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Original Article

The impact of recombinant human growth hormone on growth and development of low weight premature infants

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Abstract: Recombinant human growth hormone (rHGH) shows remarkable curative effect on premature infants' growth and development. This study analyzed the effect of rHGH on low weight premature infants. Premature infants delivered in our hospital were selected. Enzyme-linked immunosorbent assay was used to test the growth and development related indicators, insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), IGF-1/IGFBP-3, and fasting glucose. Adverse reactions were observed. After 6 months' treatment, body weight (10.4 ± 0.5 kg), length (68.1 ± 2.4 cm), and head circumference (35.8 ± 2.2 cm) in experimental group were significantly higher than that in control, at birth, and treatment for 3 months, respectively ($P < 0.05$). Experimental group performed higher body mass increasing speed, head circumference increasing speed, and length increasing speed, shorter reaching adequate feeding time through the mouth, and lower EUGR incidence ($P < 0.05$). After the treatment for 6 months, experimental group presented higher serum IGF-1 (184.2 ± 152.3 ng/mL), IGFBP-3 (5.4 ± 1.7 ng/mL), and IGF-1/IGFBP-3 (36.4 ± 4.5 ng/ml) levels than the control group, at birth, and treatment for 3 months, respectively ($P < 0.05$). Fasting glucose (5.23 ± 2.3 mmol/L) was obviously higher in the experimental group ($P < 0.05$). Four cases appeared local skin reactions (13.3%) and self-relieved. Recombinant human growth hormone could safely promote low weight premature infants growth.

Keywords: Recombinant human growth hormone, low weight premature infant, growth and development, IGF-1, IGFBP-3

Introduction

With the development of the gynecology and neonatal medical innovation and technology, which include maternal pregnant examination and treatment, neonatal intensive care, treatment of related diseases has been significant improved. Though the premature infant's quality of life has been elevated obviously, it remains a hotspot to better solve the problem of premature infant's growth and development [1]. Since premature infants abnormally leave the mother earlier, the organ function and metabolic system have not yet matured. Accordingly, premature infant faces up with the challenge of great nutrition burden for the growth and development [2]. British nutritionist Lucas proposed that infants and young children suffered from a critical period of growth and development, and good nutrition status had a lifelong influence on the organ system function [3]. Generally, short of hormones and nutrients exist in premature infants. Hypothalamus or pituitary dysfunction decreases growth hormone synthesis or secretion significantly, and even changes growth hormone structure, leading to the body growth and development retardation. It also results in short stature, metabolic disorder, important organ and system dysfunction that seriously affect quality of life [4]. Recombinant human growth hormone (rHGH) is produced by genetic engineering technology, and its application significantly promotes bone growth, organs matura-

tion and protein synthesis of preterm infants. Its wide use in the treatment of premature growth hormone deficiency proved no side effect that causes puberty and bone mature ahead of time in the growth process [5, 6]. Our study aims to evaluate the role of rHGH on the growth and development of premature infants or low birth weight infants, which may provide a future basis for the rational preparation of hormone therapy.

Materials and methods

General information

Sixty cases of premature infants delivered in The Fourth Hospital of Shijiazhuang City from Jan 2014 to Jan 2015 were enrolled. The subjects were divided into two groups: 30 cases in experimental group with 18 males and 12 females, and 30 cases in control with 16 males and 14 females. No statistical difference was observed in gender, gestational age, and weight between the two groups ($P > 0.05$) (**Table 1**).

Inclusion criteria: gestational age ≤ 32 weeks, weight ≤ 1800 g, length of stays > 14 d, and the infants reached adequate feeding through mouth at discharge.

Exclusion criteria: congenital digestive tract malformation; severe liver and kidney dysfunction; hereditary metabolic disease.

Therapeutic method

The infants in two groups were given oxygen inhalation, intravenous fluids, heat preservation, and diet guidance. Experimental group received recombinant human growth hormone (Shanghai Unilab biological engineering co., LTD., batch number: 20140748) at 0.1 U/kg once-daily via subcutaneous injection for 6 months, while the control group received no drug therapy.

Observation indicator

Growth and development related indicator detection: Infant's weight at birth, treatment for 3 months, and treatment for 6 months were measured accurate to 10 g. Measurement bed was applied to test infant's length accurate to 0.1 cm. Infant's head circumference was measured by tape accurate to 0.1 cm. Weight descent range, weight increase speed, head circumference increase speed, length increase speed, time of restore weight at birth, time to adequate oral feeding, and extra uterine growth retardation (EUGR) incidence were observed and compared.

Insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and IGF-1/IGFBP-3 detection: Peripheral blood was extracted at birth, 3 months after treatment, and 6 months after treatment and centrifuged at 3000 r/min to separate serum. The supernatant was isolated and stored at -85°C.

Enzyme-linked immunosorbent assay (ELISA) was applied to test serum IGF-1 and IGFBP-3 levels. The ELISA kit was bought from Shanghai west tang biological technology development Co., LTD. 0.75 mL ddH_2O was added to the bottle containing different amount of samples. 40 mL dense washing liquid was added into 960 ml ddH_2O to prepare the washing liquid. 600 μL Tracer was added to 12 ml CRP biotin to prepare incubation buffer. The microplate coated by streptavidin was washed by washed by washing buffer. 25 μL standard substance or sample was added to each hole together with 100 μL incubation buffer per hole. After vibrated at room temperature for 1 h, the plate was washed by washing buffer for six times. The plate was added with 100 μL substrate and vibrated at room temperature for 30 min. And then, the plate was added with 100 μL stop buffer and vibrated at room temperature for 1 min. Absorbance of plate (OD) was read at microplate reader at 405 nm to calculate IGF-1 and IGFBP-3 concentration.

Fasting blood-glucose detection: Fasting blood was extracted at birth, 3 months after treatment, and 6 months after treatment. Glucose oxidase method was used to test blood glucose (Sangon, Shanghai).

Adverse reaction comparison: Adverse reaction in two groups were observed, including skin irritation, rashes, liver and kidney function damage, hypothyroidism, systemic hypersensitivity, and scoliosis.

Data analysis

All statistical analysis was performed on SPSS17.0 software (IBM, USA). Measurement

Table 1. General information comparison

Item	Experimental group	Control group	*P* value
Cases	30	30	
Gender (male/female)	18/12	16/14	> 0.05
Gestational age (weeks)	30.5 ± 1.3	30.4 ± 1.2	> 0.05
Weight at birth (kg)	1.5 ± 0.3	1.3 ± 0.2	> 0.05
Head circumference (cm)	26.1 ± 1.1	26.8 ± 1.1	> 0.05
Height (cm)	42.3 ± 2.3	41.8 ± 2.4	> 0.05
Singletons premature infant	22 (73.3)	21 (70)	> 0.05
Twins premature infant	6 (20)	5 (16.7)	> 0.05
Multiple gestation	2 (6.7)	4 (13.3)	> 0.05
Intrauterine infection (n%)	13 (43.3)	14 (46.7)	> 0.05
Simple premature infant	26 (86.7)	25 (83.3)	> 0.05
Hypoxic ischemic encephalopathy	2 (6.7)	3 (10)	> 0.05
Amniotic fluid inhalation syndrome	2 (6.7)	2 (6.7)	> 0.05
Neonatal asphyxia (n%)	5 (16.7)	6 (20)	> 0.05
Neonatal respiratory distress syndrome (n%)	18 (60)	19 (63.3)	> 0.05
Neonatal necrotizing colitis (n%)	9 (30)	8 (23.3)	> 0.05

Table 2. Growth related indicators comparison

Item	Experimental group	Control group
Cases	30	30
Body mass (kg)		
At birth	1.5 ± 0.3	1.3 ± 0.2
3 months' treatment	4.1 ± 0.4	3.3 ± 0.2
6 months' treatment	10.4 ± 0.5*	6.2 ± 0.4
Length (cm)		
At birth	42.30 ± 2.30	41.8 ± 2.4
3 months' treatment	60.2 ± 2.3	53.2 ± 2.1
6 months' treatment	68.1 ± 2.4*	62.2 ± 1.7
Head circumference (cm)		
At birth	30.1 ± 1.6	29.8 ± 1.6
3 months' treatment	33.4 ± 2.1	31.4 ± 1.8
6 months' treatment	45.8 ± 2.2*	33.0 ± 2.0
Body mass increasing speed (g/kg/d)	2.3 ± 0.2*	1.4 ± 0.9
Head circumference increasing speed (cm/week)	0.7 ± 0.4*	0.4 ± 0.1
Length increasing speed (cm/week)	1.2 ± 0.2*	0.9 ± 0.1
Time of restore weight at birth (d)	5 (3)*	9 (1)
Reaching adequate feeding time (d)	20 (8)*	25 (9)
EUGR incidence (n%)	11 (36.7)*	18 (60)

*P < 0.05, compared with control.

data was presented as mean ± standard deviation ($\bar{x}$ ± s). T test and chi-square test were used for data comparison. P < 0.05 was considered as statistically significant.

Results

Growth related indicators detection

Growth related indicators between two groups were compared, including weight, length, head circumference, body mass descend range, body mass increasing speed, head circumference increasing speed, length increasing speed, time of restore weight at birth, reaching adequate feeding time, and EUGR incidence. No significant difference in weight, length, and head circumference between two groups was observed (P > 0.05). After 6 months treatment, body weight, length, and head circumference in experimental group were significantly higher than that in control, at birth, and 3 months' treatment, respectively (P < 0.05). Experimental group presented higher body mass increasing speed, head circumference increasing speed, and length increasing speed, shorter reaching adequate feeding time through the mouth, extended time of restore weight at birth, and lower EUGR incidence (P < 0.05) (**Table 2**).

IGF-1, IGFBP-3, and IGF-1/IGFBP-3 levels comparison

Experimental group presented higher IGF-1, IGFBP-3, and IGF-1/IGFBP-3 levels in serum, compared to control group, at birth, and 3 months treatment (P < 0.05). Control group showed no statistical difference between 3 months and 6 months (P > 0.05), while they were both higher than at birth (P < 0.05) (**Table 3**).

Table 3. Serum IGF-1, IGFBP-3, and IGF-1/IGFBP-3 comparison

Item	Experimental group	Control group
Cases	30	30
IGF-1 (ng/ml)		
At birth	39.2 ± 33.4	38.7 ± 34.2
3 months' treatment	124.8 ± 84.3$^{*,\#}$	47.2 ± 37.1$^{\#}$
6 months' treatment	184.2 ± 152.3$^{*,\#,\&}$	59.7 ± 55.3$^{\#}$
IGFBP-3 (ng/ml)		
At birth	2.4 ± 0.5	2.3 ± 0.4
3 months' treatment	4.6 ± 0.9$^{*,\#}$	2.7 ± 0.6$^{\#}$
6 months' treatment	5.4 ± 1.7$^{*,\#,\&}$	3.8 ± 0.9$^{\#}$
IGF-1/IGFBP-3		
At birth	16.2 ± 2.1	16.9 ± 2.3
3 months' treatment	21.3 ± 3.3$^{*,\#}$	17.2 ± 2.4$^{\#}$
6 months' treatment	36.4 ± 4.5$^{*,\#,\&}$	18.7 ± 2.7$^{\#}$

$^{*}P < 0.05$, compared with control; $^{\#}P < 0.05$, compared with at birth; $^{\&}P < 0.05$, compared with 3 months' treatment.

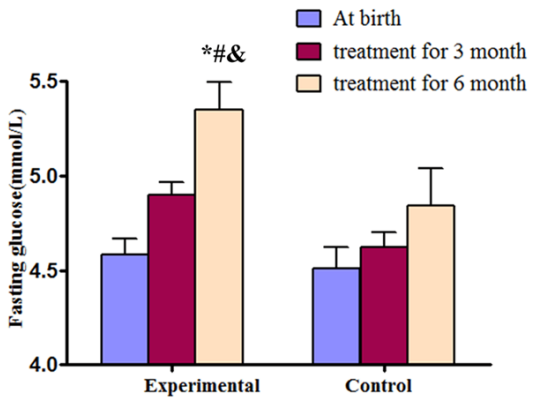

Figure 1. Fasting glucose comparison. *P < 0.05, compared with control; #P < 0.05, compared with at birth; &P < 0.05, compared with treatment for 3 months.

Adverse reaction comparison

Fasting glucose monitor result showed that there was no significant difference between two groups at birth (P > 0.05). However, after 6 months' treatment, the level in experimental group was obviously higher than that in control, at birth, and 3 months' treatment (P < 0.05) (**Figure 1**). Four cases appeared local skin irritation and rashes (13.3%), and they were self-relieved without treatment. No severe hypothyroidism, systemic anaphylaxis, or scoliosis happened during the treatment process.

Discussion

Preterm is a major cause of neonatal cripple that seriously affects infant's life and health, which easily inclines to cause physical and mental development disorder [7]. American scholar RH Clark defined EUGR as growth parameter including weight, length, and head circumference lower more than 10% of the same gestational age at birth, which was relative to the intrauterine growth retardation [8]. It has been demonstrated that Preterm infant's growth is influenced by a variety of important factors, which consist of economic level, living environment, parents' educational level, family feeding way, health care, and heredity [9, 10].

In this study, we selected low weight premature infants in our hospital as the research object. After the continuous treatment of 0.1 U/kg recombinant human growth hormone for 6 months, the body mass, length, and head circumference levels were significantly higher than the control group, at birth, and treatment for 3 months. Meanwhile, the increasing speed of body mass, head circumference, and length were also accelerated, while the time for adequate feeding was shortened, and EUGR incidence was reduced, suggesting that rHGH played a favorable role in maturation. Premature infants may appear growth speed lower than the term infant after birth for a period of time. However, growth potential still anchored for premature infants within their first six months, which facilitates them to catch up with the body development of term infant [11]. Growth hormone is a type of single polypeptide containing 191 amino acids. It weighted in 22 kD, is synthesized, stored and secreted by growth hormone cells that locate in pituitary side ring [12]. Research indicated that serum growth hormone level in premature was lower than that in the term infants. It was reported that supplement of recombinant human growth hormone could promote premature to grow 10-12 cm in height per year [13]. Clinical trials received satisfactory effect of recombinant human growth hormone in treating premature infant's growth retardation [14]. Exogenous recombinant human growth hormone can stimulate proliferation and differentiation of bone marrow cartilage cell, promote bone growth, and improve height growth speed [15].

We detected serum IGF-1, IGBP-3, and IGF-1/IGFBP-3 levels in premature at birth, treatment

for 3 months, and 6 months, and found that experimental group after 6 months' treatment presented higher serum IGF-1, IGFBP-3, and IGF-1/IGFBP-3 levels, implying that rHGH promotes IGF-1 and IGBP-3 secretion. IGF-1 and IGBP-3 are the key regulatory factors for infant's growth and development. IGF-1, as a kind of biological active peptide, shares the similarity in structure and function to insulin, and is mainly involved in embryo differentiation and closely related to growth and development through regulating glucose, fat and protein metabolism [16]. Research showed that deficiency of IGF-1 may restrict the tissue growth only up to 30% of normal levels [17]. IGF-1 binding with IGFBP-3 regulates growth and development through the involvement in GHRH-GH-IGF endocritic axis [18]. Besides, recent evidences unraveled that recombinant growth hormone stimulated the production of IGF-1 in liver, resulting in cell growth and differentiation.

Recombinant growth hormone elevates fasting glucose, and participates in glycometabolism through activating gluconeogenesis enzyme to reduce glucose utilization rate. Additionally, recombinant human growth hormone shows low incidence of adverse reactions mainly in hypothyroidism, water retention, intracranial hypertension, scoliosis, decreased insulin sensitivity, and secondary tumors, etc. Findings also indicated that no risk of type I diabetes and malignant tumor had been increased during the rHGH therapy [19]. In this study, fasting glucose level after 6 months' treatment was obviously higher than that in control, at birth, and treatment for 3 months. No severe hypothyroidism, systemic anaphylaxis, or scoliosis happened during the treatment process, in spit of 4 mild adverse cases. Similarly, previous studies also showed that rHGH promoted bone growth with no obvious adverse reaction after 4 years of follow-up [20]. Our data indicated that rHGH has therapeutic function on the premature growth recovery with good tolerance and less adverse reaction.

To sum up, recombinant human growth hormone improves the development of low weight premature infants by increasing their weight, length, and head circumference within a short period of time. It induces the rise of IGF-1 and IGFBP-3 secretion to regulate the body's endocrine and metabolic state without severe adverse reactions, which shows promising clinical popularization and application in the future.

Disclosure of conflict of interest

None.

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