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红金消结胶囊联合米非司酮治疗子宫肌瘤的疗效及对血清 Ang-2、EGF、NF-κBp65 水平的影响 *

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摘要 目的：探讨红金消结胶囊联合米非司酮治疗子宫肌瘤的疗效及对血清血管生成素 -2(Ang-2)、表皮生长因子(EGF)、核因子 -κBp65(NF-κBp65)水平的影响。**方法：**选择我院 2017 年 5 月至 2018 年 5 月接诊的 103 例子宫肌瘤患者，通过随机数表法将其分为观察组 53 例和对照组 50 例。对照组给予米非司酮治疗，观察组在对照组基础上联合红金消结胶囊治疗，两组患者在月经期间停药，均连续治疗 3 个月。比较两组的临床疗效、治疗前后血清 Ang-2、EGF、NF-κBp65、卵泡雌激素(FSH)、促黄体生成素(LH)、雌二醇(E2)水平、子宫体积与瘤体情况的变化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为 94.34%，显著高于对照组 78%，$P<0.05$)，血清 Ang-2、EGF、NF-κBp65、FSH、LH、E2 水平均显著低于对照组($P<0.05$)，子宫体积和子宫肌瘤体积均小于对照组($P<0.05$)。两组不良反应发生率比较差异无统计学意义($P>0.05$)。**结论：**红金消结胶囊联合米非司酮治疗子宫肌瘤的临床疗效显著优于单用米非司酮治疗，其可更显著改善患者性激素水平，缩小子宫和子宫肌瘤的体积，这可能与降低血清 Ang-2、EGF、NF-κBp65 水平有关。

关键词：红金消结胶囊；米非司酮；子宫肌瘤；血管生成素 -2；表皮生长因子；核因子 -κBp65
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Efficacy of Hongjin Xiaojie Capsule and Mifepristone in the Treatment of Hysteromyoma and its Effect on the Serum Ang-2, EGF and NF-kappa Bp65 Levels*

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ABSTRACT Objective: To study the efficacy of Hongjin Xiaojie Capsule and mifepristone in the treatment of hysteromyoma and its effect on the serum Ang-2, EGF and NF-kappa Bp65 levels. **Methods:** 103 patients with hysteromyoma were selected from May 2017 to May 2018 in our hospital. They were divided into the observation group (53 cases) and the control group (50 cases) by the random number table method. The control group was treated with mifepristone, while the observation group was treated with Hongjin Xiaojie Capsule on the basis of control group. The two groups of patients stopped taking medicine during menstruation and were treated continuously for 3 months. The clinical efficacy, changes of serum Ang-2, EGF, NF-kappa Bp65, uterine volume and tumors, follicular estrogen (FSH), luteinizing hormone (LH), estradiol (E2) levels and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was 94.34%, which was significantly higher than 78% in the control group ($P<0.05$); the serum levels of Ang-2, EGF, NF-kappa Bp65, FSH, LH and E2 were significantly lower than those of the control group ($P<0.05$); the uterine volume and uterine leiomyoma volume of the observation group were smaller than those of the control group($P<0.05$); there was no significant difference in the incidence of adverse reactions between the two groups($P>0.05$). **Conclusion:** The clinical efficacy of Hongjin Xiaojie Capsule combined with mifepristone in the treatment of uterine leiomyoma is significantly better than that of mifepristone alone. it can significantly improve the sex hormone level of patients and reduce the volume of uterine and uterine leiomyoma, which may be related to the reduction of serum Ang-2, EGF and NF-kappa B p65 levels.

Key words: Hongjin Xiaojie Capsule; Mifepristone; Hysteromyoma; Angiopoietin-2; Epidermal Growth Factor; Nuclear Factor-Kappa Bp65

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前言

子宫肌瘤是育龄期女性较为常见的一种生殖器肿瘤.随着人们近年来饮食生活习惯等改变，该病的发病率也呈增长趋势[1,2]。子宫肌瘤发生主要是由平滑肌细胞或结缔组织细胞良性增殖所致，其中血清血管生成素 -2 (Ang-2)、表皮生长因子(EGF)、核因子 -κBp65(NF-κBp65)在细胞增殖、凋亡过程中发挥着重要作用[3,4]。目前,临床对于瘤体较小的患者仍主要使用药物缩小肌瘤体积、抑制进展,常规的西医治疗多使用性激素抑制类药物,例如米非司酮,其通过降低体内孕激素和雌激素水平促使肌瘤的体积缩小,但用药后对人体激素水平影响较大,伴有不同程度的潮热、骨量丢失等问题出现,整体疗效欠佳[5,6]。

近年来,中医药在治疗方面注重标本兼治、总体调节,与此同时兼具疗效明显、不良反应少等优势,中医学认为诱发子宫肌瘤的病因与气血失调、正气不足等紧密相关,而通过补中益气、消结化瘀等方为化瘤治疗原则[7,8]。红金消结胶囊具有舒肝理气,软坚散结,活血化瘀,消肿止痛,提高机体免疫力等功效。红金消结胶囊中的柴胡、香附、三七能抑制胶原纤维的合成,从而促进乳腺增生组织和纤维的吸收,在消肿散结方面,红金消结胶囊配合血府逐瘀口服液,祛瘀通络止痛,相得益彰。在卵巢囊肿、乳腺小叶增生、子宫肌瘤的治疗中均有独到之处。本研究主要探讨了红金消结胶囊联合米非司酮治疗子宫肌瘤的疗效及对血清 Ang-2、EGF、NF-κB p65 水平的影响。

1 资料与方法

1.1 一般资料

选择我院 2017 年 5 月至 2018 年 5 月接诊的 103 例子宫肌瘤患者,本研究已获得伦理委员会批准进行。纳入标准:① 确诊为子宫肌瘤[9]:患者月经周期延长、月经血液量增多、腹部存在包块和压迫症状、疼痛、白带增加等症状,经腹部、盆腔超声医学检验后明确诊断为子宫肌瘤;② 患者均与《中药新药临床研究指导原则》[10]中叙述的子宫肌瘤中医标准相符:月经量多、颜色紫合并血块、经期延长淋漓不尽、下腹坠胀、腰骶酸痛,面色少华、神疲乏力、舌苔紫黯或有瘀斑,脉象沉;③ 单个瘤体最大直径≤ 6cm;④ 年龄 18~50 岁,未绝经女性;⑤ 知情同意本研究。排除标准:① 近三个月内有相关治疗史,且对本研究的结果有所影响;② 近三个月内有接受激素类药物的治疗;③ 合并子宫内膜炎、子宫肌腺症、子宫囊肿等子宫内疾病;④ 合并肺结核、梅毒、艾滋病等传入疾病;⑤ 合并严重内分泌系统和造血系统疾病、重要肾脏器官功能障碍;⑥ 精神状态异常;⑦ 患有粘膜下子宫肌瘤、子宫颈肌瘤、阔韧带肌瘤。

通过随机数表法分为观察组 53 例和对照组 50 例。观察组年龄 21~48 岁，平均 (35.74± 3.19) 岁；病程 5~21 月，平均 (13.14± 1.54)月；对照组年龄 22~49 岁,平均(35.80± 3.22)岁；病程 6~20 月,平均(13.16± 1.52)月。两组患者的一般资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 方法

对照组给予常规西医治疗,月经结束后第 1 d,口服米非司酮(规格 25 mg,厂家:浙江仙琚制药股份有限公司,国药准字 H20000649)治疗,每日睡前用药,每次 25 mg;观察组在对照组基础上,联合红金消结胶囊(规格每粒装 0.4 克,厂家:云南佑生药业有限责任公司,国药准字 Z20026032)口服治疗,每次 4 粒,一天 3 次;两组患者在月经期间均停止用药,均连续治疗 3 个月。

1.3 观察指标

① 采集治疗前、治疗后 5 mL 空腹静脉血,血液收集时间点为月经第 3~5 d,加入未放置抗凝剂的干燥管中,室温下静置 1 h,使用 3500 r/min 的速度离心,提取上层清液储存于零下 20℃的冰箱中保存备检,血清 Ang-2、EGF、NF-κBp65 的检测均使用上海信帆生物科技有限公司生产的酶联免疫吸附法(ELISA)试剂盒;② 同时测定血清性激素变化,指标包括卵泡雌激素(FSH)、促黄体生成素(LH)、雌二醇(E2),均使用深圳晶美生物工程有限公司生产的化学发光法试剂盒;③ 并使用 B 超检测单个瘤体最大直径、单个瘤体最大体积。

治疗结束后评价临床疗效[7],痊愈:患者临床症状、病体特征、子宫肌瘤完全消失;显效:月经量多、经期延长、腹部包块、疼痛、白带增加等症状基本消失,瘤体直径缩小≥ 50%;有效:月经量多、经期延长、腹部包块、疼痛、白带增加等症状部分缓解,瘤体直径缩小 25~49%;无效:上述症状无明显缓解,瘤体缩小<25%,甚至有增大肌瘤。多发肌瘤患者瘤体直径缩小情况根据直径较大的进行评价。总有效率 =(痊愈＋显效 + 有效)/ 总例数× 100%。

1.4 统计学分析

以 spss18.0 软件包处理,正态分布计量资料用均数± 标准差($\bar{x}$± s)表示,组间比较使用独立样本 t 检验,组内比较使用配对样本 t 检验，计数资料以率表示,x^2 检验,P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后,观察组临床疗效总有效率为 94.34%,显著高于对照组 78%,P<0.05),见表 1。

表 1 两组临床疗效的比较[n(%)]

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

Groups	Recovery	Effective	Valid	Invalid	Total effective rate
Observation group(n=53)	28(52.83)	17(32.08)	5(9.43)	3(5.66)	50(94.34)*
Control group(n=50)	19(38.00)	13(26.00)	9(18.00)	11(22.00)	39(78.00)

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

2.2 两组治疗前后血清 Ang-2、EGF、NF-κBp65 水平的比较

治疗后,观察组血清 Ang-2、EGF、NF-κBp65 水平均比对照组显著降低(P<0.05),见表 2。

表 2 两组治疗前后血清 Ang-2、EGF、NF-κBp65 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum Ang-2, EGF and NF-kappa Bp65 between two groups before and after treatment($\bar{x}\pm s$)

Groups		Ang-2(ng/L)	EGF(pg/mL)	NF-κB p65(ng/L)
Observation group(n=53)	Before treatment	314.25± 15.71	329.41± 18.03	80.41± 7.03
	After treatment	253.28± 6.44*#	242.37± 10.22*#	51.06± 3.22*#
Control group(n=50)	Before treatment	318.30± 13.96	331.38± 16.40	80.38± 7.10
	After treatment	290.42± 8.20*	286.20± 13.75*	63.20± 4.45*

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

2.3 两组治疗前后血清性激素水平的比较

治疗后，观察组血清 FSH、LH、E2 水平比对照组均显著降低(P<0.05)，见表 3。

表 3 两组治疗前后血清性激素比较($\bar{x}\pm s$)

Table 3 Comparison of the Serum Sex Hormones between Two Groups before and after treatment($\bar{x}\pm s$)

Groups		FSH(IU/L)	LH(IU/L)	E2(pmol/L)
Observation group(n=53)	Before treatment	5.95± 1.31	12.54± 2.38	521.26± 34.72
	After treatment	3.25± 0.55*#	5.16± 0.80*#	400.13± 20.16*#
Control group(n=50)	Before treatment	5.88± 1.36	12.59± 2.46	525.09± 22.37
	After treatment	4.42± 0.74*	9.03± 1.01*	463.40± 21.00*

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

2.4 两组治疗前后子宫体积与瘤体情况比较

治疗后，观察组子宫体积、子宫肌瘤体积均比照组显著缩小(P<0.05)，见表 4。

表 4 两组治疗前后子宫体积与瘤体情况情况比较($\bar{x}\pm s$)

Table 4 Comparison of the uterine volume and tumors between two groups before and after treatment($\bar{x}\pm s$)

Groups		Uterine volume	Hysteromyoma volume
Observation group(n=53)	Before treatment	120.54± 14.83	15.62± 3.05
	After treatment	83.16± 7.35*#	9.24± 1.28*#
Control group(n=50)	Before treatment	120.48± 15.10	15.60± 3.07
	After treatment	100.29± 8.04*	12.85± 1.63*

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

2.5 两组不良反应发生情况的比较

在治疗过程中，观察组与对照组分别 2 例和 5 例患者出现呕吐恶心，不良反应发生率分别为 3.77%、10.00%，组间差异无统计学意义(χ^2=1.575，P=0.210)。

3 讨论

近年来，子宫肌瘤的发生逐渐趋于年轻化，相关研究报告数据显示国内大约有 25%~42%的育龄女性患有此病，且倾向于多发的状态，严重影响患者生活与健康[11,12]。药物与手术切除为子宫肌瘤的主要治疗措施，手术治疗是切除子宫肌瘤病灶的有效方案，但术后产生的术后并发症易对患者的生育产生影响，降低患者健康指数与生活质量[13,14]。因此，部分患者选择抑制性激素分泌的相关口服药物抑制子宫肌瘤的发展[15,16]。米非司酮是孕激素和甾体类药物拮抗剂，口服后可在卵巢持续性发挥药效，与孕激素相结合，可抑制子宫肌瘤的生长，发挥溶解卵巢黄体、缩小肌瘤的作用，但单独用药在临床疗效方面效果不太显著，且对垂体激素中卵泡雌激素和促黄体生成素的分泌也有所影响，甚至会致使患者出现闭经的症状[17,18]。

中医中将此病归纳为"症瘕"，指出病因多为本虚标实，本虚为气血失调、正气不足，标实为血瘀、湿浊、痰饮凝结，发病多是日积月累而形成，长期的失血致使阴血亏虚、气血耗损，再加之气虚，进一步损伤机体正气，机体无力行气，致血瘀加重，瘀血更甚，因果交织，造成恶性循环，形成肿瘤[19,20]。本研究所使用的红金消结胶囊中，鸡矢藤具有抗菌和镇痛的功效，金荞麦属于蓼科植物，具有清热解毒和排脓祛瘀的作用，可有效作用于脱氧核糖核酸代谢的中间环节，从而抑制肿瘤细胞侵袭与转移，能抵抗自由基对机体的损害，提高巨噬细胞的免疫与吞噬的功能，同时能增强机体的免疫力。大红袍消炎止痛、活血调经，有利于月经周期的恢复[21,22]。现代药理学研究证实八角莲、柴胡和三七皆有抗肿瘤，促进身体免疫力提高的作用，能对子宫肌瘤的恶化起到有效预防[23,24]。与此同时红金消结胶囊中的有效成分香附兼具调经止痛、行气补血和清热解郁的功效，从而可以在治疗将调理协同进行。

Ang-2、EGF 是血管生成的核心因子，在肿瘤生长中具有重

要作用[25]。Ang-2 表达受体内肿瘤血管的发生、发展所影响，与肿瘤分期、肿瘤血管生成的数量之间存在紧密联系，有研究显示子宫肌瘤患者体内的血清 Ang-2 指标水平显著升高[26]。EGF 是通过血管内壁的内皮细胞所分泌，在未患病的女性人体中 EGF 表达平稳，在患有子宫肌瘤、乳房腺瘤、乳房纤维瘤等良性肿瘤患者体内的表达居高不下[27]。NF-κB 是拥有多个方向调节性能的转录因子，包含数量众多的蛋白因子，共同构成强大且复杂的蛋白系统，其中的 NF-κB p65 通过对信号途径产生激活作用，对消化道肿瘤、颈部肿瘤、子宫肌瘤等大多数肿瘤的形成存在紧密的联系 [28,29]。有研究证实子宫肌瘤患者血清 NF-κB p65 表达也明显高于正常组，在子宫肌瘤的发生、发展中起着重要作用，可诱导子宫平滑肌的增值、分化，促进瘤体形成[30]。本研究结果显示联合用药的患者治疗 3 个月后血清 Ang-2、EGF、NF-κBp65 均有显著的下降趋势，且子宫体积、子宫肌瘤体积明显小于对照组，可能是由于红金消结胶囊中的有效成分八角莲、柴胡、三七对肿瘤的活性具有抑制作用，金荞麦具有抑菌抗癌的作用，且八角莲、三七中的三七皂苷、金荞麦中的含大量黄酮类化合物均对血管平滑肌细胞的增值、分化具有抑制作用，因此，有利于进一步调节血清 Ang-2、EGF、NF-κBp65 的表达[30,31]。此外，联合用药的患者在临床疗效的总有效率高于对照组，可能是联合红金消结胶囊的患者性激素降低、子宫和瘤体体积缩小程度是有效内在机制之一。

综上所述，红金消结胶囊联合米非司酮治疗子宫肌瘤的临床疗效显著优于单用米非司酮治疗，其可更显著改善患者性激素水平，缩小子宫和子宫肌瘤的体积，这可能与降低血清 Ang-2、EGF、NF-κBp65 水平有关。

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