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Long-term efficacy of a triptorelin 3-month depot in girls with central precocious puberty

Kyu Hyun Park[1],
Si-Hwa Gwag[1],
Yu Jin Kim[1],
Lindsey Yoojin Chung[2],
Eungu Kang[1],
Hyo-Kyoung Nam[1],
Young-Jun Rhie[1],
Kee-Hyoung Lee[1]

[1]Department of Pediatrics, Korea University College of Medicine, Seoul, Korea
[2]Department of Pediatrics, Myoungji Hospital, Goyang, Korea

Purpose: Three-month gonadotropin-releasing hormone agonists (GnRHas) are expected to achieve better compliance in patients with central precocious puberty (CPP) compared to the monthly formulation. However, 1-month depot remains the dominant choice for conventional treatment worldwide. Our study aimed to investigate the long-term efficacy of a 3-month GnRHa for CPP treatment.
Methods: In this retrospective study, 69 Korean girls with CPP were prescribed either triptorelin pamoate (TP) 3-month depot (n=29) or triptorelin acetate (TA) 1-month depot (n=40) and were followed for 1 year after the end of treatment. Auxological, radiological, and biochemical data were collected every 6 months.
Results: Baseline characteristics were similar between the 2 groups. In the TP 3-month depot group, 27 of 29 patients (93.1%) exhibited suppressed luteinizing hormone level (below 2.5 IU/L) after 6 months of treatment, and this suppression level was reserved until the final injection. The degree of bone age advancement in the TP 3-month depot group decreased from 1.8±0.4 years at the start of treatment to 0.6±0.5 years at 1-year posttreatment. The gain in predicted adult height (PAH) 1 year after the end of treatment was similar between the TP 3-month and TA 1-month depot groups (5.2±3.1 and 5.3±2.4 cm, respectively; *P*=0.875).
Conclusion: A 3-month depot of triptorelin effectively inhibited gonadal and sex hormones, suppressed bone maturation, and increased PAH. For patient convenience, we suggest a 3-month GnRHa regimen as a promising CPP treatment option.

Keywords: Central precocious puberty, Gonadotropin-releasing hormone, Triptorelin pamoate

Highlights

- This study investigated the efficacy of 3-month versus 1-month gonadotropin-releasing hormone agonist (GnRHa) treatments for central precocious puberty in 69 Korean girls.
- The 3-month regimen effectively suppressed hormone levels, reduced bone age advancement, and increased predicted adult height.
- It presents a convenient and effective alternative to the 1-month GnRHa treatment.

Introduction

Precocious puberty is defined as pubertal development occurring before the age of 8 years in girls and 9 years in boys.[1)] Central precocious puberty (CPP) involves gonadotropin-dependent premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, which leads to increased secretion of sex steroid hormones.[2)] CPP occurs more frequently in girls and can cause premature menarche and early fusion of the growth plates, compromising adult height (AH).[1,3)] The treatment of choice for CPP is a gonadotropin-releasing hormone

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Address for correspondence:
Kee-Hyoung Lee
Department of Pediatrics, Korea University College of Medicine. 73 Goryodae-ro, Sungbuk-gu, Seoul 02841, Korea
Email: doclee@korea.ac.kr
https://orcid.org/0000-0002-4319-9019

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agonist (GnRHa), which down-regulates pituitary gonadotropin secretion.[4] This type of drug has been used since the 1980s, and its effectiveness and safety have been demonstrated.[5]

Monthly formulations of GnRHa have long been used in CPP treatment, and long-term efficacy and safety have been demonstrated in many studies.[1,6,7] Administration of 3-month depots, an extended-release form, reduced the number of injections and improved the convenience and comfort for children receiving treatment. Although several studies have investigated the short-term effect of luteinizing hormone (LH) suppression using a 3-month depot,[8-12] few long-term studies have reported its effect on suppressing bone age (BA) and increasing predicted adult height (PAH).[13-15]

Triptorelin, a synthetic GnRHa, is available in 2 formulations: acetate and pamoate salts. Although the acetate salt was the first to be developed, the pamoate salt is commonly used in slow-release formulations of pharmaceutical agents. The formulations show similar efficacy and safety profiles.[16]

Our study aimed to investigate the long-term therapeutic efficacy of CPP treatment using a triptorelin pamoate (TP) 3-month depot in female patients and to compare its effects with that of a triptorelin acetate (TA) 1-month depot.

Materials and methods

1. Subjects

In this retrospective study, we included 69 girls diagnosed with and treated for CPP at the Pediatric Endocrinology Clinic of Korea University Hospital between 2015 and 2020. CPP was diagnosed by the presence of breast development before the age of 8 years, more than 1 year BA advancement compared with chronological age (CA), and pubertal LH level ≥5.0 IU/L on a GnRH stimulation test.[17] We excluded patients with underlying conditions such as brain tumor, growth hormone deficiency, cranial irradiation, chronic disease, and those who changed formulations or received concurrent treatment with growth hormone.

2. Methods

A total of 69 girls completed the CPP treatment: 29 received TP 11.25 mg every 3 months, and 40 received TA 3.75 mg once a month. TP 3-month depot was administered in a one-vial injection without changing the dose in patients weighing 20 kg or more. Clinical and biochemical data were collected at baseline and followed up every 6 months until 1 year after treatment cessation.

For the GnRH stimulation test, synthetic GnRH (Relefact LH-RH 0.1 mg; Aventis Pharma, Frankfurt, Germany) was used, and a blood sample was collected before administration and at 30, 45, 60, and 90 minutes after injection to measure LH and follicle-stimulating hormone (FSH) levels. To evaluate the therapeutic effect, serum LH, FSH, and estradiol levels were measured 30 minutes after administration of the GnRHa during treatment every 6 months, and an LH level <2.5 IU/L was interpreted as effective pubertal suppression.[8,18] LH and FSH levels were measured using an immunoradiometric kit (Beckman Coulter, Inc., Brea, CA, USA), and estradiol levels were measured using a radioimmunoassay kit (Cisbio Bioassays, Codolet, France).

Every 6 months, 2 pediatric endocrinologists evaluated BA through left-hand radiography using the Greulich-Pyle method and calculated the PAH according to tables from Bayley and Pinneau.[19,20]

3. Statistical analyses

Data were analyzed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). We performed Student t-test to compare continuous variables between the 2 groups. Continuous variables are presented as mean±standard deviation. A *P*-value<0.05 was considered statistically significant.

4. Ethical statement

Ethical approval for this study was obtained from the Korea University Institutional Review Board (IRB) (Study approval No. 2022AN0311).

Results

1. Patient clinical and auxological characteristics

Baseline characteristics of the 69 enrolled patients are summarized in Table 1. At baseline, no significant differences were observed between the TP 3-month depot and TA 1-month

Table 1. Baseline characteristics of the triptorelin 3-month depot and 1-month depot subjects

Variable	TP 3-mo (n=29)	TA 1-mo (n=40)	*P*-value
Age (yr)	8.6±0.4	8.5±0.5	0.274
Midparental height (cm)	160.8±3.6	160.9±3.8	0.920
Height (cm)	135.4± 4.7	135.1±4.6	0.795
Height SDS for CA	0.9±0.8	1.0±0.5	0.559
Weight (kg)	33.7±5.7	34.5±4.8	0.513
BMI (kg/m^2)	18.3±2.5	18.9±2.1	0.292
BMI SDS for CA	0.6±1.2	1.0±1.0	0.202
BA (yr)	10.4±0.4	10.3±0.6	0.491
BA–CA (yr)	1.8±0.4	1.8±0.4	0.723
GnRH-stimulated LH peak (IU/L)	17.5±12.9	15.2±14.5	0.503
GnRH-stimulated FSH peak (IU/L)	14.4±12.0	16.7±6.6	0.312
Estradiol (pg/mL)	0.8±4.4	2.1±3.1	0.176
Predicted adult height (cm)	159.5±5.3	159.4±2.9	0.908

Values are presented as mean±standard deviation.
TP 3-mo, triptorelin pamoate 3-month depot; TA 1-mo, triptorelin acetate 1-month depot; SDS, standard deviation score; CA, chronological age; BMI, body mass index; BA, bone age; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

depot groups in terms of age, BA, height standard deviation score (SDS), body mass index (BMI) SDS, midparental height, PAH, initial mean GnRH-stimulated LH, FSH peak, and estradiol levels.

2. Gonadotropin and sex-hormone suppression during treatment and recovery following treatment termination

In the TP 3-month depot group, 27 of 29 patients (93.1%) showed a suppressed LH response <2.5 IU/L after 6 months of treatment. After 12 months of treatment and at the final injection, 28 patients (96.6 %) maintained this response. One patient in the TP 3-month depot group failed to achieve LH suppression, with LH levels of 3.5 IU/L at months 6 and 12 and 2.8 IU/L at the end of treatment. The mean stimulated LH levels were 1.4±1.5 and 0.5±0.3 IU/L at 6 months (P=0.005) and 0.7±0.6 IU/L and 0.5±0.4 IU/L at the end of treatment (P=0.073) in the TP 3-month and TA 1-month depot groups, respectively (Table 2). Compared with the TA 1-month depot group, the TP 3-month depot group showed slightly higher LH concentrations; however, both groups showed suppressed LH level less than 2.5 IU/L during the treatment period. Twenty patients in the TP 3-month depot group were followed for 1 year after treatment discontinuation; LH, FSH, and estradiol levels recovered to pubertal levels.

3. Assessment of growth velocity in the TP 3-month depot during the treatment period

In the treatment period, the TP 3-month depot group demonstrated growth velocities of 5.8±0.8 cm/yr and 5.6±1.0 cm/yr during the first and second years, respectively. The effects of this dosage were comparable to those of the 1-month depot group, which exhibited growth velocities of 5.8±0.8 cm/yr (P=0.998) and 5.4±0.8 cm/yr (P=0.388) in the corresponding timeframes. No significant differences were found between the 3-month and 1-month depot forms in terms of height velocity SDS during the first or second year of treatment (Table 3).

4. Clinical efficacy of TP 3-month depot for BA suppression and PAH improvement

At baseline, the TP 3-month depot group showed a BA advancement of 1.8±0.4 years. At 1-year posttreatment, the TP 3-month depot group showed a decrease in BA advancement to 0.6±0.5 years, indicating an efficacy comparable to that of

Table 3. Changes in height velocity and BA advancement after GnRHa treatment

Variable	TP 3-mo	TA 1-mo	*P*-value
Height velocity (cm)			
Year 1	5.8±0.8	5.8±0.8	0.998
Year 2	5.6±1.0	5.4±0.8	0.388
Height velocity SDS			
Year 1	-0.2±0.1	-0.2±0.1	0.797
Year 2	-0.2±0.2	-0.3±0.2	0.328
BA–CA (yr)			
Baseline	1.8±0.4	1.8±0.4	0.723
End of treatment	0.7±0.5	0.9±0.4	0.163
One year post treatment	0.6±0.5†	0.7±0.4	0.233

Values are presented as mean±standard deviation.
BA, bone age; GnRHa, gonadotropin-releasing hormone agonist; TP 3-mo, triptorelin pamoate 3-month depot; TA 1-mo, triptorelin acetate 1-month depot; SDS, standard deviation score; CA, chronological age.
†TP 3-mo (n=20).

Table 4. Changes in PAH before and after GnRHa treatment

Variable	TP 3-mo	TA 1-mo	*P*-value
PAH (cm)			
Baseline	159.5±5.3	159.4±2.9	0.908
End of treatment	164.0±4.8	164.0±3.7	0.953
One year post treatment	164.7±5.2†	164.6±3.7	0.942
ΔPAH (cm)			
End of treatment – baseline	4.5±3.8	4.7±2.9	0.832
One year post treatment – baseline	5.2±3.1†	5.3±2.4	0.875

Values are presented as mean±standard deviation.
PAH, predicted adult height; GnRHa, gonadotropin-releasing hormone agonist; TP 3-mo, triptorelin pamoate 3-month depot; TA 1-mo, triptorelin acetate 1-month depot.
†TP 3-mo (n=20).

Table 2. Changes in LH, FSH, and estradiol levels during and after GnRHa treatment

Variable	LH (IU/L)			FSH (IU/L)			Estradiol (pg/mL)		
	TP 3-mo	TA 1-mo	*P*-value	TP 3-mo	TA 1-mo	*P*-value	TP 3-mo	TA 1-mo	*P*-value
At baseline†	17.5±12.9	15.2±14.5	0.503	14.4±12.0	16.7±6.6	0.312	0.8±4.4	2.1±3.1	0.176
At 6 months‡	1.4±1.5	0.5±0.3	0.005	2.6±1.6	1.4±0.8	0.001	0.6±2.0	1.4±2.6	0.162
At 12 months‡	1.0±0.7	0.4±0.4	<0.001	3.1±1.5	1.5±0.7	<0.001	0.4±1.4	0.9±2.8	0.333
At the end of treatment‡	0.7±0.6	0.5±0.4	0.073	3.3±1.1	2.1±0.9	<0.001	0	0.6±1.8	0.034
One year posttreatment§	5.5±4.1‖	5.2±3.1	0.808	5.3±1.6‖	4.8±1.3	0.220	3.0±8.8‖	5.7±5.4	0.162

Values are presented as mean±standard deviation.
LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist; TP 3-mo, triptorelin pamoate 3-month depot; TA 1-mo, triptorelin acetate 1-month depot.
†GnRH-stimulated LH, FSH peak, and estradiol levels. ‡LH, FSH, and estradiol levels after administering a GnRHa injection. §Basal LH, FSH, and estradiol levels. ‖TP 3-mo (n=20).

the TA 1-month depot group, which exhibited a reduction to 0.7±0.4 years (*P*=0.233) (Table 3).

Prior to treatment, the PAH in the TP 3-month depot group was 159.5±5.3 cm. The gain in PAH from treatment initiation to 1-year posttreatment in this group was 5.2±3.1 cm. These results were similar to those of the TA 1-month depot group, which demonstrated a pre-treatment PAH of 159.4±2.9 cm and height gain of 5.3±2.4 cm posttreatment (*P*=0.875) (Table 4). Across all measured time points, PAH did not differ significantly between the 2 groups.

Discussion

This study aimed to evaluate the long-term therapeutic efficacy of a 3-month GnRHa formulation for CPP treatment. Our findings demonstrated successful suppression of LH level and increase in PAH among patients with CPP treated with the 3-month formulation for up to 1 year after treatment cessation. Moreover, the clinical efficacy of the 3-month formulation was comparable with that of the 1-month formulation.

GnRHa has shown well-established efficacy and safety in CPP treatment for more than 30 years.[6,7] Among GnRHa formulations, the 3-month depot has been approved in Korea since 2014, although the 1-month dosage form is preferred. Due to scheduling conflicts faced by school students and their guardians or reluctance to receive frequent injections, an increasing number of patients find it difficult to visit hospitals every month. Therefore, longer-acting GnRHas are expected to play a greater role in treatment. However, long-term studies investigating the efficacy and safety of these formulations are lacking.

The HPG axis can be assessed by measuring the concentration of unstimulated or stimulated serum, urinary gonadotropin, or sex steroid hormone levels. Measurement of LH levels after administration of a GnRHa injection is preferred over the GnRH stimulation test because the former involves a single injection and is less invasive and more cost-effective than the latter, which requires multiple blood draws and can be uncomfortable for the patient.[21] The inhibitory effect of gonadotropin after GnRHa administration was evaluated by monitoring stimulated serum LH level <2.5 IU/L during the CPP treatment period.[8,18] Stimulated LH level was effectively suppressed after treatment initiation and remained suppressed throughout the treatment period. The findings of this study were similar to those of previous studies, with 93.5% of patients showed adequate LH suppression in the first year of treatment.[8]

Although LH level was effectively suppressed to ≤2.5 IU/L in all evaluation sections, the 3-month formulation demonstrated higher mean stimulated LH level than the monthly formulation in the early treatment period. Previous research has suggested that a higher BMI status could be associated with a decrease in stimulated LH.[22,23] In this study, we found no significant difference in BMI between the 2 groups at baseline or during treatment. Fuld et al.[24] reported that leuprolide acetate 11.25 mg showed marginally inferior LH suppression compared with the monthly formulation, but effective LH and BA suppression was achieved at the second year of treatment. In our study, a single patient in the TP 3-month depot group who failed to achieve LH suppression showed a favorable treatment response with successful suppression of BA and increase of 8.1 cm in PAH at 1 year after treatment cessation.

Our study showed an increase in LH and estradiol levels after treatment cessation, indicating that gonadal function was restored and reproductive potential was not affected.[25] To date, 9 of 29 subjects in our study group have experienced menarche at a mean age of 12.7 years 17.4 months after treatment cessation.

Important characteristics of precocious puberty are faster height growth and bone maturation than among peers owing to the influence of sex hormones. After initiation of GnRHa treatment, growth velocity and bone maturation decreased to prepubertal levels. Our previous short-term study showed gradual decrease in growth velocity and degree of BA advancement (BA/CA) as treatment progressed.[8] In this study, decrease in growth velocity was confirmed and was maintained at more than 5 cm/yr on average during the treatment period. These results were not significantly different from those of the 1-month depot treatment.

In this study, we investigated the effectiveness of a 3-month GnRHa depot for CPP treatment and its impact on PAH and height gain. Our results showed that treatment with the 3-month depot led to a 5.2 cm gain in PAH, which is consistent with previous studies. Bertelloni et al.[14] treated 25 female children with CPP using quarterly triptorelin 11.25 mg and reported that AH was achieved without a significant difference in genetic potential (midparental height). Similarly, other studies using 11.25 mg of leuprolide acetate have reported an increase in PAH by 4–6 cm, with AH reaching the target height range.[13,15] Our control group, who received the monthly formulation, did not show a significant difference in PAH advancement compared with the 3-month depot group. This finding is consistent with similar studies using triptorelin 3.75 mg, which reported 5.7 cm and 6.5 cm gains in PAH.[26,27] A negative correlation was observed between age at GnRHa treatment initiation and PAH, with a decrease in the positive change in PAH as treatment initiation was delayed.[28,29] In this study, because the patient population had a relatively narrow age range, examination of changes in PAH according to age at GnRHa treatment initiation was limited.

No serious adverse effects were reported from the start of treatment to 1 year after the end of treatment. No unexpected safety concerns regarding vital signs or laboratory parameters were found during follow-up.

Our study provides valuable insights into the long-term efficacy of 3-month GnRHa treatment for the first time in Korea. However, the study has several limitations. The retrospective design, which relied on chart review, may have introduced a selection bias. Additionally, a relatively small number of subjects participated, and male patients with CPP were not included. Although we improved the accuracy of PAH by following the participants up to 1 year after the end of

treatment, final AH was not confirmed.

In conclusion, long-term follow-up showed that 3-month triptorelin depot effectively inhibited gonadal and sex hormones, suppressed bone maturation, and increased predicted AH. No serious adverse effects were observed. For the children's convenience and comfort, a 3-month triptorelin depot can serve as a suitable treatment option for precocious puberty because of its comparable effect to that of 1-month depot.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

Author contribution: Conceptualization: SHG, YJK, LYC, EK, HKN, YJR, KHL; Data curation: KHP, HKN, YJR; Formal analysis: KHP; Methodology: LYC, EK, HKN, KHL; Project administration: KHL; Visualization: KHP; Writing - original draft: KHP; Writing - review & editing: KHP, LYC, YJR

ORCID

Kyu Hyun Park: 0000-0002-4288-3820
Si-Hwa Gwag: 0000-0001-6313-2551
Yu Jin Kim: 0000-0002-9063-2006
Lindsey Yoojin Chung: 0000-0002-7447-6250
Eungu Kang: 0000-0001-6544-3599
Hyo-Kyoung Nam: 0000-0003-1512-2062
Young-Jun Rhie: 0000-0002-1250-6469
Kee-Hyoung Lee: 0000-0002-4319-9019

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