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曲普瑞林联合小剂量生长激素物治疗女童 CPP 疗效及对骨龄的影响 *

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摘要 目的:探讨曲普瑞林联合小剂量生长激素物治疗女童 CPP 疗效及对骨龄影响。**方法:**选取 2017 年 1 月至 2020 年 1 月我院收治的 200 例 CPP 女童,随机将其分为两组,对照组 100 例,给予常规治疗,研究组 100 例,给予曲普瑞林联合小剂量生长激素治疗。观察两组患者的临床疗效、治疗前后血清性激素水平、子宫容积、卵巢容积变化情况以及生长发育指标变化。**结果:**治疗后,研究组总有效率为 98%;显著高于对照组总有效率(80%, $P<0.05$)。两组 FSH、LH、 E_2 水平、子宫容积、卵巢容积均降低,骨龄、身高、PAH 均显著升高,且研究组上述指标明显优于对照组($P<0.05$)。**结论:**曲普瑞林联合小剂量生长激素物治疗女童 CPP 疗效显著,能很好的改善患者血清性激素水平、子宫容积、卵巢容积,对生长发育指标具有积极的意义,值得临床推广和应用。

关键词:曲普瑞林;小剂量生长激素;女童 CPP;疗效;骨龄

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Efficacy of Triptorelin Combined with Low-dose Growth Hormone on Central Precocious Puberty in Girls*

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ABSTRACT Objective: To investigate the efficacy of triptorelin combined with low-dose growth hormone in the treatment of girls with central precocious puberty (CPP) and its effect on bone age. **Methods:** A total of 200 girls with CPP, who were admitted to People's Hospital of Shaanxi Province from January 2017 to January 2020, were chosen as research subjects and were randomly divided into control group (n=100) and study group (n=100). The control group was given conventional treatment, and the study group was given triptorelin combined with low-dose growth hormone therapy. The clinical efficacy of, serum sex hormone levels before and after treatment, changes in uterine volume, ovarian volume, and changes in growth and development indicators of the two groups of patients were observed. **Results:** After treatment, the total effective rate (98%) in the study group was significantly higher than that (80%) in the control group ($P<0.05$). The levels of FSH, LH, E_2 , uterine volume, and ovarian volume of the two groups were reduced, and bone age, height, and PAH were significantly increased. The above indicators of the study group were significantly better than those of the control group ($P<0.05$). **Conclusion:** Triptorelin combined with low-dose growth hormone has a significant effect in the treatment of girls with CPP. It can improve the serum sex hormone levels, uterine volume, and ovarian volume of the girls with CPP. It has positive significance for growth and development indicators and is worthy of clinical promotion and application.

Key words: Triptorelin; Low-dose growth hormone; Girls' CPP; Curative effect; Bone age

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前言

女童 CPP 即女童中枢性性早熟(central precocious puberty, CPP),是指 8 岁以前的女童出现内外生殖器发育的现象,并且出现了乳房发育、阴毛等第二性征,是目前临床比较常见的内分泌疾病^[1,2]。主要为下丘脑提前分泌大量的促性腺激素释放激素,加快了性腺的发育,导致激素分泌,致使患者出现了性早熟的特征。导致患者骨龄超前并且骨骼迅速增长,最终会影响患者的身高^[4,5]。近些年,随着人们生活水平的不断提高以及饮食习惯的改变,导致女童 CPP 的发病率呈逐年上升的趋势,严重

的影响患者的心理健康和生活质量,引起临床的高度重视。因此,对于 CPP 给予及早发现及早治疗成为临床研究的关键^[5,6]。目前,临床普遍应用的治疗药物为曲普瑞林,对丘脑-垂体-促性腺轴的功能具有很好的抑制作用,能够使体内垂体促性腺激素的释放减少,能降低患者骨龄的生长速度,从而改善患者成年以后的身高。但是,长期累积大量使用曲普瑞林会急速降低患者骨龄的生长速度,因此要配合小剂量生长激素物才能有效的防止患者骨骼生长速度过慢的现象^[7,8]。本研究选取 2017 年 1 月至 2020 年 1 月我院收治的 200 例 CPP 女童,探讨曲普瑞林联合小剂量生长激素物治疗女童 CPP 疗效及对骨龄

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影响。

1 资料与方法

1.1 一般资料

选取 2017 年 1 月至 2020 年 1 月我院收治的 200 例 CPP 女童,将其随机分为两组,对照组 100 例,年龄 6~10 岁,平均(6.28±2.04)岁,病程 5~20 个月,平均(12.13±2.37)个月;研究组 100 例,年龄 7~11 岁,平均(7.38±3.36)岁,病程 6~20 个月,平均(13.02±2.56)个月。经比较,两组一般资料无差异($P>0.05$),具有可比性。

1.2 纳入与排除标准

纳入标准:(1)符合 CPP 的诊断标准;(2)患者在 8 岁前出现了乳房发育等第二性征,或是 10 岁前有月经初潮现象;(3)骨骼超出实际的年龄;(4)卵巢容积大于 1 mL,并且可见多个卵泡;(5)患者及家属均知情并签署了同意书。

排除标准:(1)因为药物或是其他原因导致的 CPP 的患者;(2)有心脑血管、或是免疫系统疾病的患者;(3)有卵巢实质性病变的患者;(4)临床资料不全的患者;(5)依从性差的患者。

1.3 方法

对照组给予常规治疗。指导患者口服钙剂,并进行健康宣教,告知患者如何选择适合的运动方式加强体育锻炼,增强免疫力。

研究组给予曲普瑞林治疗。曲普瑞林注射液(法国 Ipsen

Pharma Biotech;批准文号 H20130797;规格:1 mL: 0.1 mg),肌肉注射,每月一次,最大剂量 3.75 mg,之后每月注射剂量为 100 μ g/kg 体重,最大剂量 3.75 mg;重组人生长激素注射液(长春金赛药业股份有限公司;批准文号 国药准字 S20050025;规格:30 IU/10 mg/瓶),皮下注射,0.125~0.2 mg/kg 体重,每日一次。两组均治疗 4 个月。

1.4 评价标准

疗效及评价标准:显效:患者乳房发育、月经来潮过早等症得以缓解,并且恢复正常;有效:乳房发育、月经来潮过早等症有所缓解,生长发育未恢复正常;无效:临床症状没有缓解甚加重。

1.5 观察指标

观察两组的临床疗效、治疗前后血清性激素水平、子宫容积、卵巢容积变化情况以及生长发育指标变化。

1.6 统计学方法

应用 SPSS22.0,计量资料以($\bar{x}\pm s$)表示,比较用 t 检验;计数资料用百分比(%)表示,采用卡方检验(χ^2)。 $P<0.05$ 有统计学意义。

2 结果

2.1 两组疗效比较

研究组总有效率为 98.0%;对照组总有效率为 80.0%,两组患者总有效率比较,差异有统计学意义($P<0.05$),见表 1。

表 1 两组疗效比较(例,%)

Table 1 Comparison of efficacy between two groups(n, %)

Groups	n	Effect	Effective	Invalid	Total efficiency(%)
Study group	100	53(53.0)	45(45.0)	2(2.0)	98(98.0)*
Control group	100	36(36.0)	54(54.0)	20(20.0)	80(80.0)

Note: Compared with the control groups, * $P<0.05$.

2.2 两组血清性激素水平比较

两组治疗前 FSH、LH、 E_2 水平指标比较无差异($P>0.05$);

治疗后,研究组上述指标明显低于对照组($P<0.05$),见表 2。

表 2 两组血清性激素水平比较($\bar{x}\pm s$)

Table 2 Comparison of serum sex hormone levels between two groups ($\bar{x}\pm s$)

Groups	n	FSH(IU/L)		LH(IU/L)		E_2 (pg/mL)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Study group	100	18.70±2.17	6.64±1.13 [#]	21.85±1.94	9.17±2.18 [#]	29.89±2.55	13.38±2.46 [#]
Control group	100	18.67±2.16	12.44±1.35 [#]	21.56±1.32	16.11±2.03 [#]	29.56±2.46	21.25±2.52 [#]

Note: Compared with the control group, * $P<0.05$; compared with pretherapy, [#] $P<0.05$.

2.3 两组子宫容积、卵巢容积变化情况比较

两组治疗前子宫容积、卵巢容积变化情况比较无差异($P>0.05$);治疗后,研究组明显小于对照组($P<0.05$),见表 3。

2.4 两组生长发育指标变化比较

两组治疗前骨龄、身高、PAH 比较无差异($P>0.05$);治疗后,研究组明显高于对照组($P<0.05$),见表 4。

3 讨论

女童 CPP 是儿科临床发病率比较高的的内分泌疾病,一般是指女童在 8 岁之前就出现了乳房发育、阴毛生长或是不满 10 岁就月经来潮等第二性征^[9-11],严重的影响着患者的心理健康及生活质量,同时对患者的身体造成严重的危害,引起临床的高度重视^[12-15]。近些年,女童 CPP 的发病率逐年增加,主要的治疗手段是控制性腺轴,延缓第二性征,使患者健康成长^[16,17]。目前,比较常用的药物为曲普瑞林,能够很好的抑制雌性激素的分泌,防止第二性征的发育,延缓性成熟及骨成熟^[18-20]。曲普

表 3 两组子宫容积、卵巢容积变化比较($\bar{x} \pm s$, mL)Table 3 Comparison of uterine and ovarian volume between two groups($\bar{x} \pm s$, mL)

Groups	n	Uterine volume		Ovarian volume	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Study group	100	4.14±0.18	3.04±0.61 [#]	2.15±0.40	1.31±0.38 [#]
Control group	100	4.17±0.16	3.78±0.65 [#]	2.16±0.32	1.71±0.43 [#]

Note: Compared with the control group, * $P < 0.05$; compared with pretherapy, [#] $P < 0.05$.

表 4 两组生长发育指标变化比较($\bar{x} \pm s$)Table 4 Comparison of growth and development indicators between two groups($\bar{x} \pm s$)

Groups	n	Bone age (years)		Height (cm)		PAH (years)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Study group	100	10.36±0.19	12.66±0.45 ^{#*}	128.45±4.13	142.84±3.32 [#]	150.27±2.54	159.34±2.68 ^{#*}
Control group	100	10.28±0.17	11.84±0.42 [#]	128.67±4.12	135.64±3.35 [#]	150.26±2.47	152.27±2.60 [#]

Note: Compared with the control group, * $P < 0.05$; compared with pretherapy, [#] $P < 0.05$.

瑞林虽然能很好的抑制骨成熟,但是,又会对骨骼的发育起到了抑制的作用,直接影响患者的身高。因此,临床上将曲普瑞林与小剂量生长激素物联合使用,对于女童 CPP 的治疗的疗效显著^[20,21]。

本研究结果显示:研究组的总有效率明显优于对照组,说明曲普瑞林联合小剂量生长激素物对于女童 CPP 的治疗能够提高治疗效果。这与张莉等学者^[22,23]的研究结果相似。CPP 是由于下丘脑-垂体-性腺轴功能异常,导致性腺激素被大量的分泌和释放,激活了性腺轴功能,致使性激素分泌过多,最终患者出现第二性征等临床症状。曲普瑞林能够有效的减少雌性激素的分泌,使性腺发育进程减慢,缓解患者的临床症状。治疗后,研究组 FSH、LH、E₂ 水平指标明显优于对照组,证明曲普瑞林联合小剂量生长激素物能够改善患者血清性激素水平。这与陈赛兰^[24,25]研究结果相符。究其原因是因为曲普瑞林能够对下丘脑-垂体激素分泌起到抑制作用,阻断受体负反馈激活通路,最终使体内雌性激素水平能够达到正常的水平。治疗后,研究组子宫容积、卵巢容积变化情况明显优于对照组。证明本研究方法能够改善患者子宫及卵巢情况。这与李存桂等学者^[26,27]的研究结果相似。CPP 患者由于垂体促性腺激素的增加,使性腺发育,激素分泌增加,导致生殖器发育快速,进而使子宫体积及卵巢容积发生变化。曲普瑞林可以抑制 GnRH 的水平,使性激素分泌减少,致使患者子宫体积及卵巢容积逐渐缩小。治疗后,研究组患者骨龄、身高、PAH 等指标明显优于对照组。充分证明本研究方法能够改善患者生长发育指标。这与狄云霏等学者^[29,30]的研究结果一致。曲普瑞林能够作用于受体,使雌性激素水平降低,使患者的身高、骨龄情况得到缓解。大量的曲普瑞林能够快速的降低性激素水平,但如果长期连续使用会消耗 GnRH,产生低雌激素现象,而影响骨代谢,使骨吸收速度增加,导致骨质流失、骨密度下降。因此,配合小剂量的生长激素物能够有效的抑制生长过慢现象,使患者能够达到正常身高,健康的成长。

综上所述,曲普瑞林联合小剂量生长激素物治疗女童 CPP,能够有效的提高治疗效果。能明显改善患者血清性激素

水平,缩小患者的子宫容积及卵巢容积,使患者的身高及骨龄维持正常水平,因此及早发现及早治疗患儿具有积极的临床意义,值得广泛推广和应用。

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