

# Efficacy and Safety of Domestic Leuprorelin in Girls with Idiopathic Central Precocious Puberty: A Multicenter, Randomized, Parallel, Controlled Trial

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## Abstract

**Background:** In central precocious puberty (CPP), the pulse secretion and release of gonadotropin-releasing hormone (GnRH) are increased due to early activation of the hypothalamic-pituitary-gonadal axis, resulting in developmental abnormalities with gonadal development and appearance of secondary sexual characteristics. The CPP without organic disease is known as idiopathic CPP (ICPP). The objective of the study was to evaluate the clinical efficacy and safety of domestic leuprorelin (GnRH analog) in girls with ICPP.

**Methods:** A total of 236 girls with ICPP diagnosed from April 2012 to January 2014 were selected and were randomized into two groups. One hundred fifty-seven girls in the test group were treated with domestic leuprorelin acetate, 79 girls in the control group were treated with imported leuprorelin acetate. They all were treated and observed for 6 months. After 6-month treatment, the percentage of children with peak luteinizing hormone (LH)  $\leq 3.3$  U/L, the percentage of children with peak LH/peak follicle stimulating hormone (FSH) ratio  $< 0.6$ , the improvements of secondary sexual characteristics, gonadal development and sex hormone levels, the change of growth rate of bone age (BA) and growth velocity, and drug adverse effects between two groups were compared.

**Results:** After the treatment, the percentage of children with a suppressed LH response to GnRH, defined as a peak LH  $\leq 3.3$  U/L, at 6 months in test and control groups were 96.80% and 96.20%, respectively, and the percentage of children with peak LH/FSH ratio  $\leq 0.6$  at 6 months in test and control groups were 93.60% and 93.70%, respectively. The sizes of breast, uterus and ovary of children and the levels of estradiol ( $E_2$ ) were significantly reduced, and the growth rate of BA was also reduced. All the differences between pre- and post-treatment in each group were statistically significant ( $P < 0.05$ ), but the differences of the parameters between two groups were not significant ( $P > 0.05$ ).

**Conclusions:** Domestic leuprorelin is effective and safe in the treatment of Chinese girls with ICPP. Its effectiveness and safety are comparable with imported leuprorelin.

**Key words:** Central Precocious Puberty; Gonadotropin-releasing Hormone Analog; Idiopathic Central Precocious Puberty; Leuprorelin

## INTRODUCTION

In central precocious puberty (CPP, also known as gonadotropin-releasing hormone [GnRH]-dependent precocious puberty), the GnRH pulse secretion and release are increased due to early activation of the hypothalamic-pituitary-gonadal axis, resulting in gonadal development and appearance of secondary sexual characteristics. The CPP without organic disease is known as idiopathic CPP (ICPP). ICPP is more

common in girls, accounts for more than 80–90% of ICPP. With the improvement of living level, the incidence of ICPP has been increasing in recent years. Studies indicated that its incidence was between 1/5000 and 1/1000, and it was higher in girls than in boys.<sup>[1,2]</sup> The UK survey from 1860 to 2010 found that the sexual maturity was 6 years advanced in girls and was at least 2 years advanced in boys. American child specialists pointed out that signs and behaviors of current 10-year-old children were equivalent to past 15-year-old teenage youths. The 25% of black girls and 15% of Hispanic girls in America entered puberty at 7-year-old; the data published by the Japanese

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National Medical Center showed that within 8 years between 1995 and 2003, the age of sexual maturity in girls was 1 year advanced. The incidence of precocious puberty in children in Chinese coastal areas is 0.38%, of them the incidence of precocious puberty in girls is higher (0.67%).<sup>[3]</sup> The incidence of precocious puberty in Shanghai is 1%,<sup>[4]</sup> and the incidence of precocious puberty in Jiujiang city is 0.68%, of them it is up to 1.25% in girls, and 0.11% in boys;<sup>[5]</sup> the incidence is up to 0.74% in Zhengzhou.<sup>[6]</sup>

The objectives of CPP therapies are to inhibit premature or excessive sexual development and improve impaired adult height due to advance bone age (BA), to prevent psychosocial problems associated with prematurity and early menarche.<sup>[7-10]</sup> Currently, the preferred drug in the world for treatment of CPP is GnRH analog (GnRHa), which is a high-active derivative of GnRH.<sup>[11]</sup>

Gonadotropin-releasing hormone analog sustained-release agents are key products in the treatment of CPP, including leuprorelin acetate and triptorelin acetate.<sup>[10,12,13]</sup> Most agents of leuprorelin in China are imported branded products. In 2009, a domestic agent of leuprorelin acetate was marketed, and was studied for the treatment of endometriosis in adults. Its safety and efficacy had no difference compared with an imported agent of leuprorelin acetate. Currently, there is no large multi-center clinical study data on the comparison of domestic and imported leuprorelin acetate. In order to demonstrate the efficacy and safety of domestic leuprolide in the treatment of CPP, and based on specific patient population—children, we designed this study with caution.

## METHODS

### Study population

This trial included 236 girls with ICPP who were diagnosed in Beijing Children's Hospital, Tongji Hospital, Harbin Children's Hospital, Affiliated Hospital of Qingdao University, Shanxi Children's Hospital, and Second Hospital of Jilin University between April 2012 and January 2014. This clinical trial has been approved by the Ethics Committee of Beijing Children's Hospital, and the informed consents were obtained from all participated children and parents.

All the cases met the following inclusion and exclusion criteria. Inclusion criteria included: (1) Early appearance of secondary sexual characteristics: Girls  $\leq 8$  years; (2) Enlarged gonad: Under the B-ultrasound, the ovary volume  $> 1$  ml, more than 4 follicles with diameter  $\geq 4$  mm in unilateral ovary were observed; (3) Serum gonadotropins (including that luteinizing hormone [LH] and follicle stimulating hormone [FSH] level rose to the pubertal level): First, routine screening of baseline LH, if the baseline serum LH  $> 3.3$  U/L, the onset of gonadal axis can be determined, the condition was met; if baseline serum LH  $< 3.3$  U/L, the GnRH stimulation test was conducted; secondly, GnRH stimulation test: The stimulated peak value in the test can be used as diagnostic basis, the peak value referred to the maximum value of LH and FSH at each time-point

in the stimulation test, which occurred at 60–120 min; for detection at 60 min, with immune chemiluminescence assay, when peak LH  $> 3.3$  U/L and peak LH/peak FSH  $> 0.6$  in the GnRHa stimulation test, CPP can be diagnosed; (4) Growth velocity (GV) spurted; (5) BA exceeded: BA increased by more than 1-year compared with the actual age.

Exclusion criteria included: (1) Congenital hypothyroidism; (2) Peripheral precocious puberty: Germ cell tumors and various types of gonadal tumors; (3) Organic diseases including congenital adrenal hyperplasia, adrenal tumors, various intracranial tumors; (4) Precocious puberty resulted by central nervous system diseases; (5) Exogenous precocious puberty, such as medicines, hormones, or pollute; (6) Patient who had used corticosteroid within 3 months before enrollment; (7) ICPP patient who had used GnRHa.

Case drop-out and elimination criteria: Those who did not meet the inclusion criteria or had no follow-up information record were eliminated. The eliminated cases were not included in the efficacy analysis. The drop-out case was defined as those who did not complete the follow-up prescribed in the protocol, included: (1) Patients who requested to withdraw from the study; (2) Posed potential risks to patients based on the judgment by investigator; (3) Serious adverse events; and (4) Patients who lost to follow-up. The specific reasons should be recorded for drop-out cases, which should be included in the full analysis set (FAS) and the safety analysis set.

### Sample size estimation

There were two treatment groups in this study. The percentages of patients with “baseline serum LH  $<$  upper limit of normal (0.1 U/L)” or “peak LH in response to the drug  $< 3.3$  U/L (or peak LH/peak FSH ratio  $< 0.6$ )” at 6 months after the treatment between two groups were compared. It was expected that the mean percentage was 90%. Noninferiority test was applied,  $\alpha = 0.025$ ,  $\beta = 0.2$  (power = 80%),  $\delta = 12.5\%$ , the ratio of the test group to the control was 2:1, the estimated results: 136 cases in the test group and 68 cases in the control group, considering the factor of drop-out, it increased to 160 cases in the test group, 80 cases in the control group, a total of 240 cases.

### Methods

Cases in the study were randomized into the test group and the control group. Girls in the test group were treated with domestic leuprorelin acetate microspheres for injection (3.75 mg/vial, produced by Shanghai Livzon Pharmacy Co., Ltd., trade name: Beiyi). Girls in the control group were treated with leuprorelin acetate microspheres for injection (3.75 mg/vial, produced by Takeda Pharmaceutical Co., Ltd., Japan; trade name: Enantone), the dose in both groups was 3.75 mg, subcutaneous injection every 4 weeks for 6 months.

Central randomization was used for grouping in the study. Dynamic randomization system provided by statistical professionals from the Clinical Research Center, Shanghai University of Traditional Chinese Medicine was used for

the centralized randomization procedure. After screening every eligible patient, investigators participated in the study in each site logged in the system, entered the screening information, obtained a random number (e.g., drug number), provided corresponding investigational drug based on the random number.

The investigational medicinal product in this study is a marketed product. The product could not be designed as a double-blind study because there is the logo of the company on the package. Consequently, this trial was conducted with the investigator-isolated blinded method, in which patients were enrolled sequentially and were provided with the product. Staff who provided and injected the product received the drug according to the random numbers and did not exchange the allocating information with the observing investigators. The product was blinded to the laboratory technicians who measured blood hormones, and the doctors who conducted the genital B-ultrasound.

### Data collection

The improvements of secondary sexual characteristics (breasts, pubic hair, menstruation, armpit hair), gonadal development (pelvic B-ultrasound), and serum sex hormone level ( $E_2$ ) at 0, 3, 6 month(s) after the treatment were observed. The changes of growth rate of BA and GV at 0, 6 month(s) after the treatment were recorded, these were calculated with GV, standard deviation score of height (HtSDS). The adverse effects were monitored and recorded. The changes of renal function, blood lipids, bone metabolism, urine routine test, body mass index, injection site pain, rash or abscess, vaginal bleeding, and polycystic ovary at 0, 3, 6 month(s) after the treatment were recorded. These were estimated for causality based on the standards of China Food and Drug Administration.

Height and weight (measured by a specified person with the same tools in each center) were measured monthly for each patient during the treatment. Three measurements were conducted, and the results were averaged; BA was determined using Greulich-Pyle method; ellipsoid volume formula was used for uterus and ovary volume:  $\text{Length} \times \text{width} \times \text{depth} \times \pi/6$ . The SDS was used as calculation unit of the parameter: The HtSDS was calculated with the data of height (girl) of "A national survey on growth of children in nine cities of China, 2005" as reference,<sup>[14]</sup>  $\text{HtSDS} = (\text{measured height} - \text{mean height of the same age})/\text{standard deviation (SD) of height of the same age}$ . HtSDS for the chronology age was represented as HtSDSCA, HtSDS for the BA was represented as HtSDSBA.

### Clinical efficacy evaluation

The primary efficacy endpoints: The percentage of patients met the LH criterion at 6 months after the treatment, e.g., the percentage of patients with "baseline serum LH < upper limit of normal" or "peak LH in response to the drug < 3.3 U/L or peak LH/peak FSH ratio < 0.6."

The secondary efficacy endpoints: The improvement of secondary sexual characteristics (breasts, pubic hair, menstruation, armpit hair), gonadal development (pelvic B-ultrasound), and serum sex hormone level ( $E_2$ ) at 0, 3,

6 month(s) after the treatment were compared. The changes of growth rate of BA and GV at 0, 6 month(s) after the treatment were compared, these were calculated with GV, HtSDS.

### Statistical analysis

Statistics Analysis System (SAS) 9.2 software (USA) was used for analyses. Three analytic data sets (FAS, per protocol set [PPS], safety set [SS]) were determined. Demographic data were shown as mean  $\pm$  SD. Two-sided 95% confidence interval (CI) of the percentage difference for patients whose primary efficacy endpoint LH met its criterion was tested by noninferiority test based on 12.5% of noninferiority criteria (FAS, PPS). For all secondary efficacy endpoints, two-sided test was used in the general statistical test; independent sample *t*-test was used in the comparisons between two groups; paired *t*-test was used in the comparisons between pre- and post-treatment. A  $P \leq 0.05$  was considered as statistically significance for a tested difference (FAS). The incidences of adverse events and adverse reactions were calculated in the safety evaluation (SS).

## RESULTS

### Case distribution and baseline equilibrium

Two hundred and forty cases were included in the study. One hundred sixty cases were included in the test group (Beiyi), 3 of them were eliminated. All the PPS, FAS, and SS sets had 157 cases; 80 cases were included in the control group (Enantone), 1 of them was eliminated. All the PPS, FAS, and SS sets had 79 cases [Figure 1].

All the 236 subjects in this trial were girls with ICPP, and the demographic and clinical characteristics were shown in Table 1. In the test group, the initial age was  $6.42 \pm 1.01$  years, the initial BA was  $9.22 \pm 1.43$  years; according to Tanner's staging for puberty development, there were 71 cases of breast Stage II, 70 cases of breast Stage III, 5 cases of breast Stage IV; 17 cases of pubic hair Stage II, 3 cases of pubic hair Stage III, the remaining girls were pubic hair Stage I; menarche appeared in 10 cases; armpit

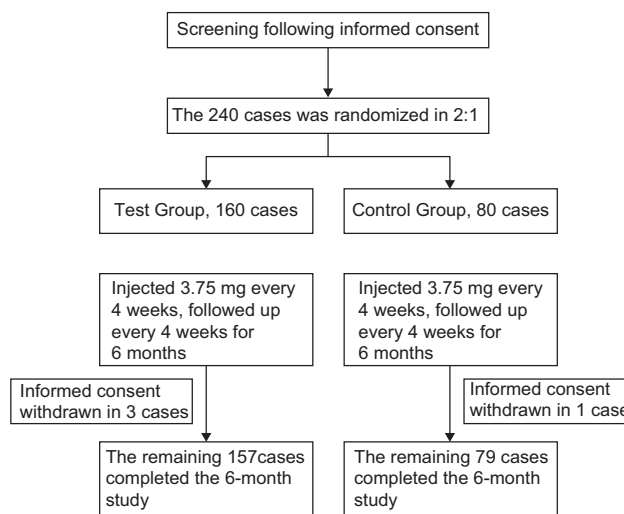
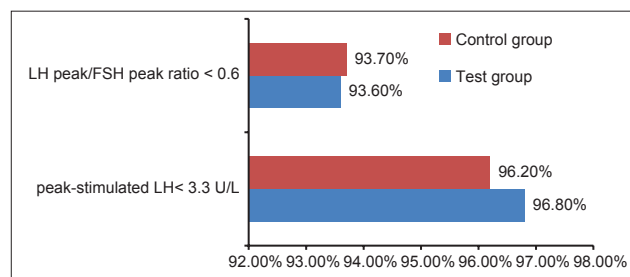


Figure 1: The treatment flow chart of the patient.

hair appeared in 3 cases. In the control group, initial age was  $6.47 \pm 0.75$  years, initial BA was  $9.21 \pm 1.18$  years; there were 53 cases of breast Stage II, 21 cases of breast Stage III, 3 cases of breast Stage IV; 4 cases of pubic hair Stage II, 1 case of pubic hair Stage III, the remaining girls were pubic hair Stage I; menarche appeared in 4 cases; armpit hair appeared in 2 cases [Table 1].

### The primary efficacy endpoint: The percentage of patients met the peak luteinizing hormone criterion

The percentage of patients with peak LH in response to the drug  $<3.30$  U/L was 96.80% and 96.20% at 6 months after the treatment in patients of the test group and the control group, respectively. There was no significant difference between two groups ( $P > 0.05$ ) [Figure 2]; the percentage of patients with peak LH/peak FSH  $<0.6$  was 93.60% and 93.70% at 6 months after the treatment in patients of two groups, respectively, there was no significant difference between two groups ( $P > 0.05$ ) [Figure 2].



**Figure 2:** Percentage of patients with peak-stimulated luteinizing hormone (LH)  $<3.3$  U/L and peak LH/follicle stimulating hormone ratio of  $<0.6$  after gonadotropin-releasing hormone stimulation test at 6 months.  $P > 0.05$ , comparison between two groups.

For FAS analysis, the percentages of patients met the peak LH criterion in both test (Beiyi) and control groups (Enantone) were 100%, the lower limit of 95% CI for the rate of difference between two groups was 0. The test group was noninferior compared with the control group based on the noninferiority criteria of 12.5%.

### Changes in secondary sexual characteristics

Patients in the test and the control groups developed manifestations that the mammary gland mass became softer and smaller, and the breast shrank. In the test group, 20 cases developed pubic hair growth before the treatment; which remained unchanged in 14 cases after the treatment, decreased slightly in 5 cases, progressed from Stage I to Stage II in 1 case. In the control group, 5 cases developed pubic hair growth before the treatment; which remained unchanged in 3 cases after the treatment, decreased slightly in 2 cases. Before the treatment, 10 cases developed menarche in the test group, and 4 cases developed menarche in the control group, all of which were disappeared at 1 month after the treatment. Before the treatment, 3 cases developed armpit hair growth in the test group, and 2 cases developed armpit hair growth in the control groups, which decreased after the treatment in 2 cases in both groups, and 1 case remained unchanged in the test group.

### Pelvic B-ultrasound

The uterus volume of patients before therapy in test and control groups was higher than the prepubertal level ( $3 \text{ cm}^3$ ), and significantly decreased at 3 months after the treatment. The differences were significant compared with the pretreatment levels in each group (all  $P < 0.05$ ). The uterus volume of patients before therapy in test and control groups decreased to the prepubertal level after 6 months treatment, the difference of those between 6 months and

**Table 1: The demographic and clinical characteristics of ICPP girls**

| Items  | Test group (n = 157) | Control group (n = 79) | t     | P     |
|--|----------------------|------------------------|-------|-------|
| Age (mean $\pm$ SD, years)   | $6.42 \pm 1.01$      | $6.47 \pm 0.75$        | 0.411 | 0.682 |
| Weight (mean $\pm$ SD, kg)   | $27.50 \pm 5.40$     | $27.3 \pm 5.00$        | 0.277 | 0.782 |
| Height (mean $\pm$ SD, cm)   | $130.00 \pm 8.00$    | $129.00 \pm 5.00$      | 1.182 | 0.238 |
| GV at 1 year before enrollment (mean $\pm$ SD, cm/year.)             | $7.43 \pm 1.36$      | $7.70 \pm 1.62$        | 1.330 | 0.185 |
| Tanner's staging of breast development (mean $\pm$ SD, stage)        | $2.44 \pm 0.67$      | $2.32 \pm 0.59$        | 1.380 | 0.169 |
| Tanner's staging of pubic hair development (mean $\pm$ SD, stage)    | $1.15 \pm 0.41$      | $1.08 \pm 0.31$        | 1.480 | 0.140 |
| Tanner's staging of armpit hair development (mean $\pm$ SD, stage)   | $1.02 \pm 0.14$      | $1.03 \pm 0.16$        | 0.311 | 0.756 |
| Uterus volume (mean $\pm$ SD, $\text{cm}^3$ )                        | $3.40 \pm 2.90$      | $3.13 \pm 2.27$        | 0.782 | 0.435 |
| Left ovary (ml)  | 2.21                 | 2.15                   | 0.183 | 0.669 |
| Number of follicles with diameter $\geq 4$ mm in the left ovary (n)  | 4.80                 | 4.66                   | 0.141 | 0.707 |
| Right ovary (ml)   | 1.96                 | 1.93                   | 0.340 | 0.560 |
| Number of follicles with diameter $\geq 4$ mm in the right ovary (n) | 4.21                 | 3.78                   | 3.863 | 0.049 |
| BA (mean $\pm$ SD, years)  | $9.22 \pm 1.43$      | $9.11 \pm 1.18$        | 0.585 | 0.599 |
| BA-CA (mean $\pm$ SD, years)   | $2.19 \pm 1.07$      | $2.18 \pm 1.00$        | 0.114 | 0.909 |
| LH (mean $\pm$ SD, U/L)  | $1.83 \pm 2.71$      | $2.14 \pm 3.14$        | 0.773 | 0.440 |
| Follicle stimulating hormone (mean $\pm$ SD, U/L)                    | $4.43 \pm 2.91$      | $4.77 \pm 3.42$        | 0.794 | 0.428 |
| Estradiol (mean $\pm$ SD, $\times 10^{-6}$ mg/L)                     | $37.1 \pm 14.7$      | $36.0 \pm 17.3$        | 0.519 | 0.604 |
| Testosterone (mean $\pm$ SD, $\times 10^{-5}$ mg/L)                  | $4.34 \pm 6.50$      | $4.57 \pm 5.78$        | 0.265 | 0.791 |
| Baseline LH (mean $\pm$ SD, U/L)                                     | $2.37 \pm 3.80$      | $2.16 \pm 2.99$        | 0.444 | 0.657 |
| Peak LH (mean $\pm$ SD, U/L)   | $16.60 \pm 7.50$     | $16.40 \pm 6.60$       | 0.237 | 0.813 |

SD: Standard deviation; ICPP: Idiopathic central precocious puberty; LH: Luteinizing hormone; BA: Bone age; GV: Growth velocity; CA: Chronology age.

3 months after the treatment was significant ( $P < 0.05$ ). The differences of the uterus volume before treatment and 3 months after the treatment between two groups were not significant (all  $P > 0.05$ ). The difference at 6 months after the treatment between two groups was significant ( $P < 0.05$ ) [Table 2]. Bilateral ovaries volume before therapy increased significantly compared with the prepubertal level (1 ml) in patients of test and control groups. It was decreasing with the course of treatment and reached the prepubertal level at 6 months after the treatment. The difference at 6 months after the treatment of two groups was significant (all  $P < 0.05$ ) compared with pretreatment. There was no significant difference between two groups before the treatment and after the treatment ( $P > 0.05$ ) [Table 2]. Follicles with diameter  $\geq 4$  mm were observed in unilateral ovary in all patients of both groups; all of these follicles decreased or disappeared after the treatment.

### Changes in hormone levels

The serum  $E_2$  level before the treatment was significantly higher than the prepubertal level ( $< 2 \times 10^{-5}$  mg/L) in patients of test and control groups, and significantly decreased at 3 months and 6 months after the treatment, the differences between pre- and post-treatment in each group were significant ( $P < 0.05$ ). There was no significant difference before and after the treatment between two groups ( $P > 0.05$ ) [Table 2].

The peak LH after GnRH stimulation test at 6 months after treatment in all patients of two groups was significantly decreased compared with that before the treatment, reached the prepubertal level ( $< 3.3$  U/L). The difference between

those at 6 months after the treatment and before the treatment was significant ( $P < 0.05$ ), there was no significant difference between two groups before the treatment ( $P > 0.05$ ), but the difference between two groups at 6 months after the treatment was statistically significant ( $P < 0.05$ ) [Table 2].

### Bone age and growth velocity

The growth rate of BA was decreased after the treatment in all patients of test and control groups. Before the treatment, the CA was  $6.42 \pm 1.01$  years and  $6.47 \pm 0.75$  years, respectively; BA was  $9.22 \pm 1.43$  years and  $9.11 \pm 1.18$  years, respectively; the difference of BA-CA was  $2.19 \pm 1.07$  years and  $2.18 \pm 1.00$  years, respectively. At 6 months after the treatment, BA was  $9.24 \pm 1.36$  years and  $9.16 \pm 1.18$  years, respectively, the difference of BA-CA was  $1.72 \pm 1.03$  years and  $1.73 \pm 0.99$  years, respectively; the growth rate of BA was significantly lower than that of CA; all the differences of these were not significant between two groups ( $P > 0.05$ ) [Table 3].

The GV was decreasing with the course of treatment after the treatment in patients of test and control groups. After 6 months of treatment, the HtSDSCA of patients in two groups was decreased from  $0.71 \pm 0.29$ ,  $0.69 \pm 0.32$  to  $0.70 \pm 0.30$ ,  $0.69 \pm 0.29$ , respectively; and the HtSDSBA was increased from  $-0.47 \pm 0.48$  and  $-0.48 \pm 0.40$  to  $-0.24 \pm 0.55$  and  $-0.21 \pm 0.57$ , respectively. All the differences between them before the treatment and 6 months after the treatment were significant ( $P < 0.05$ ), indicating that GV was catching up with BA. Before and after the treatment, GV, HtSDSCA, and HtSDSBA between two groups were not significantly different ( $P > 0.05$ ) [Table 3].

**Table 2: The sexual characters and the results of GnRH releasing test in ICPP girls before and after the leuporelin therapy**

| Items  | Before therapy    |                   | 3 months after the treatment |                    | 6 months after the treatment |                    |
|--|-------------------|-------------------|------------------------------|--------------------|------------------------------|--------------------|
|  | Test group        | Control group     | Test group                   | Control group      | Test group                   | Control group      |
| Uterus volume (mean $\pm$ SD, cm <sup>3</sup> )  | 3.40 $\pm$ 2.90   | 3.13 $\pm$ 2.27   | 2.21 $\pm$ 2.10*†            | 2.50 $\pm$ 1.63*†  | 1.99 $\pm$ 1.86*             | 1.52 $\pm$ 1.45*   |
| Left ovary volume (ml)                           | 2.21 (1.03–6.77)  | 2.15 (1.04–4.76)  | 1.29*† (0.16–5.37)           | 1.27*† (0.33–2.90) | 0.90*† (0.10–2.89)           | 0.91*† (0.26–2.32) |
| Right ovary volume (ml)                          | 1.96 (1.01–5.60)  | 1.93 (1.02–3.77)  | 1.23*† (0.14–3.72)           | 1.32*† (0.34–3.30) | 0.92*† (0.08–2.77)           | 0.90*† (0.08–2.24) |
| Estradiol (mean $\pm$ SD, $\times 10^{-6}$ mg/L) | 37.10 $\pm$ 14.70 | 36.00 $\pm$ 17.30 | 18.70 $\pm$ 6.80*†           | 18.70 $\pm$ 6.20*† | 13.50 $\pm$ 5.30*†           | 13.30 $\pm$ 5.30*† |
| Peak value of LH (mean $\pm$ SD, U/L)            | 16.60 $\pm$ 7.50  | 16.40 $\pm$ 6.60  | –                            | –                  | 1.85 $\pm$ 0.67*             | 1.58 $\pm$ 0.56*   |

\* $P < 0.05$ , versus before treatment in the same group; † $P > 0.05$ , comparison between two groups at the same time point, bilateral ovarian volume used nonparametric test (Wilcoxon test). SD: Standard deviation; ICPP: Idiopathic central precocious puberty; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone.

**Table 3: The height, weight, BA, GV, and PAH in ICPP girls before and after the leuporelin therapy (mean  $\pm$  SD)**

| Items        | Before therapy   |                  | 3 months after the treatment |                    | 6 months after the treatment |                    |
|--------------|------------------|------------------|------------------------------|--------------------|------------------------------|--------------------|
|              | Test group       | Control group    | Test group                   | Control group      | Test group                   | Control group      |
| Height (cm)  | 130 $\pm$ 8      | 129 $\pm$ 5      | 132 $\pm$ 8*†                | 131 $\pm$ 5*†      | 133 $\pm$ 8*†                | 132 $\pm$ 5*†      |
| Weight (kg)  | 27.5 $\pm$ 5.40  | 27.30 $\pm$ 5.00 | 28.10 $\pm$ 5.40*†           | 28.10 $\pm$ 5.10*† | 28.80 $\pm$ 5.50*†           | 29.10 $\pm$ 5.10*† |
| BA (years)   | 9.22 $\pm$ 1.43  | 9.11 $\pm$ 1.18  | –                            | –                  | 9.24 $\pm$ 1.36*†            | 9.16 $\pm$ 1.18*†  |
| GV (cm/year) | 7.43 $\pm$ 1.36  | 7.70 $\pm$ 1.62  | 6.28 $\pm$ 1.42*†            | 6.40 $\pm$ 1.71*†  | 4.76 $\pm$ 2.23*†            | 4.85 $\pm$ 1.65*†  |
| HtSDSBA      | -0.47 $\pm$ 0.48 | -0.48 $\pm$ 0.40 | –                            | –                  | -0.24 $\pm$ 0.55*†           | -0.21 $\pm$ 0.57*† |
| HtSDSCA      | 0.71 $\pm$ 0.29  | 0.69 $\pm$ 0.32  | –                            | –                  | 0.70 $\pm$ 0.30†             | 0.69 $\pm$ 0.29†   |

\* $P < 0.05$ , vs. before treatment in the same group; † $P > 0.05$ , comparison between two groups at the same time point. BA: Bone age; ICPP: Idiopathic central precocious puberty; SD: Standard deviation; PAH: Predicted adult height; GV: Growth velocity; HtSDSBA: Height standard deviation score for bone age; HtSDSCA: Height standard deviation score for chronology age.

## Safety

During the treatment, in the test group, 8 patients developed pain and swelling in the injection site, 5 patients appeared vaginal bleeding after the first dose of the drug; in the control group, 5 patients developed pain and swelling in the injection site, 2 patients appeared vaginal bleeding after the first dose of the drug. Swelling spontaneously alleviated about 2 weeks later without any therapeutic treatment in children of both groups, vaginal bleeding no longer appear during the subsequent course of the treatment. Thyroid, adrenal, electrolytes, bone metabolism, liver and renal function, blood lipids, glucose tolerance test, and glycosylated hemoglobin were detected before and after the treatment, and all of them were normal.

## DISCUSSION

With the improvement of living level and the impact of environmental factors, growth and development of children in our country are accelerated, the time of adolescence is advanced, in general. In recent years, the number of outpatient with precocious puberty was increasing. Precocious puberty has become the second place of pediatric endocrine disorders and the serious threat to children's mental and physical health and physical development.<sup>[15-17]</sup>

Gonadotropin-releasing hormone analogue has been used in the treatment of CPP for more than 20 years. Its efficacy and safety have been accepted in the world. GnRHa has no significant adverse effect on growth, reproduction, and bone metabolism in future in children with precocious puberty.<sup>[18-20]</sup> The age of menarche in girls with ICPP is near the normal age of menarche when the GnRHa treatment is stopped.<sup>[12]</sup>

During the treatment of GnRHa, some children may develop vaginal bleeding, the incidence of which was various in different clinical studies, was 5–9% or even 16–60%,<sup>[21]</sup> especially more common in those who had menarche. Vaginal bleeding usually occurred at 2 weeks after the first dose of the drug, occurred after the second dose in a few cases. This phenomenon is continued after 6 months in rare cases. Its duration is usually 3–5 days, even up to 11–13 days in a few patients.

The clinical study, a multi-center, randomized, parallel, positive control, prospective clinical trials, objectively evaluated the clinical effectiveness of the drug, obtained the clinical data of domestic leuprolide in the treatment of ICPP, and provided reference for the treatment of girls with ICPP. Furthermore, domestic drugs of efficacy equivalence, low-cost are very important for the relatively poor families and are also of certain significance for supporting national enterprises.

The percentage of children with an peak LH <3.3 U/L at 6 months of treatment in test and control groups were 96.80% and 96.20%, respectively, and the percentage of children with peak LH/FSH ratio <0.6 were 93.60% and 93.70%, respectively, there were no differences between the two groups, which were consistent with a foreign multi-center clinical study that the percentage of children with an peak LH <3.3 U/L at 6

months of treatment was 96.3%, and the percentage of children with peak LH/FSH ratio <0.6 was 94.4%.<sup>[22]</sup>

In this study, the mammary gland mass became softer and smaller, and the breast shrank after the treatment in test and control groups. In both groups, the development of secondary sexual characteristics such as breasts, pubic hair, and armpit hair were effectively inhibited; menstruation disappeared in children who have occurred menarche.

In the study, the uterus volume of patients in both groups before the treatment was significantly higher than the prepubertal level, and decreased to the prepubertal level after 6 months of treatment, the differences compared with pre-treatment in both groups were significant (all  $P < 0.05$ ). Bilateral ovaries volume before the treatment increased 1 ml significantly compared with the prepubertal level in patients of both groups. It was decreased to the prepubertal level at 6 months after treatment, the difference was significant (all  $P < 0.05$ ) compared with pre-treatment. Follicles with diameter  $\geq 4$  mm disappeared after the treatment in all patients of both groups. Serum sex hormone level returned to the prepubertal level in children of both groups; the GV and the growth rate of BA were decreased.

The objective of the study was to evaluate the clinical efficacy and safety of domestic leuporelin in girls with ICPP. The clinical indicators used in the study are the national and international accepted classic indicators for evaluating the degree of gonadal inhibition. The clinical observation period of the imported GnRHa was employed as the observation period of the study, which was 6 months. Therefore, this clinical study has some limitations. First, the duration of observation was short, only 6 months, the further data should be collected. The children should be followed up as long as possible up to their adulthood; second, the sample size was not large enough, the related safety data have been gradually expanded sample size, further analysis should be conducted; finally, there was no updated observation indicator in this clinical study. In future, updated indicators could be added in studies to research their scientific significances.

In conclusion, in the treatment of girls with ICPP, the efficacy and safety of domestic leuporelin were comparable with imported leuporelin. The results of this study were consistent with reported results<sup>[22-25]</sup> in literature, provided a reference for the clinical treatment of ICPP. Domestic leuporelin may safely and effectively used in the treatment of ICPP, is worthy of clinical application and promotion.

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