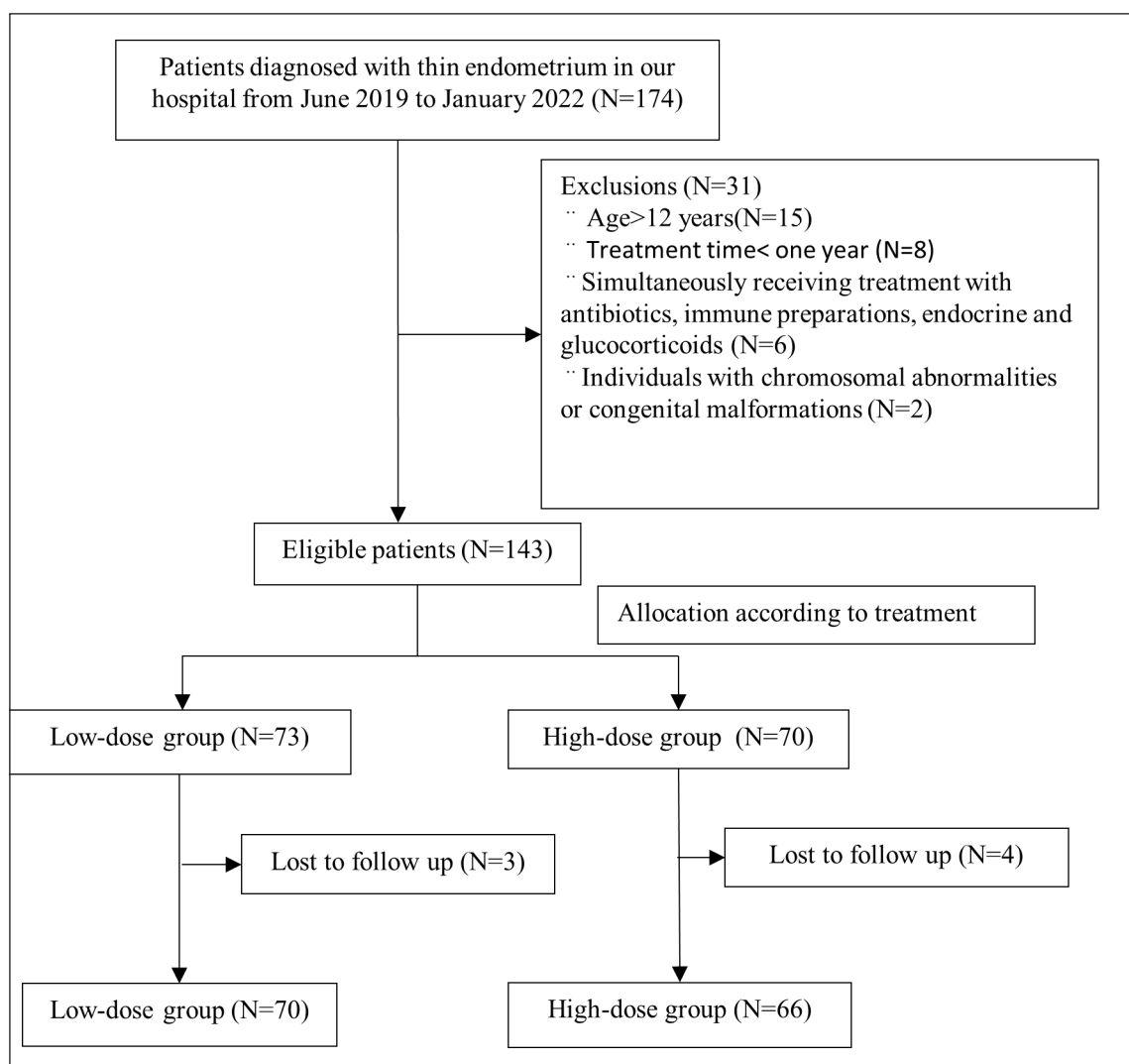


Figure 1. Study enrolment flowchart.

Inclusion Criteria

- 1) Meets GHD diagnostic criteria¹⁰.
- 2) The age before receiving treatment: 6-12 years old; received more than 1 year of treatment and has complete follow-up information.
- 3) No treatment such as antibiotics, immune and endocrine preparations, and glucocorticoids was administered within one month prior to the inclusion in the study.
- 4) Growth rate <5 cm/year.

Exclusion Criteria

- 1) Intrauterine developmental delay, chromosomal abnormalities, or congenital malformations.
- 2) Organic, consumable, nutritional, and systemic lesions.
- 3) Eating disorders.
- 4) Speech communication, emotional, and psychological disorders.
- 5) Allergic constitution.
- 6) Pituitary lesions.
- 7) Abnormal thyroid function.
- 8) Genetic metabolic disorders.

Treatment

Patients were provided dietary guidance and family members were instructed to give the child supplements containing trace elements, vitamins, calcium, etc. Every night before bedtime, subcutaneous injections of 0.1 U/ (kg·d) or 0.2 U/ (kg·d) doses of rhGH [Anhui Anke Biotechnology (Group) Co., Ltd., Anhui Province, China; Approval No. S19990021) were administered into the anterolateral part of the middle thigh and the periumbilical area. Patients were instructed to alternate injection sites. The treatment was continued for one year.

Data Collection and Indicators

The following indicators were collected: 1) Growth and development status before and one year after the treatment, including height, weight, height standard deviation (HtSDS), and growth rate. HtSDS was calculated as (height of the patient - normal height of the same age)/normal HtSDS of the same age. Growth rate was calculated as height difference before and after treatment/interval time × 12. 2) Bone age, bone density, distal radius bone mass, speed of sound (SOS) were measured using the Greulich Pyle standard atlas method before and one year after treatment. MiniOmni ultrasound bone density instrument (BeamMed, Petah Tikva, Israel) was used for detecting SOS. 3) Levels of IGF-1, Insulin-like

growth factor binding protein 3 (IGFBP-3), GH and other biochemical indicators were measured before the treatment and one year after the treatment. Briefly, supernatant from 4 ml of fasting venous blood was used, and levels of biochemical markers were detected by Siemens IMMULITE 2000 (Berlin, Germany) fully automatic chemiluminescence immunoassay analyzer and matching reagent kit. 4) Adverse reactions.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for data processing. The measurement data were represented by mean ± standard deviation (SD). Student's *t*-test was used for comparison between the two groups, and paired sample *t*-test was used for comparison within the same group before and after the treatment. Classified data were expressed in frequency and percentage (n, %), and differences between the two groups were compared using Chi-square tests. Wilcoxon rank-sum test was used for comparing ordinal data. All statistical tests were bilateral tests. *p*<0.05 indicated statistical significance.

Results

Baseline Data

A total of 136 patients met the inclusion criteria. Of them, 70 patients were in the low-dose group, and 66 patients in the high-dose group. There was no statistically significant difference in baseline data between the two groups of patients (*p*>0.05) (Table I).

Comparison of Growth and Development Between the Two Groups Before and After Treatment

There was no significant difference in height, weight, HtSDS, and growth rate between the two groups before the treatment (*p*>0.05). After the treatment, height, weight, HtSDS, and growth rate of the two groups increased compared to the baseline levels (before the treatment; *p*<0.05) and were significantly higher in the high-dose group compared to the low-dose group (*p*<0.05) (Table II).

Comparison of Bone Age and SOS Between Two Groups Before and After Treatment

There was no significant difference in bone age and SOS between the two groups before the treatment (*p*>0.05). After one year of the treatment,

Table I. Comparison of baseline data between two groups of patients.

Group	n	Gender (Male/Female)	Age (years)	BMI (kg/m ²)	Genetic target height (cm)	Tanner stage (I/II)
Low-dose group	70	33/37	8.75±1.52	18.79±1.01	166.91±4.04	45/25
High-dose group	66	37/29	9.03±1.56	18.46±0.96	167.56±4.32	39/27
χ^2/t		1.082	-1.035	1.905	-0.902	0.388
<i>P</i>		0.298	0.302	0.059	0.369	0.533

Table II. Comparison of baseline data between two groups of patients.

Time	Group	n	Height (cm)	Body weight (kg)	HtSDS (cm)	Growth rate (cm/year)
Before treatment	Low-dose group	70	108.27±6.71	21.03±2.35	-2.40±0.28	4.19±0.94
	High-dose group	66	107.61±6.26	21.77±2.41	-2.47±0.22	4.30±0.96
	<i>t</i>		0.597	-1.822	-1.671	-0.721
	<i>p</i>		0.552	0.071	0.097	0.472
After one year of treatment	Low-dose group	70	115.66±8.39 ^a	24.94±3.78 ^a	-1.83±0.22 ^a	7.38±2.47 ^a
	High-dose group	66	122.09±9.00 ^a	28.76±3.32 ^a	-1.60±0.18 ^a	14.48±3.40 ^a
	<i>t</i>		-4.313	-6.228	6.749	13.857
	<i>p</i>		<0.001	<0.001	<0.001	<0.001

HtSDS: height standard deviation; Compared within the same group before treatment, ^a*p*<0.05.

the bone age of the two groups increased compared to that before the treatment (*p*<0.05) and was significantly higher in the high-dose group compared to the low-dose group (*p*<0.05). After one year of treatment, the SOS of the two groups decreased (*p*<0.05) but was significantly higher in the high-dose group compared to the low-dose group (*p*<0.05) (Table III).

Comparison of Biochemical Indicators of Growth and Development Before and After Treatment

There was no significant difference in serum IGF-1, IGFBP-3, and GH levels between the two groups before the treatment (*p*>0.05). After one year of the treatment, serum IGF-1, IGFBP-3 and

GH levels in both groups increased compared to before treatment (*p*<0.05), with the high-dose group exhibiting significantly higher levels than the low-dose group (*p*<0.05) (Table IV).

Adverse Reactions in Both Groups After Treatment

There was no significant difference in the incidence of adverse reactions between the high-dose group (8.6%) and the low-dose group (6.1%) (*p*>0.05) (Table V).

Discussion

In this study, children with GHD were administered different doses of rhGH over the course

Table III. Comparison of bone age and SOS between two groups.

Time	Group	n	Bone age (years)	SOS (m/s)
Before treatment	Low-dose group	70	6.03±1.85	3743.17±92.35
	High-dose group	66	6.15±2.03	3715.98±83.12
	<i>t</i>		-0.368	1.801
	<i>p</i>		0.712	0.074
After one year of treatment	Low-dose group	70	9.01±1.63 ^a	3607.33±78.33 ^a
	High-dose group	66	9.90±1.54 ^a	3663.44±92.81 ^a
	<i>t</i>		-3.291	-3.818
	<i>p</i>		0.001	<0.001

HtSDS: height standard deviation; Compared within the same group before treatment, ^a*p*<0.05.

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of 1 year. Our results showed that the height, weight, HtSDS, growth rate, bone age, and SOS of the high-dose group were higher than those of the low-dose group. However, there was no significant difference in the incidence of adverse reactions among GHD children treated with different doses of rhGH. Jiang et al¹¹ treated children with GHD with high-dose and low-dose rhGH and showed that the growth rate and standard deviation score of height in both groups improved compared to the levels before the treatment. However, the improvement of the above indicators in the high-dose group was more significant, consistent with the

results of this study. Our results confirm the feasibility and effectiveness of using different doses of rhGH to treat GHD and show that a high-dose rhGH regimen can more effectively promote the growth and development of children with GHD. Zheng et al¹² showed that in adult patients who received the low-dose growth hormone treatment, the low weight incidence rate was significantly reduced, and cardiovascular risk factors were effectively controlled compared to patients who did not receive the treatment. Several studies¹³⁻¹⁵ also explored the application value of different doses of rhGH in GHD. For example, Xu et al¹³ found

Table IV. Comparison of biochemical indicators for growth and development between two groups.

Time	Group	n	IGFBP-3 (ug/ml)	IGF-1 (ng/ml)	GH (ng/ml)
Before treatment	Low-dose group	70	337.66±22.23	112.59±15.80	2.61±0.71
	High-dose group	66	342.17±25.26	109.70±15.07	2.51±0.64
	<i>t</i>		-1.107	1.089	0.854
	<i>P</i>		0.270	0.278	0.395
After one year of treatment	Low-dose group	70	521.18±28.20 ^a	196.37±20.53 ^a	3.40±0.77 ^a
	High-dose group	66	547.15±31.07 ^a	221.35±23.38 ^a	3.93±0.72 ^a
	<i>t</i>		-5.108	-6.630	-4.118
	<i>P</i>		<0.001	<0.001	<0.001
	<i>p</i>		0.001	<0.001	

IGF-1: Insulin growth factor 1; IGFBP-3: Insulin-like growth factor binding protein 3; GH: growth hormone; Compared within the same group before treatment, ^a*p*<0.05.

Table V. Comparison of adverse reactions between the two groups [n (%)].

Time	n	Abnormal thyroid function	Lower limb edema	High blood sugar	knee pain	Total occurrence rate
Before treatment	70	1 (1.4)	1 (1.4)	2 (2.9)	2 (2.9)	6 (8.6)
Time	66	0 (0.0)	2 (3.0)	1 (1.5)	1 (1.5)	4 (6.1)
χ^2						0.569
<i>p</i>						0.451

that the total effective rate of patients who received a high dose (0.2 U/kg) rhGH (experimental group) was significantly higher than that in the control group, which is consistent with the results of this study. However, the incidence of adverse reactions in the experimental group was lower than that in the control group. These results contradict our observation. We may speculate that there may be a correlation between the patient's condition and their health status, and further studies are needed to confirm the safety of different doses of rhGH in GHD. Li¹⁴ treated children with dwarfism with low-, medium-, and high-dose rhGH and showed that the positive effects observed in the high- and medium-dose groups were more prominent than those of the low-dose group. Their results confirmed the dose-dependent effect of rhGH treatment on children with GHD. Similarly, in their study, Han et al¹⁵ demonstrated that compared to low-dose rhGH, high-dose treatment regimens can more effectively promote the growth and development of children with dwarfism, with guaranteed safety, which is consistent with the conclusions of our study.

RhGH is a commonly used drug for GHD, which can induce and promote the transformation of chondrocytes in the quiescent phase to the proliferative phase, stimulate IGF-1 production, accelerate the proliferation and differentiation of chondrocytes in the proliferative phase, and promote bone growth¹⁶. Early high-dose administration of rhGH can more effectively regulate growth hormone resistance, promote physical development, and increase height in children with GHD whose epiphyses have not yet been fully closed^{17,18}. GHD is mainly caused by decreased secretion of growth hormone due to dysfunction of the hypothalamic-pituitary anterior lobe. A high-dose rhGH can compensate for the lack of GH in the body, thereby ensuring normal growth and development of the child^{19,20}.

Ertl et al²¹ pointed out that IGF-1 can directly act on target cells, mediate the biological effects of GH, and that the IGF-1 serum content is also affected by GH. IGF-1 levels can accurately reflect the functional status of the GH-IGF-1 axis and accelerate height growth through cartilage action. Thus, low levels of serum IGF-1 may indicate delayed growth and development. Additionally, IGF-1 can promote the division and proliferation of chondrocytes from different sources, accelerate the synthesis of cartilage matrix, and enhance cell enzyme activity. IGFBP-3 is a multifunctional regulatory factor that promotes bone growth. Numerous studies^{21,22} show the synergistic effect of IGF-1 and IGFBP-3

on bone growth and differentiation. As shown in the study by Haj-Ahmad et al²², IGF-BP3 is one of the IGF-1 binding proteins and key carriers. After binding IGF-1, promotes a slow increase in IGF-1 levels, which in turn regulates the level of free IGF-1 in the blood and enables it to effectively promote growth in a long-term manner. In our study, the serum levels of IGF-1, IGFBP-3, and GH in the high-dose group were significantly higher than in the low-dose group after the treatment. Our results further confirm that the higher dose of rhGH has better application value and is more beneficial for promoting the growth and development of children with GHD. We hypothesize that there may be a certain level of IGF-1 resistance reactions in GHD patients treated with rhGH, which may lower the efficiency of the treatment. Higher doses of rhGH may overcome this IGF-1 resistance reaction, enhance the levels of alkaline phosphatase and GH in the body, regulate the balance of IGF-1 and IGFBP-3, ensure bone development, and accelerate growth.

Limitations

This is a single-center retrospective study, with a small sample size and some bias in the case selection. Further multicenter prospective case-control trials including more groups with a wider range of rhGH doses should be conducted to determine the optimal treatment regimen in children with GHD.

Conclusions

Adopting high-dose rhGH treatment for GHD is safe and can more effectively upregulate IGF-1, IGFBP-3, and GH indicators, and promote the growth and development of children.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

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Ethics Approval

The study was approved by the Ethics Committee of the Anhui Children's Hospital (No.: EYLL-2022-018; Date: 23 March 2022).

Informed Consent

Patient informed consent was waived because of the retrospective nature of the study.

Authors' Contribution

T. Yang, W. Zha, X. Liang, Q. Xu, T.-T. Guo, X. He, and Y. Yuan have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. T. Yang, W. Zha and G. Zhang are involved in drafting the manuscript or revising it critically for important intellectual content. G. Zhang agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved of the final manuscript.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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