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雌激素与丹栀逍遥丸对更年期女性生殖内分泌系统及免疫功能的调节作用*

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摘要 目的:探究雌激素联合丹栀逍遥胶囊对更年期综合征妇女生殖内分泌系统及免疫功能的调节作用。**方法:**选取 2014 年 5 月至 2014 年 9 月我院收治的女性更年期综合症患者 60 例并将其随机分为两组, 其中对照组给予雌激素替代等临床常规疗法; 实验组在雌激素替代治疗基础上加用丹栀逍遥胶囊联合治疗。观察并比较两组患者生殖内分泌激素(E₂、FSH、LH)水平、T 淋巴细胞亚群(CD³⁺、CD⁴⁺、CD⁸⁺、CD⁴⁺/CD⁸⁺)比例以及 IL-2 活性的变化。**结果:**治疗后, 两组血清 E₂、CD³⁺、CD⁴⁺、CD⁴⁺/CD⁸⁺ 水平及 IL-2 活性均较治疗前显著升高, 而 FSH、LH 水平均明显低于治疗前, 且实验组治疗后 E₂、CD³⁺、CD⁴⁺、CD⁴⁺/CD⁸⁺ 水平及 IL-2 活性显著高于对照组, FSH、LH 水平均明显低于对照组, 差异均有统计学意义(P<0.05)。**结论:**雌激素联合丹栀逍遥胶囊能更加有效调节女性更年期综合征患者生殖内分泌激素水平, 提高免疫功能, 值得临床推广。

关键词:雌激素; 丹栀逍遥胶囊; 更年期综合征; 内分泌激素; 免疫功能

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Regulation of Estrogen Combined with Danzhi Xiaoyao Capsule on the Reproductive Endocrine and Immune Function of female patients with Climacteric Cyndrome*

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ABSTRACT Objective: To explore the regulatory effect of estrogen combined with Danzhi Xiaoyao Capsule on the reproductive endocrine and immune function of female patients with climacteric syndrome. **Methods:** 60 female patients with climacteric syndrome admitted in our hospital from May 2014 to September 2014 were selected and randomly divided into two groups, 30 patients in the control group were treated by the clinical routine of estrogen replacement, while the other 30 patients in the observation group were treated by dang zi xiao yao capsules based on the use of estrogen replacement therapy. After treatment, the reproductive endocrine hormone(E₂, FSH, LH) levels, the ratio of T lymphocyte subsets(CD³⁺, CD⁴⁺, CD⁸⁺, CD⁴⁺/CD⁸⁺), the changes of IL-2 activity were observed and compared between two groups. **Results:** After treatment, the E₂, CD³⁺, CD⁴⁺, CD⁴⁺/CD⁸⁺ levels and IL-2 activity of both groups were significantly higher than those before treatment (P<0.05), while the FSH, LH levels were obviously lower (P<0.05). Moreover, the E₂, CD³⁺, CD⁴⁺, CD⁴⁺/CD⁸⁺ levels and IL-2 activity of experiment group after treatment were all significantly higher than those of the control group(P<0.05), while the FSH, LH levels were obviously lower(P<0.05). **Conclusions:** Estrogen combined with Danzhi Xiaoyao capsule could effectively regulate the reproductive endocrine hormone levels and improve the immune function of female patients with climacteric syndrome, which was worthy of clinical application.

Key words: Estrogen; Dangzixiaoyao capsules; Climacteric syndrome; Endocrine hormone; Immune function

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前言

更年期综合征(menopausal syndrome, MPS)指妇女在绝经前后由于卵巢功能逐渐衰退、雌激素水平下降, 出现以植物神经系统功能紊乱为主伴有神经心理症状的一组症候群, 也称为围绝经期综合征^[1], 多发于 40-55 岁女性, 其发病原因主要为卵

巢功能减退、性激素水平下降, 临床特征表现为潮热汗出、月经不调、植物神经症状、骨质疏松、急躁易怒、失眠不寐、阴道泌尿系统疾病等^[2-4]。目前, 临床普遍采用的雌激素替代治疗无法从根本上消除患者的临床症状, 且长期大量服用会增加患者发生心脏病、乳腺癌的机率。祖国医学认为更年期综合征主要由经血不足、阴阳不调所致。近年来的研究发现^[5], 雌激素联合丹栀

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逍遥胶囊不仅能够有效改善更年期综合征,对于患者的生殖内分泌系统和免疫功能也具有调整作用。本研究通过观察患者治疗前后血清雌二醇(E₂)、卵泡刺激素(FSH)、黄体生成素(LH)、外周血 T 淋巴细胞亚群比例及 IL-2 活性水平的变化,旨在探究雌激素联合丹栀逍遥胶囊对更年期综合征妇女的生殖内分泌及免疫功能的调节作用。

1 资料与方法

1.1 一般资料

选择 2014 年 5 月至 2014 年 9 月于我院以更年期综合征为诊断而收入院的女性患者 60 例,采用随机数字表随机分为实验组和对照组。其中实验组 30 例,平均年龄(51.2±4.2)岁,平均病程(8.2±5.4)个月;对照组 30 例,平均年龄(49.8±5.3)岁,平均病程(7.1±6.3)个月。两组患者的一般资料比较无统计学差异(P>0.05),具有可比性。

1.2 诊断标准

1.2.1 西医诊断标准 参照 2002 年《中药新药临床研究指导原则》关于更年期综合征的诊断标准而拟定^[6]。其主要诊断标准包括:①发病年龄为 45~55 岁妇女;②除月经紊乱或闭经等月经病症外,还有急躁易怒、失眠多梦、潮热汗出等症状;③血清 E₂ 水平下降,FSH 及 LH 水平升高。

1.2.2 中医诊断标准 参照 2007 年“中药、天然药物治疗女性更年期综合征临床试验技术指导原则”和 2008 年《中医妇科学》中关于更年期综合征的诊断标准而拟定。其主要症状为:①发病年龄大于 40 周岁;②月经紊乱伴烘热汗出或情志急躁易怒;③心悸怔忡、斜肋部或乳房胀痛、失眠多梦、阴道干涩、夜尿频多等次要症状;④舌淡红或偏红,苔薄白或薄黄,脉弦数或细数。

1.3 纳入标准

符合更年期综合征中医、西医诊断标准;年龄 45~55 周岁,病程 6~24 个月;X 线、超声等检查无心、肝、肾等器质性病变;上述症状较为严重且要求药物治疗者;自愿参与本研究,并签署知情同意书。

1.4 排除标准

不愿参与本研究或不符合纳入标准者;有甲亢、心血管系统疾病等干扰疾病者;有较重传染性疾病患者;合并有严重肝、肾功能疾病患者;节律性失眠障碍或昼夜倒班工作者;对激素治疗有过敏史者;患有精神类疾病不能配合研究者。

1.5 治疗方法

1.5.1 对照组 参照临床常规雌激素替代疗法治疗,予结合雌激素片(Pfizer Ireland Pharmaceuticals,批准文号:H20130229),0.625 mg/d,周期性服药,服药三周停药一周,共治疗两个月^[7]。

1.5.2 实验组 在与对照组相同的常规治疗基础上加用丹栀逍遥胶囊(陕西方舟制药有限公司,批准文号:国药准字 Z20060255),1.8 g(4 粒)/次,每日两次口服,共治疗两个月。

1.6 观察指标及检测方法

检测患者用药前后血清激素(E₂、FSH、LH)水平、外周血 T 淋巴细胞亚群(CD³⁺、CD⁴⁺、CD⁸⁺)改善情况及外周血白细胞介素-2(IL-2)活性的变化。血清 E₂、FSH、LH 水平检测方法:患者治疗前和治疗后空腹抽取肘正中静脉血 2 ml,抗凝后离心处理,取上清液,用放射免疫法检测(试剂盒由上海西唐生物科技有限公司提供)。外周血 T 淋巴细胞亚群检测方法:采用免疫荧光法测定。外周血白细胞介素-2(IL-2)活性检测方法:采用 IL-2 依赖细胞 3H-TdR 参入法测量其活性水平。

1.7 统计学分析

本研究采用 SPSS19.0 统计学软件进行统计学分析,计量资料以 $\bar{x} \pm s$ 表示,采用 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者治疗前后血清 E₂、FSH、LH 水平变化的比较

入院时,两组患者血清 E₂、FSH、LH 水平比较差异无统计学意义(P>0.05);治疗后,两组血清 E₂ 水平均较治疗前显著升高,而 FSH、LH 水平均明显低于治疗前,且实验组治疗后 E₂ 水平显著高于对照组,FSH、LH 水平均明显低于对照组,差异均有统计学意义(P<0.05),如表 1。

表 1 两组患者治疗前后血清 E₂、FSH、LH 水平的比较($\bar{x} \pm s$)

Table 1 Comparison of E₂, FSH, LH levels in serum between two groups before and after treatment

Groups	E ₂ (pmol/L)		FSH(IU/L)		LH(IU/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Reference value	870.25±102.80(n=12)		29.63±7.06(n=12)		23.6±5.09(n=12)	
Control group (n=30)	449.25±80.25	693.98±83.77*	42.61±5.88	36.43±6.21*	39.51±7.01	32.55±8.14*
Experimental group (n=30)	453.22±78.21 [△]	831.56±65.36*▲	45.83±4.35 [△]	31.56±5.28*▲	38.77±3.24 [△]	29.63±4.58*▲

Note: *P<0.05, Compared with before treatment; ▲P<0.05, Compared with control group; △P>0.05, Compared with control group

2.2 两组患者治疗前后外周血 T 淋巴细胞亚群比例的比较

入院时,两组患者外周血 T 淋巴细胞亚群(CD³⁺、CD⁴⁺、CD⁸⁺、CD⁴⁺/CD⁸⁺)比较差异无统计学意义(P>0.05);经治疗后,两组患者的 CD³⁺、CD⁴⁺、CD⁴⁺/CD⁸⁺水平均较治疗前显著升高,

而 CD⁸⁺水平均明显低于治疗前,且实验组治疗后 CD³⁺、CD⁴⁺、CD⁴⁺/CD⁸⁺水平显著高于对照组,CD⁸⁺水平均明显低于对照组,差异均有统计学意义(P<0.05),如表 2。

表 2 两组患者治疗前后外周血 T 淋巴细胞亚群比例的比较($\bar{x} \pm s$)

Table 2 Comparison of the T-lymphocyte subsets in peripheral blood between two groups before and after treatment

Groups	CD ³⁺ (%)		CD ⁴⁺ (%)		CD ⁸⁺ (%)		CD ⁴⁺ /CD ⁸⁺	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Reference value	74.10± 7.35		46.590± 5.64		22.90± 4.30		2.09± 0.45	
Control group (n=30)	41.24± 7.61	59.24± 8.27*	26.24± 7.04	38.89± 5.41*	36.89± 6.511	29.14± 4.16*	0.92± 0.24	1.67± 0.34*
Experimental group (n=30)	44.79± 8.66 [△]	72.59± 8.21*▲	25.41± 5.87 [△]	43.79± 6.16*▲	37.14± 5.21 [△]	23.18± 6.18*▲	0.91± 0.18*	2.01± 0.34*▲

Note: *P<0.05, Compared with before treatment; ▲P<0.05, Compared with control group; △P>0.05, Compared with control group

2.3 两组患者治疗前后外周血 IL-2 活性的比较

入院时, 两组患者外周血 IL-2 活性水平比较差异无统计学意义(P>0.05); 经治疗后, 两组患者的外周血 IL-2 活性均较治疗前显著升高, 且实验组治疗后外周血 IL-2 活性显著高于对照组, 差异均有统计学意义(P<0.05), 如表 3。

表 3 两组患者治疗前后外周血 IL-2 活性水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the IL-2 activity in peripheral blood between two groups before and after treatment

Groups	IL-2 (U/ml)	
	Before treatment	After treatment
Reference value(n=12)	13.34± 5.81	
Control group(n=30)	2.89± 5.36	18.09± 6.47*
Experimental group(n=30)	3.01± 5.14 [△]	23.14± 6.38*▲

Note: *P<0.05, Compared with before treatment; ▲P<0.05, Compared with control group; △P>0.05, Compared with control group

3 讨论

更年期综合征是围绝经期妇女常见疾病之一^[11,12]。传统医学认为, 女性停经而子宫衰老, 此时天癸竭而冲任脉虚衰, 为绝经前后诸证的主要病机。有研究发现^[13,14], 雌激素替代疗法不能在根源上解决患者雌激素分泌不足, 停药后病情易复发。而传统医学在治疗更年期综合征时, 虽然能让卵巢功能恢复到接近育龄期水平, 但是中药治疗见效较慢, 疗程较长, 不能短时间内解决患者痛苦。有研究发现^[15], 绝经前后诸证与肝关系最为密切, 在常规雌激素疗法的基础上联合丹栀逍遥胶囊能够有效改善更年期综合征妇女的生殖内分泌及免疫功能。

有研究表明^[16], 由于衰退的卵巢产生的雌激素水平降低, 解除了雌激素对垂体的负反馈功能, 导致 FSH、LH 水平增高。这与本研究采集的更年期综合征患者血清 E₂ 水平较低, FSH、LH 水平较高是一致的。在本研究中, 仅给予雌激素替代等临床常规疗法的患者血清 E₂、FSH、LH 水平较治疗前亦有所恢复, 其原因可能为服用的雌激素补充了体内的雌激素不足, 从而重新建立垂体-下丘脑-卵巢轴的平衡, 恢复雌激素对垂体的反馈调节, 故 FSH、LH 的水平得以恢复至正常水平^[17,18]。而由于 FSH 的生成、释放受雌激素的反馈抑制较 E₂ 敏感, 因此 FSH

水平恢复较 LH 更好。

丹栀逍遥胶囊由柴胡、当归、白芍、白术、茯苓、甘草、牡丹皮、栀子组成, 方中柴胡、白芍疏肝解郁, 当归补血活血, 白术、茯苓健脾益气, 丹皮、栀子清热以除烦, 甘草调和诸药, 共奏疏肝健脾、解郁清热、养血调经之功, 从而缓解更年期综合征急躁易怒、失眠多梦、月经不调等症状。亦有学者研究证实^[19], 丹栀逍遥胶囊可降低 FSH、LH 水平, 提高 E₂ 水平, 与本研究一致。

女性进入更年期后, 其免疫功能亦开始降低, 更年期综合征患者则变化更甚。从本研究可以看出, 治疗前 T 细胞亚群中, 调高免疫应答能力的 CD³⁺、CD⁴⁺ 比例是明显低于参考值, 而调低免疫应答能力的 CD⁸⁺ 比例则高于参考值, CD⁴⁺/CD⁸⁺<1, 且 IL-2 活性水平亦低于正常值。其原因可能是由于更年期综合征患者卵巢机能减退, 产生雌激素不足, 导致 E₂ 水平下降, 免疫细胞雌激素受体随之减少, 不足量的雌激素难以维持对免疫细胞正常的刺激量, 导致免疫细胞产生的 IL-2 不足。仅给予雌激素替代等临床常规疗法的患者在服用雌激素后, CD³⁺、CD⁴⁺ 比例有所恢复, CD⁸⁺ 比例开始降低, IL-2 活性水平亦有所提高, 说明雌激素可以提高更年期综合征患者免疫功能。其机制可能为补充了足量雌激素后, E₂ 水平恢复至正常水平, 免疫细胞产生足量 IL-2, 拮抗去甲肾上腺素活性, 从而提高其免疫功能, 缓解更年期综合征症状^[20]。在雌激素替代治疗基础上加用丹栀逍遥胶囊联合治疗的患者免疫功能恢复情况更优于仅给予雌激素替代等临床常规疗法的患者, 其原因可能是由于联合了丹栀逍遥胶囊, 通过丹栀逍遥胶囊恢复冲任脉气血、调节肝脾, 使机体气血阴阳恢复至平衡水平, 从而提高机体免疫功能, 但其具体机制, 尚不十分明确, 还有待下一步进行深入研究。

综上所述, 雌激素联合丹栀逍遥胶囊能有效调节更年期综合征患者生殖内分泌激素水平, 提高免疫功能, 为治疗更年期综合征提供了新的思路和方法, 值得临床应用、推广。

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