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戊酸雌二醇联合甲羟孕酮治疗子宫内膜异位症的疗效及对血清 CA125、CA199、VEGF 水平的影响 *

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摘要 目的:探讨戊酸雌二醇联合甲羟孕酮治疗子宫内膜异位症的疗效及对血清糖类抗原 125(CA125)、糖类抗原 199(CA199)、血管内皮生长因子(VEGF)水平的影响。**方法:**选择本院 2016 年 6 月~2018 年 1 月收治的 134 例子宫内膜异位症患者,按随机数字表法分为对照组($n=76$)和观察组($n=58$),对照组采用甲羟孕酮治疗,观察组在对照组基础上联合戊酸雌二醇治疗,比较两组临床疗效,治疗前后血清 CA125、CA199、VEGF 水平,囊肿直径、月经不调评分、痛经评分和不良反应发生情况。**结果:**观察组总有效率高于对照组,差异有统计学意义($P<0.05$)。治疗前,两组血清 CA125、CA199、VEGF 水平,囊肿直径、月经不调评分、痛经评分比较差异无统计学意义($P>0.05$);治疗后,两组血清 CA125、CA199、VEGF 水平、囊肿直径、月经不调评分及痛经评分均下降,观察组低于对照组,差异有统计学意义($P<0.05$)。两组均有乏力、失眠及潮热发生,组间总副反应发生率差异无统计学意义($P>0.05$)。**结论:**戊酸雌二醇联合甲羟孕酮能够提高子宫内膜异位症的疗效,有效降低血清 CA125、CA199 及 VEGF 水平,安全性较高。

关键词:子宫内膜异位症;戊酸雌二醇;甲羟孕酮;糖类抗原 125;糖类抗原 199;血管内皮生长因子

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Curative Effect of Estradiol Valerate Combined with Medroxyprogesterone in Treatment Endometriosis and Its Impact on Serum Levels of CA125, CA199 and VEGF*

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ABSTRACT Objective: To investigate the curative effect of estradiol valerate combined with medroxyprogesterone in the treatment of endometriosis and its impact on serum levels of carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199) and vascular endothelial growth factor (VEGF). **Methods:** 134 cases of endometriosis who treated from June 2016 to January 2018 in our hospital, according to random number table method these patients were divided into the control group ($n=76$) and observation group ($n=58$), the control group was treated with medroxyprogesterone and the observation group was treated with estradiol valerate on the basis of the control group, then clinical curative effect, serum levels of CA125, CA199 and VEGF cyst diameter, menstruation to be not moved a grade, dysmenorrhea before and after treatment, and adverse reactions occur in both group were compared. **Results:** the total effective rate in the observation group was higher than that in the control group, and the difference was statistically significant ($P<0.05$). Before treatment, serum levels of CA125, CA199 and VEGF, cyst diameter, menstrual irregularness score and dysmenorrhea score of the two groups were no significant difference ($P>0.05$). After treatment, serum levels of CA125, CA199 and VEGF, cyst diameter, dysmenorrhea score and dysmenorrhea score of the two groups were all decreased, and the difference between the observation group and the control group was statistically significant ($P<0.05$). Fatigue, insomnia and hot flashes occurred in both groups, and there was no statistically significant difference in the incidence of total adverse reactions between the two groups ($P>0.05$). **Conclusion:** Estradiol valerate combined with medroxyprogesterone can improve the efficacy of endometriosis, effectively reduce the level of serum CA125, CA199 and VEGF, and has a high safety.

Key words: Endometriosis; Estradiol valerate; Medroxyprogesterone; Carbohydrate antigen 125; Carbohydrate antigen 199; Vascular endothelial growth factor

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前言

子宫内膜异位症为生育期妇女的常见疾病,显著危及患者身心健康^[1,2]。临床强调个体化治疗,其中药物治疗已成为有生育要求、经期痛经明显、无卵巢囊肿形成等患者的主要方式^[3,4]。子宫内膜异位症为激素依赖性疾病,既往研究认为^[5,6],下调机体雌激素浓度能够抑制子宫内膜生长,在改善患者症状、降低复发率等方面的疗效显著,但其可能引起低雌激素效应,导致骨质丢失及更年期症状,降低患者生活质量。最新研究表明^[7],反向添加疗法可有效减轻药物所致的低雌激素症状,戊酸雌二醇具有雌二醇药理作用,能够补充雌激素。甲羟孕酮为高效孕激素,能够通过调节垂体及下丘脑对促性腺激素的分泌,抑制排卵,导致内膜组织蜕膜化甚至萎缩^[8,9]。目前缺乏二者联合应用的系统报道,相关起效机制也尚未明确。相关研究报道^[10,11],CA125、CA199、VEGF水平与子宫内膜异位症的病变程度有着良好关系。本研究旨在分析戊酸雌二醇联合甲羟孕酮治疗子宫内膜异位症的疗效及对血清CA125、CA199、VEGF水平的影响。

1 资料与方法

1.1 一般资料

134例子宫内膜异位症患者纳入标准^[12]:伴不孕、持续加重的盆腔疼痛及粘连、痛经等症状,血清CA125浓度明显上升,经妇科触诊、超声等检查确诊为子宫内膜异位症;无子宫手术史;异位囊肿<5cm;无自身免疫系统、血液系统病变;肝肾等功能无异常;年龄24~53岁;囊肿直径3~5cm;病程1~5年。将宫内放置节育器、合并其他妇科肿瘤、近期有过甾体类激素治疗者予以排除。按随机数字表法分为对照组($n=76$)和观察组($n=58$),对照组年龄(39.06 ± 4.83)岁;病程(2.47 ± 0.81)年;囊肿直径(4.21 ± 0.57)cm;疾病分期:I期28例、II期48例。观察组年龄(38.65 ± 5.03)岁;病程(2.42 ± 0.86)年;囊肿直径(4.15 ± 0.65)cm;疾病分期:I期25例、II期33例。两组基般

资料比较无统计学差异($P<0.05$)。

1.2 方法

对照组采用甲羟孕酮治疗,在经期5d内,于深部肌肉注射150mg甲羟孕酮(生产厂家:浙江仙琚制药股份有限公司,规格:2mg/片,批号:20150918),每30d进行1次,持续治疗6次。观察组在对照组基础上联合戊酸雌二醇治疗,口服0.5mg戊酸雌二醇片(生产厂家:拜耳医药保健有限公司广州分公司,规格:0.5mg/片,批号:20150511),1次/d,持续治疗12周。

1.3 观察指标

1.3.1 临床疗效评价 治疗结束时进行,症状完全消失,盆腔提示无肿块为显效;症状显著缓解,盆腔提示无肿块;症状无改变或者加重为无效^[12]。

1.3.2 血液指标 于治疗前及治疗结束后采用放射免疫法测定血清CA125、CA199浓度,采用酶联免疫分析法测定血清VEGF浓度。

1.3.3 囊肿直径及临床评分 (1)于治疗前后采用B超诊断仪测定囊肿大小。(2)月经不调评分:无症状记为0分;行经不畅记为2分;行经不畅,颜色黯淡,有结块记为4分;行经不畅,量多,颜色黯淡,有结块记为6分。(3)痛经评分:经期无腹痛记为0分;经期仅轻微腹痛记为2分;经期腹痛明显,但看耐受记为4分;经期腹痛难忍记为6分^[12]。

1.4 统计学分析

数据处理选择SPSS18.0软件包进行,用[(例)%]表示计数资料,比较用 χ^2 检验,用($\bar{x}\pm s$)表示计量资料,比较用独立样本t检验, $P<0.05$ 则比较有统计学差异。

2 结果

2.1 两组疗效比较

观察组总有效率较对照组高93.10%比80.26%($P<0.05$),见表1。

表1 两组疗效比较[例(%)]

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

Groups	n	Effective	Effective	Ineffective	Total Effective Rate
Control group	76	26(34.21)	35(46.05)	15(18.74)	61(80.26)
Observation group	58	35(60.34)	19(32.76)	4(6.90)	54(93.10)
χ^2					4.457
P					0.034

2.2 两组血清CA125、CA199、VEGF水平比较

治疗后,观察组血清CA125、CA199、VEGF水平低于对照

组($P<0.05$),见表2。

表2 两组血清CA125、CA199、VEGF水平比较($\bar{x}\pm s$)

Table 2 Comparison of serum CA125, CA199 and VEGF levels between the two groups($\bar{x}\pm s$)

Groups	n	CA125(U/mL)		CA199(U/mL)		VEGF(U/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	76	111.06 $\pm$ 13.20	78.62 $\pm$ 9.14	103.96 $\pm$ 16.39	30.29 $\pm$ 4.26	372.90 $\pm$ 46.71	210.75 $\pm$ 33.82
Observation group	58	106.43 $\pm$ 15.29	54.30 $\pm$ 6.43	109.10 $\pm$ 14.18	18.42 $\pm$ 2.76	383.19 $\pm$ 42.85	138.07 $\pm$ 13.27
t		1.878	17.258	1.905	18.460	1.309	15.471
P		0.062	0.000	0.058	0.000	0.192	0.000

2.3 两组囊肿直径、月经不调评分、痛经评分比较

治疗后,观察组囊肿直径、月经不调评分、痛经评分较对照组低($P<0.05$),见表3。

2.4 两组副反应比较

两组总发生率比较无统计学差异($P>0.05$),见表4。

表3 两组囊肿直径、月经不调评分、痛经评分比较($\bar{x}\pm s$)

Table 3 Comparison of cyst diameter, irregular menstruation score, dysmenorrhea score between the two groups($\bar{x}\pm s$)

Groups	n	Cyst size(cm^2)		Irregular menstruation score (points)		Dysmenorrhea score(points)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	76	2.68 $\pm$ 0.32	1.78 $\pm$ 0.27	3.40 $\pm$ 0.36	1.80 $\pm$ 0.29	4.36 $\pm$ 0.59	3.58 $\pm$ 0.46
Observation group	58	2.60 $\pm$ 0.38	1.50 $\pm$ 0.20	3.27 $\pm$ 0.45	1.54 $\pm$ 0.21	4.20 $\pm$ 0.66	2.31 $\pm$ 0.32
t		1.321	6.628	1.857	5.768	1.477	17.962
P		0.188	0.000	0.065	0.000	0.142	0.000

表4 两组副反应比较[例(%)]

Table 4 Comparison of side reaction between two groups[n(%)]

Groups	n	Weak	Insomnia	Hot flashes	Total incidence rate
Control group	76	15(19.74)	13(17.11)	16(21.05)	44(58.89)
Observation group	58	13(22.41)	9(15.51)	10(17.24)	32(55.17)
χ^2		0.142	0.060	0.305	0.099
P		0.705	0.805	0.580	0.752

3 讨论

子宫内膜异位症的病情迁延,有一治疗难度^[13,14]。药物治疗是子宫内膜异位症患者的主要方式之一,既往研究已证实,孕激素能够减轻子宫内膜异位症患者的临床症状,起到良好的治疗作用^[15,16]。甲羟孕酮能够通过垂体及下丘脑负反馈作用影响性激素分泌,抑制卵巢功能,下调机体雌激素的表达,还可阻止血管新生,避免逆流内膜的种植及生长^[17]。尽管甲羟孕酮对于此类患者症状缓解有积极作用,但雌激素是维持机体骨量平衡的重要因素,其浓度过低可能引起不规则的骨量及月经缺失,有一定局限性^[18]。

近年来,药物反向添加疗法在子宫内膜异位症治疗中备受关注^[19,20]。戊酸雌二醇进入机体后可分解天然雌二醇,抑制甲羟孕酮所致的雌二醇下调,既往主要用于雌激素不足所致的闭经、更年期综合征及性腺功能不良等疾病^[21]。近年来有研究发现^[22,23],在孕激素治疗基础上加以戊酸雌二醇不会导致子宫内膜重新增殖,可有效降低复发风险。本研究结果显示,戊酸雌二醇联合甲羟孕酮组治疗后总有效率显著高于相对较高,说明二者联合治疗在临床疗效方面有一定突出作用。

子宫内膜异位症有恶性肿瘤能力,近年来有关研究发现^[24,25],多种肿瘤标志物在子宫内膜异位症表达中呈上升趋势。CA125及CA199均为癌性抗原,机体正常状态下其含量较低,可用于监测妇科肿瘤疾病的治疗及早期复发^[26,27]。血管新生在子宫内膜异位症发生中有重要作用,VEGF可为血管形成创造良好条件,通过测定以上指标改变可能有利于药物疗效的评价^[28,29]。本研究结果显示,联合治疗组治疗后以上指标下降更明显,说明二者联合治疗更能下调相关细胞因子的表达,从而在多个途径干预疾病,发挥治疗作用。进一步研究发现,联合治疗组治疗

后囊肿直径、月经不调评分、痛经评分降低更明显,证实二者联合作用能更好的促进子宫内膜异位囊肿的吸收,从而减轻临床症状。两组治疗期间均有少数患者出现轻微副反应,但均未影响后续治疗。

综上所述,戊酸雌二醇联合甲羟孕酮能够提高子宫内膜异位症的疗效,有效降低血清CA125、CA199及VEGF水平,安全性较高。

参考文献(References)

- [1] Mir O, Ropert S, Morice P, et al. Clinical Activity of Sunitinib and Regorafenib in Endometriosis [J]. Mayo Clin Proc, 2019, 94 (12): 2591-2593
- [2] Hierink MG, Poppelaars F, Klinkert ER, et al. Delay in diagnosis of endometriosis: a case report of catamenial pneumothorax[J]. Br J Gen Pract, 2015, 69(689): 626-627
- [3] Sashibhusan Dash, Sasmita Panda, Niranjana Route, et al. Role of fine needle aspiration cytology and cell block in diagnosis of scar endometriosis: A case report [J]. Journal of Cytology, 2015, 32(1): 71-73
- [4] Pliszkievicz M, Pliszkievicz M, Brzuchalski MA, et al. Bladder endometriosis - long-term efficacy of radical laparoscopic surgery [J]. Pol Merkuriusz Lekarski, 2019, 47(280): 139-143
- [5] Zambrano-Moncayo CP, López-Jaramillo JD, López-Isanoa JD, et al. Safety of the laparoscopic management of patients with deep infiltrative endometriosis in a reference center in pereira, colombia. retrospective cohorte, 2007-2016 [J]. Rev Colomb Obstet Ginecol, 2019, 70(3): 181-188
- [6] Yousef S, Jahanian Sadatmahalleh SH, Mottaghi A, et al. Dietary Phytoestrogen Intake and The Risk of Endometriosis in Iranian Women: A Case-Control Study[J]. Int J Fertil Steril, 2020, 13(4): 296-300
- [7] Koninckx PR, Ussia A, Adamyan L, et al. Heterogeneity of en-

- ometriosis lesions requires individualisation of diagnosis and treatment and a different approach to research and evidence based medicine[J]. *Facts Views Vis Obgyn*, 2019, 11(1): 57-61
- [8] Jain J, Kwan D, Forcier M. Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results From a Retrospective Study[J]. *J Clin Endocrinol Metab*, 2019, 104(11): 5148-5156
- [9] Dragoman MV, Gaffield ME. The safety of subcutaneously administered depot medroxyprogesterone acetate (104 mg/0.65 mL): A systematic review[J]. *Contraception*, 2016, 94(3): 202-215
- [10] Shin KH, Kim HH, Kwon BS, et al. Clinical Usefulness of Cancer Antigen (CA) 125, Human Epididymis 4, and CA72-4 Levels and Risk of Ovarian Malignancy Algorithm Values for Diagnosing Ovarian Tumors in Korean Patients with and Without Endometriosis[J]. *Ann Lab Med*, 2020, 40(1): 40-47
- [11] Alborzi S, Poordast T, Askary E, et al. Effects of clarithromycin on inflammatory markers and clinical manifestations in postsurgical follow-up of patients with endometriosis: a double-blinded randomized placebo-controlled clinical trial [J]. *Arch Gynecol Obstet*, 2019, 299(5): 1305-1312
- [12] Cooperative Group of Endometriosis, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Guideline for the diagnosis and treatment of endometriosis [J]. *Zhonghua Fu Chan Ke Za Zhi*, 2015, 50(3): 161-169
- [13] Biscaldi E, Barra F, Ferrero S. Magnetic Resonance Enema in Rectosigmoid Endometriosis[J]. *Magn Reson Imaging Clin N Am*, 2020, 28(1): 89-104
- [14] Lockyer EK, Schreurs A, Lier M, et al. Treatment of ovarian endometriomas using plasma energy in endometriosis surgery: effect on pelvic pain, return to work, pregnancy and cyst recurrence [J]. *Facts Views Vis Obgyn*, 2019, 11(1): 49-55
- [15] Awosile BB. Antimicrobial resistance in bacteria isolated from the uteri of horses with endometriosis[J]. *Vet Rec*, 2019, 185(19): 596-597
- [16] Antônio LGL, Rosa-E-Silva JC, Machado DJ, et al. Thalidomide Reduces Cell Proliferation in Endometriosis Experimentally Induced in Rats[J]. *Rev Bras Ginecol Obstet*, 2019, 41(11): 668-672
- [17] Oh ST. The Comparison Between 2mg Dienogest and High-Dose Medroxyprogesterone Acetate on Oral Treatment of Endometriosis [J]. *J Minim Invasive Gynecol*, 2015, 22(6S): S170
- [18] Connolly MA, Trentalange M, Zeiss CJ. Long-Term Clinical Outcomes in Diabetic Rhesus Macaques (*Macaca mulatta*) Treated with Medroxyprogesterone Acetate for Endometriosis [J]. *Comp Med*, 2016, 66(4): 343-348
- [19] Baik S, Mehta FF, Chung SH. Medroxyprogesterone Acetate Prevention of Cervical Cancer through Progesterone Receptor in a Human Papillomavirus Transgenic Mouse Model [J]. *Am J Pathol*, 2019, 189(12): 2459-2468
- [20] Omotola O, Legan S, Slade E, et al. Estradiol regulates daily rhythms underlying diet-induced obesity in female mice [J]. *Am J Physiol Endocrinol Metab*, 2019, 317(6): E1172-E1181
- [21] Kawakami M, Yokota-Nakagi N, Takamata A, et al. Endurance running exercise is an effective alternative to estradiol replacement for restoring hyperglycemia through TBC1D1/GLUT4 pathway in skeletal muscle of ovariectomized rats [J]. *J Physiol Sci*, 2019, 69(6): 1029-1040
- [22] Venegas B, De León Gordillo LY, Rosas G, et al. In rats with estradiol valerate-induced polycystic ovary syndrome, the acute blockade of ovarian β -adrenoreceptors improve ovulation [J]. *Reprod Biol Endocrinol*, 2019, 17(1): 95
- [23] Riahi-Zanjani B, Heidarzadegan M, Badibostan H, et al. Determination of 17β -estradiol in commercial pasteurized and sterilized milk samples in Mashhad, Iran [J]. *J Food Sci Technol*, 2019, 56(11): 4795-4798
- [24] Ponandai-Srinivasan S, Andersson KL, et al. Aberrant expression of genes associated with stemness and cancer in endometria and endometrioma in a subset of women with endometriosis [J]. *Hum Reprod*, 2018, 33(10): 1924-1938
- [25] Lac V, Verhoef L, Aguirre-Hernandez R, et al. Iatrogenic endometriosis harbors somatic cancer-driver mutations[J]. *Hum Reprod*, 2019, 34(1): 69-78
- [26] Margatho D, Mota Carvalho N, Eloy L, et al. Assessment of biomarkers in women with endometriosis-associated pain using the ENG contraceptive implant or the 52 mg LNG-IUS: a non-inferiority randomised clinical trial[J]. *Eur J Contracept Reprod Health Care*, 2018, 23(5): 344-350
- [27] Khodaverdi S, Amini-Moghaddam S, Almassi Nokiani F, et al. Adnexal mass with extremely high levels of CA-125 and CA19-9 but normal Human Epididymis Protein 4 (HE4) and Risk of Ovarian Malignancy Algorithm (ROMA): Endometriosis or ovarian malignancy? A case report[J]. *Int J Reprod Biomed (Yazd)*, 2018, 16(6): 413-416
- [28] Rashidi BH, Sarhangi N, Aminimoghaddam S, et al. Association of vascular endothelial growth factor (VEGF) Gene polymorphisms and expression with the risk of endometriosis: a case-control study [J]. *Mol Biol Rep*, 2019, 46(3): 3445-3450
- [29] Ansariniya H, Hadinedoushan H, Javaheri A, et al. Vitamin C and E supplementation effects on secretory and molecular aspects of vascular endothelial growth factor derived from peritoneal fluids of patients with endometriosis[J]. *J Obstet Gynaecol*, 2019, 39(8): 1137-1142