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百令胶囊联合罗氟司特治疗老年支气管哮喘的效果及对免疫功能的影响 *

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摘要 目的:研究百令胶囊联合罗氟司特治疗老年支气管哮喘的效果及对免疫功能的影响。**方法:**选择 2018 年 3 月～2019 年 3 月我院第六派驻门诊部收治的 110 例老年支气管哮喘患者,随机分为两组,每组各 55 例。对照组患者口服罗氟司特片,每次 500 mg,每天 1 次。观察组患者联合服用百令胶囊,每次 5 粒,每天 3 次。比较两组的临床控制率,治疗前后两组诱导痰中炎症因子、中性粒细胞、呼出气一氧化氮(fractional exhaled nitric oxide,FeNO)水平和免疫功能的变化。**结果:**治疗后,观察组的临床控制率为 70.91 %(39/55),明显高于对照组[40.00 %(22/55)](*P*<0.05);两组的 $CD4^+$、$CD4^+/CD8^+$ 和 $CD3^+$ 均较治疗前明显升高,且观察组的 $CD4^+$、$CD4^+/CD8^+$ 和 $CD3^+$ 明显高于对照组(*P*<0.05);两组患者诱导痰中中性粒细胞绝对值、中性粒细胞百分比、白细胞介素 -4(interleukin-4,IL-4)、FeNO、白细胞介素 -17(interleukin-17,IL-17)均较治疗前明显降低(*P*<0.05),诱导痰中的干扰素 -γ(Interferon gamma,IFN-γ)均较治疗前明显升高(*P*<0.05),且观察组诱导痰中的组中性粒细胞绝对值、中性粒细胞百分比、IL-4、FeNO、IL-17 明显低于对照组(*P*<0.05),诱导痰中的 IFN-γ 均明显高于对照组(*P*<0.05)。**结论:**百令胶囊联合罗氟司特对老年支气管哮喘患者具有显著的疗效,其机制可能与抑制中性粒细胞的激活、调节 T 淋巴细胞亚群的平衡和抑制相关炎症因子的释放相关。

关键词:百令胶囊;罗氟司特;老年支气管哮喘;免疫功能

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Clinical Efficacy of Bailing Capsule Combined with Rofluoristone in the treatment of Elderly Patients with Bronchial Asthma and Its Effect on the Immune Function*

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ABSTRACT Objective: To investigate the clinical efficacy of Bailing Capsule combined with rofluoristone in the treatment of elderly patients with bronchial asthma and its effect on immune function. **Methods:** Selected 110 elderly patients with bronchial asthma who were treated in our hospital from March 2018 to March 2019, divided into two groups randomly, each with 55 cases. The control group was treated with rofluoristone tablets orally, 500 mg each time, once a day. The observation group took bailing capsule, 5 capsules each time, 3 times a day. Compared the clinical control rate of the two groups, and observed the changes of inflammatory factors, neutrophils, exhaled FeNO level and immune function in the induced sputum of the two groups before and after treatment. **Results:** After treatment, the clinical control rate in the observation group was 70.91 % (39/55), which was significantly higher than the control group [40.00 % (22/55)] (*P*<0.05). After treatment, $CD4^+$, $CD4^+/CD8^+$ and $CD3^+$ in the two groups were significantly higher than before treatment, and the observation group were significantly higher than those in the control group (*P*<0.05). After treatment, the absolute value of neutrophils, percentage of neutrophils, IL-4, FeNO and IL-17 were significantly lower in the two groups than before treatment (*P*<0.05), and IFN-γ in the induced sputum was significantly higher than before treatment (*P*<0.05). The absolute value of neutrophils, the percentage of neutrophils, IL-4, FeNO and IL-17 in the induced sputum of the observation group were significantly lower than those of the control group (*P*<0.05), and the IFN-γ in the induced sputum was significantly higher than that of the control group (*P*<0.05). **Conclusion:** Bailing Capsule combined with rofluorostat had a significant effect on elderly patients with asthma. The mechanism may be related to the inhibition of neutrophil activation, the regulation of the balance of T-lymphocyte subsets and the inhibiting the release of related inflammatory factors.

Key words: Bailing Capsule; Rofluorast; Senile Asthma; Immune Function

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前言

支气管哮喘是一种以气流阻塞与多种炎性因子和炎症细胞浸润为主要特征的慢性呼吸道疾病[1,2]。在急性发作时,支气管哮喘患者常常表现为喘憋、咳嗽和呼吸困难,重度的哮喘发作甚至能导致心律失常以及呼吸衰竭,严重威胁其生活质量[3-5]。支气管哮喘的治疗以减少发作以及控制呼吸道症状为主,常规的治疗药物有抗胆碱能药物、糖皮质激素、茶碱类药物和支气管扩张剂,长时间应用后,患者机体会对上述药物的敏感性会不断降低,且存在多种的不良反应,如口干、头痛、声音嘶哑等[6,7]。

罗氟司特是一种新型的磷酸二酯酶 4 抑制剂,对支气管哮喘具有一定效果,但单独使用的效果并不佳。近些年来,在支气管哮喘的治疗中,中药的应用开始不断增多。百令胶囊的主要成分是冬虫夏草,能有效益精气、补肺肾,具有增强免疫功能、抗氧化以及改善肺功能等多种效果[8]。本研究主要探讨了百令胶囊联合罗氟司特治疗老年支气管哮喘的效果及对免疫功能的影响,旨在为老年支气管哮喘的临床用药提供依据。

1 资料与方法

1.1 一般资料

选择 2018 年 3 月～2019 年 3 月我院第六派驻门诊部收治的 110 例老年支气管哮喘患者,纳入标准:(1)符合相关的诊断标准[9],(2)近期没有严重的感染;(3)年龄 >60 周岁;(4)在本研究的治疗前至少 3 个月没有出爱去免疫性药物治疗;(5)知情同意。排除标准:(1)合并呼吸衰竭、肺部感染、心源性哮喘的患者;(2)患有比较严重的脑、心血管、肝脏和肾脏疾病患者;(3)血气分析发现,动脉二氧化碳分压持续不断升高,而且伴有伴进行性呼吸性酸中毒的患者;(4)患有造血系统疾病和自身免疫性疾病的患者;(5) 病情危重必须进行气管切开或者气管插管的患者。用抽签法将患者随机分为两组,观察组 55 例,男 28 例,女 27 例;年龄 60～82 岁,平均(69.34±3.19)岁;病程 4~15 年,平均(10.13±1.27)年。对照组 55 例,男 29 例,女 26 例;年龄 60～82 岁,平均(69.27±2.36)岁;病程 4~15 年,平均(10.09±1.38)年。两组的基线资料比较具有可比性(P>0.05)。

1.2 治疗方法

对照组:口服罗氟司特片(批号:120002,生产厂家:艾德凯腾生物医药公司),每次 500 mg,每天 1 次。重症患者给予氨溴索祛痰、头孢类药物抗感染、地塞米松静滴、雾化吸入多索茶碱解痉和吸氧支持治疗。观察组:联合服用百令胶囊(批号:国药准字 Z10910036,生产厂家:杭州中美华东制药),每次 5 粒,每天 3 次。1 个疗程为 60 d,总计治疗两个疗程。

1.3 观察指标

疗效标准[9]:① 临床控制:患者的第 1 秒用力呼气的容积(forced expiratory volume in one second,FEV_1) 与治疗相比升高超过 35 %或者治疗后大于 80 %的预计值,支气管哮喘症状基本消失或偶然发作,但是不需要给药;② 显效:患者的 FEV_1 值与治疗前相比升高 25 %～35 %,或治疗后可以达到预计值的 60 %～79 %,支气管哮喘症状显著缓解;③ 有效:患者的 FEV_1 值与治疗前相比升高 15 %～24 %,支气管哮喘症状轻微缓解;④ 无效:患者的 FEV_1 值和支气管哮喘症状无改善。

治疗前后,用贝克曼库尔特的流式细胞仪检测 $CD4^+$ 和 $CD3^+$ 等 T 细胞,且计算 $CD4^+/CD8^+$ 的比值。

治疗前后,收集两组患者 3 mL 的痰液,采用 ELISA 法检测诱导痰中的 IL-4、IFN-γ、IL -17 水平,采取瑞氏吉姆萨染色法检测诱导痰中的中性粒细胞绝对值以及中性粒细胞百分比,采取尚沃医疗电子公司生产的 Sunvou- D100 型纳库仑呼气分析仪检测患者的 FeNO 水平。

1.4 统计学分析

采用 SPSS 21.0 进行数据分析,两组间计量资料对比采用 t 检验,计数资料组间比较采用 χ^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床控制率的对比

治疗后,观察组的临床控制率为 70.91 %(39/55),对照组的临床控制率为 40.00 %(22/55),观察组的临床控制率显著高于对照组(P<0.05),见表 1。

表 1 两组临床控制率比较[例(%]

Table 1 Comparison of the clinical control rate between two groups [n(%)]

Groups	n	Clinical control	Effective	Valid	Invalid
Control group	55	22(40.00)	12(21.82)	10(18.18)	11(20.00)
Observation group	55	39(70.91)*	9(16.36)	7(12.73)	0(0.00)

Note: Compared with the control group, *P<0.05.

2.2 两组治疗前后免疫功能的对比

治疗前,两组 $CD4^+$、$CD4^+/CD8^+$ 和 $CD3^+$ 对比差异无统计学意义(P>0.05);治疗后,两组的 $CD4^+$、$CD4^+/CD8^+$ 和 $CD3^+$ 均比治疗前明显升高,且观察组的上述指标的水平明显高于对照组(P<0.05),见表 2。

2.3 两组诱导痰中炎症因子、中性粒细胞和 FeNO 对比

治疗后,两组诱导痰中的组中性粒细胞绝对值、中性粒细胞百分比、IL-4、FeNO、IL-17 均较治疗前明显降低(P<0.05),IFN-γ 均均较治疗前明显升高(P<0.05),且观察组诱导痰中的组中性粒细胞绝对值、中性粒细胞百分比、IL-4、FeNO、IL-17 明显低于对照组 (P<0.05),诱导痰中的 IFN-γ 均明显高于对照组(P<0.05),见表 3。

3 讨论

为支气管哮喘是一种由多种细胞包含气道结构细胞(上皮细胞以及气道平滑肌细胞等)、炎性细胞(肥大细胞、嗜酸性粒细

表 2 两组治疗前后的免疫功能对比($\bar{x}\pm s$)

Table 2 Comparison of the immune function between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	n		$CD4^+$(%)	$CD4^+/CD8^+$	$CD3^+$(%)
Control group	55	Pretherapy	33.27±4.19	0.93±0.17	59.34±11.27
		Post-treatment	40.29±6.13#	1.27±0.24#	65.31±12.68#
Observation group	55	Pretherapy	32.48±5.27	0.94±0.18	58.32±10.19
		Post-treatment	45.37±10.13*#	1.46±0.38*#	74.26±14.83*#

Note: Compared with the control group, *P<0.05; compared with pretherapy, #P<0.05.

表 3 两组治疗前后诱导痰中炎症因子、中性粒细胞和 Fe NO 对比($\bar{x}\pm s$)

Table 3 Comparison of the inflammatory factors, neutrophils and FeNO in induced sputum between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n		Absolute neutrophil value (10^6/L)	Absolute neutrophil value (%)	IL-4/(ng/L)	IFN-γ/(ng/L)	FeNO/(ppb)	IL-17/(ng/L)
Control group	55	Pretherapy	5.22±0.94	73.64±14.27	153.42±22.79	33.46±10.17	35.27±4.98	5.54±1.29
		Post-treatment	4.17±0.85#	52.36±11.49#	80.36±19.27#	47.39±12.69#	21.34±3.27#	3.68±1.07#
Observation group	55	Pretherapy	5.23±0.97	72.19±15.38	152.71±23.64	34.28±10.25	36.14±5.26	5.52±1.17
		Post-treatment	3.42±0.64*#	42.57±10.38*#	65.17±14.29*#	54.36±13.82*#	15.29±1.65*#	2.41±0.75*#

Note: Compared with the control group, *P<0.05; compared with pretherapy, #P<0.05.

胞、中性粒细胞和 T 淋巴细胞等)以及细胞组分等参与的气道慢性炎症性疾病[10-14]。患者的病理改变主要是支气管平滑肌发生显著的痉挛,分泌支气管黏液的量明显增加,且支气管黏膜出现异常性的肿胀[15-18]。现代医学认为支气管哮喘主要与遗传以及生活环境相关,大多数的患者都有家族史,而且大部分属于过敏体质,容易对牛奶、花粉、皮毛、特定的药物以及海鲜等发生过敏[19-21]。目前,最为有效的治疗药物为 β2 受体激动剂与糖皮质激素,但是部分的支气管哮喘患者还无法达到满意的控制效果[22-25]。

支气管哮喘属于中医学 " 喘证 "、" 哮证 "、" 宿痰 "、" 痰饮" 等病证的范畴。中医学认为肺脾阳虚是支气管哮喘的发病之本,正气不足则为支气管哮喘反复发作的内因,外邪入里、肺气不利,则易化热,血运不畅容易造成津液的健运不足,津液聚而生痰,不断瘀阻于肺,而肺气肃降不利,肺气郁滞,造成气道壅塞,而最终触发支气管哮喘[26]。虫夏草是百令胶囊的主要成分,入肺经和肾经,具有降虚火,益精气,保肺益肾,助肾阳,止血化痰的作用。现代医学研究表明虫草内含虫草多糖、虫草素(3 - 脱氧腺苷)、麦角甾醇、载体生物碱虫草酸、19 种氨基酸和锌、硒、锶等物质,可以明显降低机体 IL-2、肿瘤坏死因子 -α 和 IL-8 的表达水平,明显增强肾上腺皮质的功能,舒张机体的肺支气管平滑肌[27]。本研究结果显示观察组的 $CD4^+$、$CD4^+/CD8^+$ 和 $CD3^+$ 明显高于对照组,表明百令胶囊能提高免疫功能。与本研究不同的是,国内百令胶囊主要辅治对支气管哮喘患儿,改善患儿的大小气道功能,减轻炎性反应,提高临床疗效[28],但是在老年人中的应用较少,任前[29]等通过百令胶囊联合普米克令舒雾化治疗老年支气管哮喘,临床疗效显著。本研究表明百令胶囊治疗老年哮喘具有良好的效果。其原因可能为百令胶囊能保护机体的 T 细胞,明显提高受刺激后 T 淋巴细胞的转换率,增强单核 - 巨噬细胞系统的吞噬功能,进而提高免疫力。但是对于对于中医的临床辩证还需要进一步的探究。

IFN-γ 作为一种由 Th1 细胞合成的因子,还可以抑制 Th2 细胞的功能及 IL-4 的合成,对支气管哮喘的发病发挥负向的调控作用[30]。IL-4 不但能诱导 B 细胞的增殖,还可以生成免疫球蛋白 E,有效促进嗜酸性粒细胞、中性粒细胞和单核细胞等向机体的气道黏膜浸润,使气道高反应性明显加重。IL-17 可以破坏免疫衡,引起炎症反应,募集以及刺激中性粒细胞聚集于气道中。当前,FeNO 主要被应用于判断支气管哮喘患者的气道炎症水平,评估患者激素治疗的反应性以及依从性,预测哮喘的急性发作情况以及复发情况。本研究显示观察组诱导痰中的组中性粒细胞绝对值、中性粒细胞百分比、IL-4、FeNO、IL-17 明显低于对照组,诱导痰中的 IFN-γ 均明显高于对照组,与吴宗跃等[28]在患儿中的研究结果一致。同时,原爱红[33]通过建立支气管哮喘模型大鼠,给予百令胶囊,结果也显示大鼠血清 IFN-γ 的水平显著提高,IL-4 的水平显著降低,主要是通过纠正IFN-γ/IL-4 比例失衡,降低了气道炎症,也与本研究结果一致。以上结果表明百令胶囊不但可以减轻气道的黏膜水肿情况,调节 INF-γ 及 IL-4 的表达而产生免疫炎症调节效果,还能抑制中性粒细胞聚集于患者的气道黏膜,降低气道的高反应性,抑制炎性细胞释放过氧自由基以及氧化物,具有抗氧化和抗炎效果。

综上所述,百令胶囊联合罗氟司特对老年支气管哮喘患者具有显著的疗效,其机制可能与抑制中性粒细胞的激活、调节 T 淋巴细胞亚群的平衡和抑制相关炎症因子的释放相关。本研

究也存在一定的不足,样本量少,同时也没有中医的临床辩证,后续需要进一步的深入探究。

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