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加味二妙颗粒联合重组人干扰素 a2b 阴道泡腾胶囊治疗宫颈上皮内瘤变的疗效及对患者免疫功能的影响 *

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摘要 目的:探讨加味二妙颗粒联合重组人干扰素 a2b 阴道泡腾胶囊治疗宫颈上皮内瘤变的疗效及对患者免疫功能的影响。**方法:**将西北妇女儿童医院妇科门诊自 2018 年 1 月至 2019 年 1 月收治的确诊为宫颈上皮内瘤变患者 300 例作为研究对象,将其随机的分为研究组和对照组,每组各 150 例。研究组患者给予加味二妙颗粒联合重组人干扰素 a2b 阴道泡腾胶囊进行治疗,对照组患者给予重组人干扰素 a2b 阴道泡腾胶囊进行治疗,比较两组患者治疗后的临床总有效率,治疗前后 $CD3^+$、$CD4^+$、$CD8^+$、NK 细胞水平和中医证候评分的变化及不良反应的发生情况。**结果:**治疗后,研究组临床总有效率为 91.33 %,明显高于对照组(74.67 %,$P<0.05$)。两组治疗后 $CD3^+$、$CD4^+$、$CD8^+$、NK 细胞水平均较治疗前明显升高,且研究组以上指标显著高于对照组($P<0.05$)。研究组治疗后中医证候评分降低程度明显优于对照组,其不良反应发生率为 10.00 %,明显低于对照组(28.67 %,$P<0.05$)。**结论:**与单用重组人干扰素 a2b 阴道泡腾胶囊治疗相比，加味二妙颗粒联合使用重组人干扰素 a2b 阴道泡腾胶囊治疗宫颈上皮内瘤变患者可显著提高患者的免疫功能,缓解症状,提高治疗效果,且安全性更高。

关键词:宫颈癌;宫颈上皮内瘤变;感染蛋白;二妙颗粒;重组人干扰素 a2b 阴道泡腾胶囊

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Clinical Efficacy of Jiawei Ermiao Granules Combined with Recombinant Human Interferon A2b Vaginal Effervescent Capsule in the Treatment of Cervical Intraepithelial Neoplasia and Its Effect on the Immune Function*

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ABSTRACT Objective: To investigate the clinical efficacy of Jiawei Ermiao Granules combined with recombinant human interferon a2b vaginal effervescent capsule in the treatment of cervical intraepithelial neoplasia and its effect on the immune function. **Methods:** 300 patients with cervical intraepithelial neoplasia who were admitted to the gynecological clinic of Northwest Women's and Children's Hospital from January 2018 to January 2019 were randomly divided into study group and control group, there were 150 patients in each group. The patients in study group were treated with Jiawei Ermiao Granules and recombinant human interferon a2b vaginal effervescent capsules. The patients in control group were treated with recombinant human interferon a2b vaginal effervescent capsules. These indexes were compared in the two groups which include the clinical total effective rate, the changes of $CD3^+$, $CD4^+$, $CD8^+$, NK cell level before and after treatment, the changes of TCM syndrome scores and the occurrence of adverse reactions. **Results:** After treatment, the total effective rate of the study group was 91.33%, which was significantly higher than that of the control group (74.67%, $P<0.05$). The levels of $CD3^+$, $CD4^+$, $CD8^+$ and NK cells after treatment were significantly higher than that before treatment, and the study group of the above-mentioned indexes was significantly higher than that of the control group ($P<0.05$). After treatment, the reduction of syndrome score in the study group was significantly better than that of the control group. The incidence of adverse reactions was 10.00%, which was significantly less than that of the control group (28.67%, $P<0.05$). **Conclusion:** Compared to the treatment with recombinant human interferon a2b vaginal effervescent capsule, the treatment with Jiawei Ermiao Granules combined with recombinant human interferon a2b vaginal effervescent capsule can significantly improve the immune function, relieve symptoms, improve the therapeutic effect of patients, and possess higher safety in cervical intraepithelial neoplasia.

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前言

宫颈癌(cervical cancer)是临床发病率仅次于乳腺癌的女性生殖系统常见恶性肿瘤,也是造成全球女性癌症患者死亡的主要原因[1]。大量研究资料显示在宫颈癌发生、发展过程中,高危型人乳头瘤病毒(Human papilloma virus,HPV)起着重要的作用[2,3]。宫颈癌原位癌好发于为 30～35 岁,浸润癌好发于 45～55 岁。近几十年,由于宫颈细胞学筛查的普遍应用,癌前病变和宫颈癌可以早期发现和治疗,宫颈癌的发病率和死亡率已有显著的下降[4,5]。

宫颈上皮内瘤变 (Cervical intraepithelial neoplasia,CIN)发生进展至宫颈癌是需要一个过程,其可以有效的反映宫颈癌发病进展的过程，对 CIN 进行及时的干预和治疗能够阻止宫颈癌前病变进展[6]。CIN 的患者多采用药物、物理或手术治疗,且均能获得一定的效果。目前,临床上用于治疗宫颈癌和癌前病变的常用药物是重组人干扰素 a2b 阴道泡腾胶囊[7],对于抵抗病毒感染,消除宫颈炎症,提高机体免疫力十分有效。近年来研究表明加味二妙颗粒治疗 CIN 合并 HPV 感染有一定的实用性和可行性[8],但还缺少临床前实验,因此本研究采用加味二妙颗粒联合重组人干扰素 a2b 阴道泡腾胶囊治疗 CIN 患者,观察治疗后疗效及患者免疫功能的变化，为 CIN 的治疗提供新的思路及临床前实验验证。

1 资料与方法

1.1 一般资料

选择西北妇女儿童医院妇科门诊 2018 年 1 月至 2019 年 1 月收治的确诊为 CIN 的 300 例患者，将其随机分为研究组 150 例和对照组 150 例,两组基本资料的对比差异无统计学意义(P＞0.05),具有可比性,详见表 1。

表 1 两组的一般资料的比较

Table 1 Comparison of the general data between the two groups

Groups	Cases	Age (years)	Average age (years)	CIN Stage II	CIN Stage III
Research group	150	22~50	38.62± 5.19	62(41.33)	88(58.67)
Control group	150	20~48	38.21± 4.98	59(39.33)	91(60.67)
x^2/t	-	-	0.582	0.927	
P	-	-	＞0.05	＞0.05	

1.2 纳入、排除标准

纳入标准:所有患者证实经阴道镜活检和宫颈液细胞学检测均为 CIN,年龄＞18 周岁,存在性生活史,HPV 检测结果为阳性,月经周期规律[9,10],并且伴有中度或重度宫颈上皮瘤样病变(CINⅡ期 ~Ⅲ期)。

排除标准:排除有过敏体质和精神障碍疾病,合并有严重心、肝、肾、肺和血液系统疾病,合并有严重生殖道炎症,出于哺乳期或妊娠期的患者。

本次研究获得了医院伦理委员会的批准同意,患者均知情且签署同意书。

1.3 研究方法

对照组：本组患者使用重组人干扰素 a2b 阴道泡腾胶囊(商品名:辛复宁;批准文号:国药准字 S20050075;生产企业:上海华新生物高技术有限公司;规格:80 万 IU/ 粒)进行治疗,直接将本品放置于阴道后穹隆接近宫颈口处,睡前使用,每次 1 粒,隔日一次,9 粒为一疗程。

研究组:在对照组治疗的基础上联合使用加味二妙颗粒进行治疗,方剂基本组成:黄柏、炒苍术、生薏仁、重楼、蛇舌草、板蓝根、土茯苓、炒白术各 10 g,加水煎煮,经期前 10 d 口服,每日一剂,早晚分服用,每月连续服 10 d,治疗 3 个月为一个疗程,临床治愈后即停用,临床观察 2 个疗程。

两组均治疗 6 个月,月经周期停用。

1.4 观察指标

临床疗效[12,13]:根据 CIN 管理指南来对两组患者的治疗效果进行评价，显效：治疗后经阴道镜检查宫颈醋酸上皮消失,HPV 检查结果阴性;有效:治疗后阴道镜检查宫颈醋酸上皮厚度变薄,面积缩小,HPV 检测结果至少一种是阴性;无效:治疗前后患者症状无任何改善甚至病情恶化加重。临床总有效率为显效率 + 有效率。

细胞检测:治疗前后,于患者清晨且空腹的状态下采集患者周静脉血并置于抗凝管中,加入相关鼠抗人克隆抗体,根据说明书使用 Beckman-Coultet XL 流式细胞仪检测 T 细胞亚群和 NK 细胞活性。

中医证候积分:根据《中医病症诊断疗效标准》观察患者治疗前后中医证候计分变化情况,得分越低表明患者症状越轻微[14]。

不良反应:记录两组患者治疗过程中不良反应发生率。

1.5 统计学方法

采用 SPSS19.0 分析处理数据,以%和($\bar{x}\pm s$)分别表示计数资料和计量资料，使用 x^2 或 t 检验进行组间比较，以 P＜0.05 时为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，研究组临床总有效率为 91.33%，对照组为 74.67%，研究组明显高于对照组($P<0.05$)，详见表 2。

表 2 两组临床疗效的比较

Table 2 Comparison of the clinical effects between two groups

Groups	Cases	Significant effect	Effective	Invalid	Total efficiency
Research group	150	71(47.33)	66(44.00)	13(8.67)	137(91.33)
Control group	150	53(35.33)	59(39.33)	38(25.33)	112(74.67)
x^2	-	-	-	-	4.392
P	-	-	-	-	＜0.05

2.2 两组治疗前后 $CD3^+$、$CD4^+$、$CD8^+$、NK 细胞水平的比较

两组治疗前 $CD3^+$、$CD4^+$、$CD8^+$、NK 细胞水平比较差异无统计学意义($P>0.05$)，而治疗后各项指标在均较治疗前显著升高，且研究组患者明显高于对照组($P<0.05$)，见表 3。

表 3 两组治疗前后 $CD3^+$、$CD4^+$、$CD8^+$、NK 细胞水平的比较

Table 3 Comparison of the $CD3^+$, $CD4^+$, $CD8^+$, NK cell levels between two groups before and after treatment

Groups	Subgroup	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	NK(%)
Research group(n=150)	Before treatment	34.78± 4.31	24.19± 2.64	23.93± 2.19	43.12± 5.29
	After treatment	46.58± 5.20*#	30.32± 3.10*#	29.04± 2.48*#	50.47± 7.38*#
Control group(n=150)	Before treatment	34.69± 4.74	24.24± 2.58	23.11± 2.29	43.46± 5.18
	After treatment	39.11± 4.92*	27.08± 2.73*	26.42± 2.15*	46.11± 6.95*

Note: *$P<0.05$ means compared with before treatment; #$P<0.05$ means compared with the control group after treatment.

2.3 两组治疗前后中医证候评分和不良反应的发生情况比较

治疗后，研究组中医证候评分明显低于对照组，其不良反应发生率为 10.00%，明显低于对照组(28.67%，$P<0.05$)，见表4。

表 4 两组中医证候评分和不良反应的发生情况比较

Table 4 Comparison of TCM Syndrome Scores before and after treatment and incidence of adverse reactions between two groups

Groups	Cases	TCM syndrome score		Feel sick and vomit	Dizziness, headache	Irregular menstruation	Heat	Total
		Before treatment	After treatment					
Research group	150	7.38± 1.29	1.32± 0.56	4	6	3	2	15(10.00)
Control group	150	7.42± 1.31	3.26± 0.74	10	15	12	6	43(28.67)
x^2/t	-	0.382	4.194					3.294
P	-	＞0.05	＜0.05					＜0.05

3 讨论

宫颈癌是女性常见的恶性肿瘤之一，严重影响患者的生活质量和生命安全。HPV 感染的低危患者在疾病初期通过激活自身免疫系统，及时清除病毒可达到治愈的目的，少部分高危型感染的患者体内病毒会发生免疫逃逸，如果不重视会最终引起癌变[15,16]。大量研究证实 CIN 能对宫颈癌进行早期筛查、早期诊断、早期干预，及时清除 HPV 感染，增强机体抵抗力，可明显的阻止病变进一步发展[17-19]。临床治疗 CIN 方法包括高频电刀宫颈环切术、电烙术等手术，但对机体存在不同程度的破坏性，尤其对年轻的女性而言会对生育功能造成影响，同时也存在较高的复发率[20,21]。

局部使用重组人干扰素 a2b 阴道泡腾胶囊治疗宫颈癌前病变患者可达到强化巨噬细胞吞噬功能、调节机体免疫机制[22]，加快 NK 细胞对病毒的杀伤作用，增加 T 淋巴细胞亚群的表达，促进特异性的抗原肽复合物和肿瘤细胞结合，释放穿孔素、颗粒酶，溶解、杀灭肿瘤靶细胞，诱导使其凋亡，同时会加快肿瘤细胞细胞的清除速率[23,24]。本研究结果显示在常规使用重组人干扰素治疗的基础上联合使用加味二妙颗粒进行治疗的总有效率明显高于单用重组人干扰素治疗，T 淋巴细胞亚群和 NK 细胞水平明显升高，中医证候积分显著降低。中医治疗讲究整体观念、辨证论治、治病求本，可以从根本上调节机体自身气血津液之间的关系[25]。加味二妙颗粒由黄柏、炒苍术、生薏仁、重楼、蛇舌草、板蓝根、土茯苓、炒白术组成，方中黄柏性寒味苦，具有清热解毒、燥湿的功效[26]；炒苍术性温、味辛苦，具有燥湿健脾，祛风散寒的功效；生薏仁性微寒，味甘淡，具有利湿健

脾、舒筋除痹的功效；重楼性微寒，味苦，具有清热解毒、消肿止痛的功效[27]；蛇舌草性寒味苦寒，具有清热解毒、消痈散疖、利尿除湿的功效；板蓝根性寒味先微甜后苦涩，具有清热解毒的功效；土茯苓性平，味甘淡，具有解毒、除湿、利关节的功效[28]；炒白术属于补虚药，具有健脾益气的功效，上述诸药合奏清热燥湿，健脾益气的功效，尤其对湿热下注型合并 HPV 持续性感染的 CIN 患者疗效显著，联合使用重组人干扰素 a2b 阴道泡腾胶囊可共同调节机体的免疫力，修复免疫损伤，有效的增加了机体的抵抗力，提高对 HPV 的清除率，增加了局部应用干扰素的局限性，而且使用中药治疗毒副作用比较小，安全性高[29,30]。

综上所述，与单用重组人干扰素 a2b 阴道泡腾胶囊治疗相比，加味二妙颗粒联合使用重组人干扰素 a2b 阴道泡腾胶囊治疗宫颈上皮内瘤变患者可显著提高患者的免疫功能，缓解症状，提高治疗效果，且安全性更高。

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