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米非司酮联合桂枝茯苓丸治疗子宫内膜异位症的临床效果分析 *

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摘要 目的:分析米非司酮联合桂枝茯苓丸治疗子宫内膜异位症的临床效果。**方法:**106 例子宫内膜异位症患者按抽签法分为对照组(n=53)与实验组(n=53),对照组采用米非司酮治疗,实验组基于对照组加以桂枝茯苓丸治疗,比较两组的临床疗效,治疗前后血清癌抗原 125(CA125)、癌抗原 199(CA199)、血管内皮生长因子(VEGF)、超氧化物歧化酶(SOD),白细胞介素 -6(IL-6)、白细胞介素 -8(IL-8)、肿瘤坏死因子 -α(TNF-α)、超敏 C 反应蛋白(hs-CRP)、血浆黏度、全血黏度、红细胞聚集指数的变化。**结果:**实验组的治疗总有效率为 94.33%,显著高于对照组,差异有统计学意义(P<0.05)。实验组治疗后血清 CA125、CA199、VEGF、SOD、IL-6、IL-8、TNF-α、hs-CRP 水平、血浆黏度、全血黏度、红细胞聚集指数均明显低于对照组(P<0.05)。**结论:**米非司酮联合桂枝茯苓丸治疗子宫内膜异位症的临床疗效确切,可能与其抗炎、抗氧化和改善血液流变学作用有关。

关键词:子宫内膜异位症;米非司酮;桂枝茯苓丸;临床疗效

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Clinical Efficacy of Mifepristone Combined with Guizhi Fuling Capsule in The Treatment of Endometriosis*

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ABSTRACT Objective: To analyze the clinical effects of mifepristone and guizhi fuling capsules on the endometriosis and serum levels of cancer antigen 125 (CA125) and cancer antigen 199 (CA199). **Methods:** 106 cases with endometriosis who were treated in our hospital were selected and randomly divided into the control group and the experimental group with 53 cases in each group. The patients in the control group were treated with mifepristone, while the patients in the experimental group were treated with guizhi fuling capsule on the basis of the control group. Then the clinical curative effect, serum levels of CA125, CA199, vascular endothelial growth factor (VEGF), superoxide dismutase (SOD), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), hypersensitive c-reactive protein (hs-CRP), whole blood viscosity, plasma viscosity and erythrocyte aggregation in the two groups were observed and compared before and after the treatment. **Results:** The effective rate of the experimental group was significantly higher than that of the control group(P<0.05); The serum levels of CA125, CA199, VEGF, SOD, IL-6, IL-8, TNF-α, hs-CRP, whole blood viscosity, plasma viscosity and erythrocyte aggregation indexes of the experimental group were significantly lower than those of the control group(P<0.05). **Conclusion:** Mifepristone and guizhi fuling capsule had better clinical effects on the endometriosis, which could reduce the serum levels of CA125 and CA199.

Key words: Endometriosis; Mifepristone; Guizhi fuling capsule; Clinical curative effect

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前言

子宫内膜异位症为妇科常见疾病,大部分患者可出现继发性痛经、不育、性交痛、月经改变等典型临床表现,严重影响患者的生活质量[1,2]。子宫内膜异位症虽为良性病变,但存在局部浸润生长和转移等恶性肿瘤的能力[3]。血清癌抗原 125(CA125)及癌抗原 199(CA199)是机体常见肿瘤标志物,广泛存在于宫颈上皮、输卵管、子宫内膜等组织中,其水平与病变程度有着紧密联系[4,5]。子宫内膜异位症目前主要以药物及保守手术治疗为主,但手术创伤较大,临床应用有一定限制性[6]。米非司酮可与孕激素受体起到拮抗作用,桂枝茯苓丸现已广泛开展于妇科疾病治疗中。本研究主要探讨了采用米非司酮联合桂枝茯苓丸治疗子宫内膜异位症患者的临床效果及其可能机制,现报道如下。

1 资料与方法

1.1 一般资料

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选择 2014 年 1 月 ~2016 年 7 月于我院就诊的 106 例子宫内膜异位症患者，本研究患者及家属均已签署知情同意书，同时通过医院伦理委员会审核，按抽签法分为对照组(n=53)与实验组(n=53)。纳入经中西医明确诊断为卵巢巧克力囊肿；未见手术指征，且自愿行药物保守治疗；近期未接受激素治疗；无免疫系统、内分泌系统、血液系统病变；未合并其他妇科疾病[7]。排除心、肝肾等基础疾病；相关药物禁忌症；癫痫、恶性肿瘤等。对照组年龄 22~40 岁，平均(31.48± 2.36)岁；病程 6~25 月，平均(12.67± 3.29)月；囊肿直径 3~5 cm，平均(4.33± 0.42) cm；疾病分期：Ⅰ期有 11 例，Ⅱ期有 42 例。实验组年龄 21~43 岁，平均(32.51± 2.54)岁；病程 5~27 月，平均(13.42± 3.56)月；囊肿直径 3~5 cm，平均(4.26± 0.47) cm；疾病分期：Ⅰ期有 14 例，Ⅱ期有 39 例。两组一般资料比较差异无统计学意义(P>0.05)，具有可比性。

1.2 治疗方法

对照组采用米非司酮治疗，每次口服 12.5 mg 米非司酮(25 mg/ 片)，每日 1 次。实验组基于对照组加以桂枝茯苓丸治疗，每次口服 6 g 桂枝茯苓丸(6 g/ 丸)，由桂枝 8 g、茯苓 10 g、赤芍 10 g、丹皮 10 g、桃仁 10 g、淫羊藿 15 g 等组成)，每日 2 次，1 疗效为 1 个月，两组均持续治疗 3 个疗程。

1.3 观察指标

(1)临床疗效评估[8]：治疗结束时评估临床疗效。痊愈：临床体征及症状全部消失，盆腔包块消失；显效：临床体征及症状显著缓解，盆腔包块缩小在 50%以上；临床体征及症状有所缓解，盆腔包块缩小在 30%以上；无效：临床体征及症状未见缓解或者加剧。治愈、显效、好转均为有效。

(2)指标检测：收集患者治疗前后空腹外周静脉血 4 mL，肝素抗凝后采用血清分离机以 3000 r/min 分离 10 min，放置 -80℃环境中待检。血清 CA125、CA199 水平采用放射比浊法检测，试剂盒分别来自江苏中邦制药有限公司、丹东市通远药业有限公司；采用酶联免疫吸附法检测血管内皮生长因子(VEGF)、试剂盒来自沈阳富东制药有限公司，超氧化物歧化酶(SOD)、试剂盒来自昆明龙津药业有限公司；采用电化学发光法检测白细胞介素 -6(IL-6)、试剂盒来自湖北荷普药业集团公司，白细胞介素 -8(IL-8)、试剂盒来自重庆天圣制药有限公司，肿瘤坏死因子 -α(TNF-α)、试剂盒来自吉林省天光药业有限公司，超敏 C 反应蛋白(hs-CRP)、试剂盒来自丹东市通远药业有限公司；血浆黏度、全血黏度、红细胞聚集指数采用血液分析仪检测。

1.4 统计学分析

选择 SPSS18.0 软件行数据统计，计量资料用均数± 标准差($\bar{x}$± s)表示，用 t 检验比较，计数资料用[(n)%]表示，用 x^2 检验比较，等级资料用秩和检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者临床疗效比较

实验组有效率为 94.33%，显著高于对照组，差异有统计学意义(P<0.05)，见表 1。

表 1 两组患者临床疗效比较[(例)%，n=53]

Table 1 Comparison of the clinical curative effect between two groups[(n)%, n=53]

Groups	Cure	Markedly	Better	Invalid	Effective rate
Control group	17(30.07)	19(0.35)	4(7.55)	13(24.53)	40(75.47)
Observation group	32(60.37)	12(22.64)	6(11.32)	3(5.66)	50(94.33)△

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

2.2 两组患者治疗前后血清 CA125、CA199 水平比较

治疗前，两组血清 CA125、CA199 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 CA125、CA199 水平均均较治疗前显著降低，且实验组下降更明显，差异均有统计学意义(P<0.05)，见表 2。

表 2 两组患者治疗前后血清 CA125、CA199 水平比较($\bar{x}$± s，n=53)

Table 2 Comparison of the serum CA125 and CA199 levels between the two groups before and after the treatment ($\bar{x}$± s, n=53)

Groups	Time	CA125(U/mL)	CA199(U/mL)
Control group	Before treatment	112.46± 16.11	102.69± 14.57
	After treatment	82.60± 11.72#	48.53± 6.85#
Observation group	Before treatment	110.58± 15.72	104.57± 15.23
	After treatment	57.42± 8.11△ #	17.26± 2.42△ #

Note: Compared with control group, △ P<0.05; Compared with before treatment, #P<0.05.

2.3 两组患者治疗前后血清 VEGF、SOD 水平比较

治疗前，两组血清 VEGF、SOD 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 VEGF、SOD 水平均较治疗前显著降低，且实验组明显低于对照组，差异均有统计学意义(P<0.05)，见表 3。

2.4 两组患者治疗前后血清 IL-6、IL-8、TNF-α、hs-CRP 水平比较

治疗前，两组血清 IL-6、IL-8、TNF-α、hs-CRP 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 IL-6、IL-8、TNF-α、hs-CRP 水平均较治疗前显著降低，且实验组下降更明显，差异均有统计学意义(P<0.05)，见表 4。

2.5 两组患者治疗前后血液动力学指标水平比较

治疗前，两组血液动力学指标水平比较差异无统计学意义

(P>0.05)；治疗后，两组血浆黏度、全血黏度、红细胞聚集指数均较治疗前显著降低，且实验组下降更明显，差异均有统计学意义(P<0.05)，见表 5。

表 3 两组患者治疗前后血清 VEGF、SOD 水平比较($\bar{x}\pm s$，n=53)

Table 3 Comparison of the serum VEGF and SOD levels between the two groups before and after the treatment($\bar{x}\pm s$, n=53)

Groups	Time	VEGF(U/mL)	SOD(ng/L)
Control group	Before treatment	372.69± 53.16	563.38± 80.43
	After treatment	206.57± 29.46#	305.51± 43.56#
Observation group	Before treatment	370.85± 52.86	561.49± 80.16
	After treatment	142.11± 20.28△#	249.85± 35.59△#

Note: Compared with control group, △P<0.05; Compared with before treatment, #P<0.05.

表 4 两组患者血清治疗前后 IL-6、IL-8、TNF-α、hs-CRP 水平比较($\bar{x}\pm s$，n=53)

Table 4 Comparison of the serum IL-6, IL-8, TNF-α and hs-CRP levels between the two groups before and after the treatment($\bar{x}\pm s$, n=53)

Groups	Time	IL-6(ng/L)	IL-8(ng/L)	TNF-α(ng/L)	hs-CRP(mg/L)
Control group	Before treatment	33.46± 4.76	43.60± 6.14	2.58± 0.36	5.93± 0.16
	After treatment	17.39± 2.42#	20.32± 2.85#	1.36± 0.19#	2.46± 0.36#
Observation group	Before treatment	32.58± 4.59	42.11± 6.05	2.54± 0.38	5.85± 0.82
	After treatment	15.42± 2.11△#	17.54± 2.44△#	1.21± 0.19△#	2.10± 0.32△#

Note: Compared with control group, △P<0.05; Compared with before treatment, #P<0.05.

表 5 两组患者治疗前后血液动力学指标水平比较($\bar{x}\pm s$，n=53)

Table 5 Comparison of the hemodynamic indexes between the two groups before and after the treatment($\bar{x}\pm s$, n=53)

Groups	Time	Plasma viscosity(mPa·s)	Whole blood viscosity (mPa·s)	Erythrocyte aggregation index
Control group	Before treatment	1.68± 0.26	12.39± 1.86	3.79± 0.46
	After treatment	1.23± 0.19#	8.73± 1.24#	2.04± 0.29#
Observation group	Before treatment	1.66± 0.23	12.56± 1.79	3.82± 0.42
	After treatment	1.15± 0.16△#	7.85± 0.83△#	1.76± 0.22△#

Note: Compared with control group, △P<0.05; Compared with before treatment, #P<0.05.

3 讨论

子宫内膜异位症的治疗原则是清除病灶，缓解疼痛，恢复生育功能及降低复发可能性[9]。外科治疗的疗程虽短，且对疼痛及生育功能有一定的改善效果，但其浸润、扩散等特点容易降低临床效果[10]。研究显示子宫内膜异位症手术操作时容易出现破裂，降低病灶清除率，增加复发风险。因此，临床上子宫内膜异位症首选药物治疗[11]。子宫内膜异位症作为一种卵巢依赖性疾病，机体孕、雌激素可于异位内膜增殖中起到关键作用[12]。米非司酮是常用的孕激素类药物，对机体黄体酮受体有着较强的亲和性，可使孕酮与受体的结合产生抑制，对卵泡的生长发育及分泌形成影响，诱导子宫内膜细胞出现凋亡、坏死，从而使内膜结构组织增生受到抑制，造成子宫内膜出现萎缩、退化等，促进病灶坏死及吸收[13]。但仍有学者报道单用米非司酮的效果不稳定，病灶缩小速度慢，且部分患者病情几乎无改善[14]。此外，米非司酮可结合糖皮质激素受体，长时间服用可对糖皮质激素产生抵抗，从而引起多种副反应[15]。

祖国医学认为子宫内膜异位症是由寒邪入侵胞宫，致肾气衰弱，使淤血留滞，冲任调失，血气不通，从而引起不育、痛经、腹部包块等症状[16]。临床治疗应以畅通经络、调节气血、活血化瘀为主[17]。桂枝茯苓丸当以桂枝和茯苓为君药，桂枝性味温、甘，入心肺、膀胱经，可温阳散寒，畅通经络，解表扶阳；茯苓性味平，入胃、脾肝经，可养神安脾，利水肾湿[18]。同时辅以赤芍祛淤凉血、止痛清热，丹皮凉血清热，散寒止痛，桃仁解毒消痈、活血祛淤。诸药共奏调和气血、温阳化淤、消痈散结之功，且药性平和，温寒相宜，化淤却不耗血[19]。现代药理表示桂枝可使血管扩张，抗炎镇痛；茯苓可增强机体免疫力，符合中医 " 扶正祛邪" 之理念[20]。本研究结果显示米非司酮联合桂枝茯苓丸治疗后的有效率达 94.33%，显著高于单用米非司酮，提示两者联合治疗能够更有效促进患者的恢复。有研究显示子宫内膜异位症患者血清 CA125 及 CA199 浓度显著高于正常者，且可随病情进展相应上升 [21]。本研究结果显示联合桂枝茯苓丸治疗后 CA125 及 CA199 水平显著降低，提示两者联合治疗可有效去除病灶，控制疾病进展。

VEGF 是子宫内膜于异位组织中生存的重要条件，VEGF 能够诱导血管内皮细胞发生有丝分裂，导致血管通透性增加，促进血管新生，为子宫内膜的生长提供营养[22]。同时，子宫内膜异位症患者抗氧化能力相对较弱，无法有效清除机体的氧自由基，从而导致组织细胞膜及病灶产生脂质过氧化，细胞膜的通透性增加，多种水解酶释放，进而引起系列病理改变[23]。本研究

结果显示米非司酮联合桂枝茯苓丸治疗后，患者血清 VEGF 及 SOD 水平显著降低，提示两者联合治疗能够阻断病灶的生长条件，增强机体清除氧自由基的能力。临床研究显示子宫内膜异位症患者多伴不同程度的炎症反应，从而引起病灶组织出现渗出，及其他生化改变[24]。本研究结果显示米非司酮联合桂枝茯苓丸治疗后炎性因子水平显著低于单用米非司酮治疗，提示两者联合治疗可使局部炎症反应减轻，避免进一步损伤。此外，子宫内膜异位症患者多伴血流流变学异常，表现出血液黏度增加，本研究结果显示米非司酮联合桂枝茯苓丸治疗可有效改善患者的血液流变学，可能有助于减轻患者的痛经症状。

综上，米非司酮联合桂枝茯苓丸治疗子宫内膜异位症的临床疗效确切，可能与其抗炎、抗氧化和改善血液流变学作用有关。

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