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Letrozole Effect on Final Height of Patients with Constitutional Delay of Growth and Puberty

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ABSTRACT

Introduction: The inhibitory effect of aromatase on predicted adult height and near final height has been studied in patients with constitutional delay of growth and puberty (CDGP). **Aim:** This is the first study aimed at verifying the letrozole (Lz) effect on final height of patients with CDGP. **Material and Methods:** In this study 8 patients with CDGP underwent treatment with Lz (2.5 mg/day) for a year, and 8 patients with CDGP, who did not receive Lz were followed –up to reaching final height. Height discrepancy was calculated by subtracting PAH from final height measurement. **Results:** the final height for Lz and Control Groups were 171 ± 4.5 cm and 168.8 ± 4.1 cm respectively. The final heights for Lz group were significantly ($p=0.04$) higher than the control group. Final height in comparison with PAH at the beginning of the study showed significant difference ($p=0.022$) in Lz group whereas the difference was not significant ($p=0.8$) in control group. For height discrepancy the measurements were +1.9 cm and +0.1 cm for Lz and control group respectively with significant difference ($p=0.04$). **Conclusion:** Our study, which is the first one in evaluating the impact of Lz on FH, illustrated that Lz treatment will ultimately lead to augmentation of FH in boys with CDGP.

Keywords: Letrozole, Constitutional Delay of Growth, Puberty, Final Height, Treatment.

1. INTRODUCTION

The constitutional delay of growth and puberty (CDGP) is the most common cause of short stature and delayed puberty in boys (1, 2).

From early years of birth in particular at two years old, the stature range of patients with CDGP starts deviating from normal height growth and slowly moves under the 5th curve for age and gender (3, 4). Eventually the final height (FH) does not reach to the normal level or around mid-parental height (MPH) (5-7). Both male and female require estrogen hormone for bone maturation and epiphyseal plate closure which ends in cessions of growth.

Estrogen production is mediated by aromatase enzymatic activity on testosterone, thus estrogen synthesis can be inhibited by aromatase inhibitors in boys followed by delaying bone maturation (8).

These in turn increase the predicted adult height (PAH) as well as near final height (9). Aromatase inhibitors have been used in various studies to argument the PAH and near final height in CDGP, Idiopathic Short Stature (ISS) patients (10-17).

2. AIM

However, no report has been registered on the effect of aromatase inhibitor treatment on FH. Taking into account the above points, main objectives of our study are, to analyze Lz effect on FH of patients with CDGP.

3. MATERIAL AND METHODS

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Clinical Trial Code: RCT 201112238496 N1 (Related to the first research).

Study design and subject selection

This study is complementary to previously performed clinical trial (16). The above clinical trial in 2010 was conducted on 14 boys affected by CDGP, who referred to the clinic for their short stature or delayed puberty. No etiological factor was found in their history, physical examination, laboratory test for their short stature or delayed puberty. All boys treated

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with Lz 2.5mg/day for one year and followed up for six months and study terminated after 18 months.

Patients PAH at the basal level changed from 172.5±5.4 cm to 175.2±4.3 cm and 174.9±5.4 cm after 12 and 18months respectively. Of the 14 patients eight were followed up to reaching FH, we marked them as Lz group in this study. Additionally 8 boys with CDGP who did not receive Lz and followed up to reaching FH, selected as a control group. Bone age equal or greater than 17 years or growth velocity less than 1cm per year was considered as a final height. The study was approved by ethic committee of the Institute of Endocrinology and Metabolisms, affiliated to the Iran University of Medical Sciences. All research condition was explained to each patient in advance and written consents were taken.

Measurements

Heights and weights in patients were measured by standard weight scale and stadiometer. Comprehensive physical examination and puberty staging were performed by an endocrinologist using Taner stages (18). Bone age was determined based on left hand graphic image, using Greulich and Pyle method (19). PAH was calculated based on Bayley - Pinneau method (20). Blood tests including blood sugar, insulin, cholesterol, triglyceride, LDL, HDL, SGOT, SGPT, 250HD3, Alk.ph, ph, Ca, and CBC were done. Fertility of patients was checked by semen analysis test. Lateral and anterior radiographic images of spine were done. Spiral disks morphology, and disk and vertebral abnormalities were also conducted by MRI. Bone mineral density in spine and femoral region were determined by Double Emission X-ray Absorptiometry (DEXA). Height discrepancy calculated by the deducting PAH from FH.

Statistical analysis

Results for quantitative variable were presented by mean and standard deviation (Mean+SD) and for qualitative variables expressed by percentages. Student t-test were used to compare quantitative variables, and Chi-Square test to compare qualitative variables. P values<0.05 considered significant, and SPSS version 21 software was used for statistical analysis.

2. RESULTS

Mean of chronologic age for Lz and control group were 23.3± 0.8 year and 19.8 ±1.6 year respectively (P=0.002). The mean for FH in Lz and control group were 171±4.5 cm and 168.8 ± 4.1 cm respectively. Consequently the FH in Lz group was significantly higher (P=0.04) than those in control group. The anthropometrics data for both groups at the beginning and end of study are presented in Table 1. Patients data depicted in Table 1 at the beginning of study showed no significant differences in both group. The difference in height standard deviation score (SDS) at the onset of study and FH SDS in both group was significant. Lz treated boys had a greater increment FH SDS over pretreatment height SDS, with a significant difference (P=0.012). The PAH measurements in Lz and control groups were 169.2± 3.7 cm and 168.9 ± 3.6 cm respectively, at the onset of study with no significant difference (P=0.872). Comparison of FH with PAH

Characteristics	Letrozole group Mean(± SD) (N=6)	Control group Mean(± SD) (N=6)	P – Value
Age(year)			
Study Onset	15.5(0.67)	14.8(0.60)	
Study Ending	23.43(0.80)	19.93(1.55)	0.002
Height (cm)			
Study Onset	149.53(5.66)	148.33(4.31)	0.688
Study Ending	171.17(4.57)	168.83(4.13)	0.044
Height (SDS)			
Study Onset	-3.38(0.82)	-2.76(2.27)	0.173
Study Ending	-0.84(0.56)	-1.14(0.52)	0.353
Weight (kg)			
Study Onset	37.5(6.22)	40.16(2.85)	0.363
Study Ending	61.98(8.78)	57.66(13.15)	0.519
BMI(kg/m2)			
Study Onset	16.73(2.21)	18.23(1.76)	0.223
Study Ending	21.16(3.12)	20.62(3.82)	0.794
Bone age (year)			
Study Onset	12.85(1.32)	12.58(0.82)	
Study Ending	23.3(0.8)	19.8(1.6)	
Predicted Adult Height (cm)	169.26(3.70)	168.91(3.62)	0.872
Study Onset			

Table 1. Anthropometrics characteristics of patients in both Lz and control group at the onset and end of the study

Parameter	Lz Group Mean±SD	Control Group Mean±SD	P-Value
Triglyceride			
Onset of Study	75.33(10.40)	74.5(4.59)	0.863
End of Study	98.83(31.40)	51.39(20.98)	0.937
Cholesterol			
Onset of Study	138(19.83)	139.5(7.60)	0.868
End of Study	139.16(12.31)	172.16(50.53)	0.175
HDL			
Onset of Study	40.66(8.47)	40.83(5.03)	0.968
End of Study	46.16(7.49)	50.50(9.89)	0.412
LDL			
Onset of Study	85.66(19.64)	72.16(7.52)	0.147
End of Study	80.33(11.46)	92.66(30.82)	0.392

Table 2. Comparison of mean quantity for lipids in Lz and control group at the onset and end of study. HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein

at the beginning of study in Lz group showed significant difference (P=0.022) but in control group difference was not significant (P=0.898). The height discrepancy in Lz group was +1.9 cm and in control group +0.1, with a significant difference in both group (p=0.04). None of the patients in both group had vertebral body deformity when their vertebral morphology and structure was examined by MRI. Nonetheless, one patient from each group suffered from inter vertebral disk abnormality and one patient from control group had end plate abnormalities. Spine x-ray did not reveal any sign for compression fracture, other spinal abnormality in either group. The BMD evaluation for femur and spine was done by DXA method in which the mean Z-score for femur at the end of study in Lz and control group were -1.64 and -1.44 respectively, with no significant difference in both groups (P=0.793). The mean Z-score for spine at the end of

study in Lz group was -0.859 and in control group -1.12 with no significant difference ($p=0.687$). Lipid profile at the end of the study in both Lz and control group are illustrated in separately in Table 2. The results indicated no significant difference between lipid profiles of both groups.

The semen analysis identified one patient in Lz group as azospermy (sperm Count $< 5M/ml$, semen Volume < 1.5 ml, mobility $< 5\%$ and sperm morphology $< 4\%$). However the sperm analysis was normal in the remaining patients of Lz group as well as the entire control group.

3. DISCUSSION

Treatment of patients with CDGP is usually done by given adequate assurance to patient, low dose testosterone, and following up patient till they reach the FH. Recent studies have shown that these patients don't achieve the normal FH or the MPH (5-7). Thus Lz treatment, and in some cases growth hormone, have shown promising grounds in augmenting FH in these patients. Our study the first of its kind (assessed Lz effect on FH) demonstrated a significant increase in FH of Lz group in comparison to the control group. SDS final height in contrast to initial PAH (at the onset of study) was significantly higher in Lz group than those in the control group. Moreover the height discrepancy in Lz group was significantly higher than the control group. In 2001, for the first time, in a randomized clinical trial (RCT) study, conducted by Wickman et al, Lz effect studied on PAH of 23 boys with CDGP (10)

According to their results, the PAH in Lz group increased 5.1 cm. In another RCT study by hero et al. 31 boys with ISS were treated with Lz and placebo indicated increased PAH of 5.9 cm and height SDS of 0.7 SDS in Lz group in contrast to the control group (12). Salehpoor et al. reviewed 91 boys with predicted short stature treated by Lz, oxandrolone and placebo for two years (17). In their results significant increase in PAH, 6.1 cm ($p < 0.05$), was reported in Lz group in comparison to oxandrolone group. In another study, Mauras et al., the combined effect of anastrozole and growth hormone in 50 boys with growth hormone deficiency was examined (21). After 36 months follow-up, they found an augmented PAH in patients treated by both growth hormone and anastrozole (up to 6.7 ± 1.4 cm). In aforementioned, our clinical trial, all boys with CDGP treated with Lz 2.5mg/day for one year and followed up for six months and study terminated after 18 months. Patients PAH at the basal level changed from 172.5 ± 5.4 cm to 175.2 ± 4.3 cm and 174.9 ± 5.4 cm after and 18 months respectively (16)

The aforementioned studies are supportive of our results. On the other hand the study Shams et al. in 2014 on 27 boys with short stature and rapid puberty progression condition, consists of those with less than 18 months (7 boys) and other with 18-30 months (20 boys), who were treated with anastrozole (22). In the first group (treated < 18 month) no augment in PAH or SDS height was detected, whereas in the second group (treated for 18-30 month), slight and insignificant increase in PAH, a small decrease in progression of bone age, to chronolog-

ic age, and no noticeable change in SDS height were detected. The later study was conducted in boys with ISS, with the bone age of > 13 years, and rapid pubertal progression condition, without a data for control group to make comparison analysis, whereas our study contained boys with delayed puberty and CDGP. We moreover employed a control group for contrast analysis. The progression of puberty in Shams patients required longer treatment period to obtain better results, to find slight augment in PAH in longer treated patients. In 2001, Hero et al. studied 9 boys with CDGP who were pre-treated with Lz and testosterone (Lz+T) for a year long, and made the follow up till boys reached their near-final height (15). They demonstrated that boys in Lz+T group, in contrast to testosterone and placebo group had taller near-final height (175.8 cm vs. 169.1 cm, $p=0.04$). Furthermore, boys in Lz+ T group had greater increase in SDS height than those in pretreatment SDS height ($+1.4$ SDS vs. $+0.8$ SDS, $P=0.03$). A wide variety of studies have taken place to verify the effect of Lz on patients height with CDGP, growth hormone deficiency as well as patients with ISS. In all these studies short term growth outcomes like growth velocity, SDS height and PAH have been analyzed but no study has been done on patients' final height. Only one study by hero et al. has been performed to verify near-final height.

Mc Grath and coworkers in a systematic met analysis study, using aforementioned studies, concluded that no data is available in regard to augmentation of FH. This makes judgment on Lz effectiveness, extremely difficult (23). Our study is the only one that illustrates aromatase inhibitors effect Lz on the FH. Aromatase inhibitors have opened new prospects in the areas of increasing FH for various diseases with an impact on the height.

4. CONCLUSION

Our study, which is the first one in evaluating the effect of Lz on FH, illustrated that Lz treatment will ultimately lead to augmentation of FH in boys with CDGP.

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