Efficacy Comparison of Two Brands of Triptorelin in Treatment of Idiopathic Central Precocious Puberty

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In treating central precocious puberty, the monthly formulations of gonadotropin-releasing hormone agonists are the main formulations that have been used. Triptorelin is a gonadotropin-releasing hormone agonist and is approved to be used in central precocious puberty as a 1 mo formulation. This study aimed to compare the efficacy and adverse effects of a subcutaneous formulation of Triptorelin (Varipeptyl) with Diphereline during a double-blinded randomized clinical trial. Girls with idiopathic central precocious puberty were randomly allocated to Group A (intramuscular injection of Diphereline 3.75 mg, IPSEN, France) and Group B (subcutaneously injection of Variopeptyl 3.75 mg, Varian Pharmed, Iran) repeated every 28 d for 3 mo. Hormonal changes, also adverse effects and efficacy endpoints were measured at baseline and mo 3. Out of 35 girls with confirmed central precocious puberty, 18 cases were assigned to take Diphereline (group A) and 17 cases to take Variopeptyl (group B). Mean level of estradiol had a decrease of 31.7±11 pg /ml (p value: 0.00) in group A and 27.3±10 pg /ml (p value: 0.00) in group B. The mean luteinizing hormone's level reduced 3/1±2/3 IU/L (p value: 0.00) in group A and 1.6±0.9 IU/L (p value: 0.00) in group B. No significant side effects were seen. 3 patients in group B had nodules at the injection site and one patient in each group had minimal vaginal bleeding. This study demonstrated that the efficacy of Variopeptyl is as same as Diphereline in suppressing the hypothalamic-pituitary-gonadal axis and can be a substitute for Diphereline.

Key words: Gonadotropin-releasing hormone agonists, precocious puberty, subcutaneous injections, monthly formulations

Central Precocious Puberty (CPP) alludes to precocious activation of the Hypothalamic-Pituitary-Gonadal (HPG) axis and its incidence has been estimated to be 1 in 5000 to 10 000 children[1-3]. Idiopathic CPP is significantly more common in girls[4]. Precocious puberty is defined for the girls as the outset of puberty before the age of 8[5,6]. The goal of treatment in CPP is to suppress the production of gonadotropin and gonadal sex steroids. Such suppression stops and regresses the symptoms of CPP, precludes the risks of early menarche, normalizes growth velocity, and reduces epiphyseal maturation[7-9].

The Gonadotropin-Releasing Hormone (GnRH) agonists are the best option for CPP treatment[10,11]. These drugs through the downregulation of GnRH receptors, suppress gonadotropin secretion, resulting in the diminution of sex hormones to prepubertal levels[12-14].

Sufficient hormonal suppression in children with CPP is usually achieved by 1 mo therapies with depot formulations[7,15]. In the treatment of CPP, the monthly depot forms of GnRH agonists are the main formulations that have been used[16,17]. They provide a steady release of drug and improve remarkably the outcome of treatment without relevant long-term or short-term side effects[13,16,17]. Triptorelin is a synthetic GnRH analog and its 1 mo formulation

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is approved for use in CPP in several countries[3,18].

In the present research, we compared the efficacy and side effects of two brands of Triptorelin, Diphereline 3.75 mg manufactured by IPSEN (France) and Variopeptyl 3.75 mg manufactured by Varian Pharmed (Iran) in treating the girls with idiopathic central precocious maturity after 3-time injections administrated every 28 d.

This study is a double-blinded randomized clinical trial and is registered with the Iranian Registry of Clinical Trials (Number: IRCT20170225032759N1). The investigation was endorsed by the Ethical Panel of Shahid Sadoughi Medical Sciences University. Participants were girls with idiopathic central precocious maturity who were referred to the Paediatric Endocrinology Clinic of Shahid Sadoughi. Data were collected from January to June 2016. Girls aged <8 y (2 y-8 y), with proven CPP defined as the onset of sex characteristics (breast development) and the Luteinizing Hormone's (LH) pubertal response to GnRH stimulation (LH peak ≥7IU/l) included in this trial. The exclusion criteria were aged >8 y, evaluative brain tumours, gonadotropin-independent gonadal or adrenal sex steroid secretion, earlier treatment with a GnRH analog with cyproterone acetate or medroxyprogesterone, and probable concurrent disease. After providing verbal information regarding the topic and purpose of the study to the parents, they gave a written informed consent. Participation in this trial was voluntary. The sum of patients eligible for the study was 38 but 3 cases were excluded from the study owing to lack of regular use of the drug. Randomly, the subjects were divided into 2 groups. Group A took an Intramuscular (IM) injection of Diphereline 3.75 mg (IPSEN, France) repeated every 28 d for 3 mo. Group B administrated Subcutaneously (SC) injection of Variopeptyl 3.75 mg (Varian Pharmed, Iran) repeated every 28 d for 3 mo.

Physical, Clinical examinations were made ahead of and during treatment at each follow-up visit once every 28 d. In all patients, LH, FSH, and estradiol were measured in blood samples obtained at morning hours before starting the treatment and 24 h after the third injection. Peak GnRH-stimulated LH testing has been usually utilized for recording HPG suppression during CPP therapy[17]. In this study, we evaluated unstimulated (basal) LH. LH and FSH were evaluated by immunochemiluminometric assay with a lower limit of diagnosis of 0.02 IU/l for both hormones. Estradiol was measured by radioimmunoassay with a detection limit of 5 pg/ml. During the clinical assessment, weight, height, and Body Mass Index (BMI) were determined at d 0 and 84. In all cases, BMI was calculated as weight (kg) divided by the body height square (m^2)[9,19]. Pubertal development (pubarche and thelarche) was assessed using the Tanner and Marshall criteria[20].

The criteria for adequate suppression were defined as discontinuation or regression in breast development and achieving a basal LH level of <0.60 IU/L(21). Also, estradiol level ≤20 pg/ml (74 pmol/l), was defined as the threshold for sufficient sex steroid hormone suppression[7].

The Statistical Package for the Social Sciences (SPSS) program, version 18.0 (SPSS Inc., Chicago IL, United States of America (USA)) was used for statistical evaluation. The continuous data are indicated by mean±Standard Deviation (SD) and the qualitative data are expressed by percentages. For continuous data, Paired T-test was utilized to delineate the significant difference of variables in each group, and for comparison of the means between the groups, Levene's test was used. We used the Wilcoxon Signed Ranks Test for comparing qualitative data in each group and the Mann-Whitney U test to compare two groups. The $p<0.05$ was considered as statistically significant.

35 girls with confirmed CPP were randomly divided into two groups. 18 patients were allocated to group A (Diphereline) and 17 patients were allocated to group B (Variopeptyl treatment). The mean age in group A was 6.5±0.68 y (range=5-7.5) and in B, was 6.2±1.34 y (range=3-7.5).

Clinical findings are shown for both groups in Table 1. In group A after the end of the 3 mo treatment, the mean height increased 2.72±0.8 cm (p value: 0.00) and in group B, the mean height increase was 1.19±1.30 cm (p value: 0.00). At the end of treatment, we had a weight gain of 2.25±0.71 kg (p value: 0.00) in group A and 1.7±0.6 kg (p value: 0.00) in group B. At mo 3, BMI increase of 0.55±0.6 kg/m^2 (p value: 0.00) in group A and 0.34±0.4 kg/m^2 (p value: 0.005) observed in group B. No difference was determined in terms of height, BMI and weight between groups receiving Diphereline or Variopeptyl treatment ($p>0.05$).

At the start of treatment, 22 % of cases in group A and 29 % of cases in group B were in the thelarche stage III, 78 % in group A, and 71 % in group B were in the thelarche stage II. Evaluations at mo 3 showed that breast development in all girls in both groups

regressed one Tanner stage. The p value after the comparison of the thelarche stage between two groups before treatment was 0.916 and after treatment was 0.928, we detected no significant difference between the two groups.

At the start of treatment 33 % of cases in group A, were at pubarche stage II and 67 % in the pubarche stage I, and their puberty did not change after the end of 3 mo and no response to treatment was observed (p value: 1.00) In group B, 48 % of cases at the start of treatment was in the pubarche II stage and 52 % in the pubarche I stage, whose maturity stage did not change after the end of the 3 mo treatment, and no response to treatment was observed (p value: 1.00). The p value obtained after comparison of the pubarche stage between two groups before and after the treatment was 0.411 and 0.411, respectively, which showed no significant difference between the two groups.

Endocrine data at initiation and mo 3 are shown in Table 2. We can identify that the mean estradiol plasma concentrations significantly decreased in both groups. The mean level of estradiol measured in patients had a decrease of 31.7±11 pg /ml (p value: 0.00) in group A and 27.3±10 pg/ml (p value: 0.00) in group B.

The mean LH level reduced 3/1±2/3 IU/L (p value: 0.00) in group A and 1.6±0.9 IU/L (p value: 0.00) in group B. The mean FSH level decreased 3.7±2.3 IU/L (p value: 0.00) in group A and 2.6±2.2 IU/L (p value: 0.00) in group B. Data showed (Table 2), at the mo 3 both medicines did not have significant differences in reduction of estradiol, LH and FSH levels.

In general, both drugs were tolerated well. 3 cases (17 %) in group B had nodules at the injection region; redness, itches, or any discomfort were not reported. This adverse effect was not observed in any subjects in group A. Also, one girl in group A (4.8 %) and one in group B (5.5 %) reported vaginal bleeding. No other abnormal reactions were reported. The early withdrawal was not observed from any of these events.

Triptorelin is a GnRH agonist and is approved for use in CPP (18). Triptorelin is produced with different brand names, including Decapeptyl and Diphereline. An Iranian corporation (Varian Pharmed) has designed a 1 mo (SC) formulation of Triptorelin under the marketing name of Variopeptyl. In the current research, we compared the efficacy of this product with the commonly used (IM) formulation, Diphereline. Filicori *et al.*[22] showed, that Both IM and SC Triptorelin administration induced ovarian function and pituitary suppression during the study, although the IM route may cause higher plasma Triptorelin concentrations. In the short period, the SC administration may achieve more sustained plasma Triptorelin levels and more prolonged efficacy over the long-run. After 2 mo of the last SC injection, sexual hormones were at low levels and Triptorelin concentrations were still discernible. Liang *et al.*[23] concluded, that SC administration of GnRHa 3.75 mg at 6 w intervals has good clinical efficacy on ICCP. Besides, the longer interval of injection because of less pain and cost-saving could be more acceptable by families and children and thus improves patient compliance. This study showed that in terms of efficacy Variopeptyl is similar to Diphereline, sex steroid hormones, and gonadotropin were reduced to prepubertal levels. Both medicines suppressed estradiol effectively as would be expected, estradiol levels were underneath the defined threshold for suppression (≤20 pg/ml). Lee *et al.*[21] concluded that measuring basal LH levels can be utilized as a surrogate to peak-stimulated LH testing for monitoring of HPG suppression. Basal LH levels <0.60 can be considered as measures of suppression. Therefore, in this study, we assessed the basal LH level and since the mean basal LH levels are <0.60, both groups showed adequate suppression.

Many studies are reporting that GnRHa therapy does not affect height gain, especially after 6 y of age (24-26), but in our study, we observed increased mean height with both medicines, but prolonged follow-up investigations are required to assess the effectiveness of improving adult height.

There are different results about the effect of GnRHa treatment on BMI during and after treatment. Some studies showed GnRHa treatment increased BMI[15,26,27]. By contrast, in other studies, it was reported that GnRHa treatment decreased BMI[28,29] or had no effect on BMI[30,31]. Paterson *et al.*[27] evaluated 46 girls with precocious puberty who completed goserelin treatment, at the start of treatment girls were considerably overweight and during therapy observed a slight increase in adiposity. In our study, we had a similar result that GnRH agonist treatment increased BMI during treatment. Karamizadeh *et al.*[19] concluded, the more BMI at beginning of therapy is associated with more weight gain after treatment.

TABLE 1: CHANGES IN ANTHROPOMETRIC DATA AFTER 3 MO OF TREATMENT IN TWO GROUPS

		Group A	Group B	P value
Height (cm)	Before treatment	123.69±4.98	122.35±10.4	0.635
	At end of treatment	126.41±5.17	125.52±10.52	0.757
Weight (kg)	Before treatment	25±4.18	25.47±6.06	0.79
	At end of treatment	27.25±4.55	27.20±5.95	0.98
BMI (kg/m^2)	Before treatment	16.30±2.01	16.84±2.21	0.449
	At end of treatment	16.85±1.93	17.19±1.91	0.6

Note: Results are given as mean±SD

TABLE 2: CHANGES IN LH, FSH, AND ESTRADIOL CONCENTRATIONS IN TWO GROUPS

		Group A	Group B	P value
Estradiol (pg/ml)	Before treatment	40.16±14.23	37.29±11.40	0.516
	At mo 3	8.46±3.80	9.94±2.51	0.189
LH level (IU/l)	Before treatment	3.64±2.41	2.19±1.02	0.029
	At mo 3	0.53±0.28	0.58±0.26	0.6
FSH level (IU/l)	Before treatment	4.61±2.58	3.56±2.43	0.227
	At mo 3	0.87±0.33	0.96±0.36	0.436

Note: Data are given with mean±SD

However some studies reported, when patients reached the final height, they returned to their pre-treatment BMI[6]. As we found in the present study, both medicines could stop sexual development, suppress sex steroid hormone and gonadotropin secretion, and were well tolerated. Nevertheless, our research has some limitations. We think that the low number of cases involved in the study and the short time of it are the factors that reduce its power. Long-term comparative studies including patients in larger number are now needed on this subject.

This study's results indicate that Variopeptyl 3.75 mg manufactured in Iran, is as efficient as Diphereline 3.75 mg, manufactured in France for treating idiopathic central premature puberty and can be a good substitute for it. Since the main drug is more expensive, we conclude that the use of Variopeptyl represents a cost-effective option for the treatment of CPP and could be used as an alternative to Diphereline.

Ethical approval:

This study is registered with Iranian Registry of Clinical Trials (Number: IRCT20170225032759N1). The investigation was approved by the Ethical Panel of Shahid Sadoughi Medical Sciences University.

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The authors declared no conflict of interests.

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