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Comparison of Continuous Versus Intermittent Administration of Triptorelin on the Final Height of Girls with Idiopathic Precocious Puberty

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Abstract

Background: It has long been reported that gonadotropin releasing hormone (GnRH) analogs can improve final height of patients with idiopathic precocious puberty (IPP). This study aimed at comparing 2 different doses of GnRH agonist, triptorelin, on the adult height of girls with IPP.

Methods: From July 2013, sixteen girls with IPP were randomly divided to 2 groups. The first Group received 1 intramuscular injection of triptorelin 0.3 mg/kg of body weight on a monthly basis, and the second group received this at months 1 to 6, 10 to 15, and 19 to 24. They did not receive triptorelin at months 7 to 9 and 16 to 18.

Results: Patients in Group 1 received a total of 7.2 mg/kg of triptorelin during a 2-year follow up while the Group 2 received 5.4 mg/kg triptorelin or about 39.6 mg less than the other group during the same period of follow up. No side effects were noted in Group 2 receiving lower dose of triptorelin, yet, 2 cases with gray hair and 1 case with mild rash were reported in the group receiving the higher dose. No statistically significant difference was found between the 2 groups regarding height after 2 years.

Conclusions: Treatment of IPP can be performed with triptorelin doses of less than 0.3 mg/kg per month, with the same height increment and lower side effects.

Keywords: Triptorelin, Idiopathic Precocious Puberty, Gonadotropin Releasing Hormone Analog, Height

1. Background

For more than 20 years, gonadotropin releasing hormone (GnRH) analogs have been used in the treatment of idiopathic precocious puberty (IPP) (1, 2). By influencing the pituitary gland, the release of follicular stimulating hormone (FSH) and luteinizing hormone (LH) is stimulated by triptorelin, a synthetic form of hypothalamic GnRH, and its analogs (1, 2). Endogenous GnRH release is pulsatile and reined by several modulators including sex hormones. A long-acting GnRH, when used for a long duration, induces desensitization of pituitary GnRH receptors and final block of secretion after a short period of LH release. With adequate therapy, secondary sexual maturation is suppressed in a reversible manner, taking about 3 to 12 months after discontinuation (2, 3). Several side effects, including sexual dysfunction, gastrointestinal upset, mood disorders, breast swelling, graying of hair, dry skin, alterations in liver function, menopausal symptoms, rash, tumor flare, urticaria, acne, and hair loss have been reported (1, 3, 4). The occurrence of these side effects is assumed to be directly related to the dose of the drug, thus, every effort should be made to reduce the dose with noticeable influence on the final outcome (5). In this regard, maintaining the pharmaceutical effects of the agent with the lowest possible dosage is the goal of many studies in this field.

This prospective study aimed at comparing the final heights of patients with IPP in 2 groups treated with 2 different doses of triptorelin during a 2-year follow up.

2. Methods

From July 2013, sixteen girls with a mean age of 7.05 years with diagnosis of IPP were chosen and followed up during the study. Other causes of precocious puberty were ruled out by means of clinical and paraclinical tests consisting of ultrasonography of abdomen, pelvic area, and adrenal glands, assessment of bone age, computed tomog-

raphy (CT) scan, Magnetic resonance imaging (MRI) of the brain (with and without contrast), which were performed for all cases after obtaining written informed consent from the patients' parents. Androgen response to ACTH test (Cosyntropin test) and adrenal ultrasonography were performed to exclude congenital adrenal hyperplasia (CAH). Based on the manifestations of secondary sexual characteristics at the age of 8 years or younger, or the occurrence of menarche in these patients before the age of 10 years, final diagnosis of IPP was considered (6).

The patients were divided in a random manner to 2 equal groups, each including 8 girls. Group 1 received long-acting GnRH agonist triptorelin (IPSEN Pharma Biotech, Signes, France) with a dosage of 0.3 mg/kg, intramuscularly (IM), every month for a total of 24 months. Group 2 received triptorelin with a dosage of 0.3 mg/kg IM at months 1 to 6, 10 to 15, and 19 to 24. They did not receive triptorelin at months 7 to 9 and 16 to 18.

The study protocol was clarified for the patients and their parents, and written informed consent was obtained. Patients' data including age, weight, height, Tanner stages of puberty, bone age, growth rate, and estimated adult height were determined in the first visit and also before each injection, every month. The participants were followed up for at least 2 consecutive years. During each visit, height, weight, secondary sexual manifestations such as pubic hair, breast growth, occurrence of menarche, and any side effects of the drug, were evaluated carefully by a trained physician.

The protocol of the study was approved by the research ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran.

For the statistical analyses, the SPSS software version 21.0 was used and the data were compared by non-parametric Student's t test. P values of ≤ 0.05 were considered statistically significant.

3. Results

The range of patients' age was between 6 and 7.9 years with a mean of 7.05 years. The difference between age and height of the patients in Groups 1 and 2 were not statistically significant at the first visit.

Patients in Group 1 received a total of 7.2 mg/kg triptorelin during a 2-year follow up while Group 2 received 5.4 mg/kg triptorelin during the same period of follow up.

Although a mean difference of 0.5 cm between heights of the 2 groups was observed between continuous versus non-continuous administration of triptorelin, it was not significant. Mean predicted adult height in group 1 was 158 $\pm$ 8.6 cm, while in group 2 this was 159 $\pm$ 7.6 cm with no considerable difference between the 2 groups. Sex maturity rates (SMR) and attained heights in each visit in group 1, who received continuous triptorelin therapy, and Group 2, which received non-continuous triptorelin therapy, are shown in Tables 1 and 2. Comparing the heights of patients in Groups 1 and 2 in each visit indicated no statistical difference (Table 3). Mean height before each injection in both groups and their statistical differences are shown in Table 3.

Bone ages before therapy in groups 1 and 2 were 8.9 $\pm$ 1.2 years and 9.1 $\pm$ 1.4 years, respectively; after the therapy they were 9.5 $\pm$ 0.9 and 9.6 $\pm$ 0.8 years, respectively. None of the P values was significant.

No untoward side effect was noted in Group 2, which received a lower dose of triptorelin, yet, 2 cases of gray hair and 1 case of mild rash were reported in Group 1, which received a higher dose (continuous triptorelin therapy).

4. Discussion

Currently, GnRH analogs are the treatment of choice for precocious puberty as a discrete pediatric disease with substantial physical and psycho-social sequela (5, 7). Primarily, treatment of precocious puberty should be directed towards management of the underlying causes. Some studies indicated that medical treatments are more effective in reduction of bone age progression and suppression of puberty in comparison to surgical therapies (5, 8, 9).

In one study, Bertelloni et al. collected information about the final height of children with central precocious puberty (CPP), who had received no treatment due to delayed diagnosis or rejection by parents (10); they found that the long-term main consequence was reduced adult height. Indeed, untreated individuals depicted a final height of nearly 3 standard deviations below the mean for their values of reference (10). Another study showed that treatment with quarterly triptorelin, similar to monthly administration, permitted to achieve an adult height adequate for mid-parental height in girls with precocious puberty (11). Chiocca et al. evaluated 17 patients (16 girls and 1 boy) with precocious puberty receiving triptorelin 11.25 mg treatment every 90 days and reported suppressed LH peak as well as estradiol levels (12). Compared with other studies, they declared that their treatment method seemed to be more beneficial from first treatment-cycle than that of other GnRH analogs administered quarterly at similar doses. Recently, reports have shown that Histrelin, a GnRH analog, as a subdermal hydrogel implant, decreased stimulated LH concentrations quickly and suppression was maintained for 1 year in 36 subjects (33 girls) (13). After the first year, the authors followed a subset of

Table 1. Sex Maturity Rates (SMR) and Heights in Group 1 Including Eight Girls With Idiopathic Precocious Puberty (IPP) at First Visit and After a Two-Year Follow Up on Continuous Triptorelin Therapy[a]

No	Age, y/mo	SMR		Height in Centimeters in Each Visit								
		Breast	Pubic hair	1st visit	3[b]	6[b]	9[b]	12[b]	15[b]	18[b]	21[b]	24[b]
1	7	II	I	112	114.8	116.3	117.5	118	119	119.2	120.6	121.5
2	7/4	II	I	110	113	115	116	116.5	117.5	118.7	120	121
3	6	II	II	116	118.5	120	121	122	123	123.8	125	125.9
4	6/4	II	II	113	115	116.8	117.5	119	119.6	120.8	122	125
5	7/4	II	II	119	121.3	123	124.4	125.5	126	127.4	128.5	129
6	7/9	II	I	120	123	125	126.55	127.8	129	130.5	131.2	132
7	6/11	II	I	115	117.5	119	119.5	120.5	121.6	122.5	123.2	124
8	7/8	II	II	118	120	122.5	123	124	125.3	126.5	127.7	128.5

Abbreviation: SMR, Sex maturity rate according to tanner classification.
[a] Continuous triptorelin therapy: one injection of 0.3 milligram per kilogram every month.
[b] Months after first visit.

Table 2. Sex Maturity Rates (SMR) and Heights in Group 2 Including Eight Girls With Idiopathic Precocious Puberty (IPP) at First Aisit and After a Two-Year Follow up on Non-Continuous Triptorelin Therapy[a]

No	Age, y/mo	SMR		Height in Centimeter in Each Visit								
		Breast	Pubic hair	1st visit	3[b]	6[b]	9[b]	12[b]	15[b]	18[b]	21[b]	24[b]
1	6/2	II	II	109	112	114	116.8	118	119.2	120.5	122.5	123.2
2	7	II	II	116	118.8	120.5	122.5	123.7	124.2	125.8	127	128.2
3	6/9	II	I	118	120.5	122	123.5	124.8	126.3	128	129.5	130.7
4	7/6	II	I	114	116.7	118.5	120	121.5	123	124.5	126.2	128
5	7	II	II	115	118	120.3	121.8	123.3	124.5	125.8	127.2	129.5
6	7/8	II	I	111	114.6	116.5	118.5	120	121.5	122.8	124.3	125.8
7	7/9	II	II	121	123	124.8	126	126.8	128	129.5	130.4	131.3
8	6/9	II	II	112	114	115	116.5	118	118.5	119.2	120.2	121.5

Abbreviation: SMR, sex maturity rate tanner classification.
[a] Non-continuous triptorelin therapy: one injection of 0.3 milligram per kilogram at months 0, 3, 6, 12, 15, 18, 24 but no injection at months 9 and 21.
[b] Months after first visit.

Table 3. Mean and P Value of Height (Centimeter) in Group I and II After 24 Months

Visit	1st Visit	3[a]	6[a]	9[a]	12[a]	15[a]	18[a]	21[a]	24[a]
Group I	115.37	117.88	115.37	120.68	121.66	122.62	125.86	124.77	125.86
Group II	114.50	117.20	118.95	120.70	122.01	123.15	124.51	125.91	127.27
P value	0.598	0.636	0.636	1	0.916	0.793	0.636	0.600	0.49

[a] Months after first visit.

31 patients having a second implant inserted for another year (14). In a number of the girls previously treated with depot leuprolide-acetate injections, LH levels at study entry were lower, yet, were similarly suppressed at 1 and 2 years from the start of the study (13, 14). Over the course of the study, predicted adult height increased by 5.1 cm in comparison with the baseline predictions. Some adverse events, mainly pain and bruising at the implant insertion site, were seen in 61% of the patients. The implants became relatively brittle after 1 year, and breakage of the device at removal was common (13, 14). Using the implants designed to work for 2 consecutive years also showed similar outcomes compared to using the implants for 1 year (15).

Side-effects, such as gastrointestinal upset, dry skin, alteration in liver function, rash, urticaria, acne, and hair loss have been reported for GnRH analogs (2, 4). These side effects were dose-dependent and could be decreased by reducing the drug dose without affecting the final results (2, 4).

In this study, 16 girls with final diagnosis of IPP were divided to 2 equal groups. During 24 months of follow up, patients with continuous triptorelin administration received a total of 7.2 mg/kg of triptorelin, and the other group with non-continuous administration received a total of 5.4 mg/kg or about 39.6 mg of triptorelin less than the other group. During follow up, suppression of hypothalamus-

pituitary-gonadal axis in both groups was ensured by checking serum estradiol concentrations of more than 10 pg/mL and LH/FSH less than 1, using the chemiluminescence test (16). No statistically significant differences were noted regarding the height of the 2 groups in visits as well as in the last visit in month 24.

4.1. Conclusions

Regarding the outcome of the present study, treatment of IPP and suppression of hypothalamus-pituitary-gonadal axis can be performed by prescribing lower dose of GnRH agonist while maintaining the therapeutic effects and reducing the side effects.

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Footnotes

Authors' Contribution: Prof Zohreh Karamizadeh and Dr Forough Saki performed the study design and gathered the data. Dr Ahmad Reza Rasekhi and Prof Sara Kashef helped with gathering the data and patients' follow-ups. Dr Soheil Ashkani-Esfahani helped in data gathering and analysis, writing the manuscript's draft and editing. All the authors helped in writing and revising the manuscript.

Conflicts of Interest: None declared

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