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Original Article

The effects of a gonadotropin-releasing hormone analogue combined with a healthy lifestyle on girls with idiopathic central precocious puberty

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Abstract: Objective: To investigate the combination of a gonadotropin-releasing hormone analog (GnRHa) and healthy lifestyle to treat girls with idiopathic central precocious puberty (ICPP). Methods: Eighty-six girls diagnosed with ICPP were selected as the study cohort and divided into two equal groups: the control group, which received GnRHa only, and the intervention group, which received GnRHa and other interventions, such as diet and exercise, to promote a healthy lifestyle. Various indicators, including the physiological parameters, the uterus and ovary volumes, the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and the incidence of adverse reactions, were analyzed before and after the treatment. Results: After the treatment, the predicted adult height (PAH) values in both groups of children were significantly increased compared to the values before the treatment, and the bone age difference/chronological age difference ratio (ΔBA/ΔCA), the growth velocity (GV), and theuterus and ovary volumes were significantly reduced; these differences were statistically significant ($P<0.05$). Furthermore, the PAH, ΔBA/ΔCA, and GV of the intervention group were significantly improved compared to the control group ($P<0.05$). The FSH and LH levels decreased significantly after the treatment in both groups, and the intervention group levels were significantly lower than the control group levels ($P<0.05$). After the treatment, the incidence of adverse reactions in the intervention group was significantly lower than it was in the control group (4.65% vs. 18.60%) ($P<0.05$). Conclusion: GnRHa combined with a healthy lifestyle is both effective and safe for the treatment of ICPP in girls.

Keywords: Gonadotropin-releasing hormone analog, healthy lifestyle, idiopathic central precocious puberty, therapeutic effect

Introduction

Precocious puberty is characterized by premature pubertal development, manifested in the development of internal and external genitalia and secondary sex characteristics in girls and boys before the age of eight or nine years [1].

Studies have shown that, with the rapid social and economic development and the improvement in living conditions and diet, the age of puberty in children around the world has dropped [2-4]. The incidence of precocious, or earlier than normal, puberty has increased significantly and is higher in girls than in boys. There are several classifications of precocious puberty, of which idiopathic central precocious puberty (ICPP) is the most common [5]. ICPP affects children's physiological growth and development and mental health to varying degrees. In severe cases, it can affect a child's normal life and learning status [6]. Finding a safe and effective ICPP treatment has become urgent.

Gonadotropin-releasing hormone analog (GnRHa) is effective for inhibiting the secretion of sex hormones and delaying the development of secondary sex characteristics. At present, GnRHa is mainly used to treat children with ICPP. Studies have shown that GnRHa is highly effective at retarding the growth rate and height of children [7]. However, the same research found that treating ICPP with GnRHa alone may cause adverse reactions such as obesity. Studies have found that the etiology of ICPP is complex and is related to various factors such as lifestyle, diet, exercise, social

environment, and genetics [8]. Unhealthy lifestyles are closely related to an increased incidence of precocious puberty. Previous research has shown that unhealthy lifestyles (such as frequent Western snacks, tonics, and the frequent watching of emotional programs) are associated with precocious puberty [9, 10]. Currently, the majority of studies have dealt with the clinical effects of drug treatment for ICPP, but there are few studies on the effects of drugs combined with healthy lifestyles. This study explores the clinical effect of GnRHa in combination with healthy lifestyles on girls with ICPP.

Materials and methods

Research subjects

A total of 86 ICPP girls admitted to The Second People's Hospital of Yueqing from December 2018 to June 2019 were selected as the study cohort. The control group (n=43) received GnRHa only, and the intervention group (n=43) received GnRHa in combination with a healthy lifestyle intervention. The average age of the control group was 8.13±0.53 years with a bone age of 10.43±0.48 years. The average age of the intervention group was 8.16±0.49 years with a bone age of 10.29±0.38 years. The general clinical data (including age, bone age, and BMI) of the two groups of children were compared, and the differences were not statistically significant (P>0.05). This study was approved by the Ethics Committee of The Second People's Hospital of Yueqing, and the guardians of the children voluntarily signed informed consents.

Methods

Inclusion criteria: All the children in the study were newly diagnosed, and their treatments were scheduled after their diagnoses. A child met the ICPP diagnostic criteria [11] if: 1. The girl's secondary sex characteristics appeared early, namely, breast development occurring before the age of eight or menstruation occurring before the age of 10; 2. The bone age exceeded the actual age by one year or more; 3. There were no growth hormone deficiencies, intracranial tumors, or systemic disorders; 4. The child had complete clinical data.

Exclusion criteria: 1. Children with combined immune system and severe cardiovascular and cerebrovascular diseases; 2. Children with other acute and chronic diseases; 3. Children with ICPP caused by drugs; 4. Children who were lost on follow-up.

Treatment regimen: The children in both groups received GnRHa treatment (Takeda Pharmaceutical Company Limited, Hikari Plant, Japan). Medication method: The initial dose was 80-100 g/kg, according to the weight of the child, administered by subcutaneous injection. Subsequently, the patients were injected, according to the drug use specification instructions, once every four weeks at a dose of 60-90 g/(kg·times). The treatment cycle was 18 months. The patients were followed up regularly for a year at three-month intervals, and the girls' related growth indicators were recorded. In addition to the GnRHa treatment, the intervention group was also treated with healthy lifestyle interventions, including the avoidance of plasticized products (products processed using plastic as the main raw material, such as plastic tableware, children's toys, and school supplies), a regular bedtime before 21:00 each day and a certain amount of exercise every day. The maximum exercise intensity was determined using an age reduction algorithm, and a range of 50%-80% of the maximum intensity was selected during the exercises. Each exercise time lasted for 20-30 min (adjusted appropriately depending on the exercise intensity), and the patients were exercised every 2-3 days. Watching emotional shows was avoided. In terms of eating habits, the children avoided eating Western-style fast food, off-season vegetables and fruits, nutritional supplements, puffed foods, high-protein diets, and poultry [12].

Outcome measures: The girls' relevant indicators were compared before and for 12 months after treatment. The indicators were: the predicted adult height (PAH), determined by the Bayley-Pinneau method [13], the ratio of the bone age difference/actual age difference (ΔBA/ΔCA), measured by the "The Standards of Skeletal Maturity of Hand and Wrist for Chinese-China 05 V.-Revised Centile Curves of Skeletal Maturity" [14], the growth velocity (GV); the uterine and ovarian volumes, measured using B ultrasound; changes in the FSH

Table 1. General clinical data

Group	Control group	Intervention group	t	P
Age of disease onset (year)	7.43±0.36	7.61±0.51	1.891	0.062
Age of admission (year)	8.13±0.53	8.16±0.49	0.273	0.786
BMI (kg/m^2)	16.07±1.84	16.32±2.01	0.602	0.549
Bone age (year)	10.43±0.48	10.29±0.38	1.5	0.137
Breast development age (year)	7.32±0.63	7.28±0.52	0.321	0.749
Menstrual onset age (year)	9.62±0.62	9.49±0.47	1.096	0.276

Note: BMI: Body mass index.

Table 2. Comparison of the physiological parameters

Group	Control group	Intervention group	t	P
PAH				
Before treatment	152.54±3.93	153.61±3.02	1.416	0.161
After treatment	156.01±3.28***	157.58±2.21***	2.603	0.011
ΔBA/ΔCA				
Before treatment	10.48±0.95	10.53±0.87	0.255	0.8
After treatment	0.94±0.31***	0.68±0.27***	4.147	<0.001
GV (cm/year)				
Before treatment	9.58±0.95	9.42±0.89	0.806	0.423
After treatment	5.73±1.23***	4.95±1.92***	2.243	0.028

Note: PAH: Predicted adult height; ΔBA/ΔCA: the bone age difference/chronological age difference value; GV: growth velocity. Compared with before the treatment, ***P<0.001.

and LH levels, and the occurrence of adverse reactions, principally including obesity, endocrine disorders, local itching, and flaky rash. The occurrence rate of the adverse reactions was calculated by the formula: occurrence rate of adverse reactions (%) = number of adverse reactions/total number of the group * 100%. After the patient was discharged from the hospital, a follow-up call was conducted every three months to determine the effects of the treatment on the child, to guide the parents of the child on how to take the medicine and when to return to the hospital for re-examination, and to provide treatment advice if adverse reactions occurred. The follow-up period was one year.

Statistical analysis

The data in this study were analyzed using SPSS 20.0 software. The measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), independent samples t-tests were used for the comparisons, and paired sample t-tests were used for the comparisons before and after treatment and were expressed as t. The count data were expressed as cases or percentages, χ^2 tests were used for comparisons and expressed as χ^2. P<0.05 was considered statistically significant.

Results

General data

Before the treatment, it was found that all the children were overweight. Comparing the ages of disease onset, ages of admission, BMI, bone ages, breast development ages, and menstrual onset ages in the two groups showed that there were no significant differences (P> 0.05), as shown in **Table 1**.

Comparison of the physiological parameters

A comparison of the changes in the various indicators of the children in the two groups before and after the treatment showed that the differences in the PAH, ΔBA/ΔCA, and GV before the treatment in the two groups were not statistically significant (P>0.05) (**Table 2**) After the treatment, the PAH values in the two groups were higher than they were before the treatment, but the ΔBA/ΔCA and GV were lower than they were before the treatment. The PAH in the intervention group was higher than it was in the control group, and the ΔBA/ΔCA and GV were lower than they were in the control group (**Table 2**). The differences were statistically significant (P<0.05).

Comparison of the uterine and ovarian volumes

Before the treatment, there were no significant differences in the uterine and ovarian volumes between the two groups of patients (P>0.05); after the treatment, the uterine and ovarian volumes in the two groups were significantly reduced compared with the volumes before the treatment (**Table 3**). The differences were statistically significant (P<0.05).

Table 3. Comparison of the uterine and ovarian volumes

Group	Control group	Intervention group	t	P
Uterine volumes (cm^3)				
Before treatment	4.63±1.25	4.58±1.32	0.167	0.868
After treatment	3.01±0.51***	2.98±0.45***	0.289	0.773
Ovarian volume (cm^3)				
Before treatment	2.29±0.62	2.32±0.51	0.245	0.807
After treatment	1.76±0.25###	1.74±0.13###	0.078	0.938

Note: Compared with the uterine volumes before the treatment, ***P<0.001; compared with the ovarian volumes before the treatment, ###P<0.001.

Table 4. Comparison of the hormone levels

Group	Control group	Intervention group	t	P
LH (U/L)				
Before treatment	19.32±3.25	19.46±3.32	0.198	0.844
After treatment	14.36±1.32***	13.69±1.21***	2.454	0.016
FSH (U/L)				
Before treatment	5.42±1.15	5.52±1.09	0.414	0.68
After treatment	2.79±1.25###	2.27±1.03###	2.105	0.038

Note: LH: Luteinizing hormone; FSH: follicle-stimulating hormone. Compared with LH before the treatment, ***P<0.001; compared with FSH before the treatment, ###P<0.001.

Comparison of the hormone levels

Before the treatment, there were no significant differences in the LH and FSH levels between the two groups of children (P>0.05), but after the treatment, the LH and FSH levels in the children were significantly lower than they were before the treatment; these differences were statistically significant (P<0.001) (**Table 4**; **Figure 1**). The LH and FSH levels in the intervention group were significantly lower than they were in the control group, and the differences were statistically significant (P<0.05) (**Table 4**; **Figure 1**).

Occurrence of adverse reactions

After treatment, the rate of the occurrence of adverse reactions was compared between the two groups of children, and it was found that rate in the intervention group was significantly lower than it was in the control group, with a significant difference (P<0.05) (**Table 5**).

Discussion

ICPP is caused by the activation of the hypothalamic-pituitary-gonadal (HPGA) axis leading to the early initiation of puberty and resulting in premature sexual development, which, in turn, affects the child's adult height [15]. From a girl's perspective, early sexual development can cause psychological and behavioral problems, including feelings of fear and inferiority, and patients with severe symptoms can develop diseases such as polycystic ovarian syndrome (PCOS) [16]. The etiology of ICPP is complicated and is largely related to external hormones or hormone-like substances, obesity, or genetic factors [17-20]. This study retrospectively analyzed the clinical data of ICPP girls in The Second People's Hospital of Yueqing to explore the effects of clinical treatment for ICPP using GnRHa combined with a healthy lifestyle.

GnRHa, a commonly used drug for the treatment of ICPP, inhibits gonadotropin secretion by competitively binding to GnRH receptors, leading to the gradual regression of sex characteristics, slowing bone maturity, and improving the PAH in children [21]. We found that the PAH in untreated children with ICPP is significantly higher than it is in children treated with GnRHa, indicating the efficacy of GnRHa in addressing ICPP [22]. Wang Miao et al. [23] selected 50 female children with ICPP and treated them with different doses of GnRHa. Our results showed that, after the treatment, the PAH in both groups was significantly improved and the ΔBA/ΔCA ratio and GV were significantly reduced, indicating that GnRHa can slow bone maturity to a normal linear relationship with age and is also effective in improving the PAH of children with ICPP. A previous study analyzed the factors related to precocious puberty among children aged 4-10 years and found that the incidence of precocious puberty in children with unhealthy lifestyles was significantly higher than it is in children with healthy lifestyles [24]. This study also found that, compared with the before-treatment values, the children in both groups had significantly higher PAH after treatment, with significantly lower ΔBA/ΔCA and GV values, which is essentially consistent with our results. At the same time, our results

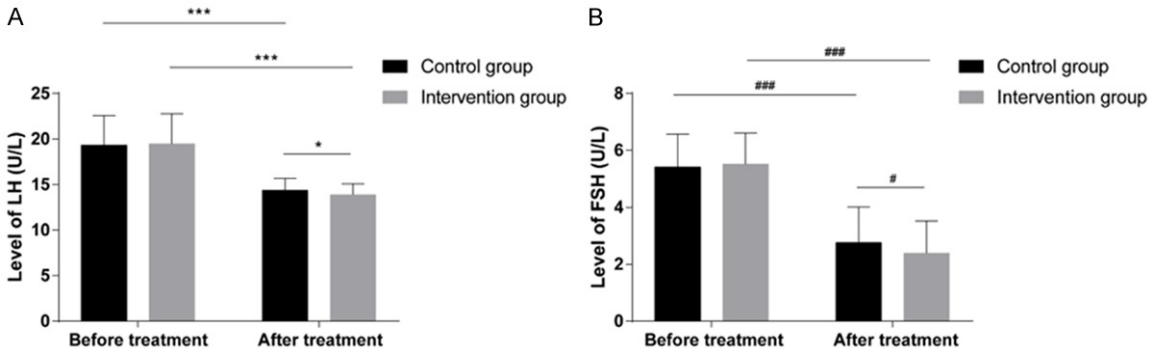

Figure 1. Comparison of the hormone levels. A: Level of LH; B: Level of FSH. LH: luteinizing hormone; FSH: follicle-stimulating hormone. Compared with LH before the treatment, ***P<0.001; compared with LH after the treatment, *P<0.05; compared with FSH before the treatment, ###P<0.001; compared with FSH after the treatment, #P<0.05.

Table 5. The occurrence of adverse reactions

Group	Control group	Intervention group	χ^2	P
Obesity	3	0	1.382	0.24
Endocrine disorders	2	0	0.512	0.474
Local itching	2	1	0	1
Flaky rash	1	1	0.512	0.474
Rate of adverse reactions (%)	18.6	4.65		
χ^2	4.074			
P	0.044			

showed that, compared with the control group, the PAH in the intervention group was significantly improved, and the ΔBA/ΔCA and GV values were significantly lower. These results suggest that GnRHa drug treatment has a beneficial therapeutic effect on children with ICPP and that this effect is enhanced by a healthy lifestyle, which may be related to factors such as physical exercise during treatment.

The abnormal feedback function of HPGA will cause an abnormal secretion of sex hormones such as LH and FSH, the main mechanism underlying the onset of ICPP in children [25]. Therefore, clinically, LH and FSH are often used as important indicators to evaluate the effects of treatment on ICPP in children [26]. This study found that, after the treatment, the LH and FSH levels in the two groups of children were significantly lower than they were before the treatment, and, furthermore, that the intervention group showed significantly lower values than the control group. The results suggest that GnRHa combined with a healthy lifestyle is not only effective in improving hormone metabolism in children with ICPP, but that healthy lifestyle factors are able to enhance the effects of the GnRHa treatment. We investigated the presence of adverse reactions in the children and found that, after treatment, adverse reactions were significantly lower in the intervention group, suggesting that GnRHa combined with a healthy lifestyle improves the efficacy of ICPP treatment.

There are, nevertheless, several limitations to this study: first, the sample size was relatively small, which may lead to biased results, and second, this was a single-center study, which may affect the universality of the results. The study will be considered for inclusion in a future multi-center study.

In conclusion, the use of GnRHa combined with a healthy lifestyle can significantly improve the PAH in children with ICPP while reducing the GV and improving their hormonal metabolism. The treatment is both efficacious and safe, so it is thus suitable for application in clinical practice.

Disclosure of conflict of interest

None.

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