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苏黄止咳胶囊联合舒利迭对咳嗽变异性哮喘患者肺功能、免疫功能及诱导痰炎性介质的影响*

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摘要 目的:探讨苏黄止咳胶囊联合舒利迭对咳嗽变异性哮喘(CVA)患者肺功能、免疫功能及诱导痰炎性介质的影响。**方法:**选取2017年1月-2019年12月期间我院收治的93例CVA患者,按照随机数字表法分为对照组(n=46)和研究组(n=47),对照组患者给予舒利迭治疗,研究组在对照组的基础上联合苏黄止咳胶囊治疗,比较两组患者疗效、肺功能、免疫功能、诱导痰炎性介质以及不良反应情况。**结果:**研究组治疗2个疗程后的临床总有效率高于对照组($P<0.05$)。两组患者治疗2个疗程后第1秒用力呼气容积(FEV1)、用力肺活量(FVC)以及呼气峰值流量(PEF)、CD4⁺、CD4⁺/CD8⁺均较治疗前升高,且研究组高于对照组($P<0.05$)。两组患者治疗2个疗程后CD8⁺以及诱导痰白介素-6(IL-6)、白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)水平均较治疗前降低,且研究组低于对照组($P<0.05$)。两组不良反应发生率比较无差异($P>0.05$)。**结论:**舒利迭联合苏黄止咳胶囊治疗CVA患者,可有效改善患者肺功能、免疫功能,降低诱导痰炎性介质水平,且不增加不良反应发生率,安全可靠,疗效显著。

关键词:舒利迭;咳嗽变异性哮喘;苏黄止咳胶囊;肺功能;免疫功能;诱导痰炎性介质

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The Effect of Suhuang Zhike Capsule Combined with Seretide on Pulmonary Function, Immune Function and Induced Sputum Inflammatory Mediators in Patients with Cough Variant Asthma*

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ABSTRACT Objective: To investigate the effect of Suhuang Zhike capsule combined with Seretide on pulmonary function, immune function and induced sputum inflammatory mediators in patients with cough variant asthma (CVA). **Methods:** 93 patients with CVA who were admitted to our hospital from January 2017 to December 2019 were selected, they were randomly divided into control group (n=46) and study group (n=47) by random number table method. Patients in the control group were treated with Seretide, while those in the study group were treated with Suhuang Zhike capsule on the basis of the control group. The therapeutic effect, lung function, immune function, induced sputum inflammatory mediators and adverse reactions were compared between the two groups. **Results:** The total clinical effective rate of the study group at 2 courses after treatment was higher than that of the control group ($P<0.05$). The forced expiratory volume in the first second (FEV1), vital capacity (FVC), peak expiratory flow (PEF), CD4⁺, CD4⁺/CD8⁺ of the two groups at 2 courses after treatment were higher than those before treatment, and those of the study group were higher than those of the control group ($P<0.05$). The levels of CD8⁺, interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α) in induced sputum of the two groups were lower than those before treatment, and those of the study group were lower than those of the control group ($P<0.05$). There was no difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Suhuang Zhike capsule combined with Seretide is effective in the treatment of patients with CVA. It can effectively improve the lung function and immune function, reduce the level of induced sputum inflammatory mediators, and do not increase the incidence of adverse reactions. It is safe and reliable.

Key words: Seretide; Cough variant asthma; Suhuang Zhike capsule; Lung function; Immune function; Induced sputum inflammatory mediators

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前言

咳嗽变异性哮喘(Cough variant asthma,CVA)是以咳嗽为唯一或主要临床表现的特殊类型哮喘,并伴有气道高反应性、气道嗜酸性细胞炎症以及气道重塑,症状多发生在夜间或凌晨,烟雾、灰尘和冷空气等可诱发或加重症状^[1-3]。CVA 的治疗原则基本与支气管哮喘相同,皆以阻止疾病进展、改善临床症状为主^[4]。沙美特罗替卡松吸入气雾剂(舒利迭)被推荐为治疗 CVA 的药物之一,可获得一定的疗效,但存在停药后易复发,且长期使用毒副作用较大的缺点^[5,6]。苏黄止咳胶囊具有疏风宣肺、止咳利咽的功效,临床常用于感冒后咳嗽,咳嗽反复发作等病症^[7]。本研究通过对我院收治的部分 CVA 患者给予苏黄止咳胶囊联合舒利迭治疗,疗效明确,整理如下。

1 资料与方法

1.1 一般资料

选取 2017 年 1 月-2019 年 12 月期间我院收治的 CVA 患者 93 例,纳入标准:(1)诊断标准参考《咳嗽变异性哮喘的诊断与鉴别诊断》^[8];(2)患者及其家属知情本次研究且已签署了同意书;(3)入院前 1 个月内未接受过其他治疗者;(4)应用常规止咳化痰药和抗生素后未得到明显缓解;(5)对本次研究使用药物无禁忌症者;(6)支气管激发试验提示阳性。排除标准:(1)因其他原因引起的慢性咳嗽;(2)妊娠或哺乳期妇女;(3)精神异常不能配合完成本次研究者;(4)嗜酸性粒细胞性支气管炎、变应性咳嗽、支气管结核、胃食管反流性咳嗽者;(5)未能遵从医嘱服药者;(6)合并心肝肾等重要脏器障碍者。根据随机数字表法将患者分为对照组(n=46)和研究组(n=47),其中对照组男 25 例,女 21 例,年龄 24~59 岁,平均(38.91±4.37)岁;病程 4 个月~3 年,平均(1.96±0.37)年;体质量指数 21~26 kg/m²,平均(23.27±0.82)kg/m²。研究组男 27 例,女 20 例,年龄 22~61 岁,平均(39.25±5.36)岁;病程 6 个月~3 年,平均(2.05±0.42)年;体质量指数 20~26 kg/m²,平均(23.51±0.97)kg/m²。两组一般资料比较无差异(P>0.05),临床基础资料组间具有可比性。

1.2 治疗方法

两组均给予止咳、平喘、抗炎等常规治疗,在此基础上,对

照组予以舒利迭(Laboratoire GlaxoSmithKline,规格:每瓶 60 揅/120 揅,每揅含沙美特罗 25 μg 和丙酸氟替卡松 125 μg,批准文号 H20140382)治疗,每次 1 吸,早晚各 1 次。研究组在对照组的基础上联合苏黄止咳胶囊(规格:每粒装 0.45 g,国药准字 Z20103075,扬子江药业集团北京海燕药业有限公司)治疗,口服,3 粒/次,3 次/d。7d 为 1 个疗程,两组均治疗 2 个疗程。

1.3 观察指标

(1)于治疗前、治疗 2 个疗程后采用 6200 型肺功能仪(美国 SensorMedics 公司)检测两组患者的用力肺活量(Forced vital capacity,FVC)、第 1 秒用力呼气容积(Forced expiratory volume in the first second,FEV1)以及呼气峰值流量(Peak expiratory flow,PEF)。(2)采用门诊复查或电子询问等方式随访 3 个月,记录两组治疗临床总有效率。总有效率=显效率+有效率^[9]。其中无效:咳嗽等临床症状未见改善甚至加重。有效:治疗后 7 d 内咳嗽等临床症状有所改善,随访 3 个月左右无复发迹象。显效:治疗后 7 d 内咳嗽等临床症状消失,随访 3 个月左右无复发迹象。(3)记录两组治疗期间不良反应情况。(4)于治疗前、治疗 2 个疗程后取两组患者空腹静脉血 4 mL,经离心半径 12 cm,3600 r/min 离心 15min,取上清液,置于冰箱中保存备用,采用 FACSCalibur 流式细胞仪(美国 BD 公司生产)检测 T 淋巴细胞亚群:CD4⁺、CD8⁺,计算 CD4⁺/CD8⁺ 比值。(5)采集两组患者治疗前、治疗 2 个疗程后的诱导痰,采用酶联免疫吸附试验法(试剂盒均购自上海钰博生物科技有限公司)检测白介素-6(Interleukin-6,IL-6)、白介素-8(Interleukin-8,IL-8)、肿瘤坏死因子-α(Tumor necrosis factor-α,TNF-α)水平。

1.4 统计学方法

采用 SPSS20.0 进行数据分析。计数资料以例数及率的形式表示,行卡方检验。计量资料均为正态资料,以均值±标准差($\bar{x} \pm s$)的形式表示,行 t 检验。检验标准设置为α=0.05。

2 结果

2.1 两组疗效比较

研究组治疗后的临床总有效率 87.23%(41/47)高于对照组 69.57%(32/46),差异有统计学意义(P<0.05)。详见表 1。

表 1 两组疗效比较 例(%)

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

Groups	Effective	Valid	Invalid	Total effective rate
Control group(n=46)	8(17.39)	24(52.17)	14(30.43)	32(69.57)
Study group(n=47)	14(29.79)	27(57.45)	6(12.77)	41(87.23)
χ^2				4.299
P				0.038

2.2 两组肺功能指标比较

两组治疗前 FVC、FEV1、PEF 比较无差异(P>0.05);两组治疗 2 个疗程后 FEV1、FVC、PEF 均较治疗前升高,且研究组高于对照组(P<0.05)。详见表 2。

2.3 两组免疫功能指标比较

两组患者治疗前 CD4⁺、CD8⁺、CD4⁺/CD8⁺ 比较差异均无统计学差异(P>0.05);两组患者治疗 2 个疗程后 CD4⁺、CD4⁺/CD8⁺ 均较治疗前升高,且研究组高于对照组(P<0.05),CD8⁺ 较治疗前降低,且研究组低于对照组(P<0.05)。详见表 3。

表 2 两组肺功能指标比较($\bar{x} \pm s$)Table 2 Comparison of lung function indexes between the two groups($\bar{x} \pm s$)

Groups	FEV1(L)		FVC(L)		PEF(L/s)	
	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment
Control group(n=46)	2.68± 0.42	2.97± 0.36*	3.62± 0.43	4.07± 0.39*	3.57± 0.53	4.06± 0.42*
Study group(n=47)	2.74± 0.36	3.31± 0.33*	3.56± 0.38	4.64± 0.55*	3.52± 0.38	4.61± 0.53*
t	0.740	4.749	0.713	5.754	0.524	5.539
P	0.461	0.000	0.477	0.000	0.602	0.000

Note: compared with before treatment, * $P<0.05$.表 3 两组免疫功能指标比较($\bar{x} \pm s$)Table 3 Comparison of immune function indexes between the two groups($\bar{x} \pm s$)

Groups	CD4 ⁺ (%)		CD8 ⁺ (%)		CD4 ⁺ /CD8 ⁺	
	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment
Control group(n=46)	31.73± 5.51	35.96± 5.61*	30.56± 4.76	27.63± 3.58*	1.04± 0.28	1.30± 0.24*
Study group(n=47)	31.58± 6.47	40.79± 5.42*	30.62± 5.82	24.17± 3.73*	1.03± 0.25	1.69± 0.26*
t	0.122	4.223	0.054	4.562	0.182	7.512
P	0.903	0.000	0.957	0.000	0.856	0.000

Note: compared with before treatment, * $P<0.05$.

2.4 两组诱导痰炎性介质比较

两组患者治疗前诱导痰 IL-6、IL-8、TNF- α 水平比较差异均无统计学差异 ($P>0.05$); 两组患者治疗 2 个疗程后诱导痰

IL-6、IL-8、TNF- α 水平均较治疗前降低, 且研究组低于对照组 ($P<0.05$)。详见表 4。

表 4 两组诱导痰炎性介质比较($\bar{x} \pm s$)Table 4 Comparison of induced sputum inflammatory mediators between the two groups($\bar{x} \pm s$)

Groups	IL-6(ng/L)		IL-8(ng/L)		TNF- α (ng/L)	
	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment	Before treatment	2 courses after treatment
Control group(n=46)	32.31± 4.13	24.11± 3.12*	19.13± 2.26	14.46± 2.92*	9.35± 1.62	7.27± 0.84*
Study group(n=47)	32.06± 3.73	15.20± 2.62*	19.21± 3.27	8.74± 1.86*	9.29± 1.48	5.18± 0.72*
t	0.306	14.926	0.137	11.292	0.187	12.892
P	0.760	0.000	0.891	0.000	0.852	0.000

Note: compared with before treatment, * $P<0.05$.

2.5 两组不良反应发生率比较

治疗期间, 对照组出现皮疹、心动过速各 1 例, 头痛、腹泻腹痛各 2 例, 不良反应总发生率为 13.04%(6/46); 研究组出现腹泻腹痛 3 例, 头痛、面部潮红、心动过速、皮疹各 1 例, 不良反应总发生率为 14.89%(7/47); 两组不良反应发生率比较无差异 ($\chi^2=0.066, P=0.797$)。

3 讨论

CVA 是气道慢性炎症性疾病, 是慢性咳嗽的常见原因, 国内多中心调查结果显示 CVA 约占慢性咳嗽原因的三分之一^[10]。虽然 CVA 在临床较为常见, 但因其缺乏特异性症状及体征, 往往易被漏诊及误诊。CVA 的发病诱因复杂, 遗传、免疫状

态失衡及病毒感染等多种因素均可诱导疾病发生^[11]。随着研究的深入, 临床研究发现^[12], CVA 的本质是多种细胞因子参与介导的慢性炎症性过程。而机体内多种细胞分泌炎性介质参与炎症反应, 可损伤患者支气管粘膜及肺功能, 进而导致患者免疫功能下降^[13]。因此, 临床在治疗的过程中, 应在改善患者症状的基础上, 尽可能减轻疾病对患者肺功能及免疫功能的影响。现临床有关 CVA 的治疗尚无统一方案, 舒利迭是临床常用于治疗 CVA 的药物之一, 该药物由长效 β_2 受体激动剂与糖皮质激素复合组成, 其中丙酸氟替卡松抗炎效果显著, 可抑制肺部肥大细胞介质的释放, 进而缓解哮喘症状, 减少全身性的不良反应; 而沙美罗特具有扩张支气管的效果, 有效改善咳嗽症状。两药联合应用, 可发挥扩张气道及抗炎的双重作用^[14-16]。中西医结合

合治疗是近年来的流行治疗趋势^[7]。苏黄止咳胶囊的主要成分为麻黄、紫苏叶、五味子、前胡、蝉蜕、地龙等成分,其中麻黄为君药,祛风散寒;五味子为臣药,敛收肺气,祛痰止咳;前胡为佐药,可增肺之宣降;蝉蜕、地龙等可促风邪疏散,缓解气道炎症^[18,19]。

本次研究结果显示,研究组治疗后的临床总有效率高于对照组,且研究组患者肺功能的改善情况优于对照组,表明苏黄止咳胶囊联合舒利迭治疗的可行性及有效性。既往已有研究证实^[20],苏黄止咳胶囊能够通过抑制气道炎性细胞分泌炎性因子、松弛支气管平滑肌、保护上皮细胞缓解CVA患者气道痉挛,对肺功能具有一定的改善作用。与本次研究结果基本一致。CVA是由多种细胞因子参与的一种慢性炎症性过程,IL-6、IL-8、TNF- α 作为临床常见的炎性因子,其中IL-6的主要作用是促进炎性细胞与内皮细胞结合,加重气道炎性反应^[21];IL-8可促进中性粒细胞、T淋巴细胞的趋化作用,损伤内皮细胞,导致微循环障碍,引起组织坏死而造成机体组织脏器损伤^[22];TNF- α 是炎性反应中最先出现的炎性因子,可激活淋巴细胞而促进其他细胞因子的合成和释放,还可调节其他组织的代谢活性^[23]。随着机体上述细胞因子的增多,可刺激免疫效应细胞而导致机体免疫功能紊乱^[24]。其中T淋巴细胞分泌失衡是导致CVA的重要病理机制^[25,26]。本研究结果中,两组患者免疫功能、诱导痰炎性介质水平均得到显著改善,且苏黄止咳胶囊联合舒利迭治疗者的改善效果更佳。这可能是因苏黄止咳胶囊的药物成分中:五味子可镇咳化痰,提高机体免疫;麻黄能够促进支气管舒张,减轻气道反应;前胡可使呼吸道的黏液分泌增加,且可阻止支气管痉挛;地龙能够拮抗组胺,消除病毒^[27,28]。上述药物成分可有效控制细胞因子的大量释放,阻止炎性细胞的损害,免疫反应的激活,进一步阻止疾病进展^[29,30]。另两组不良反应发生率比较无差异,可见苏黄止咳胶囊联合舒利迭治疗安全可靠。

综上所述,苏黄止咳胶囊联合舒利迭治疗CVA患者,疗效显著,可有效改善肺功能、免疫功能,降低诱导痰炎性介质水平,且不增加不良反应发生率,安全可靠。

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