doi: 10.13241/j.cnki.pmb.2018.08.029

桂枝茯苓胶囊联合米非司酮对子宫肌瘤患者的临床疗效及对血清 VEGF、MMP-9、CA125、E2 水平的影响 *

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摘要 目的:研究桂枝茯苓胶囊联合米非司酮对子宫肌瘤患者的临床疗效及对血清血管内皮生长因子(VEGF)、基质金属蛋白酶-9(MMP-9)、糖类抗原(CA125)、性激素[卵泡雌激素(FSH)、黄体生成素(LH)、雌二醇(E2)]水平的影响。**方法:**选取 2014 年 5 月至 2015 年 4 月我院收治的子宫肌瘤患者 76 例,根据患者入院顺序分为观察组和对照组,38 例每组。对照组使用米非司酮完成治疗,观察组在对照组治疗基础上联合桂枝茯苓胶囊完成治疗。比较两组患者临床疗效,治疗前后血清 VEGF、MMP-9、CA125、E2 水平的变化。**结果:**治疗后,观察组临床总有效率显著高于对照组[89.47%(34/38)比 60.53%(23/38)](P<0.05);两组患者血清 FSH、LH、E2、VEGF、MMP-9、CA125 水平均较治疗前显著降低(P<0.05),和对照组相比,观察组以上指标显著降低(P<0.05)。观察组和对照组不良反应的发生率比较差异无统计学意义(P>0.05)。**结论:**桂枝茯苓胶囊联合米非司酮治疗子宫肌瘤可显著提高其临床疗效,且安全性高,可能与其能有效降低子宫肌瘤患者血清 VEGF、MMP-9、CA125、FSH、LH、E2 水平有关。

关键词:桂枝茯苓胶囊;米非司酮;子宫肌瘤;临床疗效

中图分类号:R711.74 **文献标识码:**A **文章编号:**1673-6273(2018)08-1540-04

Clinical Efficacy of Guizhi Fuling Capsule Combined with Mifepristone in the Treatment of Patients with Uterine Leiomyoma and Effects on the Serum VEGF, MMP-9, CA125 and E2 Levels*

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ABSTRACT Objective: To study the clinical efficacy of guizhi fuling capsule combined with mifepristone in the treatment of patients with uterine leiomyoma and its effects on the levels of serum vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), carbohydrate antigen (CA125), sex hormones [follicle estrogen (FSH), luteinizing hormone (LH), estradiol (E2)]. **Methods:** 76 cases of patients with uterine fibroids treated in our hospital from May 2014 to April 2015 were selected and divided into the observation group and the control group according to the order of admission. The control group was treated with mifepristone. The observation group was treated with Guizhi Fuling Capsule on the basis of control group. The clinical efficacy, changes of the levels of serum VEGF, MMP-9, CA125 and E2 before and after treatment were compared between two groups. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group [89.47%(34/38) vs 60.53%(23/38)](P <0.05). The levels of serum FSH, LH, E2, VEGF, MMP-9 and CA125 in both groups were significantly lower than those before treatment (P <0.05). Compared with the control group, the above indexes in the observation group were significantly decreased (P <0.05). There was no significant difference in the incidence of adverse reactions between the observation group and the control group (P> 0.05). **Conclusion:** Guizhi Fuling Capsule combined with mifepristone could significantly improve the clinical efficacy in the treatment of uterine fibroids with high safety, which might be related to effective reduce of the levels of serum VEGF, MMP-9, CA125, FSH, LH and E2.

Key words: Guizhi Fuling capsule; Mifepristone; Uterine fibroids; Clinical efficacy

Chinese Library Classification(CLC): R711.74 Document code: A

Article ID: 1673-6273(2018)08-1540-04

* 基金项目:陕西省自然科学基金项目(2013JM4012)

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(收稿日期:2017-07-08 接受日期:2017-07-30)

前言

子宫肌瘤是妇科较为常见的一种良性肿瘤,在育龄妇女中的发病率达20%左右,主要是由于子宫平滑肌组织增生而形成的[1]。常常认为子宫肌瘤的萎缩时期是在绝经后,若子宫肌瘤较小,基本上无任何临床症状,不需采取有效的措施予以治疗,仅需定期监测即可[2]。然而,当子宫肌瘤体积较大、并且伴有明显的临床症状时,比如压迫盆腔邻近器官、痛经、月经过多时,则需采取手术治疗,但是上述方式会给育龄妇女生育以及自身健康带来严重影响[3]。

目前,中西医结合治疗子宫肌瘤越来越受到重视和青睐[4]。米非司酮作为较为新型的一种抗孕激素药,常常运用在更年期功能性子宫出血、抗早孕、子宫肌瘤等治疗中;桂枝茯苓胶囊具有活血化瘀、消癥块的作用。为给临床在治疗子宫肌瘤患者提供更多可借鉴之处,本研究主要探讨了桂枝茯苓胶囊联合米非司酮对子宫肌瘤患者的临床疗效及对血清血管内皮生长因子(VEGF)、基质金属蛋白酶-9(MMP-9)、糖类抗原(CA125)、性激素[卵泡雌激素(FSH)、黄体生成素(LH)、雌二醇(E2)]水平的影响。

1 材料与方法

1.1 一般资料

选取2014年5月至2015年4月我院收治的子宫肌瘤患者76例。纳入标准:① 患者的临床诊断和《新编妇产科疾病诊疗学》[5]中的子宫肌瘤诊断标准相符;② 近5个月内未进行过激素类药物治疗;③ 对本次研究中的药物无禁忌症。排除标准:① 宫颈管内及子宫内膜恶性病变者;② 肝、肾、脑、心等重要脏器疾病者;③ 心血管、血液疾病者。本次研究已取得我院伦理委员会批准,及得到患者及家属同意。

根据患者入院顺序分为观察组和对照组,38例每组。观察组中,年龄为28~51岁,平均(39.87± 2.94)岁;肌瘤直径为1~4cm,平均(2.35± 0.42)cm;浆膜下肌瘤13例,黏膜下肌瘤9例,肌壁间肌瘤11例,混合型肌瘤5例;贫血程度:轻度21例,中度13例,重度4例。对照组中,年龄为27~52岁,平均(40.02± 2.92)岁;肌瘤直径为1.2~3.8cm,平均(2.32± 0.39)cm;浆膜下肌瘤14例,黏膜下肌瘤10例,肌壁间肌瘤10例,混合型肌瘤4例;贫血程度:轻度23例,中度12例,重度3例。两组患者年龄、肌瘤直径等方面比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组借助米非司酮(生产厂家:海新华联制药有限公司,规格:10 mg/片,生产批号:20140204)完成治疗,睡前口服,25 mg/次,1次/天,观察组在此治疗基础上加以桂枝茯苓胶囊(生产厂家:江苏康缘药业股份有限公司,规格:0.31 g× 10粒/盒,生产批号:20140214)完成治疗,4粒/次,3次/天,均连续治疗3个月。

1.3 临床疗效评价

根据参考文献[6]评判两组患者临床疗效,标准包括治愈、显效、有效、无效。治疗后,经阴道B超检查,提示子宫大小正常且肌瘤消失,实验室有关指标恢复至正常状态则为治愈;经治疗后,通过阴道B超检查,提示肌瘤三维径线缩小程度≥ 1/2,有关实验室指标恢复至正常则为显效;治疗后,通过阴道B超检查,肌瘤三维径线缩小程度为1/3~1/2,并且实验室有关指标明显改善则为有效;治疗后,患者临床症状、体征及实验室指标并未发生变化,甚至加重则为无效。总有效 = 治愈 + 显效 + 有效。比较两组患者治疗前后血清VEGF、MMP-9、CA125、性激素水平[卵泡雌激素(FSH)、黄体生成素(LH)、雌二醇(E2)],分别在治疗前和治疗后抽取两组患者5 mL的空腹静脉血,离心15 min,转速3000 r/min,分离血清后,提取上清液,放置在-50℃低温箱中待测,使用酶联免疫吸附法检测VEGF、MMP-9水平,使用放射免疫法检测CA125、性激素水平。由北京研吉生物试剂有限公司提供VEGF、MMP-9、CA125、FSH、LH、E2试剂盒。

1.4 统计学处理

选取spss11.5软件包对本次实验数据予以处理,用($\bar{x}\pm s$)表示计量资料,组间比较采用t检验,用[n(%)]表示计数资料,组间比较采用x^2检验,以P<0.05为差异存在统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组临床总有效率显著高于对照组[89.47%(34/38)比60.53%(23/38)](P<0.05),见表1。

表1 两组患者临床疗效的比较[例(%)]

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

Group	Case	Curement	Effective	Valid	Invalid	Total effective
Observation	38	14(36.84)	14(36.84)	6(15.79)	4(10.53)	34(89.47)*
Control	38	4(10.53)	3(7.89)	16(42.11)	15(39.47)	23(60.53)

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

2.2 两组患者治疗前后血清性激素水平的比较

治疗前,两组患者血清FSH、LH、E2水平比较差异无统计学意义(P>0.05);治疗后,两组患者血清FSH、LH、E2水平均较治疗前显著降低(P<0.05),且观察组以上指标的水平明显低于对照组(P<0.05),见表2。

2.3 两组患者治疗前后血清VEGF、MMP-9、CA125水平的比较

治疗前,两组患者血清VEGF、MMP-9、CA125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、CA125水平均较治疗前显著降低(P<0.05),且观察组以上指标的水平明显低于对照组(P<0.05),见表3。

2.4 两组患者不良反应发生情况的比较

在治疗期间,观察组中有1例患者发生呕吐、2例患者伴

表 2 两组患者治疗前后血清性激素水平的比较($\bar{x}\pm s$)

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

Item	Control(n=38)		Observation(n=38)	
	Before treatment	After treatment	Before treatment	After treatment
FSH(U·L^{-1})	24.45± 2.32	20.87± 2.04*	24.48± 2.36	16.14± 1.34*#
LH(U·L^{-1})	18.43± 1.43	14.65± 1.21*	18.49± 1.47	10.03± 1.02*#
E2(pmol·L^{-1})	19.87± 1.76	8.86± 0.87*	19.82± 1.72	4.38± 0.43*#

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

表 3 两组患者治疗前后血清 VEGF、MMP-9、CA125 水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the serum VEGF, MMP-9, CA125 levels before and after treatment between two groups($\bar{x}\pm s$)

Item	Control(n=38)		Observation(n=38)	
	Before treatment	After treatment	Before treatment	After treatment
VEGF(ng·L^{-1})	421.32± 40.15	197.65± 18.76*	422.07± 40.08	105.66± 10.43*#
MMP-9(ng·L^{-1})	1314.21± 125.32	1032.16± 102.34*	1315.02± 126.03	824.32± 81.03*#
CA125(U·mL^{-1})	20.52± 2.14	17.87± 1.34*	20.59± 2.18	14.43± 1.02*#

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

有恶心、3 例患者发生食欲下降;对照组中发生恶心、呕吐的患者分别为 2 例,4 例患者伴有食欲下降。两组患者的不良反应发生率比较差异无统计学意义(P>0.05)。

3 讨论

子宫肌瘤也被称之为子宫纤维样瘤、子宫纤维肌瘤,大部分患者的病理过程属于良性, 也有少数患者伴有恶性病变,在临床中子宫肌瘤主要表现为月经异常、经期延长、不规则阴道出血、子宫增大、贫血、白带增多、压迫症状等[7,8]。子宫肌瘤的发病机制尚未完全明确,但研究表明其与雌激素水平变化存在着密切关系,孕激素同样是子宫肌瘤的重要诱因,对子宫肌瘤的发生发展具有极其重要的作用[9]。目前,子宫肌瘤的治疗主要以激素替代疗法和子宫切除为主,其中保守治疗主要以促性腺激素释放素激动药、米非司酮、雄激素等西药为主[10,11]。

米非司酮在抗孕激素药中属于较为新型的一种,能和孕酮相竞争受体,进而阻碍孕激素活性,导致排卵停滞,同时还会在非竞争性抗雌激素作用下对下丘脑 - 垂体 - 卵巢轴发挥阻碍的作用,抑制孕酮在子宫肌瘤中的扩血管功能,以至于绒毛受损、蜕膜细胞坏死,肌瘤发生萎缩[12-14]。在更年期功能性子宫出血、抗早孕、子宫肌瘤等治疗中使用米非司酮均可获得较好的效果[15]。

中医学将子宫内肌瘤划为 " 症瘕 " 范畴,认为子宫肌瘤是因为气血运行受阻、湿邪所侵、胞宫受寒所致,脏腑气血失调、情志过激而导致脉络不畅、气血凝血,进而发生此病[16-18]。因此,临床治疗可通过缓消癥块、活血化瘀的方式完成治疗。桂枝茯苓胶囊主要由芍药、桃仁、丹皮、茯苓、桂枝组合而成,芍药、丹皮能活血散瘀、同时具有凉血作用,进而消退瘀久所化之热,味苦而微寒,芍药还可以缓急止痛;桃仁味苦甘平,有活血化瘀的作用,借助此药物能化瘀消癥;茯苓渗湿祛痰,健脾益胃,具有消癥之功,均属于佐药,辅之正气;桂枝温通血脉,辛甘而温,行瘀滞,多为君药[19-22]。在上述诸多药物联合作用下能发挥缓消癥块功能,活血化瘀的作用[23]。在现代药理学看来,桂枝茯苓胶囊能有效增强患者机体免疫功能,具有抗肿瘤、扶正祛邪的作用,除此之外,还能有效抑制血小板聚集、抗血栓,改善微循环,进而实现缓消瘤块、活血化瘀的目的[24-26]。本研究采用桂枝茯苓胶囊联合米非司酮治疗子宫肌瘤患者,结果显示患者的临床疗效提高至 89.47%(34/38), 临床疗效临床显著高于单纯米非司酮治疗者,同时联合治疗所产生的不良反应和单纯米非司酮相比无明显差异,提示加以桂枝茯苓胶囊治疗子宫肌瘤的安全性较高。

VEGF 能有效促使新生血管的生长及形成,血清 VEGF 在子宫肌瘤中呈现出高表达,并且病情严重程度和 VEGF 表达存在着密切关联性[27,28]。MMPs 在机体的许多病理生理过程中均发挥着参与性作用,属于较为重要的一种蛋白水解酶,对细胞外基质降解过程均发挥着极其重要的作用。MMP-9 是 MMPs 家族中最大的分子量,主要来自于巨噬细胞、中性粒细胞、结缔组织细胞,对细胞外基质的主要成分具有降解的作用,对血管内皮细胞的出芽具有促进作用,有利于新生血管的形成[29,30]。本研究中,桂枝茯苓胶囊联合米非司酮治疗的子宫肌瘤患者血清 FSH、LH、E2、VEGF、MMP-9、CA125 水平均显著降低, 这可能是桂枝茯苓胶囊联合米非司酮有效提高子宫肌瘤患者临床疗效的重要机制之一。

总之,桂枝茯苓胶囊联合米非司酮治疗子宫肌瘤可显著提高其临床疗效,且安全性高,可能与其能有效降低子宫肌瘤患者血清 VEGF、MMP-9、CA125、FSH、LH、E2 水平有关。

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