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孕三烯酮联合米非司酮对子宫内膜异位症患者血清 VEGF、MMP-9、sICAM-1 水平的影响*

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摘要 目的: 研究孕三烯酮联合米非司酮治疗子宫内膜异位症患者的临床效果及对患者血清血管内皮生长因子(vascular endothelial growth factor, VEGF)、基质金属蛋白酶-9(matrix metalloprotein-9, MMP-9)、可溶性细胞黏附因子-1(soluble Intercellular adhesion molecule-1, sICAM-1)水平的影响。**方法:** 选择 2017 年 6 月至 2018 年 10 月在我院进行治疗的子宫内膜异位症患者 96 例,根据治疗方案不同分为观察组和对照组,对照组给予孕三烯酮治疗,观察组在对照组的基础上联合米非司酮治疗。治疗后,观察和比较两组的临床疗效,治疗前后血清 VEGF、MMP-9、sICAM-1 水平及临床症状、体征的变化。**结果:** 治疗后,观察组总有效率显著高于对照组 ($P < 0.05$), 两组患者血清 VEGF、MMP-9、sICAM-1 水平均较治疗前显著减低 ($P < 0.05$), 且观察组血清 VEGF、MMP-9、sICAM-1 水平均明显低于对照组($P < 0.05$);两组患者治疗后痛经、非经期下腹痛、性交痛、子宫直肠窝结节粘连、子宫直肠窝触痛以及子宫活动受限的发生率均较治疗前显著降低,且观察组以上症状体征的发生率明显低于对照组($P < 0.05$)。**结论:** 采用孕三烯酮联合米非司酮治疗子宫内膜异位症可有效提高其临床疗效,且安全性较高,可能与其显著降低患者血清 VEGF、sICAM-1、MMP-9 水平有关。

关键词: 子宫内膜异位症;米非司酮;孕三烯酮;血管内皮生长因子;基质金属蛋白酶-9;可溶性细胞黏附因子-1

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Clinical Efficacy of Trienone Combined with Mifepristone in the Treatment of Endometriosis and its Effects on the Serum Levels of VEGF, MMP-9, sICAM-1*

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ABSTRACT Objective: To investigate the clinical efficacy of trienone combined with mifepristone in the Treatment of Endometriosis and its effects on the serum Levels of vascular endothelial growth factor (VEGF), matrix metalloprotein-9 (MMP-9), soluble intercellular adhesion molecule-1 (sICAM-1). **Methods:** 96 cases of patients with endometriosis treated from June 2017 to October 2018 in our hospital were selected and divided into the observation group and the control group according to different treatment. The control group was treated with trienone, while the observation group was treated with ultrasound guided the injection without water ethanol unite mifepristone for 6 months. Then the clinical effect, changes of serum VEGF, MMP-9, sICAM-1 levels and clinical symptoms and signs before and after treatment were observed and compared between two groups. **Results:** After treatment, the total effective rate of observation group was higher than that of the control group ($P < 0.05$), the serum VEGF, MMP-9, sICAM-1 levels in both groups after the treatment were lower than those before treatment ($P < 0.05$), which were higher in the observation group than those of the control group ($P < 0.05$). The Clinical symptoms of Observation group were better than those of the control group ($P < 0.05$). **Conclusion:** Trienone combination with mifepristone can achieve ideal curative effect in the treatment of endometriosis with high safety, it may be related to the decrease of VEGF, sICAM-1, MMP-9 levels.

Key words: Endometriosis; Mifepristone; Trienone; Vascular endothelial growth factor; Matrix metalloprotein-9; Soluble Intercellular adhesion molecule-1

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前言

子宫内膜异位症是指子宫内膜出现在子宫腔内膜外与宫体肌层外区域,从而引发增生、浸润等情况所导致的一种疾病,

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是临床妇科中较常见疾病之一,具有较高的发病率,且其发病率在近几年有明显增高的趋势,近四成的患者伴有不孕症,对患者的身心健康具有极大影响^[1,2]。目前,子宫内膜异位症的主要治疗手段分为手术治疗与药物治疗。单纯药物治疗主要是通过抑制卵巢生理功能达到治疗的目的,临床效果较差,易出现骨质疏松、肝功能损伤等副作用。单纯手术虽免去了药物治疗的副作用,但其复发率较高^[3]。因此,寻找一种的达到理想效果同时副作用较小的治疗方案具有重要的临床意义。

米非司酮为一种新型的抗孕激素,具有抗糖皮质激素活性,但无抗雌性激素、无孕激素活性,同时具有抑制排卵及干扰内膜的完整性的作用,临床通常用于抗早孕、引产等^[4]。近几年有相关研究显示米非司酮用于子宫内膜异位症的治疗具有较好的临床效果^[5]。但使用孕三烯酮联合米非司酮用于子宫内膜异位症术后辅助治疗的研究较为罕见。为明确其治疗效果,本研究主要探讨孕三烯酮联合米非司酮对子宫内膜异位症患者的治疗效果及对患者血清 VEGF、MMP-9、sICAM-1 水平的影响。现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2015 年 6 月至 2016 年 3 月在我院进行治疗的子宫内膜异位症患者 120 例,纳入标准:(1)病理检测且临床症状符合子宫内膜异位症;(2)对本研究知情并同意,同时按要求复诊。排除标准:(1)患有其它妇科病症;(2)入院前 3 个月内使用过其他激素药物。将入选患者根据治疗方案不同分为两组,观察组 60 例,年龄 28~41 岁,平均年龄(35.43± 4.75)岁;其中阴道后穹窿触痛结节 37 例,卵巢巧克力囊肿 17 例,其中 3 例为双侧性,合并不孕者 20 例。对照组 60 例,年龄 27~42 岁,平均年龄(35.96± 5.04)岁;其中阴道后穹窿触痛结节 35 例,卵巢巧克

力囊肿 18 例,其中 4 例为双侧性,合并不孕者 22 例。两组患者上述一般资料相比差异均无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

两组患者均在行腹腔镜术后的第 1 周给予药物治疗。对照组口服孕三烯酮,2 次/周,2.5 mg/次;观察组在对照组基础上口服米非司酮(临沂市仁华药品有限责任公司,25 mg,201500417),1 次/天,12.5 mg/次,连续服用 6 个月。

1.3 观察指标

临床疗效;治疗前后血清 VEGF、MMP-9、sICAM-1 水平变化;临床症状、体征变化;治疗后 6 个月后及治疗后 1 年患者生活质量。

于治疗前后收集两组外周血 3 mL,离心处理后取上清液置于 -80℃ 环境中待检,其血清 VEGF、MMP-9、sICAM-1 水平均使用酶联免疫吸附法进行检测。

疗效评价标准参照相关文献进行^[6]:(1)显效:临床症状完全消失,且 B 超检查为发现盆腔包块,妇科检测无阳性体征;(2)有效:临床症状有所缓解,且 B 超检查为发现盆腔包块,妇科检测无阳性体征;(3)无效:临床症状无明显改善,且 B 超检查仍发现盆腔包块。

1.4 统计学分析

选择 spss18.0 进行数据统计,本研究计量资料比较采用 t 检验,计数资料比较采用 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,观察组的总有效率 91.30%,显著高于对照组(74.00%, $P<0.05$),详见表 1。

表 1 两组患者临床疗效比较[例(%)]

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

Groups	n	Excellent	Progress	Invalid	Total effective
Observation group	46	17(36.96)	25(54.34)	4(8.70)	42(91.30) ^a
Control group	50	13(26.00)	24(48.00)	13(26.00)	37(74.00)

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

2.2 两组治疗前后血清 VEGF、MMP-9、sICAM-1 水平的比较

治疗前,两组患者血清 VEGF、MMP-9、sICAM-1 水平比较差异无统计学意义 ($P>0.05$);治疗后,两组患者血清 VEGF、MMP-9、sICAM-1 水平均较治疗前明显降低,且观察组以上指

标水平平均明显低于对照组($P<0.05$),详见表 3。

2.3 两组治疗前后临床症状、体征的发生率比较

治疗前,两组患者痛经、非经期下腹痛、性交痛、子宫直肠窝结节粘连、子宫直肠窝触痛以及子宫活动受限的发生率比较

表 2 两组治疗前后血清 VEGF、MMP-9、sICAM-1 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum VEGF, MMP-9 and sICAM-1 levels between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	VEGF (ng/mL)	MMP-9(pg/mL)	sICAM-1(ng/L)
Observation group	46	Before treatment	422.43± 89.43	281.75± 30.65	512.78± 54.75
		After treatment	123.71± 34.91 ^{ab}	128.83± 15.11 ^{ab}	272.75± 30.42 ^{ab}
Control group	50	Before treatment	431.51± 92.74	278.97± 29.26	513.21± 53.33
		After treatment	193.32± 45.82 ^b	197.81± 20.12 ^b	322.87± 34.35 ^b

Note: Compared with the control group, ^a $P<0.05$; Compared with before the operation, ^b $P<0.05$.

无明显差异($P>0.05$);治疗后,两组上述症状均得到显著改善,腹痛、性交痛、子宫直肠窝结节粘连、子宫直肠窝触痛以及子宫发生率均较治疗前显著降低($P<0.05$),且观察组痛经、非经期下活动受限的发生率均明显低于对照组($P<0.05$)。详见表 3。

表 3 两组治疗前后临床症状发生率比较[例(%)]

Table 3 Comparison of the incidence of clinical signs between the two groups before and after treatment[n(%)]

Groups	n	Time	Dysmenorrhea	Hypogastralgia		Uterine rectum nodules adhesion	Rectum of the uterus is painful	Uterine activity restriction
				for non-menstrual period	Dyspareunia			
Observation group	46	Before treatment	37(80.43)	8(17.39)	15(32.61)	30(65.22)	36(75.00)	24(52.17)
		After treatment	0(0.0)ab	2(4.35) ^{ab}	2(4.35) ^{ab}	4(8.70)ab	4(8.70)ab	0(0.0)ab
Control group	50	Before treatment	41(82.00)	8(16.00)	17(34.00)	32(64.00)	39(78.00)	25(50.0)
		After treatment	6(10.0) ^b	7(14.00) ^b	8(16.00) ^b	10(20.0) ^b	11(22.00) ^b	8(16.00) ^b

Note: Compared with the control group, ^a $P<0.05$; Compared with before treatment, ^b $P<0.05$.

2.4 两组患者不良反应发生情况的比较

观察组服药期间有 2 例出现轻度恶心症状,1 例患者出现多汗、轻微潮热症状,但均能忍耐,停药后症状自行消失。对照组患者未出现不良反应。两组不良反应的发生情况比较差异无统计学意义($P>0.05$)。

3 讨论

子宫内膜异位症是因子宫内膜细胞由于某种原因导致其生长在子宫腔外或嵌入子宫肌层中,发生机制目前尚未明确,但有研究认为免疫异常、腹膜腔功能失调等也是导致子宫内膜异位症较为重要的病因,患者临床主要表现为痛经、性交痛、月经异常、慢性盆腔痛等^[7-10]。子宫内膜异位症的治疗主要通过改善盆腔疼痛的程度以及患者的受孕率,疼痛的强度与发生的位置、嵌入的深度与直接关系,由于机体的神经是分布于表面,因此嵌入越深患者所感知到的疼痛越为强烈^[11]。子宫内膜异位症伴不孕症,其原因为患者盆腔纤维征粘连,从而会产生多种物质抑制受精^[12]。临床治疗通常分为手术治疗与药物治疗,国内外大量的临床研究显示单纯依靠手术或药物治疗子宫内膜异位症的效果均不理想,同时复发率较高。因此,获取一种对子宫内膜异位症的有效治疗方案具有极高的临床价值。

我们通过总结多年的临床经验,同时参阅国内外相关临床实践报告中提出在子宫内膜异位症术后可应用孕三烯酮联合米非司酮进行辅助治疗,其机制可能为米非司酮对下丘脑-垂体-卵巢性轴不会产生明显的影响,且不良反应较少,可提高临床疗效。此外,米非司酮通过与受体结合使卵巢功能受到抑制,诱发闭经从而使异位的子宫内膜组织萎缩达到治疗目的^[13]。研究显示米非司酮在辅助治疗子宫内膜异位囊肿的治疗中具有较好的效果,且不会诱发低雌激素症状以及其他代谢方面的不良反应^[14,15]。孕三烯酮作为临床常用的孕激素,具有抗孕激素以及抗雄激素的作用,通过抑制促性腺激素的分泌,从而有效的控制卵巢的分泌功能;此外孕三烯酮可直接作用于子宫内膜以及子宫内膜受体,发挥其作用使子宫内膜与异位子宫内膜萎缩^[16,17]。孕三烯酮能够安全有效的硬化子宫内皮细胞,且对周围的正常的卵巢组织则不会造成损害。以往的临床研究显示妇科疾病患者在经过硬化治疗后其周期仍保持正常,且部分不孕症患者治疗后可再怀孕,说明孕三烯酮对卵巢功能的影响

轻微。因此,我们认为孕三烯酮联合米非司酮治疗子宫内膜异位症具有一定的理论与实践基础。本研究结果显示联合治疗后其临床疗效显著高于孕三烯酮治疗的患者,虽在联合治疗后,部分患者出现药物副作用,但停药后均显著改善,可见孕三烯酮与米非司酮联合治疗子宫内膜异位症为一种合理有效的治疗方案。

子宫内膜异位症是一种血管生成依赖性疾病,在其发生发展中 VEGF 具有重要的作用,机体 VEGF 水平的升高,促进了新生血管的生长,同时增加了血管的通透性,使血浆蛋白加速渗透,从而形成高度血管化基质,为子宫内膜异位症的发生提高了良好的基质条件,从而加速病情发展^[18,19]。另有文献显示^[20]对于子宫内膜异位症患者均会存在一定程度的免疫调节异常,相关研究显示患者血清 sICAM-1 均显著高于正常值,与本研究结果相符^[21,22]。sICAM-1 是一种膜表面糖蛋白,具有一定的介导作用,同时可对细胞之间的信号进行传递^[23-25]。相关研究显示患者的病情越严重起血清 sICAM-1 水平则越高^[26]。另有研究显示^[27]sICAM-1 可阻断 CTL 与肿瘤细胞的结合,间接削弱 NK 细胞在免疫监视中的作用。本研究中,患者经治疗后血清 VEGF、sICAM-1 均显著降低,且联合治疗降低幅度较大。可见,患者在病情得到好转后体内血清 VEGF、sICAM-1 也逐渐恢复正常,因此患者血清 sICAM-1 水平的升高有可能是一种自我保护机制。

MMP-9 是机体中的一种较为重要的酶,具有降解基底膜以及细胞外基质的作用,而基底膜、细胞外基质的降解过程对子宫内膜异位症的发生具有重要影响,可诱发血管内皮细胞新生,促进组织细胞间的黏附作用^[28,29]。机体在正常状态下,MMP-9 与 TIMP-1 水平同等,但子宫内膜异位症则会增加 MMP-9 水平,使 MMP-9/TIMP-1 比例失衡,从而造成一系列的病理改变^[30]。本研究通过联合应用孕三烯酮与米非司酮,使其发挥协同作用,促进了内膜萎缩,使 MMP-9/TIMP-1 比例失衡得到改善,从而降低了 MMP-9 水平。

综上所述,采用孕三烯酮联合米非司酮治疗子宫内膜异位症可有效提高其临床疗效,且安全性较高,可能与其显著降低患者血清 VEGF、sICAM-1、MMP-9 水平有关。

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