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Evaluation Study on the Effect of Leuprolide Acetate Extended-Release Microspheres for Injection in Pediatric Precocious Puberty

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Abstract: *Objective:* This study aimed to evaluate the therapeutic effects of leuprolide acetate extended-release microspheres for injection in children with pediatric precocious puberty. *Methods:* A total of 110 cases of pediatric precocious puberty admitted between January 2019 and December 2021 were selected and randomized into two groups using a random number table, with 55 cases in the control group and 55 cases in the experimental group. The control group received conventional treatment, while the experimental group was treated with leuprolide acetate extended-release microspheres for injection. The therapeutic effects were observed, and changes in sex hormone levels, ovarian volume, growth indices, and the incidence of adverse reactions were statistically compared between the groups. *Results:* The experimental group demonstrated superior outcomes in terms of sex hormone levels, ovarian volume, and growth indices compared to the control group. Additionally, the incidence of adverse reactions in the experimental group was significantly lower ($P < 0.05$). *Conclusion:* The application of leuprolide acetate extended-release microspheres for the treatment of pediatric precocious puberty is associated with improved therapeutic effects and higher safety.

Keywords: Leuprolide acetate; Pediatric precocious puberty; Sex hormone level; Ovarian volume; Growth indicators

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1. Introduction

Central precocious puberty (CPP) is a common pediatric endocrine disorder characterized by the premature development of internal and external genital organs and secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, resulting from the early activation of the hypothalamic-pituitary-gonadal axis (HPGA) [1-3]. This condition is significantly more prevalent in girls, with an incidence rate 5–10 times higher than in boys [1-3].

The rapid physical development associated with CPP is disproportionate to the child's psychological and chronological age, often leading to the premature closure of growth plates, which negatively impacts final adult height. This mismatch has profound implications for the physical and mental well-being of affected children, attracting considerable concern from families and society at large [4,5]. As a result, identifying safe and effective therapeutic options for these children has become a pressing need.

This study investigates the therapeutic effects of leuprolide acetate extended-release microspheres on bone age and sex hormone levels in 110 children with precocious puberty, providing evidence for its efficacy and safety.

2. Materials and methods

2.1. General information

A total of 110 children with pediatric precocious puberty were enrolled in this study between January 2019 and December 2021. All participants were cognitively sound, without speech communication disorders or cognitive dysfunction, and met the diagnostic criteria for central precocious puberty in China [1].

Exclusion criteria: (1) Children who did not receive treatment with gonadotropin-releasing hormone agonists; (2) Children with other acute or chronic diseases; (3) Children treated with growth hormone or other sex hormone drugs.

The 110 participants were randomly divided into two groups: the experimental group (n = 55) and the control group (n = 55). The ages of the children ranged from 4 to 10 years, with a mean age of 7.11 ± 2.35 years in the control group and 7.60 ± 2.24 years in the experimental group.

Prior to the study, the families of the children were fully informed about the purpose, procedures, and significance of the research. Written consent was obtained from all families. The baseline characteristics of age, gender, and disease distribution between the two groups showed no statistically significant differences ($P > 0.05$).

2.2. Treatment methods

(1) Control group treatment: Children in the control group received oral administration of megestrol acetate (H31020875) manufactured by Shanghai Xinyi Tianping Pharmaceutical Co., Ltd. The medication was given twice daily, with a dosage of 2 mg per administration.

(2) Experimental group treatment: Children in the experimental group received the same treatment as the control group, supplemented with Leuprolide Acetate Extended-Release Microspheres (H20093809) produced by Beijing Boente Pharmaceutical Co., Ltd. This drug was administered subcutaneously once per month at a dosage of 90 μg/kg. The dosage was adjusted according to the children's height.

Both groups underwent continuous treatment for one year.

2.3. Observation indexes

(1) Sex hormone levels: Sex hormone levels, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and serum estradiol (E2), were evaluated. Early morning fasting venous blood samples were collected, centrifuged, and analyzed using the Myriad CL8000 automated luminescence immunoassay analyzer.

(2) Ovarian volume and growth index: Ovarian volume measurements included assessments of the left and right ovaries. Growth indicators encompassed bone age and height.

(3) Adverse reaction incidence: Adverse reactions were recorded and included symptoms such as allergies, dizziness, cough, and fatigue.

2.4. Statistical analysis

Data analysis was performed using SPSS 21.0 statistical software. Categorical data were expressed as [*n* (%)], and continuous data were expressed as mean ± standard deviation (SD). Statistical comparisons were conducted using the χ^2 test for categorical data and the *t*-test for continuous data. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of sex hormone levels between groups

After treatment, the FSH levels in the experimental group were 2.57 ± 0.59 U/L, LH levels were 1.43 ± 0.43 U/L, and E2 levels were 11.33 ± 3.94 ng/L, which showed significant differences compared to the control group ($P < 0.05$). Detailed results are provided in **Table 1**.

Table 1. Comparison of sex hormone levels between groups before and after treatment (mean ± SD)

Groups	FSH (U/L)		LH (U/L)		E2 (ng/L)	
	Before	After	Before	After	Before	After
Experimental group (n = 55)	2.26 ± 0.65	2.57 ± 0.59	3.69 ± 0.58	1.43 ± 0.43	34.21 ± 4.21	11.33 ± 3.94
Control group (n = 55)	4.18 ± 0.63	3.69 ± 0.60	3.74 ± 0.63	3.55 ± 0.40	33.81 ± 4.41	14.65 ± 3.66
t	15.730	9.623	0.433	26.771	0.487	4.579
P	0.000	0.000	0.666	0.000	0.628	0.000

3.2. Comparison of ovarian volume and growth index between groups

After treatment, the left ovarian volume in the experimental group was 1.54 ± 0.27 cm^3, the right ovarian volume was 1.35 ± 0.24 cm^3, the bone age was 8.77 ± 0.38 years, and the height was 130.46 ± 2.86 cm, all of which showed significant differences compared to the control group ($P < 0.05$). Detailed results are presented in **Table 2**.

Table 2. Comparison of ovarian volume and growth index between groups before and after treatment (mean ± SD)

Groups	Left ovarian volume (cm^3)		Right ovarian volume (cm^3)		Bone age (years)		Height (cm)	
	Before	After	Before	After	Before	After	Before	After
Experimental group (n = 55)	2.25 ± 0.35	1.54 ± 0.27	2.32 ± 0.22	1.35 ± 0.24	9.07 ± 0.44	8.77 ± 0.38	125.44 ± 2.37	130.46 ± 2.86
Control group (n = 55)	2.30 ± 0.43	1.98 ± 0.36	2.27 ± 0.32	2.07 ± 0.27	9.12 ± 0.46	9.02 ± 0.40	124.85 ± 3.43	128.50 ± 2.75
t	0.669	7.251	0.955	14.781	0.583	3.360	1.050	3.664
P	0.505	0.000	0.342	0.000	0.561	0.001	0.296	0.000

3.3. Comparison of incidence rates of adverse reactions between groups

In the experimental group, adverse reactions, including allergy, dizziness, cough, and tiredness, occurred in 7 cases, resulting in a total incidence rate of 12.73%. This rate was significantly lower than that in the control group ($P < 0.05$). Details are shown in **Table 3**.

Table 3. Comparison of incidence rates of adverse reactions between groups [*n* (%)]

Group	Allergy	Dizziness	Cough	Tiredness	Total incidence rate
Experimental group (n = 55)	2 (3.64)	3 (5.45)	1 (1.82)	1 (1.82)	7 (12.73)
Control group (n = 55)	4 (7.27)	7 (12.73)	2 (3.64)	3(5.45)	16 (29.09)
χ^2					4.453
P					0.035

4. Discussion

Central precocious puberty results from the premature activation of the hypothalamic-pituitary-gonadal axis, leading to the early release of gonadotropin-releasing hormone (GnRH) and its abnormal secretion patterns. This, in turn, promotes increased secretion of LH and FSH, causing premature activation of the gonads and the appearance of secondary sexual characteristics [6]. In female children, key manifestations include premature breast development, the growth of pubic hair, and menarche [7]. The primary objectives of treatment for central precocious puberty are to inhibit the activity of the hypothalamic-pituitary-gonadal axis, control symptoms of precocious puberty, delay epiphyseal closure, and enhance final adult height [8].

The mechanism of action of gonadotropin-releasing hormone analogs (GnRHa) involves binding to GnRH receptors in anterior pituitary gonadotroph cells. Initially, this induces a transient surge in LH and FSH secretion (referred to as the “flare effect”). Subsequently, the receptors in pituitary target cells are downregulated, suppressing the hypothalamic-pituitary-gonadal axis and reducing the secretion of LH, FSH, and gonadal hormones. This process effectively regulates sexual development, delays bone age progression, and preserves the growth potential of the epiphyseal plates, ultimately aiding in achieving an improved final adult height [1]. The effectiveness of GnRHa in promoting final adult height remains a topic of debate. However, Guaraldi *et al.* [9], in a review of 22 studies across various countries, reported that the majority of patients achieved adult heights comparable to their genetic potential [10].

Leuprolide acetate, a GnRHa, functions as a luteinizing hormone analog, stimulating the pituitary gland to release luteinizing hormone while subsequently reducing gonadotropin levels [11]. This mechanism provides therapeutic benefits for managing precocious puberty [12,13]. Studies have demonstrated that GnRHa treatment, including the use of leuprolide acetate, significantly improves the final adult height of girls, with treated individuals achieving heights closer to or exceeding their genetic potential [14,15].

Serum LH, primarily secreted by adenohypophysis cells, accelerates the conversion of cholesterol into sex hormones within gonadal cells, promotes follicular maturation, increases estrogen levels, and facilitates ovulation and luteinization, thereby advancing sexual development. Similarly, serum FSH, also secreted by the pituitary gland, supports follicular development and maturation while promoting estrogen secretion. Among estrogens, E2 is the most active and significant hormone, serving as a marker of gonadal activation. Elevated levels of serum LH, FSH, and E2 can thus indicate the progression of puberty in affected children.

In the present study, treatment with leuprolide acetate extended-release microspheres led to a significant reduction in LH levels compared to the control group. This finding indicates that leuprolide acetate effectively inhibits ovarian function and exerts a strong suppressive effect on the hypothalamic-pituitary-gonadal axis. This suppression reduces serum sex hormone levels, delays the progression of precocious puberty, and improves ovarian volume and growth parameters. These outcomes are consistent with the findings of Ma *et al.* [16].

Leuprolide acetate extended-release microspheres have been shown to effectively reduce sex hormone levels in children with precocious puberty, improve premature development, and enhance final adult height. By delaying reproductive system development, this treatment allows children to achieve growth and development appropriate for their age. Furthermore, it demonstrates high safety and a low incidence of adverse effects, making it a valuable and practical option for widespread clinical application.

Disclosure statement

The authors declare no conflict of interest.

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