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定坤丹联合复宫宁颗粒治疗子宫内膜异位症的疗效及对血清 MCP-1、sICAM-1、CA125 水平的影响*

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摘要 目的:探讨定坤丹联合复宫宁颗粒治疗子宫内膜异位症的疗效及对血清单核细胞趋化蛋白-1(MCP-1)、可溶性细胞间粘附分子(sICAM-1)、CA125 水平的影响。**方法:**选择 2014 年 12 月至 2016 年 12 月我院接诊的 96 例子宫内膜异位症患者,通过随机数表法将其分为观察组(n=48)和对照组(n=48)。对照组给予醋酸亮丙瑞林微球注射液联合定坤丹治疗,观察组在对照组基础上联合复宫宁颗粒治疗,两组均连续治疗 3 个疗程。比较两组治疗前后卵泡生成激素(FSH)、黄体生成激素(LH)、雌二醇(E₂)及血清 MCP-1、sICAM-1、CA125 水平的变化,临床疗效及不良反应的发生情况。**结果:**治疗后,观察组临床疗效总有效率明显高于对照组(93.75% vs. 70.83%, $P<0.05$),FSH、LH 明显低于对照组, E₂ 明显高于对照组($P<0.05$);两组血清 MCP-1、sICAM-1、CA125 较治疗前均显著降低($P<0.05$),观察组以上指标明显低于对照组($P<0.05$)。此外,观察组潮热、多汗、阴道出血总发生率明显低于对照组($P<0.05$)。**结论:**与醋酸亮丙瑞林微球注射液联合定坤丹治疗相比,定坤丹联合复宫宁颗粒治疗子宫内膜异位症的效果更好,其可有效改善患者卵巢内分泌功能,缓解临床症状,其内在机制可能和降低血清 MCP-1、sICAM-1、CA125 水平相关。

关键词:子宫内膜异位症;定坤丹;复宫宁颗粒;单核细胞趋化蛋白-1;可溶性细胞间粘附分子;CA125

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Efficacy of Dingkundan Combined with Fugongning Granule in the Treatment of Endometriosis and Its Effects on the Serum MCP-1, sICAM-1 and CA125 Levels*

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ABSTRACT Objective: To study the efficacy of Dingkundan combined with fugongning granule in the treatment of endometriosis and its effects on the serum monocyte chemotactic protein-1 (MCP-1), soluble intercellular adhesion molecule (sICAM-1) and CA125 levels. **Methods:** 96 patients of endometriosis who were treated in our hospital from December 2014 to December 2016 were selected. According to the random number table, those patients were divided into the observation group (n=48) and the control group (n=48). The control group was treated with leuporelin acetate microsphere injection combined with Dingkundan, the observation group was treated by fugongning granule on the basis of control group, both groups were continuously treated for 3 courses. The changes of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E₂), serum MCP-1, sICAM-1, CA125 levels before and after treatment, the clinical efficacy and the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate of observation group was higher than that of the control group(93.75% vs. 70.83% $P<0.05$); the FSH and LH were significantly lower than those of the control group, and the E₂ was significantly higher than that of the control group ($P<0.05$); the serum MCP-1, sICAM-1 and CA125 levels were significantly lower in the observation group than that of the control group($P<0.05$). In addition, the total incidence of hot flashes, hyperhidrosis and vaginal bleeding in the observation group was significantly lower than that of the control group ($P<0.05$). **Conclusion:** Compared with leuporelin acetate microsphere injection combined with Dingkundan, Dingkundan combined with fugongning granule is more effective in treating endometriosis, which can effectively improve the ovarian endocrine function and alleviate clinical symptoms, its intrinsic mechanism may be related to the decrease of serum MCP-1, sICAM-1 and CA125 levels.

Key words: Endometriosis; Dingkundan; Fugongning granule; Monocyte chemotactic protein-1; Soluble intercellular adhesion molecule; CA125

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前言

子宫内膜异位症是临床上常见的妇科疾病,主要指患者横膈、腹股沟等子宫腔之外的部位发生子宫内膜组织,多在盆腔中生殖器官内以及相邻的器官腹膜面上呈现,可有结节、包块出现,引发性交痛、月经疼痛、不孕等症状,严重威胁女性生殖健康^[1,2]。醋酸亮丙瑞林又被称作促性腺激素释放激素,生物活性较高,可抑制垂体分泌促性腺激素,是指子宫肌瘤、子宫内膜异位症的常用药物,但该药物不良反应较多,且长期使用激素类药物可降低自然妊娠率,影响患者预后^[3]。

随着祖国医学的不断发展,中医治疗在该病中也体现出独特的优势。定坤丹具有调经活血、理气镇痛等效;复宫宁颗粒在临床上具有温经行气、活血化瘀、补肾益精等功效^[4]。近年来,国内外研究证实血清单核细胞趋化蛋白-1(MCP-1)、可溶性细胞间粘附分子(sICAM-1)、CA125水平的变化有助于评价子宫内膜异位症的疗效^[5,6]。因此,本研究主要探讨了定坤丹联合复宫宁颗粒子宫内膜异位症的疗效及其对血清MCP-1、sICAM-1、CA125水平的影响,结果如下。

1 资料与方法

1.1 一般资料

选择我院2014年12月至2016年12月接诊的96例子宫内膜异位症患者。纳入标准^[7]:①符合子宫内膜异位症诊断标准,伴有不同程度的非经期下腹痛、性交痛、月经痛、月经不调等;②年龄20~40岁;③知情同意此次研究。排除标准^[8]:①近3个月内取过其余治疗;②对研究药物过敏;③合并心、肝、肾等重要脏器功能障碍;④精神病史。通过随机数表法将患者分为2组,每组各48例。观察组年龄21~38岁,平均(29.87±1.54)岁;病程3个月~6年,平均(3.35±0.69)年;已婚34例,未婚11例。对照组年龄23~39岁,平均(29.96±1.50)岁;病程4个月~6年,平均(3.42±0.65)年;已婚32例,未婚13例。两组一般资料比较均无显著差异($P>0.05$),具有可比性。

1.2 治疗方法

对照组:在患者月经周期第1~5d,给予1次醋酸亮丙瑞林

微球注射液(规格3.75mg,厂家:上海丽珠制药有限公司,国药准字H20093852)的皮下注射,3.75mg/次,并于月经第5d开始口服定坤丹(规格7g,厂家:山西广誉远国药有限公司,国药准字Z20059003),7g/次,2次/d,连续用药15d;以一个月经周期为1疗程,连续治疗3个疗程。

观察组:联合复宫宁颗粒(规格10g,厂家:浙江爱生药业有限公司,国药准字Z20010177)的口服,于经期开始第1d服药,10g/次,3次/d,连续用药7d,以一个月经周期为1疗程,连续治疗3个疗程。

1.3 观察指标

1.3.1 性激素水平检测 于治疗前、治疗后月经干净后3~5d抽取3mL静脉血,检测卵泡生成激素(FSH)、黄体生成激素(LH)、雌二醇(E_2)的变化,均采用放免法测定,试剂盒购于深圳晶美生物公司。

1.3.2 血清因子水平检测 于治疗前、治疗后抽取3mL静脉血,检测血清MCP-1、sICAM-1、CA125的表达,均采用酶联免疫吸附法检测,试剂盒均购于美国R&D systems公司。

1.3.3 不良反应的发生情况 包括潮热、多汗、阴道出血等。

1.4 疗效评定标准

显效:患者非经期下腹痛、月经痛、性交痛等症状消失,盆腔内无肿物;有效:非经期下腹痛、月经痛、性交痛等症状有所缓解,但盆腔内仍有肿物;无效:非经期下腹痛、月经痛、性交痛等症状仍未消失,甚至加重,盆腔内肿物未消失。以显效+有效为总有效率。

1.5 统计学分析

以SPSS18.0软件包处理数据,计量资料用均数±标准差($\bar{x} \pm s$)表示,组间比较采用t检验,计数资料以[例(%)]表示,组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,观察组临床疗效总有效率为93.75%,明显高于对照组(70.83%, $P<0.05$),见表3。

表1 两组临床疗效的比较[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=48)	28(58.33)	17(35.42)	3(6.25)	45(93.75)*
Control group(n=48)	19(39.58)	15(31.25)	14(29.17)	34(70.83)

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

2.2 两组治疗前后性激素水平的比较

治疗后,两组FSH、LH、 E_2 较治疗前均明显改善($P<0.05$),观察组FSH、LH水平明显低于对照组, E_2 水平明显高于对照组($P<0.05$),见表2。

2.3 两组治疗前后血清MCP-1、sICAM-1、CA125比较

治疗后,两组血清MCP-1、sICAM-1、CA125水平较治疗前均显著降低($P<0.05$),观察组血清MCP-1、sICAM-1、CA125水平明显低于对照组($P<0.05$),见表3。

2.4 两组不良反应发生情况的比较

观察组潮热、多汗、阴道出血总发生率为6.25%,明显低于对照组(22.92%, $P<0.05$),见表4。

3 讨论

子宫内膜异位症是育龄女性中的常见病症,其发病率可高达15%,发病机制尚未完全明确。研究显示该病属于性激素依赖性,和卵巢分泌激素密切相关,因此目前对于该病的治疗主要采取激素类药物^[9,10]。醋酸亮丙瑞林是由视丘下部所产生的黄体生成激素释放激素类似物,可调节垂体分泌功能,减少卵巢分泌甾类物质,缩小子宫内膜病灶,从而改善临床症状^[11]。

表 2 两组治疗前后性激素水平的比较($\bar{x} \pm s$)Table 2 Comparison of the sex hormone levels between two groups before and after treatment($\bar{x} \pm s$)

Groups		FSH(IU/L)	LH(IU/L)	E ₂ (pg/mL)
Observation group(n=48)	Before treatment	5.72± 0.45	15.43± 2.10	452.31± 34.85
	After treatment	3.12± 0.25* [#]	7.24± 1.30* [#]	721.29± 38.94* [#]
Control group(n=48)	Before treatment	5.79± 0.41	14.28± 2.14	453.02± 34.56
	After treatment	4.28± 0.30*	9.38± 1.60*	579.15± 37.29*

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

表 3 两组治疗前后血清 MCP-1、sICAM-1、CA125 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum MCP-1, sICAM-1 and CA125 hormone levels between two groups before and after treatment($\bar{x} \pm s$)

Groups		MCP-1(ng/L)	sICAM-1(ng/mL)	CA125(U/mL)
Observation group(n=48)	Before treatment	197.85± 25.42	401.21± 22.74	54.73± 8.02
	After treatment	131.23± 18.17* [#]	229.23± 15.43* [#]	21.82± 3.04* [#]
Control group(n=48)	Before treatment	198.12± 25.78	400.57± 23.19	55.93± 8.36
	After treatment	174.95± 20.34*	280.23± 17.28*	34.50± 4.52*

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

表 4 两组不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reaction between two groups[n(%)]

Groups	Hot flashes	Hyperhidrosis	Colporrhagia	Total incidence rate
Observation group(n=48)	1(2.08)	2(4.16)	0(0.00)	3(6.25)*
Control group(n=48)	3(6.25)	5(10.42)	3(6.25)	11(22.92)

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

中医认为子宫内膜异位症的发病机制为“血瘀”，主要是由于经血不畅，致使部分经血在宫内淤积，难以排除体外，形成盆腔血瘀；且疾病病程较长，瘀血反复产生，对人体肺腑、气血、经血功能均会产生影响，进一步加重病情；瘀阻胞脉、冲任，引发不孕，瘀血积于体内，形成包块，阻滞气血，不通则痛。因此，对于该病的治疗应以活血化瘀为主^[12,13]。定坤丹主要包括三十味中药，其中白芍、人参、当归、白术、阿胶等可补血益气、滋养肾脏、令肝气调达，益母草、五灵脂、西红花、红花等具有活血化瘀、逐瘀通经等效；而在复宫宁颗粒中，莪术、三棱可散结消肿、活血消癥，蒲黄、红花可通经活血、止痛消瘀，菟丝子、巴戟、淫羊藿可补肾益精、散寒温里，白芍可养血、止痛，延胡索可行气活血，主要联合，共奏温经行气、活血化瘀、补肾益精之效。

本研究显示联合用药的患者 FSH、LH 明显降低，E₂ 明显升高，且临床疗效高达 93.75%，明显优于对照组，显示出联合用药更有助于改善患者卵巢功能，缓解临床症状。现代药理学显示定坤丹中鹿茸、鹿角霜等药物可增加卵巢、垂体、子宫血流量，对子宫起到兴奋作用，提高卵巢受体功能，而白芍、柴胡、枸杞子等可提高子宫孕激素受体含量，改善盆腔微循环^[14,15]。此外，Laganà AS 等^[16]报道也证实复宫宁颗粒中的有效成分可调节子宫内膜异位症患者内分泌功能，并具有扩张血管、调节血液粘稠度、缓解疼痛等作用，对内膜异位病灶的生长产生抑制作用。此外，联合用药可降低醋酸亮丙瑞林所产生的不良反应，如联合用药的患者潮热、多汗、阴道出血总发生率明显低于单独用药患者，也显示出用药安全性。这和 Pabalan N 等^[17]研究具有相似性。

MCP-1 是由巨噬细胞和单核细胞特异性的化学趋化和激

活因子，近年来研究表明 MCP-1 在盆腔粘连的形成起着关键作用，其通过对单核细胞、成纤维细胞产生的趋化作用，引发盆腔粘连^[18,19]。Chang KK 等^[20]研究显示在子宫内膜异位症患者中，MCP-1 的表达明显高于正常人。在异位内膜的发生、发展中，细胞外基质的破坏发挥着重要的作用^[21,22]。sICAM-1 属于免疫球蛋白超家族，主要附着于异位内膜的细胞、基质，参与着子宫内膜的存活、增殖、分裂等过程^[23,24]。有研究表明子宫内膜异位症患者血清 sICAM-1 水平呈明显增高，且经过有效治疗后，其表达降低，和疾病的发展、发展关系密切^[25,26]。CA125 是一种肿瘤标志物，主要在宫颈上皮、子宫内膜、输卵管、腹膜中存在，各种体液中均存在高浓度表达。在 80% 的卵巢癌患者中，血清 CA125 的表达可呈明显增加，其可用于盆腔良、恶性肿瘤的诊断指标^[27]。近年来有较多研究显示子宫内膜异位症、子宫肌腺病患者血清 CA125 的表达也明显升高^[27,28]。

本研究显示两种用药方式的患者治疗后血清 MCP-1、sICAM-1、CA125 的表达均明显降低，但联合用药的患者降低程度更加明显，可能是由于定坤丹中有效成分可促进子宫平滑肌收缩，且可增加巨噬细胞细胞的吞噬作用，减少单核细胞、成纤维细胞的趋化，缓解病情；且复宫宁颗粒可促进子宫内膜细胞凋亡，对细胞趋化活性具有抑制作用，有助于降低炎症化学递质的释放，且复宫宁颗粒还对细胞外基质的降解具有抑制作用，可抑制子宫内膜的增生和分化，继而前起到抑制内膜异位病灶的生长^[29,30]。我们认为这可能是联合复宫宁颗粒患者血清 MCP-1、sICAM-1、CA125 水平降低程度更明显的作用机制，但具体原因仍需进一步深入研究。

综上所述，与醋酸亮丙瑞林微球注射液联合定坤丹治疗相

比, 定坤丹联合复宫宁颗粒治疗子宫内膜异位症的效果更好, 其可有效改善患者卵巢内分泌功能, 缓解临床症状, 其内在机制可能和降低血清 MCP-1、sICAM-1、CA125 水平相关。

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