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血清 VEGF, IGF-1 和 CA125 水平与子宫动脉栓塞术(UAE)治疗子宫腺肌症的相关性

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摘要 目的:探讨血清血管内皮生长因子(VEGF)、胰岛素样生长因子-1(IGF-1)和 CA125 水平和子宫动脉栓塞术(UAE)治疗子宫腺肌症的相关性。方法:选择接受子宫动脉栓塞术治疗的 39 例子宫腺肌症患者作为患者组,取同时期参加健康体检的 30 名健康者作为健康对照组。用 ELISA 法检测子宫腺肌症患者子宫动脉栓塞术前和术后不同时间点血清 VEGF、IGF-1、CA125 的水平,评估子宫动脉栓塞术后的患者的疗效。结果:34 例痛经患者术后 1 个月开始改善,最终 29 例完全缓解,有效率 85.2%。患者组治疗前血清 VEGF、IGF-1、CA125 水平均显著高于健康对照组($P<0.05$)。子宫动脉栓塞术治疗后,患者组血清 IGF-1、VEGF 和 CA125 的水平与治疗前相比均显著降低,术后 6 月,恢复正常水平。结论:血清 IGF-1、VEGF、CA125 的变化可能在子宫动脉栓塞术治疗子宫腺肌症中作为疗效和预后评估指标。

关键词: 血管内皮生长因子;胰岛素样生长因子-1;糖类抗原 125;子宫动脉栓塞术

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Clinical Significance of Serum VEGF, IGF-1 and CA125 Levels in the Uterine Artery Embolization Treatment for Uterine Adenomyosis

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ABSTRACT Objective: To investigate the correlation of serum concentration of vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF 1) and CA125 with uterine artery embolization (UAE) in the treatment of uterine adenomyosis. **Methods:** 39 cases of uterine adenomyosis patients were chosen as patient group and received uterine artery embolization, 30 healthy subjects were selected as control. The serum concentrations of VEGF, IGF 1, CA125 before and after the operation were quantified by ELISA at different time points. The curative effect after uterine artery embolization was evaluated. **Results:** After 1 month of UAE, in 34 patients with dysmenorrhea, 29 cases turned to be complete remission with its final efficiency of 85.2%. The VEGF, IGF 1 and CA125 concentrations in serum of patient group were significantly higher than those of normal control group before UAE treatment ($P<0.05$). After uterine artery embolization, the serum concentrations of IGF 1, VEGF and CA125 of patient group decreased significantly. After 6 months of UAE treatment, all indicators turned to be at normal level. **Conclusion:** The changes of serum IGF - 1, VEGF and CA125 concentrations could be taken as curative effect and prognosis marker of uterine artery embolization in the treatment of uterine adenomyosis.

Key words: VEGF; IGF-1; CA125; Uterine artery embolization

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前言

子宫腺肌病是一种良性的子宫病变,是一个由子宫内膜组织遍布到子宫肌层的非肿瘤的过程,同时伴随着子宫平滑肌的增生肥大^[1],一般通过组织学分析确诊^[2]。目前,子宫腺肌症的治疗方法包括子宫切除术、药物治疗、微创手术。随着微创技术的进步,近年来,一些新的技术被广泛应用于治疗子宫腺肌病,包括磁共振成像引导聚焦超声(MRgFUS)^[3]和子宫动脉栓塞术(U-

terine artery embolization, UAE)^[4]等。子宫动脉栓塞术是治疗子宫腺肌病的新方法,作为一项微创技术有望成为子宫腺肌病的一线治疗方法。

研究表明血管内皮生长因子(VEGF)、胰岛素样生长因子 1 (IGF-1)在子宫腺肌症的发生过程中起重要作用^[5],主要参与血管生成。而血清 CA125 在子宫腺肌症等多种恶性肿瘤疾病患者中表达升高^[6-8]。为了解 VEGF、IGF-1 和 CA125 水平的变化在子宫动脉栓塞术治疗子宫腺肌症中的意义,本研究选择我院自 2010 年 3 月至 2015 年 9 月因子宫腺肌病住院的行子宫动脉栓塞术治疗的 39 名患者,检测了子宫动脉栓塞术前和术后血清 VEGF、IGF-1 和 CA125 水平的变化,现报道如下。

1 资料与方法

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1.1 研究对象

选取 2010 年 3 月至 2015 年 9 月在我院妇产科因子宫腺肌病住院并自愿接受双侧子宫动脉栓塞术治疗的 39 名子宫腺肌病患者为研究对象,平均年龄为 43.5 岁(27~54 岁),患者均已婚已育。栓塞术前行血常规、肝肾功能、凝血功能、心电图、胸片检查均未发现手术禁忌,盆腔核磁共振成像(MRI)检查结果显示均符合子宫腺肌病影像学特征。患者纳入标准:经过临床表现、妇科体征、影像学诊断为子宫腺肌症的患者。排除子宫肌瘤、卵巢子宫内膜异位症的患者。对照组是同时期参与体检的 30 例健康人,平均年龄 42.6 岁(26-62 岁),无妇科疾病史,年龄、体重等基本参数与患者组无统计学差异($P>0.05$)。

1.2 子宫动脉栓塞术手术方法

39 名患者先后由两名介入科主任医师使用同一操作方法完成,患者取仰卧位,常规消毒铺巾,2%利多卡因局麻右侧股动脉穿刺道,以改良 Seldinger 技术成功穿刺右侧股动脉,置入导管鞘,在 DSA 造影下采用经鞘引入 5Fsiml 造影导管分别选择性插管至双侧髂内动脉、子宫动脉造影,观察子宫动脉走行、病灶分布、子宫血供等详细情况,证实导管正确进入子宫动脉后,经导管注入栓塞剂栓塞子宫动脉,栓塞后造影复查见仅留子宫动脉主干且显影正常,邻近正常组织血流通畅。术毕拔除导管及鞘,压迫止血弹力绷带加压包扎右侧股动脉穿刺区域 5-10 分钟,患者生命体征平稳,送回病房。

1.3 ELISA 测定

抽取所有患者术前及术后晨起空腹静脉血 5 mL,分装 2 管,1 管内置入 2 mL 静脉血,置于 -4℃ 冰箱保存待测。血清 VEGF、IGF-1、CA125 测定采用酶联免疫吸附实验法测定。分别使用上海生工 VEGFR165、IGF-1、CA125 酶联免疫检测试剂盒,操作方法参考说明书,取同时期 30 名健康体检者做对照参考。患者指标测量时间:术前 1 周、术后 1 周、术后 1 个月、术后 3 个月、6 个月。

1.4 痛经程度

在术前和术后随访时间内,采用 "慢性疼痛分级量表" 评估患者的痛经症状,根据结果分类为完全缓解、明显好转、中度

改善、无效。随访时间为术前 1 个月、术后 6 个月、术后 1~5 年的每一年随访一次,随访截止时间为 2016 年 2 月。

1.5 统计学方法

本研究采用 SPSS 20.0 版统计软件进行数据分析,计数资料率的比较应用 χ^2 检验,计量资料的比较应用 t 检验、重复测量方差分析。 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 手术基本情况

2010 年 3 月至 2015 年 9 月,因子宫腺肌病住院的 39 名患者均成功实施双侧子宫动脉栓塞术,手术平均操作时间为 60.0 ± 5.0 min (25.1-140.5 min),平均住院天数 3.4 ± 0.7 天(3.0-6.0 天)基本情况见表 1。

表 1 成功施行子宫动脉栓塞术住院患者的基本参数(n=39)

Table 1 The basic parameters of the patients receiving UAE

Parameters	Results
Age (year)	43.5 ± 2.5 (27.0~54.5)
Weight (kg)(kg)	60.3 ± 3.5 (46.1-74.9)
Operation time (min)	60.0 ± 5.0 (25.1-140.5)
Hospital stays (day)	3.4 ± 0.7 (3.0-6.0)

39 名随访患者中,术前有明显痛经的患者 34 名,治疗后(1.0 ± 0.6)个月患者的痛经开始有所缓解,29 例缓解(完全缓解 + 部分缓解),2 例中度改善,3 例无效。总有效率达 85.2%。疗效维持时间为(50 ± 21)个月。

2.2 两组不同时点血清 VEGF、IGF-1 水平的比较

手术前,患者组与健康组血清 VEGF 水平分别为 142.5 ± 56.6 $\mu\text{g/mL}$ 、 76.5 ± 34.1 $\mu\text{g/mL}$,组间差异具有显著统计学意义($P=0.045<0.05$)(表 2)。经过子宫动脉栓塞术后,患者血清 VEGF 含量在术后 1 周有显著的下降,相对于术后 1 周,术后 1 个月 VEGF 血清水平有所回升($P=0.049<0.05$),术后 6 个月恢复到正常值(相比于正常人, $P=0.342>0.05$)。

表 2 两组不同时点血清 VEGF 水平的比较($\mu\text{g/mL}$)

Table 2 Comparison of the serum VEGF level at different time points between two groups ($\mu\text{g/mL}$)

Groups	Before UAE	After UAE			
		1 week	1 month	3 months	6 months
Patients	142.5 ± 56.6	$85.2 \pm 23.8^{*a}$	$98.6 \pm 34.2^{*b}$	86.8 ± 42.7^b	81.7 ± 43.5^c
Controls	76.5 ± 34.1				
P	0.045	0.041	0.049	0.297	0.342

注: * 表示 $P<0.05$,^a 相对于手术前浓度显著改变。^b 相对于术后一周,浓度显著改变。

Note: * compared with before UAE, ^b compared with 1 week after UAE, ^c compared with controls * $P<0.05$.

手术前,患者组与健康组血清 IGF-1 水平分别为 135.4 ± 44.6 $\mu\text{g/mL}$ 、 121.5 ± 45.2 $\mu\text{g/mL}$,组间差异具有显著统计学意义($P=0.042<0.05$)(表 3)。经过子宫动脉栓塞术后,患者血清 IGF-1 含量在术后 1 周有显著的下降,相对于术后 1 周,术后 1 个月 IGF-1 血清水平有所回升($P=0.036<0.05$),术后 6 个月恢复到正常值(相比于正常人, $P=0.146>0.05$)。

2.3 两组不同时点血清 CA125 水平的比较

手术前,患者组与健康组血清 CA125 水平分别为 121.8 ± 60.1 U/mL、 22.5 ± 3.7 U/mL,组间差异具有显著统计学意义($P=0.001<0.05$)(表 4)。经过子宫动脉栓塞术后,患者血清 CA125 含量在术后 1 月内有短暂的上升。术后 3 个月时明显下降($P=0.019<0.05$),6 个月即恢复到正常水平,其水平为 27.8 ± 11.2 U/mL(相比于正常人, $P=0.263>0.05$)。

表 3 两组不同时点血清 IGF-1 水平的比较(μg/mL)

Table 3 Comparison of the serum IGF-1 level at different time points between two groups(μg/mL)

Groups	Before UAE	After UAE			
		1 week	1 month	3 months	6 months
Patients	135.4± 44.6	70.1± 20.3 ^a	97.5± 26.9 ^{ab}	102.5± 52.8 ^{ab}	110.1± 55.3 ^c
Controls	121.5± 45.2				
P	0.042	0.007	0.036	0.042	0.146

Note: ^a compared with before UAE, ^b compared with 1 week after UAE, ^c compared with controls * P<0.05.

表 4 两组不同时点血清 CA125 水平的比较(U/mL)

Table 4 Comparison of the serum CA125 level at different time points between two groups (U/mL)

Groups	Before UAE	After UAE			
		1 week	1 month	3 months	6 months
Patients	121.8± 60.1	122.4± 40.7	135.6± 21.5	51.6± 22.8 ^a	27.8± 11.2 ^b
Controls	22.5± 3.7				
P	0.001	0.562	0.139	0.019	0.263

Note: ^a compared with before UAE, ^b compared with controls, * P<0.05.

3 讨论

目前研究认为子宫腺肌症的发生可能与内分泌因素、免疫基质以及血管生成因子共同作用有关。子宫内膜异位的发生有粘附、侵袭和血管生成三个基本步骤,发生过程中需要新生血管提供血液。研究显示 VEGF、IGF-1、CA125^[9-11]在子宫腺肌症的发生中起到重要作用。VEGF^[12]是重要的生长因子,主要刺激血管内皮细胞增殖。患有腺肌病的鼠血管直径、面积、子宫肌层血管面积均显著增加^[13]。IGF-1 是一种肿瘤自分泌因子,在多种肿瘤中表达,刺激细胞生长和增殖^[14]。子宫腺肌症中内膜细胞生长和增殖的影响因子目前研究的较少,而 IGF-1 可能通过调节雌激素起到影响细胞分化的作用^[15]。研究普遍认为抗雌激素治疗可以抑制子宫腺肌症的发展^[16]。而在鼠腺肌症模型中同样发现 IGF 的 mRNA 表达水平与子宫腺肌症显著相关^[17],说明 IGF-1 的局部表达与子宫内膜异位相关。血清 CA125 是肿瘤相关抗原,在卵巢癌的筛查、诊断、疗效监测、预后判定及卵巢癌随访中起重要作用,在子宫腺肌症中表达相对提高^[18]。

子宫内膜血液供应主要来自于子宫动脉及其分支,子宫动脉栓塞术是阻断子宫腺肌病病灶的血液供应^[19,20],导致异位的子宫内膜坏死,导致子宫体积缩小,月经量减小,因而 VEGF、IGF-1、CA125 的浓度也会随之发生变化。本研究中,在子宫动脉栓塞术(UAE)治疗前,相对于健康对照组,子宫内膜异位症患者血清 VEGF、IGF-1、CA125 的浓度均显著高于对照组,治疗后其浓度均呈现显著下降。栓塞后 1 周,VEGF 和 IGF-1 即呈现显著下降的趋势,说明 VEGF、IGF-1 在子宫腺肌症发生的过程中起到重要作用,其原因可能是由于栓塞后缺氧和栓塞,IGF-1 和 VEGF 表达在术后初期被抑制,随后表达开始恢复正常。CA125 浓度在栓塞术后 1 周开始变化,术后 1 月有一定的上升,可能的原因是子宫动脉栓塞术后早期,异位内膜和增生的结缔组织缺血、缺氧水肿,细胞膜受体功能障碍,使细胞溶解,细胞内 CA125 进入血液,因此 CA125 有所上升。而随时间进展,CA125 浓度在术后 3 月开始下降,并在术后 6 月恢复正常水平,说明子宫动脉栓塞术在治疗子宫腺肌病治疗是一个缓

慢过程。

尽管子宫动脉栓塞术治疗子宫腺肌病从长期角度来看有一定的无效率和复发率^[21],但其治疗子宫腺肌病的短期疗效显著,微创治疗有利于减轻患者的痛苦,是代替子宫切除术的有效方法。术后 1 个月,部分患者痛经程度开始改善,最终有 29 例患者达到缓解,总有效率达 85.2%。行子宫动脉栓塞术后 6 月,子宫内膜异位症患者血清 VEGF、IGF-1、CA125 所有指标均恢复到健康人水平,表明血清 IGF-1、VEGF、CA125 的变化可能在子宫动脉栓塞术治疗子宫腺肌症中作为疗效和预后评估指标。

参考文献(References)

- [1] Pontis A, D'Alterio MN, Pirarba S, et al. Adenomyosis: a systematic review of medical treatment[J]. Gynecol Endocrinol, 2016 Jul 5: 1-5
- [2] Struble J, Reid S, Bedaiwy MA. Adenomyosis: A Clinical Review of a Challenging Gynecologic Condition [J]. J Minim Invasive Gynecol, 2016, 23(2): 164-185
- [3] Ferrari F, Arrigoni F, Miccoli A, et al. Effectiveness of Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) in the uterine adenomyosis treatment: technical approach and MRI evaluation[J]. Radiol Med, 2016, 121(2): 153-161
- [4] Wang S, Meng X, Dong Y. The evaluation of uterine artery embolization as a nonsurgical treatment option for adenomyosis [J]. Int J Gynaecol Obstet, 2016, 133(2): 202-205
- [5] Mu Y, He J, Yan R, et al. IGF-1 and VEGF can be used as prognostic indicators for patients with uterine fibroids treated with uterine artery embolization[J]. Exp Ther Med, 2016, 11(2): 645-649
- [6] Mu Y, Hu X, He J, et al. Serum levels of vascular endothelial growth factor and cancer antigen 125 are related to the prognosis of adenomyosis patients after interventional therapy [J]. Int J Clin Exp Med, 2015, 8(6): 9549-9554
- [7] Høgdall E. Approaches to the detection of ovarian cancer [J]. Scand J Clin Lab Invest Suppl, 2016, 245: S49-53
- [8] Colloca G, Venturino A, Governato I. CA125-related tumor cell kinetics variables after chemotherapy in advanced ovarian cancer: a systematic review[J]. Clin Transl Oncol, 2016, 18(8): 813-824

(下转第 2049 页)

- [13] Sadoghi P, Liebensteiner M, Agreiter M, et al. Revision surgery after total joint arthroplasty: a complication-based analysis using world-wide arthroplasty registers[J]. J Arthroplasty, 2013, 28(9): 1329-1332
- [14] Schroer WC, Berend KR, Lombardi AV, et al. Why are total knees failing today? Etiology of total knee revision in 2010 and 2011 [J]. J Arthroplasty, 2013, 28(17): 116-119
- [15] Del Buono A, Denaro V, Maffulli N. Genetic susceptibility to aseptic loosening following total hip arthroplasty: a systematic review [J]. Br Med Bull, 2012, 101(4): 39-55
- [16] New drugs and dosage forms [J]. Am J Health Syst Pharm, 2015, 72(23): 2002
- [17] Ross GD. Role of the lectin domain of Mac-1/CR3 (CD11b/CD18) in regulating intercellular adhesion [J]. Immunol Res, 2002, 25(15): 219-227
- [18] Hayashi H, Nakahama K, Sato T, et al. The role of Mac-1 (CD11b/CD18) in osteoclast differentiation induced by receptor activator of nuclear factor-kappaB ligand [J]. FEBS Lett, 2008, 582(3): 3243-3248
- [19] Sucur A, Katavic V, Kelava T, et al. Induction of osteoclast progenitors in inflammatory conditions: key to bone destruction in arthritis [J]. Int Orthop, 2014, 38(11): 1893-1903
- [20] Lochner K, Fritsche A, Jonitz A, et al. The potential role of human osteoblasts for periprosthetic osteolysis following exposure to wear particles[J]. Int J Mol Med, 2011, 28(15): 1055-1063
- [21] Liu GD, Yu HJ, Ou S, et al. Human beta-defensin-3 for the diagnosis of periprosthetic joint infection and loosening [J]. Orthopedics, 2014, 37(6): e384-e390
- [22] Cherian JJ, Jauregui JJ, Banerjee S, et al. What Host Factors Affect Aseptic Loosening After THA and TKA? [J]. Clin Orthop Relat Res, 2015, 473(23): 2700-2709
- [23] Stihsen C, Radl R, Keshmiri A, et al. Subsidence of a cementless femoral component influenced by body weight and body mass index [J]. Int Orthop, 2012, 36(10): 941-947
- [24] Kapadia BH, Issa K, Pivec R, et al. Tobacco use may be associated with increased revision and complication rates following total hip arthroplasty[J]. J Arthroplasty, 2014, 29(2): 777-780
- [25] Toman J, Iorio R, Healy WL. All-polyethylene and metal-backed tibial components are equivalent with BMI of less than 37.5[J]. Clin Orthop Relat Res, 2012, 470(10): 108-116
- [26] Kim KJ, Rubash HE, Wilson SC, et al. A histologic and biochemical comparison of the interface tissues in cementless and cemented hip prostheses[J]. Clin Orthop Relat Res, 1993(18): 142-152

(上接第 2063 页)

- [9] Konopka B, Skasko E, Kluska A, et al. Changes in the concentrations of receptors of insulin-like growth factor-I, epithelial growth factor, oestrogens and progestagens in adenomyosis foci, endometrium and myometrium of women during menstrual cycle [J]. Eur J Gynaecol Oncol, 1998, 19(1): 93-97
- [10] Huang TS, Chen YJ, Chou TY, et al. Oestrogen-induced angiogenesis promotes adenomyosis by activating the Slug-VEGF axis in endometrial epithelial cells[J]. J Cell Mol Med, 2014, 18(7): 1358-1371
- [11] Sheth SS, Ray SS. Severe adenomyosis and CA125 [J]. J Obstet Gynaecol, 2014, 34(1): 79-81
- [12] Vasta S, Di Martino A, Zampogna B, et al. Role of VEGF, Nitric Oxide, and Sympathetic Neurotransmitters in the Pathogenesis of Tendinopathy: A Review of the Current Evidences [J]. Front Aging Neurosci, 2016, 8: 186
- [13] Zhou YF, Matsuda M, Skaamotos, et al. Changes in Uterine Microvessels as a Possible Pathogenic Factor in the Development of Adenomyosis Induced by Pituitary Grafting in Mice [J]. Acta Histochem Cytochem, 1999, 32(5): 387-391
- [14] Li Y, Yang T, Li J, et al. Inhibition of multiple myeloma cell proliferation by ginsenoside Rg3 via reduction in the secretion of IGF-1[J]. Mol Med Rep, 2016, 14(3): 2222-2230
- [15] 郝群. 血管生成因子在子宫内位异位症中的研究进展[J]. 国外医学妇产科分册, 2001, 28(4): 236-238
- [16] Hirata T, Izumi G, Takamura M, et al. Efficacy of dienogest in the treatment of symptomatic adenomyosis: a pilot study [J]. Gynecol Endocrinol, 2014, 30(10): 726-729
- [17] Kudoh M1, Susaki Y, Ideyama Y, et al. Inhibitory effects of a novel aromatase inhibitor, YM511, on growth of endometrial explants and insulin-like growth factor-I gene expression in rats with experimental endometriosis[J]. J Steroid Biochem Mol Biol, 1997, 63(1-3): 75-80
- [18] Agic A, Djalali S, Wolfler MM, et al. Combination of CCR1 mRNA, MCP1, and CA125 measurements in peripheral blood as a diagnostic test for endometriosis[J]. Reprod Sci, 2008, 15(9): 906-911
- [19] Bae SH, Kim MD, Kim GM, et al. Uterine Artery Embolization for Adenomyosis: Percentage of Necrosis Predicts Midterm Clinical Recurrence[J]. J Vasc Interv Radiol, 2015, 26(9): 1290-1296.e2
- [20] 魏宏, 任帅, 高万里等. 子宫动脉栓塞术治疗子宫腺肌病的临床观察[J]. 中国妇产科临床杂志, 2010, 11(5): 349-351
- [21] Wei Hong, Ren Shuai, Gao Wan-li, et al. Clinical study on adenomyosis treated with uterine embolization[J]. Chin J Clin Obstet Gynecol, 2010, 11(5): 345-351
- [21] Yu L, Wu T, Spain J, et al. Uterine artery embolization for the treatment of adenomyosis: questions for long-term efficacy [J]. J Vasc Interv Radiol, 2012, 23(3): 430-432
- Hao Qun. The progress of VEGF in uterine adenomyosis [J]. Foreign Medical Sciences(Obstet Gynecol Fascicle), 2011, 28(4): 236-238