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Evaluation of Therapeutic Response to Triptorelin Acetate in Girls with Central Precocious Puberty in Kashan University Pediatric Endocrinology Clinic from 2011 to 2017

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Abstract

Introduction and Objective: The standard treatment for central precocious puberty is the use of gonadotropin-releasing hormone agonists; nevertheless, there is still no agreement on those who have not acquired adequate control of puberty with a standard dose of GnRh agonist. Therefore, this study was conducted aiming to determine the response ratio to the Triptorelin Acetate Treatment Program in adequate control of the central precocious puberty of girls referred to endocrinology clinic of Kashan University of Medical Sciences from 2011 to 2017. Materials and Methods: This study as cohort study was performed on 48 girls suffering from central precocious puberty. The treatment with treptorelin acetate was performed once every 28 days, and a clinical examination and measurement of estradiol, LH and FSH levels were performed once every 3 months. The cases without adequate control of puberty based on clinical, laboratory and radiological criteria were treated with a 25-day regimen and in case of the lack of adequate control of puberty, the interval of medicine injection was reduced to 21 days. To analyze the data, the statistical SPSS V.16 software was used. Findings: Totally, 13 (27%) children responded to the once in 28-day regimen and 35 (73%) children were regarded in the once in 25-day treatment due to the lack of adequate control, of which 20 (57%) children were treated and 15 (43%) children were treated with the once in 21-day regimen due to the lack of adequate control, that finally adequate control was created in all patients. Conclusion: In girls suffering from central precocious puberty, that adequate control of puberty is not created by 28-day standard regimen, this aim can be achieved by reducing the injection intervals.

Key words: Central Precocious Puberty, Gonadotropin-Releasing Hormone Agonists, Triptorelin Acetate.

Introduction

Puberty includes the physical, hormonal, and physiological transition of a person from childhood to adulthood that in girls is through estrogen along with changes in the genital system and breast, as well as fat distribution increase and change in the body, especially in the hip area. (Brito et al., 2016) In terms of definition, central precocious puberty is a disease that depends on the GnRH hormone and often occurs in girls before the age of eight and in boys before the age of 9, (Carel et al., 2009) and studies have shown that more prevalence of this disease is in girls. (Antoniazzi and Zamboni, 2004) In a study performed in this field in Iran, central precocious puberty is considered to include the beginning of puberty before the age of 7.72 years old and the average age of puberty in girls has been estimated equal to 10.46 ± 1.47. (Salek Ardestani et al., 2007) Another similar study has estimated precocious puberty including puberty before 7.42 years and the average age of beginning puberty as the age of 9.74 years, (Razzaghi Azar et al., 2006) indicating a relative similarity in the scientific definition of this disease. Of course, epidemiological studies performed on this disease have indicated the reduction of puberty age in girls (Feibelmann et al., 2015) and boys (Alikasifoglu et al., 2015).

Different treatment methods and medicines are used to treat central precocious puberty, among which medroxyprogesterone, cyproterone acetate, and gonadotropin-releasing hormone (GnRH) agonists can be mentioned. (Seminara et al., 2010) However, investigations performed show that some of the complications of precocious puberty, such as height shortness can only be prevented by treatment with GnRH agonists that are proposed as a real treatment of precocious puberty, and medroxyprogesterone or cyproterone acetate do not have

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preventive power in this case. (Carel et al., 1999) Therefore, the use of GnRH agonists has long been considered as the main treatment of central precocious puberty (Carel et al., 2009). Among the GnRH agonists, the medicines such as leuprolide, triptorelin, goserelin and buserelin can be mentioned. (Kaplowitz, 2009)

Various studies have been conducted about the treatment effects of various GnRH agonists, including triptorelin, on the suppression of sexual development and the reduction of bone puberty, but there is still no theoretical agreement about various treatment formulas, including type of treatment, treatment intervals, treatment dosage, and medicine prescription method. (Kaplowitz, 2009) Another important point about the treatment of central precocious puberty is evaluation and differentiation of adequate suppression gonadotropin from its inadequate suppression, because inadequate suppression may lead to progression of puberty and bone age increase of the patient. In this regard, the physician can prevent the emergence of complications resulted from inadequate suppression by altering the formula, method, (Mul et al., 1999; Brito et al., 2004) or the treatment alternate, (Strich et al., 2013) if the inadequacy of treatment is observed, and this point makes the importance of evaluating and assessing the adequacy of treatment twofold.

In order to evaluate the response to the treatment, measuring the estradiol level can be exploited, that its accuracy and efficiency are of course less than measuring the LH serum level, (Zec et al., 2012) while measuring the LH serum level is a suitable method in evaluating the response to treatment. (Klein et al., 2016) Studies performed in this field show that measuring LH several hours after the treatment with leuprolide or triptorelin can be used as a proper indicator for evaluating the adequacy of treatment (Brito et al., 2004; Strich et al., 2013). The sensitivity of the morning base level of LH measurement test has been reported between 60% and 100% in diagnosing the central precocious puberty that this difference is considered as a result of the difference in the amount of cutoff and various laboratory assessment methods. (Brito et al., 2008)

According to the stated points, since there is still no consensus treatment method concerning the treatment of central precocious puberty, this study was conducted aiming to determine the response ratio to the Triptorelin Acetate Treatment Program in adequate control of the central precocious puberty of girls referred to Endocrinology clinic of Kashan University of Medical Sciences from 2011 to 2017.

Materials and Methods

This study was performed as descriptive and all female children referred to Endocrinology clinic of Kashan University of Medical Sciences during the years 2011-2017 who had symptoms of precocious puberty in the clinical examination (appearance of thelarche or pubarche in the girls under the age of 8 years or the emergence of menarche in the girls under the age of 9 years) and based on the laboratory and radiological findings, and clinical evidence, their central precocious puberty was confirmed and by controlling clinical and laboratory conditions, they were treated with GnRH agonist and had received at least 6 months of regular treatment with triptorelin acetate. The exclusion criteria included irregular visits and the presence of underlying diseases or genetic syndromes or chronic receiving of specific medicine with regard to a chronic disease.

The calculation of the sample size was done using the formula of estimating a ratio:

$$n = \frac{Z\left(_{1-\frac{\alpha}{2}}\right)^2 * p * (1 - p)}{d^2}$$

α = The first type error = 0.5%; d = The maximum acceptable error = 5%
P = The frequency of response to the treatment based on the executor's pilot study = 98%
n = 30

That based on these parameters, the minimum required sample size was estimated 30 people, and in this study 48 patients were studied.

The participants in this study were initially treated with triptorelin acetate medicine with the treatment dose of 3.75 mg muscular once every 28 days and were followed up with the same clinical, laboratory, and radiological indices each month up to six months, and if puberty was not suppressed, the medicine intervals were reduced to once every 25 days and were reduced to every 21 days, if not responded. Then, the response ratio to the treatment period was compared with intervals of 28 days, 25 days, and 21 days. It should be mentioned that only the information of those patients was investigated in this study, that based on the clinical examinations and hormonal and radiological investigations, central precocious puberty was approved in them, and had the indication of the onset of treatment with GnRH agonist (tryptrilin acetate), and had passed the treatment period and the periodic investigations were done on them.

The general variables investigated in the population under study included height, weight, BMI and Sexual Maturation Rating (SMR), which were extracted from the data recorded when admitting the patients. To investigate the treatment effects of the new formula of triptorelin, the height and weight of patients recorded three months after the initiation of treatment and then every three months by a fixed and trained person, were used. It should be mentioned that Harpenden Stadiometer was used to measure the height of all patients, and to assess their weight, the SECA scale was used.

To collect data, a questionnaire including main variables, demographic information and underlying variables (such as age, birth weight, height, cause of referring, age of puberty symptoms start, history of specific medicine consumption and history of systemic diseases) were used. In addition to the recorded information, the systemic examinations including the investigations results of cardio-pulmonary, blood pressure, goiter, and hyperthyroid and hypothyroid symptoms, skin, hair, stomach and genital changes (general health) were investigated, and evidence of other diseases causing precocious puberty including cushing, symptoms of hyperandrogenism (sound violence, hirsutism, and clitoromgaly), pelvic mass (ovarian mass, adrenal mass) were considered in investigating the patients' file.

All children were examined by a pediatric endocrinologist, and the determination of their Sexual Maturity Rating (SMR) in every examination was carried out according to the Tanner's scale (86). In all people, the bone age was measured by performing left hand wrist and fingers radiography based on Greulich and Pyle criteria (87) during the treatment period. The Predicting Adult Height (PAH) of patients was also investigated using Bayley-Pinneau tables. (Bayley and Pinneau, 1952)

In this study, SPSS V.16 software was used to analyze the data. In this regard, the description of the variables was first performed. For quantitative variables, central and dispersion indices, and for qualitative variables frequency distribution tables were prepared. To compare quantitative variables in various groups (treatment at various intervals), if the parametric tests conditions were established, the analysis of variance of repetitive measures, and in case of failure to meet the condition of parametric tests, Friedman test was used. The significance level was considered 0.05.

Findings

In this study, totally 70 girls referred to a clinic with central precocious puberty were studied and treated with GnRh agonist (tryptrilin acetate). Eventually, according to the observance of the inclusion and exclusion criteria, and equalizing and eliminating confounding factors, 48 people were investigated. The mean age of children at the first visit was calculated 7.45 ± 1.31 years, the average age of beginning treatment was calculated 7.81 ± 1.06 years and the average age of the last visit was calculated 12.22 ± 2.22 years. The frequency distribution of the age of treated children has been presented in Table 1.

Table 1: Frequency Distribution of Age of the Treated Children

Variable	Number	Minimum	Maximum	Mean	Standard Deviation
Age (Years) of Client	48	2.08	9.67	7.45	1.31
Age (Years) Onset of Treatment	48	4.08	9.67	7.81	1.06
Age (Years) End of Treatment	48	8.25	17.16	12.12	2.22

In this study, the regimen change was applied from 28 days to 25 days based on the mentioned conditions at the time interval of 0.91 ± 0.54 years (3 months to 27 months) and the regimen change was performed from 25 days to 21 days at the time interval of 0.75 ± 0.55 years (3 months to 28 months). After starting the treatment with 28-day intervals, in the clinical examination 32 people (66.7%) had clinical regression at the stage of breast tanner, and in 16 people (33.3%) no regression or progression was observed at the stage of breast tanner.

Tables 2 to 4 are related to the changes in the stages of breast tanner at various stages of the study and indicate the clinical aspect of controlling puberty. Considering the total clinical, laboratory and radiological symptoms, 35 people entered the 25-day treatment, that clinically, 25 people (71.4%) had no puberty suppression clinically before the onset of the 25-day treatment, that after the treatment, 31 people (88.2%) had reached puberty suppression clinically ($p < 0.001$) (Table 2).

Table 2: The frequency of Puberty Suppression before and after the First Change

Variable	Number before Change	Percentage	Number after Change	Percentage	P Value*
Clinical Puberty Suppression	10	28.6	31	88.2	0.001<
Lack of Clinical Puberty Suppression	25	71.4	4	11.8	
Total	35	100	35	100	

* McNemar Test

Regarding the total clinical and laboratory and radiological symptoms, 15 people entered the 21-day treatment, that clinically before the onset of 21-day treatment, 11 people (64.7%) had no puberty suppression that after the 21-day treatment, 15 people (93.8%) reached the desired result of puberty suppression clinically ($p = 0.008$) (Table 3).

Table 3: Frequency of Puberty Suppression before and after the Second Change

Variable	Number before Change	Percentage	Number after Change	Percentage	P Value*

Clinical Puberty Suppression	6	40	14	92.9	0.008
Lack of Clinical Puberty Suppression	9	60	1	7.1	
Total	15	100	15	100	

* McNemar Test

Table 4: The laboratory and Radiological Changes in Terms of Various Treatment Regimens

Variable	Number	LH Change SD ±X	FSH Change SD ±X	Estradiol Change SD ±X	Progress Rate of Bone Age SD ±X
Changes before and after the beginning of medicine	48	±1.46 -0.12 P: 0.540	±2.1 -0.91 P: 0.005	± 5.7 -7.44 P: 0.082	±0.61 0.98
Changes before and after the first change	35	±1.50 -0.52 P: 0.045	2.50 -0.29 ± P: 0.984	±8.4 -18 P:0.053	0.63 0.76±
Changes before and after the second change	15	±1.49 -0.67 P:0.018	±2.1 -1.1 P:0.069	±6.9 -50 P: 0.019	±0.36 0.35

Wilcoxon signed test

Estradiol Level:

Investigating the results obtained from this study showed that estradiol changes in 13 people who did not need to change the dose were obtained in the direction of significant decrease ($p < 0.05$), but in 35 people who needed regimen change no significant estradiol changes were reported ($p > 0.05$), that in these people, the 25-day treatment was started. Of the 35 people who were located at a 25-day regimen treatment, regarding the total clinical, radiological, and laboratory criteria, the dose change to 21-day once regimen was performed for 15 people. The regimen change from 28 days to 25 days based on the mentioned conditions at the time interval of 0.91 ± 0.54 years (3 months to 27 months) and the regimen change from 25 days to 21 days at the time interval of 0.75 ± 0.55 years (3 months to 28 Month) was performed. Twenty people who did not need to change the dose, the estradiol change in the direction of significant decrease ($p < 0.001$) was obtained, and 15 people needed to change the dose, that the estradiol level was also measured before and after the change of dose to 21 days that the difference was reported as significant ($p < 0.05$).

LH level:

The pre-treatment LH level was compared with post-treatment LH level with with 28-day intervals, and no significant difference was found ($p = 0.153$). However, the LH level before and after the dose change to 25-day was investigated and the difference was significant ($p = 0.45$). The LH level before and after the dose change to 21-day was also investigated and the difference was not significant ($p = 0.108$).

Progression of Bone Age:

In the 28-day regimen, 59.3% of the bone age progression rate of less than one year was obtained for one year of the calendar age, and 40.7% of the bone age progression rate of more than one year was calculated for one year of the calendar age. Also, in the 25-day regimen, 71.4% of the bone age progression rate of less than one year was obtained for one year of the calendar age, and 28.6% of the bone age progression rate of more than one year was obtained for one year of the calendar age. In the 21-day regimen, 92.9% of the bone age progression rate of less than one year was calculated for one year of the calendar age, and 7.1% of the bone age progression rate of more than one year was calculated for one year of the calendar age. The bone age progression rate before and after the 28-day regimen of 0.98 ± 0.61 years was obtained for one year of calendar age progression, that for children whose treatment regimen was changed to 25 days was calculated 0.76 ± 0.63 years for one year of calendar age progression and concerning children whose treatment regimen was changed to 21 days, 0.35 ± 0.36 years was obtained for one year of the calendar age progression ($P = 0.053$)

Determining PAH (Predicting Adult Height) in Terms of Various Treatment Intervals:

Based on the Chi-square and Kruskal Wallis statistical tests, the bone age of 40 children (83.3%) under study were more advanced than one year of calendar age at the start of treatment and 8 people (16.7%) had normal bone age (within the range of ± 1 year of the calendar age). In general the bone age on average was 2.07 ± 1.06 years more than the calendar age. Predicting adult height before starting treatment on average was calculated 153 ± 5.33 cm. Predicting adult height (PAH) of the time interval between the bone age before the start of treatment and the last bone age on average was calculated 2.6 ± 1.24 (31 months ± 14) (ranging from 8 to 70 months). The final predicting adult height on average was 157 ± 4.6 cm.

The difference in PAH before the start of treatment with the last PAH on average was obtained 4.2 ± 4 cm (13.46 to -3.86), indicating that PAH has improved about 4 cm by treatment. In 15 children who were followed up to the adult height, the adult height difference with the predicted height before treatment was obtained 4 ± 5 cm (-3.6 to 11.23). Also, among children who did not have a treatment regimen change, and children about whom 1 or 2 change(s) were performed, no significant difference in respect of PAH change was found (P = 0.233).

Relationship of the Ratio of Adequate Control of Clinical Puberty with BMI Percentile of a Child at Various Treatment Intervals:

Investigating the results obtained from this study did not show a relationship between the need for medicine dose change and BMI-SDS (P = 0.573). Also, the need to change the medicine dose did not have relationship with the age at the start of the treatment (p = 0.268) or the weight at the start of the treatment (p = 0.984).

Discussion

Statistical analysis of the results obtained from this study showed that the need for medicine dose change does not have a relationship with the weight at the start of treatment that indicates that the use of a constant dose regardless of weight can be reasonable. In some studies, such as Freire (2016) and Lee et al. (2011), GnRHa dose has been selected based on the weight of the child at the start of treatment. But, in some studies, the medicine dose has started regardless of the weight of the child. (Zung et al., 2015; Kendirci et al., 2015) Also, in this study, the need to change the medicine dose did not show a relationship with age at the start of the treatment or the weight at the start of the treatment. In a similar study performed by Freire (2016), similar results to the present study were also obtained.

In a similar study, Lee et al. (2011) investigated the effect of depot- leuprolide acetate form in the treatment of central precocious puberty in 2011. In that study, compared to our study, the starting medicine dose was used 2 times higher, and in spite of consuming at least 2 times of the medicine, 5 people needed to increase the dose. Of course, the medicine used in that study was leuprolide, but in this study, triptorelin acetate was used. In another similar study, Kendirci et al. (2015) conducted a study about the effect of treatment with analogue GnRh in children with central precocious puberty. In this study, 62 girls with central precocious puberty were treated with 3.75 mg of leuprolide every 28 days, that in 53 patients (85.5%), it resulted in adequate control of puberty and it has been increased in 9 remaining people 3 months after the start of treatment with a treatment dose of 7.5 mg. Nine months after the start of treatment, 3 people (5.7%) did not still have adequate control of Hypothalamic Hypophyseal Gonadal axis; while, puberty was clinically stopped and the medicine dose was not changed in these patients. In this study, doubling medicine dose has been used; while, in the present study, none of the children show the need to double the medicine dose.

There are various policies for deciding for a child with a primary standard dose of adequate control of puberty. This policy can increase medicine dose or reduce medicine injection intervals. In some studies about medicine dose increase, medicine dose has been doubled, (Freire et al., 2016; Leeet al . ,2011; Kendirci et al., 2015) which can result in an increase of 2 times (100%) of the cost of treatment and possible complications. But the method used in this study included the reduction of medicine injection intervals, which in the first change from 28 to 25 days once, had only 10.7% increase in cost, while this change in 57.7% of treated children resulted in adequate control of puberty and only 15 people (about 40%) did not still have adequate control of puberty, of which the treatment interval number was reduced to 21 days, that the cost of treatment only was increased 25% compared to the start of initial medicine dose, but it led to adequate control of puberty in all children under the study. Of course, a child still had uncontrolled puberty clinically (breast tanner), while in laboratory and radiological respect, there was suppression of the Hypothalamic Hypophyseal Gonadal axis, so the method chosen in this study seems to be an appropriate proposal for monitoring treatment in girls suffering from central precocious puberty. Clinically in the present study, the reduction of injection intervals to 25 days once could result in a clinical response (regression or the lack of progression of the tanner stage) in 87.5% of patients, and in the 21-day group, the reduction of injection intervals could also lead to a clinical response (regression or progression of the tanner stage) in 93.8% of the patients.

Conclusion

The results obtained from this study showed that the desired result could be achieved by decreasing the intervals of injections of triptorelin acetate (25 days and 21 days) in girls with central precocious puberty who were not treated with the standard 28-day regimen. Also, some central precocious puberty patients who had not responded to the standard 28-day treatment, by reduction in the injection intervals to 25 days once, achieved the result, indicating that there is no need to immediately switch from 28-day treatment to the 21-day treatment, and by the 25 days once treatment, both the proper result can be achieved, and less cost and complications can be imposed on the patient.

In this study, it has been shown that about 73% of children need reduction of medicine intervals in the 28-day regimen for adequate control of puberty, so that in cases that the referring girls suffer from advanced central precocious puberty with advanced bone age and low predicting adult height, in order to maintain their maximum potential height, the treatment should be used once in 25 days from the beginning, and this policy can lead to adequate control of puberty in 67.75%. And if in the advanced central precocious puberty with

advanced bone age and low predicting adult height, the once in 21 days treatment is applied in order to maintain the maximum potential adult height, it can lead to adequate control of puberty in all children.

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