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Original Research Article

Effect of leuprorelin plus growth hormone on serum luteinizing hormone, follicle-stimulating hormone, and estradiol levels in children with idiopathic central precocious puberty

Song Zhao, Yingying Cui*
Shiyan Maternal and Child Health Laboratory, Linyin Avenue, Shiyan City, Hubei Province, China

For correspondence:* ***Email:* *yinqiao12456323@126.com*

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Abstract

Purpose: *To evaluate the effects of leuprorelin plus growth hormone on serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) levels in children with idiopathic central precocious puberty.*
Methods: *A total of 102 girls with idiopathic central precocious puberty who met the inclusion criteria between April 2020 and September 2021 were enrolled in this study, and assigned randomly to either a control group given leuprorelin only, or a combined treatment group given leuprorelin plus growth hormone. There were 51 cases in each group. The parameters/indices evaluated include sex hormone levels (serum LH, FSH, and E2), height standard deviation scores (HtSDS), predicted adult height (PAH), and insulin-like growth factors-1 (IGH-1).*
Results: *Patients administered combined therapy showed lower levels of LH, FSH, and E2 than those on mono-therapy ($p < 0.05$). Leuprorelin plus growth hormone resulted in significantly higher HtSDS and PAH, and lower IGF-1 levels compared with those who received leuprorelin ($p < 0.05$).*
Conclusion: *The combination of leuprorelin and growth hormone effectively reduces the serum levels of LH, FSH, and E2 in children with idiopathic central precocious puberty, and improves their linear growth rate and adult height. However, economic benefits and patient acceptance should be considered in future studies to assess its overall applicability.*

Keywords: *Leuprorelin, Growth hormone, Idiopathic central precocious puberty, Luteinizing hormone, Follicle stimulating hormone, Estradiol*

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INTRODUCTION

With the rapid socioeconomic development in recent years, the prevalence of precocious puberty in children has been escalating over the years [1]. Idiopathic central precocious puberty is a common pediatric endocrine disorder in clinical practice with a high risk of morbidity. It manifests as early onset of menarche (appearance of menstruation before the age of 10 years) in girls or the emergence of secondary sexual characteristics before the age of 8 years in girls

(9 years in boys) [2]. The disease is more prevalent in girls than in boys. Clinical research has shown that its pathogenesis is mainly related to the premature activation of hypothalamic, pituitary, and gonadal axis functions and elevated levels of sex hormones in affected children [3]. Due to the early development of secondary sexual characteristics, early closure of epiphysis, and accelerated linear growth, children with idiopathic central precocious puberty show a higher height in childhood but a smaller height and poor cognitive abilities in adulthood [4].

At present, the clinical treatment of pediatric patients is mostly carried out with gonadotropin-releasing hormone analogues, among which leuprorelin is extensively used. It delays the bone age in children, reduces gonadal synthesis, effectively inhibits the overproduction of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2), slows down the development of secondary sexual characteristics, and eventually improves their linear growth rate and predicted adult height (PAH) [5]. However, Zhang *et al* suggested that monotherapy of leuprorelin failed to balance skeletal growth and may result in sudden height gain or excessive growth rate [6].

Idiopathic central precocious puberty is also clinically managed by the administration of growth hormone, produced synthetically using genetic engineering techniques. The protein structure and amino acid content and sequence of synthetic growth hormones are identical to that of growth hormones secreted by the human pituitary gland. Nevertheless, controversies exist in clinical practice regarding its efficacy [7]. To this end, the present study was undertaken to evaluate the effects of leuprorelin plus growth hormone on serum LH, FSH, and E2 levels in children with idiopathic central precocious puberty.

METHODS

Participants

The present study recruited 102 girls with idiopathic central precocious puberty who met the inclusion criteria between April 2020 and September 2021 and assigned them via random number table method to either a control group receiving leuprorelin or a combined treatment group given leuprorelin plus growth hormone, with 51 patients in each group. All children's families and guardians understood the content of this study and voluntarily signed the informed consent form, and the study was approved by the ethics committee of the Shiyan Maternal and Child Health Laboratory, Linyin Avenue, Shiyan City, Hubei Province, (approval no. 20200002). In addition, all procedures were performed in line with the protocols of Declaration of Helsinki [8].

Inclusion criteria

Patients who met the relevant clinical diagnostic criteria for idiopathic central precocious puberty, with a diagnosis confirmed by relevant pathological examination, a normal length and body mass at birth, whose parents were of normal height without family history of dwarfism, and whose bone age was more than 1 year advanced were included.

Exclusion criteria

Patients with precocious puberty with the conversion from peripheral type to central type, other serious medical conditions, a family history of dwarfism, or intolerance to the test drug were excluded.

Treatments

The two groups received leuprorelin through subcutaneous injection at an initial dose of 100 μg/kg with a maximum dose of 3.75 mg for a single administration, once every 4 weeks. The injection sites were the buttocks, abdomen, or upper arms. The vital signs and physical condition of the patients were strictly monitored during the treatment: height and body mass were monitored every 3 months, and ovarian uterine ultrasound and gonadotropin-releasing hormone analogue excitation tests were performed [9]. The gonadal axis suppression was observed and analyzed, and the dose of leuprorelin was adjusted accordingly. The interval between each review of bone age was six months, and the growth of height in adulthood was predicted according to height trends [9]. The duration of treatment was 1 year.

The combined treatment group received 0.10 - 0.15 IU/kg of growth hormone (Kinsai Pharmaceutical, State Drug Administration S20150029) through subcutaneous injection once daily 30 min before bedtime. The patient's blood and urine routine examination indices, thyroid function, liver function, kidney function, blood glucose, and glycosylated hemoglobin were closely monitored during the treatment [10]. The patients were followed up every 3 months after discharge. The duration of treatment was 1 year.

The medication would be discontinued if any of the following criteria were present in the patients: The difference between true age and bone age is no more than 1 year; Height after 1 cycle of treatment is close to the genetic target height value (sum of parents' height - 13 cm)/2; Bone age was 11 - 12 years [11].

Parameters evaluated

Sex hormone levels

Fasting venous blood was collected from each patient, and the levels of estradiol E2 were measured using a fully automated immunoassay analyzer. The GnRHa stimulation test was performed, and the levels of LH and FSH in the two groups were recorded and compared 1 h after stimulation.

Growth and development of the affected children

Bone age, height, weight, body mass index, and laboratory parameters were collected in the GnRHa stimulation test, and height standard deviation scores (HtSDS) and predicted adult height (PAH) of the patients were measured.

Growth factors

Serum insulin-like growth factor-1 (IGF-1) levels were determined using electrochemilumi-nescence immunoassay.

Statistical analysis

The data in the present study were analyzed using Statistical Packages for the Social Sciences (SPSS) software (version 22.0). Measurement data are expressed as mean ± standard deviation (SD) and tested using a t-test. Count data are expressed as cases (%) and tested using the chi-square (χ^2) test. Statistically significant differences were indicated at $p < 0.05$.

RESULTS

Baseline clinical profiles

The two arms were well-balanced in the baseline clinical profiles of the patients ($p > 0.05$; Table 1).

Sex hormone levels

Children with combined therapy showed lower levels of LH, FSH, and E2 versus those on mono-therapy ($p < 0.05$, Table 2).

Children's growth

Leuprorelin plus growth hormone resulted in significantly higher HtSDS and PAH than leuprorelin ($p < 0.05$, Table 3).

Table 1: Baseline clinical profiles (mean ± SD, n = 51)

Parameter	Combined treatment group	Control group	t/χ^2	*P*-value
Age (years)	8-11	8-11	0	1.0
Mean age (years)	9.21±0.30	9.24±0.26	0.54	0.59
Height (cm)	120-140	123-141	0.01	0.92
Mean height (cm)	134.32±5.03	135.18±6.50	0.747	0.457
Bone age (years)	10.39±0.39	10.44±0.37	0.664	0.508
BMI (kg/m^2)	17.42±2.86	17.46±2.94	0.07	0.944
Treatment onset age (years)	6.23±0.26	6.19±0.38	0.62	0.537
Ratio of bone age to true age	1.81±0.18	1.77±0.16	1.186	0.238
Pre-treatment predicted height (cm)	148.57±3.24	147.76±4.56	1.034	0.304

Table 2: Sex hormone levels (mean ± SD, n = 51)

Parameter	Time component	Combined treatment group	Control group	T	*P*-value
LH (IU/L)	Before treatment	5.31±0.60	5.37±0.62	0.497	0.62
	After treatment	2.23±0.24	3.79±0.38	24.788	<0.001
FSH (mU/mL)	Before treatment	7.80±0.32	7.84±0.43	0.533	0.595
	After treatment	4.39±0.45	7.12±0.41	32.025	<0.001
E_2 (pg/mL)	Before treatment	29.13±2.94	29.24±2.52	0.203	0.84
	After treatment	17.33±3.48	21.78±2.33	7.588	<0.001

Table 3: Children's growth (mean ± SD, n = 51)

Group	HtSDS (points)		PAH(cm)	
	Before treatment	After treatment	Before treatment	After treatment
Combined treatment group	-2.14±0.15	-1.47±0.08	149.9±4.9	157.2±4.2
Control group	-2.12±0.12	-1.79±0.11	151.5±5.3	153.6±4.6
t	0.744	16.802	1.583	4.127
P-value	0.459	<0.001	0.117	<0.001

Table 4: Growth factor (mean ± SD, n = 51)

Group	IGF-1	
	Before treatment	After treatment
Combined treatment group	351.54 ± 32.85	253.87 ± 22.38
Control group	358.69 ± 34.17	167.42 ± 19.22
T	1.077	20.928
P-value	0.284	<0.001

Growth factor

Leuprorelin plus growth hormone resulted in significantly lower IGF-1 levels than leuprorelin ($p < 0.05$, Table 4).

DISCUSSION

Precocious puberty is a common pediatric endocrine disorder that refers to the early onset of puberty, indicating that the first menstruation occurs before the age of 10 years in females or the enlargement of the gonads and the development of secondary sexual characteristics before the age of 8 years in male [12]. Its incidence has been increasing in recent years. The disease is divided into peripheral precocious puberty and central precocious puberty based on the pathogenesis and clinical manifestations, of which central precocious puberty, also called GnRH-dependent precocious puberty, is triggered by organic hypothalamic-pituitary lesions, such as tumors and inflammatory diseases [13]. Precocious puberty is called idiopathic central precocious puberty if no obvious central pathology is found. In girls, more than 80 % of central precocious puberty is idiopathic central precocious puberty, while in boys, more than 80 % is triggered by central organic pathology [12]. The premature maturation and hyperfunction of the hypothalamic-pituitary-gonadal axis lead to the premature establishment of the central GnRH-Gn pulse release rhythm, which promotes the overproduction of LH and FSH and consequently the development of the gonads [14]. Bone age in children with idiopathic central precocious puberty is usually accelerated, resulting in early skeletal fusion growth and reduced PAH. Studies have shown that inhibition of the abnormal developmental process of puberty in children with idiopathic central precocious puberty increases the growth cycle of children and improves their adult height.

The specific manifestations of idiopathic central precocious puberty are: The premature appearance of secondary sexual characteristics, the rapid development of reproductive organs, and early menarche may cause psychological disorders. Although the affected children have short-term accelerated skeletal growth, early osteosacral healing, and advanced bone age, their low intellectual and psychological development increases the psychological burden of the affected children [15]. Thus, early diagnosis and interventions are of great significance for the clinical management of idiopathic central precocious puberty. In recent years, clinical practice has shown that leuprorelin, as one of the gonadotropin-releasing hormone analogues is effective and safe in the treatment of idiopathic central precocious puberty. It effectively inhibits the excessive secretion of luteinizing hormone, follicle-stimulating hormone, and estradiol, reduces gonadal synthesis, and delays gonadal development. Moreover, it effectively slows down bone age, prevents early menstruation, and postpones breast development, thereby inhibiting the process of pubertal development [16].

There are several concerns when implementing leuprorelin treatment. First, the injection site is the buttocks (the subcutaneous fat of the buttocks is thick, which avoids important blood vessels and nerves), the abdomen, or the upper arm (the lower edge of the deltoid muscle of the upper arm has less subcutaneous fat and is rich in blood vessels, which is conducive to the absorption of drugs) under the skin. Secondly, to avoid strong local irritation, the injection site should be changed each time. Thirdly, because leuprorelin injection may lead to thrombosis, it is important to check the injection needle during

injection to avoid insertion into the blood vessel and to warn the child not to rub the injection site after the injection [17]. Studies have shown that a high dose of leuprorelin alone is expensive, and some adverse effects such as erythema, sclerosis, pruritus, vomiting, and nausea may occur during the treatment, while a small dose fails to successfully inhibit the secretion of the gonadal axis. Hence, the use of leuprorelin alone for the treatment of idiopathic central precocious puberty may result in sudden height gain or excessive growth rate.

Growth hormone is produced synthetically using genetic engineering technology, and its protein structure and amino acid content and sequence are identical to those of growth hormone secreted by the human pituitary gland, which is common in clinical practice for the management of dwarfism. The proper use of drug doses accelerates bone regeneration and promotes longitudinal growth in children and adolescents, and also consolidates and enhances the efficacy of gonadotropin-releasing hormone analogs. Chen *et al*. found high effectiveness of growth hormone treatment in improving the height and growth rate of children with idiopathic dwarfism [18]. The results of the study have demonstrated that children with combined therapy exhibited lower levels of LH, FSH, and E2 than those on monotherapy. The results suggested that leuprorelin plus growth hormone for idiopathic central precocious puberty was more effective in reducing the sex hormone level in the patients than the monotherapy of leuprorelin. Moreover, leuprorelin plus growth hormone resulted in significantly higher HtSDS and PAH, and lower IGF-1 levels versus leuprorelin. Thus leuprorelin plus growth hormone inhibits the abnormal progression of bone age maturation by suppressing the sex hormone effect and effectively improving PAH in the patients.

In addition, long-term administration of growth hormone is associated with the following risks: Overgrowth of organ tissues that results in gigantism. Peculiar facial features such as thickened skull, prominent cheekbones, and protruding jaws. Increased risk of cardiomyopathy, arteriosclerosis, and malignant tumors. Therefore, clinicians must strictly control the scope of application and the applicable dose. The vital signs and physical condition of the children should be strictly monitored, and their clinical treatment effects, compliance, prognosis expectation, and treatment cost should be comprehensively evaluated, so as to develop a scientific, systematic, and standardized treatment plan.

Limitations of this study

This study had some limitations. In terms of participants, only Chinese participants were included in this study, and the effect may have been influenced by cultural factors. Therefore, multicenter research should be considered to reduce influence of cultural differences. In terms of observation duration, the time was shorter, and there may be some bias in the evaluating its effectiveness. Thus, a longer observation time is needed.

CONCLUSION

The combination of leuprorelin and growth hormone effectively reduces the serum levels of LH, FSH, and E2 in children with idiopathic central precocious puberty and improves their linear growth rate and adult height. However, economic benefits and patient acceptance should be considered in future studies to assess its overall applicability.

DECLARATIONS

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Ethical approval

This study was approved by the ethics committee of the Shiyan Maternal and Child Health Laboratory, Linyin Avenue, Shiyan City, Hubei Province, (approval no. 20200002).

Availability of data and materials

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

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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