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加味射干麻黄汤对重度支气管哮喘患者血清 ECP、LPO、FeNO 及肺功能的影响*

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摘要 目的:探讨加味射干麻黄汤对重度支气管哮喘患者血清嗜酸性粒细胞阳离子蛋白(ECP)、脂质过氧化物(LPO)、呼出气一氧化氮(FeNO)及肺功能的影响。**方法:**选择 2015 年 9 月至 2017 年 9 月我院接诊的 96 例重度支气管哮喘患者进行研究,通过随机数表法分为观察组(n=48)和对照组(n=48),在常规治疗基础上,对照组给予异丙托溴铵溶液、甲泼尼龙琥珀酸钠治疗,观察组联合加味射干麻黄汤治疗,均连续治疗 4 周。比较两组临床疗效、治疗前后中医证候积分、肺功能、血清 ECP、LPO 及 FeNO 的变化和不良反应。**结果:**治疗后,观察组临床疗效总有效率为 91.67%(44/48),明显高于对照组的 72.92%(35/48)($P<0.05$);治疗后,两组各中医证候积分、肺功能、血清 ECP、LPO 及 FeNO 较治疗前均显著改善($P<0.05$);中医证候积分中,观察组治疗后喘息、咳嗽、咳痰、胸闷、哮鸣音积分均明显低于对照组,肺功能中,观察组第 1 秒用力呼出量(FEV1)、FEV1/用力肺活量(FEV1/FVC)均明显高于对照组,呼气峰值流速(PEF)昼夜变异率明显低于对照组,且观察组血清 ECP、LPO 及 FeNO 明显比低于对照组,差异均具有统计学意义($P<0.05$);两组治疗期间不良反应比较无显著差异($P>0.05$)。**结论:**在重度支气管哮喘患者中应用加味射干麻黄汤效果显著,可有效改善肺功能及临床症状,其内在机制可能和调节气道慢性炎症反应、氧化应激反应,降低血清 ECP、LPO 及 FeNO 的表达相关,且用药安全性高,值得应用推广。

关键词:重度支气管哮喘;加味射干麻黄汤;嗜酸性粒细胞阳离子蛋白;脂质过氧化物;呼出气一氧化氮;肺功能

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Effect of Jiawei Shegan Mahuang Decoction on serum ECP, LPO, FeNO and Lung Function in Patients with Severe Bronchial Asthma*

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ABSTRACT Objective: To study the effect of Jiawei Shegan Mahuang Decoction on serum eosinophil cationic protein (ECP), lipid peroxide(LPO), exhalation of nitric oxide(FeNO) and lung function in patients with severe bronchial asthma. **Methods:** 96 patients of severe bronchial asthma who received therapy from September 2015 to September 2017 in our hospital were selected as research objects, according to random number table, those patients were divided into the observation group (n=48) and the control group (n=48), on the basis of routine treatment, the control group was treated with ipratropium bromide, methylprednisolone sodium succinate, while the observation group was combined with Jiawei Shegan Mahuang Decoction, they were treated continuously for 4 weeks. The clinical efficacy and the changes of TCM syndrome score, lung function, serum ECP, LPO and FeNO before and after treatment and adverse reaction were compared between the two groups. **Results:** After treatment, the total effective rate of clinical efficacy in the observation group was 91.67% (44/48), which was significantly higher than that of the control group 72.92% (35/48)($P<0.05$); after treatment, the scores of syndromes, lung function, serum ECP, LPO and FeNO between the two groups were significantly improved compared with those before the treatment($P<0.05$); in the TCM syndrome score, the scores of pant, coughin, expectoration, chest tightness, wheezing ralei in the observation group were significantly lower than those in the control group, in the lung function, the 1 second forced expiratory volume (FEV1) and the forced vital capacity of FEV1/ (FEV1/FVC) in the observation group were significantly higher than those in the control group, the peak expiratory flow (PEF) diurnal variation rate was significantly lower than those in the control group, the serum ECP, LPO and FeNO in the observation group were significantly lower than those in the control group, the difference has statistical significance ($P<0.05$); there was no significant difference in the adverse reaction between the two groups during the treatment($P>0.05$). **Conclusion:** Jiawei Shegan Mahuang Decoction is well for severe bronchial asthma, which can effectively improve the pulmonary function and clinical symptoms, its internal mechanism may be associated with the regulation of chronic airway inflammation, oxidative stress, and the reduction of the expression of serum ECP, LPO and FeNO, and high safety of drug use, it is worthy of application and promotion.

Key words: Severe bronchial asthma; Jiawei Shegan Mahuang Decoction; Eosinophil cationic protein; Lipid peroxide; Exhalation of

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前言

支气管哮喘是临床上常见的呼吸内科疾病,随着环境污染、工业化不断发展,其发病率已呈逐年增长趋势,患者可出现喘息、咳嗽、胸闷、呼吸困难等症状,已严重影响人们的生活质量及身体健康^[1]。该病的发病机制较为复杂,多数学者认为和气道慢性炎症反应、氧化应激反应等存在着密切关系,其中嗜酸性粒细胞阳离子蛋白(ECP)、脂质过氧化物(LPO)、呼出气一氧化氮(FeNO)在疾病的发生、发展中起着重要作用^[2,3]。目前对于该病的治疗通常采取抗炎、解痉平喘等对症处理措施,该方式在大部分轻、中度患者中可获得满意疗效,但用于重度支气管哮喘中效果欠佳^[4]。随着祖国医学的不断发展,中医药在支气管哮喘中也取得明显的优势,中医中认为,该病的发病机制和“痰瘀互结”密切相关,致使气道阻塞、肺失宣降,对其的治疗应以化痰止咳、散寒宣肺等为主^[5,6]。因此,本研究旨在探讨在重度支气管哮喘患者中应用加味射干麻黄汤的治疗优势,并观察其对患者血清 ECP、LPO 及 FeNO 的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2015 年 9 月至 2017 年 9 月我院接诊的 96 例重度支气管哮喘患者进行研究,研究已获得我院伦理委员会批准实施。纳入标准:①符合重度支气管哮喘诊断标准^[7];②第 1 秒用力呼出量(FEV1)<60%预计值,呼吸频率>30 次/分;③年龄≥18 岁,病程≥1 年;④签署本研究知情同意书。排除标准:①入院前 1 个月内使用过全身糖皮质激素;②合并呼吸道感染、真菌感染、肺结核等严重传染性疾病;③合并心功能不全、慢性阻塞性肺疾病加重期、甲状腺功能亢进等疾病者;④肝肾功能严重障碍;⑤意识障碍,无法配合治疗;⑥对研究药物过敏。通过随机数表法分为 2 组,每组 48 例。观察组男 27 例,女 21 例;年龄 21~49 岁,平均(36.45±7.30)岁;病程 2~14 年,平均(7.48±1.42)年。对照组男 28 例,女 20 例;年龄 23~50 岁,平均(36.83±7.14)岁;病程 2~15 年,平均(7.55±1.37)年。两组一般资料无显著差异(P>0.05),具有可比性。

1.2 方法

两组均给予平喘、解痉、吸氧、祛痰、维持水电解质平衡、酸碱平衡等常规处理措施。

对照组给予异丙托溴铵溶液(规格 2.5 mL,厂家:Laboratoire Unither,国药准字 H20150173)的雾化吸入,剂量 2.5 mL,每次 8 h,甲泼尼龙琥珀酸钠(规格 40 mg,厂家:Pfizer Manu-

facturing Belgium NV,国药准字 H20130301)静脉滴注,剂量 40 mg,2 次/d。

观察组在上述基础上,给予加味射干麻黄汤治疗,药方组成射干、炙麻黄、桔梗、大枣、五味子、杏仁、陈皮、紫苑各 10 g,半夏 15 g,细辛 5 g,水煎剂 400 mL,1 剂/d,早晚各服用 1 次。两组均连续治疗 4 周。

1.3 观察指标

1.3.1 中医证候积分 于治疗前、后,参照《中药新药临床研究指导(试行)》^[8]中相关内容,评价喘息、咳嗽、咳痰、胸闷、哮鸣音中医证候积分的变化,得分越高,提示各症状越严重。

1.3.2 肺功能 于治疗前、后,使用美国 Sensormedics 肺功能仪对 FEV1、FEV1/用力肺活量(FEV1/FVC)、呼气峰值流速(PEF)昼夜变异率进行检测。

1.3.3 血清 ECP、LPO 及 FeNO 于治疗前、后,抽取 5 mL 空腹静脉血,以 3000 r/min 的速度离心 10 min,使用酶联免疫吸附法(ELISA)检测血清 ECP、LPO,试剂盒均购于上海工研生物技术有限公司,并在专业技师指导下,使用 FeNO 检测仪 NIOX MINO 进行,在测定时,令受试者完全排出肺部存留气体,采用 50 mL/s 的呼吸流速连续呼气 10 s,叮嘱患者呼吸过程中保持气流均匀,90 s 后得到结果,单位以 ppb 表示。

1.4 疗效评价标准

参照《中药新药临床研究指导(试行)》^[8],根据患者喘息、咳嗽、咳痰、胸闷、哮鸣音症状积分进行评价,计算公式:疗效率(%)=(治疗前证候总分-治疗后证候总分)/治疗前证候总分×100%;痊愈:患者各临床症状、体征得到消失,疗效率≥95%;显效:各临床症状、体征得到明显缓解,疗效率 70%~94%;有效:各临床症状、体征部分缓解,疗效率 30%~69%;无效:各临床症状改善程度不明显,甚至加重,疗效率<30%。以治愈+显效+有效为总有效率。

1.5 统计学分析

以 SPSS18.0 软件包处理实验数据,计量资料均为正态分布,用均数±标准差($\bar{x} \pm s$)表示,组间比较采用独立样本 t 检验,计数资料组间比较采用 χ^2 检验,以 P<0.05 表示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,观察组临床疗效总有效率为 91.67%,明显比对照组的 72.92%高(P<0.05),见表 1。

表 1 两组临床疗效比较[n(%)]

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

Groups	Cure	Effective	Valid	Invalid	Total effective rate
Observation group(n=48)	13(27.08)	19(39.58)	12(25.00)	4(8.33)	44(91.67)*
Control group(n=48)	9(18.75)	11(22.92)	15(31.25)	13(27.08)	35(72.92)

Note: vs the control group, 和对照组比较,*P<0.05.

2.2 两组中医证候积分比较

治疗前,两组喘息、咳嗽、咳痰、胸闷、哮鸣音中医证候积分比较无显著差异($P>0.05$),治疗后,两组各中医证候积分较治

疗前均显著降低($P<0.05$),观察组喘息、咳嗽、咳痰、胸闷、哮鸣音中医证候积分均明显比对照组低($P<0.05$),见表2。

表2 两组中医证候积分比较($\bar{x}\pm s$,分)

Table 2 Comparison of the TCM syndrome score between two groups ($\bar{x}\pm s$, scores)

Groups		Pant	Cough	Expectoration	Chest tightness	Wheezing rale
Observation group (n=48)	Before treatment	3.49± 0.41	3.54± 0.46	3.37± 0.39	3.46± 0.43	3.52± 0.33
	After treatment	1.42± 0.27**	1.49± 0.30**	1.38± 0.29**	1.37± 0.20**	1.43± 0.26**
Control group (n=48)	Before treatment	3.54± 0.40	3.47± 0.52	3.42± 0.36	3.40± 0.41	3.47± 0.36
	After treatment	2.59± 0.31*	2.52± 0.37*	2.26± 0.33*	2.39± 0.35*	2.44± 0.27*

Note: Vs the before treatment,和治疗前比较, * $P<0.05$; vs the control group,和对照组比较, ** $P<0.05$.

2.3 两组肺功能比较

治疗前,两组FEV1、FEV1/FVC、PFE昼夜变异率比较无显著差异($P>0.05$),治疗后,两组FEV1、FEV1/FVC较治疗前均

显著升高,PFE昼夜变异率显著降低($P<0.05$),观察组FEV1、FEV1/FVC均明显高于对照组,PFE昼夜变异率明显比对照组低($P<0.05$),见表3。

表3 两组肺功能比较($\bar{x}\pm s$)

Table 3 Comparison of the pulmonary function between two groups ($\bar{x}\pm s$)

Groups		FEV1(L)	FEV1/FVC(%)	PEF diurnal variation rate(%)
Observation group (n=48)	Before treatment	1.48± 0.25	49.56± 5.69	35.86± 3.17
	After treatment	2.77± 0.36**	82.30± 7.53**	15.83± 1.30**
Control group (n=48)	Before treatment	1.52± 0.24	49.29± 5.82	36.10± 3.05
	After treatment	2.29± 0.28*	70.17± 6.34*	22.59± 2.01*

Note: Vs the before treatment, 和治疗前比较, * $P<0.05$; vs the control group,和对照组比较, ** $P<0.05$.

2.4 两组血清ECP、LPO、FeNO比较

治疗前,两组血清ECP、LPO、FeNO比较无显著差异($P>0.05$);治疗后,两组血清ECP、LPO、FeNO较治疗前均显著降

低($P<0.05$),观察组血清ECP、LPO、FeNO明显比对照组低($P<0.05$),见表4。

表4 两组血清ECP、LPO、FeNO比较($\bar{x}\pm s$)

Table 4 Comparison of the serum ECP, LPO and FeNO between two groups ($\bar{x}\pm s$)

Groups		ECP(pg/L)	LPO(nmol/L)	FeNO(ppb)
Observation group (n=48)	Before treatment	21.38± 2.42	18.59± 2.31	73.49± 15.27
	After treatment	7.42± 1.15**	7.10± 1.02**	41.62± 8.42**
Control group (n=48)	Before treatment	21.93± 2.19	18.27± 2.40	74.16± 14.89
	After treatment	13.10± 1.47*	11.27± 1.59*	52.19± 10.34*

Note: Vs the before treatment,和治疗前比较, * $P<0.05$; vs the control group,和对照组比较, ** $P<0.05$.

2.5 两组不良反应比较

治疗期间,对照组出现3例胃肠道不适,1例口干,1例咽部不适,总发生率为10.42%,观察组出现2例胃肠道不适,2例口干,总发生率为8.83%两组不良反应总发生率比较无显著差异($P>0.05$)。

3 讨论

支气管哮喘已是目前全国范围内对人体健康造成严重威胁的慢性疾病之一,可根据发作严重程度分为轻度、中度、重度及危重度,对于轻中度的患者多数可根据对症处理后缓解病情,但仍有8%的患者难以有效控制症状,最终进展成重度支气管哮喘,若未得到及时的治疗,可出现低氧血症、酸中毒、二氧

化碳潴留等严重并发症^[9,10]。

中医中将支气管哮喘纳入“哮病”范畴,可由于饮食不节、外感风寒、劳累过度等刺激,致使痰阻气道、肺失宣降,诱发哮喘,故而对其的治疗应以化痰止咳、散寒宣肺等为主^[11,12]。射干麻黄汤原方出自《金匮要略》,主要用于治疗寒哮证,之后被后人称为哮喘的主方,本研究根据支气管哮喘的证候特点,在原方基础上进行加味,主要药方组成包括射干、炙麻黄、桔梗、大枣、五味子、杏仁、陈皮、紫苑、半夏、细辛,其中射干可清热解毒、化痰平喘;炙麻黄可祛风散寒、平喘宣肺;桔梗可宣肺祛痰、利咽排脓;大枣可补脾益气;五味子可益气生津、滋肾敛肾;杏仁可宣降肺气、且可通过疏利开通之效促使平喘止咳;陈皮可化痰燥湿、理气平喘;紫苑消痰温肺、止咳祛痰;半夏化痰燥湿、

止呕降逆;细辛开窍祛风、散寒行水。全方共奏化痰止咳、散寒宣肺等效。

本研究结果显示,联合加味射干麻黄汤的患者喘息、咳嗽、咳痰、胸闷、哮鸣音症状以及肺功能的改善程度明显优于单纯西药治疗的患者,且临床疗效总有效率高达 91.67%,提示联合加味射干麻黄汤在缓解临床症状、改善肺功能中效果更具有优势,分析由于单独西医治疗组中异丙托溴铵溶液、甲泼尼龙琥珀酸钠均为对症治疗,无法有效的去除病因,而加味射干麻黄汤方中各药物通过多靶点、多方面的治疗特点,进一步改善肺功能,提高临床疗效。在现代药理学中也显示,射干麻黄汤具有降低痰液粘稠度、促进气道纤毛运动、令痰液排出等优势,是呼吸系统疾病的治疗良方^[13,14]。且本研究中两组患者不良反应无显著差异,也体现出中医药治疗安全性高的优势。

气道慢性炎症是该病发病的重要因素,嗜酸粒细胞趋化因子主要产生于支气管和肺,在机体变态反应中发挥着重要作用,而 ECP 作为活化的嗜酸细胞分泌的核糖核酸酶,也是引发气道炎症的重要因子,已有较多报道证实,ECP 的增加可致使气道痉挛及气道高反应,可作为评估监测疾病严重程度的指标^[15,16]。LPO 作为饱和脂肪酸在自由基作用下所形成的过氧化物,对免疫具有抑制作用,且可增加血小板聚集,损伤体内细胞,Navarrete BA 等^[17]研究认为,对 LPO 的检测可了解机体自由基、过氧化脂质代谢和疾病的关系,在较多疾病的诊断、预后及抗氧化治疗中均具有积极意义。谢轶群^[18]的报道也指出,在支气管哮喘患者中,在气道炎症作用下,可刺激机体大量生成 LPO,和疾病严重程度之间呈正相关。FeNO 是近年来临床上新发现的反应呼吸道炎症的指标,且具有无创、简单、重复性高等优点,目前对于 FeNO 的检查已受到临床学者重视,Shimoda T 等^[19]实验中也显示,FeNO 可有效区别呼吸道炎症类型、评估呼吸道炎症严重程度、判断吸入糖皮质激素治疗疗效,在了解哮喘控制情况及预测哮喘急性发作中作用关键。

本研究结果显示,联合加味射干麻黄汤的患者,血清 ECP、LOP 及 FeNO 的降低程度明显优于单独西医治疗的患者,通过分析是由于加味射干麻黄汤中麻黄、五味子等均具有抗炎、抗氧化应激等作用,隋博文等^[20]动物试验也显示,加味射干麻黄汤可增加小鼠血清干扰素- γ 的表达,令肺组织抗氧化能力提高,继而缓解气道免疫炎症反应。这也可能是联合射干麻黄汤的患者肺功能改善程度、临床疗效更佳的内在机制之一。但本研究时间较短,对于该方式用于重度支气管哮喘患者的远期疗效上仍需进一步深入研究。

综上所述,在重度支气管哮喘患者中应用加味射干麻黄汤效果显著,可有效改善患者肺功能及临床症状,其内在机制可能和调节气道慢性炎症反应、氧化应激反应,降低血清 ECP、LOP 及 FeNO 的表达相关,且用药安全性高,值得应用推广。

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果较单一用药更突出。

综上所述,松龄血脉康胶囊联合立普妥治疗老年高血压患者疗效显著,不仅能维持动态血压的正常水平,且能显著改善 Fibulin-3、Lp(a)、MCP-1 水平,且降脂效果良好。

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