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罗格列酮结合二甲双胍对多囊卵巢综合征患者胰岛素抵抗指数的影响及临床疗效*

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摘要 目的:探讨罗格列酮与二甲双胍联合给药对多囊卵巢综合征(PCOS)患者胰岛素抵抗指数(HOMA-IR)的变化影响与临床效果的评价。**方法:**回顾性选取我院收治的 PCOS 患者 127 例列为研究样本,按照用药方案差异分为两组,对照组 62 例采用二甲双胍进行治疗;研究组 65 例采用罗格列酮联合二甲双胍治疗。观察并比较两组患者治疗前后 HOMA-IR、血清性激素水平、排卵率及副反应发生情况。**结果:**治疗后,研究组 HOMA-IR 低于对照组,排卵率高于对照组($P<0.05$);研究组患者血清 E2 及 T 水平低于对照组,而 FSH 及 SHBG 水平高于对照组($P<0.05$);两组患者副反应发生率比较,差异无统计学意义($P>0.05$)。**结论:**罗格列酮辅助二甲双胍治疗 PCOS 可显著改善患者 HOMA-IR,对性激素平衡有良好作用,副作用较小。

关键词:多囊卵巢综合征;罗格列酮;胰岛素抵抗指数

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Effect of Rosiglitazone Combined with Metformin on Insulin Resistance Indexes in Patients with Polycystic Ovary Syndrome and Its Clinical Curative Effect*

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ABSTRACT Objective: To investigate the effects of rosiglitazone and metformin on insulin resistance index (HOMA-IR) in patients with polycystic ovary syndrome (PCOS) and evaluate the clinical effect. **Methods:** 127 PCOS patients were retrospectively selected and according to the different treatment methods, the patients were divided into two groups. 62 cases in the control group were treated with metformin, and another 65 cases in the study group were treated with rosiglitazone combine metformin. Then the HOMA-IR, serum sex hormone levels, ovulation rate and side effects of the two groups were observed and compared. **Results:** After the treatment, the HOMA-IR in the study group was significantly lower than that of the control group, while the ovulation rate was significantly higher ($P<0.05$). The serum levels of E2 and T in the study group were significantly lower than those of the control group, while the FSH and SHBG were higher ($P<0.05$). There was no statistically significant difference about the side effect rate between the two groups ($P>0.05$). **Conclusions:** Rosiglitazone combine metformin can significantly improve the HOMA-IR and balance the serum levels of sex hormones of patients with PCOS, which is effective and safe.

Key words: Polycystic ovary syndrome; Rosiglitazone; Insulin resistance index

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前言

多囊卵巢综合征(PCOS)发于生育期女性,是发病率较高的内分泌综合征,也是导致育龄期女性不孕的重要因素^[1]。在我国女性中多囊卵巢综合征的发病率约为 6.5%,通常具有无排卵、月经稀发、闭经、肥胖及不孕等症状,严重危害女性身心健康^[2,3]。据相关文献报道,超过 60%的 PCOS 和胰岛素抵抗有密切相关性^[4,5]。因此,调节胰岛素分泌水平可对治疗 PCOS 产生

积极影响。以往临床多采取二甲双胍治疗 PCOS,二甲双胍为一类双缩脲类胰岛素增敏剂,不仅能够抑制肝糖原异生,还可显著降低胰岛素抵抗,加快无氧代谢^[6]。尽管二甲双胍具有较好疗效,但其乳酸中毒和胃肠道不适等副作用也一直困扰着医学研究人员^[7,8]。罗格列酮为噻唑烷二酮类胰岛素增敏剂,可增加细胞对葡萄糖的利用率,以此达到降糖目的^[9]。虽然罗格列酮联合用药方案得到了临床上的肯定,但关于不同用药方案对 PCOS 患者具体指标的研究仍较为缺乏^[10]。因此本研究通过比

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较两种方案对 PCOS 患者临床疗效与 HOMA-IR 改变水平,旨在找到治疗 PCOS 更好的方式。

1 资料与方法

1.1 一般资料

回顾性选择我院 2013 年 7 月至 2015 年 7 月收治的 PCOS 患者,纳入标准^[12-14]:①均为合法的育龄期女性,即 20~50 周岁;②彩超诊断、实验室检查和临床表现均与 PCOS 相符,确诊为 PCOS;③均签署知情同意书,全程按时按量服药;④患者肝肾功能正常。排除标准^[6]:①3 个月内有调月经、促排卵、降糖调脂治疗史者;②合并甲亢、甲减及其他代谢病或慢性病者;③其他因素造成的多囊卵巢、月经异常及性激素紊乱者。本研究经我院医学伦理委员会批准,符合伦理要求。将达到上述要求的 127 例病例按照服药方式不同分为两组,对照组单纯采取二甲双胍治疗,共收集 62 例病例,均龄(31.12±3.48)岁,病程 2~11 年,均(3.82±1.87)年,体质量(26.15±1.87);研究组基于对照组,加用罗格列酮治疗,纳入病例 65 例,均龄(33.07±4.96)岁,病程 3~9 年,均(4.65±2.13)年,体质量(26.41±1.38),两组年龄、病程与体质量等一般资料无显著差异($P>0.05$)。

1.2 治疗方法

对照组服用盐酸二甲双胍缓释片(厂家:上海信谊万象药业公司;国药准字:H20050699;批号:20130516、20141029);从月经时服用,初始剂量为 0.25 g,tid,连续用药 5 d,5 d 后将剂量增至 1 g,tid,与饭同食。研究组基于对照组,联用罗格列酮片(厂家:成都恒瑞制药公司;国药准字:H20030569;批号:

20130619、20150213);于月经或撤退性出血起以 4 mg/次,单日 1 次。两组均于持续用药 3 个月后比较疗效。

1.3 观察指标

取治疗前后入选者空腹状态下的外周血 2 mL,进行空腹血糖(FPG)和空腹血清胰岛素(FINS)的测定。 $HOMA-IR=FPG \times FINS/22.5$ 。如果 $HOMA-IR \geq 1.66$,即为胰岛素抵抗^[15-17]。于治疗前后入选者月经第 3 d 使用光化学检测仪(由霍夫曼·罗氏公司提供,型号为 E170 型)对患者雌二醇(E2)、睾酮(T)、卵泡刺激素(FSH)、性激素结合球蛋白(SHBG)进行测定,比较各组治疗前后血清性激素水平变化。于下次月经来潮前 14~16 天进行盆腔彩超检测,观察患者卵泡数目。两种药物治疗 PCOS 可能存在的副作用有多汗、呕吐、水肿、贫血、乳酸中毒、便秘等。

1.4 统计学方法

数据分析采用 SPSS.18.0 程序,副作用和排卵率等计数资料表达形式为率(%),组间比较采用 χ^2 检验,血清性激素指标等计量资料表达式为(均数±标准差),组内差异以成组 t 检验,组间差异比较以 LSD-t 检验,以 $P<0.05$,为有统计学意义。

2 结果

2.1 两组患者治疗前后 HOMA-IR 及排卵率比较

治疗前,两组 HOMA-IR 和排卵率无显著差异(P 均 >0.05),治疗后,两组 HOMA-IR 显著下降,排卵率显著上升(P 均 <0.05)。研究组 HOMA-IR 显著低于对照组,排卵率显著高于对照组(P 均 <0.05)。见表 1。

表 1 两组患者治疗前后 HOMA-IR 及排卵率比较

Table 1 Comparison of HOMA-IR and ovulation rate between the two groups before and after the treatment

Groups	n	HOMA-IR		Ovulation rate	
		Before treatment	After treatment	Before treatment	After treatment
Study group	65	4.09±0.74	1.36±0.82 ^a	27.69%	72.31% ^a
Control group	62	4.01±0.71	2.56±0.69 ^a	27.42%	51.61% ^a
Statistics		1.942	10.873	1.065	11.785
P		>0.05	<0.05	>0.05	<0.05

Note: compared with before treatment, ^a $P<0.05$.

2.2 两组患者治疗前后血清性激素水平比较

治疗前,两组 E2、T、FSH、SHBG 表达量差异不显著(P 均 >0.05),治疗后,两组血清性激素指标均显著改善,研究组

E2、T 指标显著低于对照组,FSH、SHBG 表达显著高于对照组(P 均 <0.05),见表 2。

表 2 两组患者治疗前后血清性激素水平比较

Table 2 Comparison of serum sex hormone index between two groups before and after the treatment

Groups	n	E2(pmol/L)		T(nmol/L)		FSH(U)		SHBG(nmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	65	545.28±26.44	195.24±18.56 ^a	2.43±0.16	0.58±0.09 ^a	2.74±3.56	10.54±0.12 ^a	26.09±12.20	73.54±6.12 ^a
Control group	62	526.79±22.13	336.73±21.47 ^a	2.35±0.14	1.03±0.11 ^a	2.52±2.97	5.87±0.12 ^a	26.12±13.16	49.18±7.45 ^a
t		1.569	13.7125	1.497	11.476	1.381	12.721	1.874	13.092
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with before treatment, ^a $P<0.05$.

2.3 两组患者治疗期间副反应发生情况比较

研究组副反应发生率为 23.09%,其中水肿 5 例、贫血 3

例、多汗 3 例、便秘 2 例、呕吐 2 例;对照组副反应发生率为 20.97%,其中乳酸中毒 4 例、呕吐 5 例、便秘 3 例、贫血 1 例。两组副反应发生率比较,差异无统计学意义($P>0.05$)。

3 讨论

PCOS 作为内分泌紊乱综合征多发的疾病之一,具有排卵功能紊乱或无排卵及女性雄激素高于男性正常水平的特征^[1]。其病理机制可能为患病女性卵巢内在病变使生理分泌发生改变,造成 T 异常升高,下丘脑-垂体 FSH 分泌紊乱,引起胰岛素抵抗,使 SHBG 合成受到影响, E2 表达异常升高,由此造成了育龄期女性无法合成成熟卵泡甚至不能排卵的后果^[12-15]。本研究选取与胰岛素分泌相关的 HOMA-IR 和血清性激素 FSH、SHBG、E2、T 指标作为观察指标具有一定科学依据,以临床副作用作为用药疗效的附加项目符合医学严谨性^[16]。本研究选取临床表现较为一致、病情诊断明确、血清性激素指标和胰岛素分泌相关指标较为匹配的研究样本作为分析对象具有比较价值^[17]。本研究显示,治疗后研究组 HOMA-IR、E2、T 均显著低于对照组,FSH、SHBG 均显著高于对照组(P 均 <0.05),说明罗格列酮配合二甲双胍用药对调节患者胰岛素和性激素分泌有显著作用。这可能与罗格列酮为高选择性、强效激动剂,具有提高胰岛素敏感性的作用,可显著改善 FINS 的表达水平,缓解胰岛素抵抗,降低了内分泌水平异常对机体的侵害,从而改善机体内分泌系统的内环境,缓解血清性激素指标 SHBG、T、FSH 和 E2 异常表达,逐步排卵功能恢复正常周期,加强卵泡成熟度,提高排卵率,这与研究中研究组排卵率显著高于对照组($P<0.05$)相符合^[18-20]。同时,本研究还发现,研究组副作用和对照组无显著差异($P>0.05$),说明两组用药安全性较为一致,同时也证明了罗格列酮具有很高的安全性。通过对本研究产生药物副作用的病例进行了解,二甲双胍副作用主要为乳酸中毒、呕吐和便秘,而罗格列酮主要副作用为水肿、贫血和多汗,且两种药物的副作用均较为轻微,未引起器质性改变。尽管本研究对 PCOS 临床用药做了一定分析,但关于胰岛素分泌异常所致的肥胖体质与非肥胖体质的对比仍欠缺详细研究,更为细致的 PCOS 治疗方案仍需进行大样本实验。

综上所述,罗格列酮和二甲双胍共同治疗 PCOS 具有显著改善患者胰岛素分泌、控制患者胰岛素抵抗,改善患者血清性激素指标表达的优势,且副作用较小,药物价格合理,临床可行性高。

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