Original Article

The effect of triptorelin and leuprolide on the level of sex hormones in girls with central precocious puberty and its clinical efficacy analysis

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Background: This study aimed to explore the effects of triptorelin and leuprolide on serum hormone levels and the clinical efficacy of girls with idiopathic central precocious puberty (ICPP).

Methods: Retrospective analysis was performed on 128 girls with ICPP who were diagnosed and treated in our hospital from January 2017 to January 2020, including 71 girls in the leuprolide group and 57 girls in the triptorelin group. The differences of serum sex hormone level, ovarian volume, uterine volume, follicle diameter, bone age, growth rate (height change within half a year), maturity (bone age/living age), and other aspects between the two groups of girls were compared.

Results: Before treatment, there was no significant difference in the baseline levels of sex hormones [estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH)] between the triptorelin group and the leuprorelin group ($P>0.05$). After 1 year of treatment, serum levels of E2 and FSH in the triptorelin group were lower than those in the leuprolide group ($P<0.05$). There was no significant difference in LH levels between the two groups after 1 year of treatment ($P>0.05$). At baseline, there was no significant difference in the ovarian volume, follicle diameter, and uterine volume between the triptorelin group and the leuprolide group ($P>0.05$). After 1 year of treatment, the ovarian volume, follicle diameter, and uterine volume of the girls in the triptorelin group were all lower than those in the leuprolide group ($P<0.05$). Before treatment, there was no statistical difference in bone age, growth rate, and maturity between the triptorelin group and the leuprolide group ($P>0.05$). After 1 year of treatment, the growth rate and maturity of participants in the triptorelin group were lower than those in the leuprolide group ($P<0.05$). There was no significant difference in bone age between the two groups after 1 year of treatment ($P>0.05$).

Conclusions: For girls with ICPP, triptorelin is superior to leuprolide in reducing sex hormone level, reducing uterine volume, follicle diameter, ovarian volume, slowing down the growth rate, and decreasing maturity. Triptorelin should be selected as a priority for the treatment of girls with ICPP.

Keywords: Central precocious puberty; leuprolide; triptorelin; sex hormones

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Introduction

Precocious puberty refers to the appearance of secondary sexual characteristics in female children before 8 years old and male children before 9 years old (1,2). Central precocious puberty is due to the hypothalamus prematurely increasing the secretion and release of gonadotropin-releasing hormone (GnRH), which activates the function of the gonadal axis in advance. The incidence of central precocious puberty is about 1/5,000 to 1/10,000. According to different causes, it can be divided into idiopathic and secondary. Idiopathic central precocious puberty (ICPP) accounts for about 80% to 90% of the total (3,4). The incidence rate of precocious puberty is increasing year by year throughout the world, which may be related to the changes in the living environment and exogenous hormones (5-7). The incidence rate of precocious puberty in girls is higher than that in boys. The specific clinical manifestations of the disease are rapid increases in weight and height, and the appearance of axillary and pubic hair. In girls, rapid breast growth and early menarche also present. In boys, testicular development and penis growth become increased. Precocious puberty can be divided into central precocious puberty, peripheral precocious puberty, and partial precocious puberty. The disease affects children's bodies and causes severe psychological problems, resulting in mental disorders or behavioral abnormalities (8). Therefore, clinicians attach great importance to the disease. In China, triptorelin and leuprolide are the most commonly used in GnRH analogues, but there is no uniform standard or opinion on which drug, dosage and regimen are preferred. Triptorelin and leuprolide are commonly used in treating ICPP, but comparative analysis of the two drugs has been scarce. This study compared the effects of triptorelin and leuprolide on serum hormone levels and clinical efficacy in girls with ICPP, thus providing a reference for clinical medication decision-making. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-352).

Methods

Case collection

We performed a retrospective analysis of 128 girls with ICPP diagnosed and treated in our hospital from January 2017 to January 2020, including 71 girls treated with triptorelin and 57 girls treated with leuprolide. The inclusion criteria were as follows: (I) informed consent signed by the legal guardian of the child; (II) the child met the diagnostic criteria of ICPP, referring to the "*Recommendations on the diagnosis and treatment of central (true) precocious puberty*" (Chinese Medical Association, 2017 edition); (III) had not received any previous treatment. The exclusion criteria were as follows: (I) combined with other cardiovascular and cerebrovascular diseases, liver or kidney dysfunction; (II) central precocious puberty caused by space-occupying tumor, central nervous system infection, injury, or dysplasia; (III) had participated in other clinical studies within 3 months. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xiaoshan Hospital Affiliated to Hangzhou Normal University (No.: 2020-037) and informed consent was taken from all the patients.

Therapeutic method

The children in the triptorelin group were injected tripraline acetate subcutaneously at a dose of 100 μg/kg once a month. The children in the leuprolide group were injected with leuprolide acetate under the skin. The initial dose was 90 μg/kg once a month, and after 3 months of continuous subcutaneous injection, they received an adjusted dose of 60–80 μg/kg. The two groups were treated at least 12 months.

Observation index

The two groups were followed up for more than 1 year. The main outcome measures were as follows: (I) determination of serum sex hormones before and after treatment for 1 year. The venous blood of the girls was collected. The contents of estradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in serum were determined by immunoluminescence assay. (II) The changes of reproductive organs: ovarian volume, follicle size, and uterine volume of the two groups were measured by B-ultrasound before treatment and 1 year after treatment. (III) The height, weight, bone age, growth rate (height change within half a year), and maturity (bone age/actual age) were measured before and 1 year after treatment. The calculation formula referred to the 7th edition of "*Practical pediatrics*".

Statistical analysis

The data were analyzed using R software (http://www.

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Table 1 Comparative analysis of the general situation of two groups of ICPP girls

General information	Triptorelin group (n=57)	Leuprolide group (n=71)	t	P value
Age (years)	6.56±1.48	6.84±1.27	–1.151	>0.05
Height (cm)	134.4±6.2	133.7±5.8	0.658	>0.05
Weight (kg)	24.6±4.2	25.8±6.3	–1.234	>0.05
Bone age (years)	9.24±0.66	9.19±0.73	0.402	>0.05

ICPP, idiopathic central precocious puberty.

Table 2 Comparative analysis of serum sex hormones in two groups of ICPP girls

Sex hormones	Triptorelin group (n=57)	Leuprolide group (n=71)	t	P value
E2				
Before treatment	33.45±16.39	34.76±15.11	–0.469	>0.05
1 year after	21.76±10.21	15.43±9.38	3.648	<0.05
LH				
Before treatment	14.21±7.12	15.37±6.41	–0.968	>0.05
1 year after	5.10±2.31	4.42±2.55	1.563	>0.05
FSH				
Before treatment	15.02±6.43	14.31±5.72	0.660	>0.05
1 year after	5.64±2.07	4.47±1.91	3.318	<0.05

ICPP, idiopathic central precocious puberty; E2, estradiol; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

R-project.org/) and related R packages. The count data were expressed in the form of a percentage [n (%)], and the chi-square test was used. Measurement data were expressed as mean ± standard deviation ($\bar{x}$±s), the *t*-test was used, and P<0.05 indicated statistical significance.

Results

Comparative analysis of the general situation of two groups of ICPP girls

Before treatment, there was no significant difference in age, height, weight and bone age between the two groups (P>0.05) (*Table 1*).

Comparative analysis of serum sex hormones in the two participant groups

Before treatment, there was no significant difference in the levels of sex hormones (E2, LH, FSH) between the two groups (P>0.05). After 1 year of treatment, the levels of E2 and FSH in serum of participants in the triptorelin group were lower than those in the leuprolide group, with statistical significance (P<0.05), but there was no statistical difference in LH between the two groups after 1 year of treatment (P>0.05) (*Table 2*).

Comparative analysis of the changes of reproductive organs in two groups

Before treatment, there was no significant difference in ovarian volume, follicle diameter, and uterine volume between the triptorelin group and the leuprolide group (P>0.05). After 1 year of treatment, the ovarian volume, follicle diameter, and uterine volume of the girls in the triptorelin treatment group were smaller than those in the leuprolide group, with statistical significance (P<0.05) (*Table 3*).

Comparative analysis of growth indexes of two groups

Before treatment, there was no significant difference in bone age, growth rate, and maturity between the triptorelin group and the leuprolide group (P>0.05). After 1 year of

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Table 3 Comparative analysis of the changes of reproductive organs in two groups of ICPP girls

Reproductive organs	Triptorelin group (n=57)	Leuprolide group (n=71)	t	P value
Ovarian volume (mL)				
Before treatment	2.71±1.49	3.01±1.11	–1.305	>0.05
1 year after	1.97±0.98	1.56±0.83	2.562	<0.05
Follicle diameter (mm)				
Before treatment	6.32±2.01	6.11±1.94	0.599	>0.05
1 year after	5.47±1.39	4.18±1.51	4.975	<0.05
Uterine volume (mL)				
Before treatment	3.02±1.31	3.43±1.47	–1.645	>0.05
1 year after	2.38±1.07	2.01±1.00	2.017	<0.05

ICPP, idiopathic central precocious puberty.

Table 4 Comparative analysis of growth indexes of two groups of ICPP girls

Growth indexes	Triptorelin group (n=57)	Leuprolide group (n=71)	t	P value
Bone age (years)				
Before treatment	9.24±0.66	9.19±0.73	0.402	>0.05
1 year after	9.11±0.61	8.46±0.44	6.996	>0.05
Growth rate (cm/half year)				
Before treatment	4.47±0.49	4.51±0.38	–0.520	>0.05
1 year after	3.24±0.31	2.14±0.27	21.442	<0.05
Maturity				
Before treatment	1.31±0.14	1.27±0.19	1.326	>0.05
1 year after	1.24±0.17	1.11±0.11	5.226	<0.05

ICPP, idiopathic central precocious puberty.

treatment, the growth rate and maturity of girls in the triptorelin treatment group were lower than those in the leuprolide treatment group, with statistical significance (P<0.05), but there was no statistical difference in bone age between the two groups after 1 year of treatment (P>0.05) (*Table 4*).

Discussion

Precocious puberty is a common endocrine disease, and its incidence rate in China is increasing annually (9). The increase may be related to the improvement of our people's living standards and rich material life. The increase of children's food intake, increase of hormone disrupting substances in daily life, and the excessive nutrition of children are the main reasons for precocious puberty (10-12). Precocious puberty involves the premature arrest of children's bone growth, significantly impacts children's height, and causes a series of psychological problems such as early sexual behavior and psychosexual disorders (13-15). Epidemiological studies have shown that about 18% of children experience precocious puberty, and its incidence in girls is 5 times that of boys in China. How to administer drugs reasonably is one of the clinical problems presented by precocious puberty.

Triptorelin and leuprolide are GnRH analogs. Their pharmacological mechanism is to competitively bind to GnRH receptors to reduce gonadotropin secretion by the pituitary gland. They are mainly used to treat endometriosis, hysteromyoma, prostate cancer, central

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precocious puberty, and other diseases (16-18). Triptorelin is 35 times more effective than GnRH and has a long half-life, so triptorelin can maintain the therapeutic level for a long time. After triptorelin was stopped, its inhibitory effect on the pituitary gland disappeared quickly. Leuprolide has a strong affinity with GnRH receptors, which not only inhibits the pituitary gland and reduces gonadotropins, but also reduces the sensitivity of the ovaries and testes to gonadotropins. Studies have also shown that triptorelin and leuprolide treatment in children with central precocious puberty can lead to increased fat mass and an increased risk of obesity in the future (19).

This study found that before treatment, there was no significant difference in age, height, weight, bone age, sex hormone (E2, LH, FSH), ovarian volume, follicle diameter, uterine volume, bone age, growth rate, and maturity between the triptorelin treatment group and leuprolide treatment group. After 1 year of treatment, the serum E2 and FSH levels in the triptorelin group were lower than those in the leuprolide group, but there was no significant difference in LH between the two groups. After 1 year of treatment, the ovarian volume, follicle diameter, and uterine volume in the triptorelin group were smaller than those in the leuprolide group; at the same time, the growth rate and maturity of girls in the triptorelin treatment group were lower than those in the leuprorelin treatment group ($P<0.05$), but there was no significant difference in bone age between the two groups after 1 year of treatment ($P>0.05$). Previous studies have mostly compared the clinical effect of leuprorelin and medroxyprogesterone on the disease and compared leuprorelin and medroxyprogesterone and monotherapy. The results of other reliable studies do not align with our results. This study was a retrospective analysis, and the sample size was small. The findings of this study require verification through larger sample sized, prospective studies.

We recommend that triptorelin be used for the treatment of girls with ICPP. Dosage and schedule of medication need to emphasize the principle of individualization. For children who cannot be well controlled or cannot achieve the expected treatment goals, we recommend shortening the interval between medications or increasing the dosage of medications. During treatment, the child's development, growth rate, hormone level, and bone age should be closely monitored, and the function of the gonadal axis should be assessed. In treatment, attention should also be paid to the social and psychological impact of the children and their parents, and early psychological evaluation and psychological intervention should be carried out.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-352

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-352). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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 procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xiaoshan Hospital Affiliated to Hangzhou Normal University (No.: 2020-037) and informed consent was taken from all the patients.

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