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舒血宁注射液联合布地耐德对 COPD 急性加重期患者血清 MMP-9，IL-6，IL-8，TNF-α 及肺功能的影响 *

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摘要 目的：探讨舒血宁注射液联合布地耐德对慢性阻塞性肺病(COPD)急性加重期患者血清基质金属蛋白酶 -9(MMP-9)、白细胞介素 -6(IL-6)、白细胞介素 -8(IL-8)、肿瘤坏死因子 -α(TNF-α)及肺功能的影响。**方法：**将 112 例 COPD 急性加重期患者参照随机数表法分作对照组与观察组，每组各 56 例。对照组采用布地奈德治疗，观察组基于对照组加以舒血宁注射液治疗。比较两组总有效率，治疗前后血清 MMP-9、IL-6、IL-8、TNF-α、丙二醛(MDA)、超氧化物歧化醇(SOD)水平、二氧化碳分压($PaCO_2$)、血氧分压(PaO_2)，气峰流速(PEF)、最大呼气中期流速(MMEF)、用力肺活量(FVC)、$CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 及不良反应的发生情况。**结果：**观察组总有效率显著高于对照组 94.64% vs 80.35 %(P<0.05)。观察组治疗后血清 MMP-9、IL-6、IL-8、TNF-α、MDA 水平、$PaCO_2$、$CD8^+$ 均明显低于对照组(P<0.05)，血清 SOD 水平、PaO_2、PEF、MMEF、FVC、$CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均明显高于对照组(P<0.05)。两组不良反应的发生情况比较差异无统计学意义(P>0.05)。**结论：**舒血宁注射液联合布地奈德治疗 COPD 急性加重期患者的疗效确切，可降低血清 MMP-9、IL-6、IL-8、TNF-α 水平，改善肺功能，减轻氧化应激并改善动脉血气及免疫功能。

关键词：慢性阻塞性肺病急性加重期；舒血宁注射液；布地奈德；细胞因子；肺功能

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Influence of Shuxuening Injection Combined with Budesonide on Serum Levels of MMP-9, IL-6, IL-8 and TNF-α and Lung Function of COPD Patients with Acute Aggravating Period*

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ABSTRACT Objective: To investigate the influence of shuxuening injection combined with budesonide on the serum levels of matrix metalloproteinases-9 (MMP-9) and interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α(TNF-α) and lung function of chronic obstructive pulmonary disease (COPD) patients with acute aggravating period. **Methods:** 112 cases of COPD patients with acute aggravating period were divided into the control group and the observation group with 56 cases in each group. The control group was treated by budesonide, while the observation group was treated based on the control group combined with Shuxuening injection. The total effective rate, serum levels of MMP-9, IL-6, IL-8, TNF-α, propylene glycol (MDA), superoxide disproportionation alcohol (SOD), CO_2 partial pressure ($PaCO_2$), blood oxygen partial pressure (PaO_2), peak velocity of flow (PEF), maximum mid expiratory gas flow velocity (MMEF), forced vital capacity (FVC), $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, and the occurrence of adverse reactions before and after the treatment were compared between two groups. **Results:** The total effective rate of observation group was higher than that of the control group (94.64% vs 80.35 %, P<0.05). After the treatment, the serum levels of MMP-9, IL-6, IL-8, TNF-α, MDA, $PaCO_2$, $CD8^+$ of observation group were lower than those of the control group (P<0.05). The serum levelof SOD, PaO_2, PEF, MMEF, FVC, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ of observation group were higher than those of the control group (P<0.05). The occurrence of adverse reactions showed no difference between the two groups (P>0.05). **Conclusion:** Shuxuening injection combined with budesonide was effective in the treatment of COPD patients with acute aggravating period, which could decrease the serum levels of MMP-9, IL-6, IL-8 and TNF-α, improve the lung function, reduce the oxidative stress and improve the arterial blood gas and immune function.

Key words: Chronic obstructive pulmonary disease with acute aggravating period; Shuxuening injection; Budesonide; Cytokines; Lung function

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前言

慢性阻塞性肺病(COPD)是一种肺部的破坏性疾病,以气流受限且不全部可逆为主要特征，多呈进行性的发展。COPD急性加重期的病情程度比较严重，可加重咳嗽及呼吸急促,增加咳痰量,细菌或者病毒感染是急性加重的主要诱因[1]。研究表明气道重塑是COPD的进展和转归主要因素,基质金属蛋白酶-9(MMP-9)可参与气道重塑,同时白细胞介素-6、8(IL-6、IL-8)、肿瘤坏死因子-α(TNF-α)等炎性因子可加重气道炎症反应,影响COPD的转归[2,3]。布地奈德作为一种肾上腺皮质激素,可降低患者气道的高反应状态,改善其临床症状,但其临床效果欠佳[4]。有研究显示在布地奈德基础上加用中医配方治疗可增加疗效,舒血宁注射液作为一种中药提取剂可促进氧自由基的清除、改善微循环、提高细胞免疫活性等,现已广泛应用于COPD急性加重期治疗,但其作用机制的报道尚未完全阐明[5]。本研究主要探讨了舒血宁注射液联合布地耐德对COPD急性加重期患者血清相关因子及肺功能的影响。

1 资料与方法

1.1 一般资料

选择2013年5月~2016年5月与我院就诊的112例COPD急性加重期患者。纳入标准[6]:(1)均符合COPD相关诊断标准:慢性咳痰、咳嗽比气流受限出现的时间早,肺部X线胸片提示可有肺部紊乱、增粗等变化、也可见肺气肿,第1秒用力呼气容积/用量肺活量在0.7以下、气流存在受限、无法全部逆转;(2)符合COPD急性加重期诊断标准[7]:咳嗽及呼吸急促加重、脓痰及咳痰量增多,运动耐量降低,呼吸道感染是急性加重的唯一诱因;(3)无肺部其他疾病;(4)心肝肾等主要脏器无严重异常;(5)无恶性肿瘤。排除严重呼吸衰竭、近期有免疫抑制剂使用史,急性创伤或者感染,免疫系统异常,糖皮质激素相关禁忌症者。本研究家属及患者均签署知情同意书,且符合医院伦理委员会规定,参照随机数表法分组。对照组有29例男,有27例女;年龄55~73岁,平均(63.21± 2.89)岁。观察组有26例男,有30例女;年龄53~75岁,平均(63.85± 3.11)岁。两组性别分布及年龄等比较差异均无统计学意义(P>0.05),有可比性。

1.2 治疗方法

两组均予以维持电解质平衡、祛痰、平喘、营养支持、抗感染、持续低流量氧疗等常规治疗。对照组采用布地奈德治疗,将2 mg布地奈德(广东莱达制药有限公司,规格5 mL:20 mg,国药准字H20103795,批号130421)与10 mL的0.9%氯化钠注射液稀释后行压缩雾化吸入治疗,早晚各进行1次。观察组基于对照组加以舒血宁注射液治疗,将15 mL舒血宁注射液(江西神田制药有限公司，规格2 mL，国药准字Z14021871，批号130416)溶于250 mL 0.9%氯化钠注射液中,按静脉滴注给药,早晚各使用1次,两组均持续治疗14天,并于治疗结束时评估疗效,对期间不良反应进行记录。

1.3 观察指标

1.3.1 疗效评价 临床控制:症状和体征消失,未见实验室指标异常,生活无需外界帮助;显效:症状及体征显著减轻,实验室指标基本无异常;好转:症状和体征有一定缓解,可见部分实验室指标异常;无效:症状和体征无变化甚者加重,临床控制、显效、好转均视作总有效[8]。

1.3.2 血液指标检测 于治疗前后抽取患者2 mL空腹动静脉血,以3000 r/min分离10 min,低温保存待检。MMP-9、IL-6、IL-8、TNF-α按酶联免疫双抗体夹心法检测。二氧化碳分压($PaCO_2$)、血氧分压(PaO_2)使用血气分析仪检测。丙二醇(MDA)按硫代巴比妥酸比色法检测,超氧化物歧化醇(SOD)按黄嘌呤氧化酶法检测。$CD3^+$、$CD4^+$予以流失细胞术检测。

1.3.3 肺功能检测 于治疗前后使用肺功能仪检测呼气峰流速(PEF)、用力肺活量(FVC)、最大呼气中期流速(MMEF)。

1.4 统计学分析

选择SPSS18.0行数据统计,计量资料用($\bar{x}$± s)表示,组间比较用t检验，计数资料用[(例)%]表示，用x^2检验比较,以P<0.05为差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

观察组总有效率为94.64%,显著高于对照组,差异具有统计学意义(P<0.05),见表1。

表1 两组临床疗效的比较[(例)%,n=56]

Table 1 Comparison of the curative effect between two groups[(n)%, n=56]

Items	Control group	Observation group
Clinical control	6(10.71)	10(17.85)
Markedly	11(19.64)	16(28.57)
Better	28(50.00)	27(48.21)
Invalid	11(19.64)	3(5.35)
Total effective rate	45(80.35)	53(94.64)△

Note: compared with control group △ P<0.05.

2.2 两组治疗前后血清MMP-9、IL-6、IL-8、TNF-α水平的比较

治疗前，两组血清MMP-9、IL-6、IL-8、TNF-α水平比较差异无统计学意义 (P>0.05)；治疗后，两组血清MMP-9、IL-6、IL-8、TNF-α水平均较治疗前显著降低，且观察组明显低于对照组(P<0.05),见表2。

2.3 两组治疗前后肺功能的比较

治疗前,两组PEF、MMEF、FVC水平比较差异无统计学意义(P>0.05);治疗后,两组PEF、MMEF、FVC均较治疗前上升,且观察组上升更明显(P<0.05),见表3。

表 2 两组治疗前后血清 MMP-9、IL-6、IL-8、TNF-α 水平的比较($\bar{x}\pm s$,n=56)

Table 2 Comparison of the serum MMP-9, IL-6, IL-8, TNF-α levels between two groups before and after the treatment($\bar{x}\pm s$, n=56)

Items	Time	Control group	Observation group
MMP-9(μg/L)	Before treatment	132.60± 16.50	133.25± 1.60
	After treatment	94.73± 11.81#	67.84± 8.46△ #
IL-6(ng/L)	Before treatment	172.36± 21.53	171.80± 21.35
	After treatment	150.83± 18.79#	121.64± 17.34△ #
IL-8(mg/L)	Before treatment	47.65± 5.95	46.93± 5.88
	After treatment	32.71± 4.12#	18.90± 2.35△ #
TNF-α(μg/L)	Before treatment	35.89± 4.49	36.24± 4.51
	After treatment	11.36± 1.42#	7.25± 0.91△ #

Note: compared with control group △ P<0.05; compared with before treatment #P<0.05.

表 3 两组治疗前后肺功能的比较($\bar{x}\pm s$,n=56)

Table 3 Comparison of the lung function between two groups before and after the treatment ($\bar{x}\pm s$, n=56)

Items	Time	Control group	Observation group
PEF(L/s)	Before treatment	3.45± 0.43	3.43± 0.42
	After treatment	5.50± 0.68#	6.39± 0.79△ #
MMEF(L/s)	Before treatment	1.16± 0.14	1.15± 0.13
	After treatment	1.98± 0.25#	2.93± 0.36△ #
FEC(L)	Before treatment	2.41± 0.30	2.40± 0.30
	After treatment	2.75± 0.36#	2.89± 0.35△ #

Note: compared with control group △ P<0.05; compared with before treatment #P<0.05.

2.4 两组治疗前后 $PaCO_2$、PaO_2 水平的比较

治疗前，两组 $PaCO_2$、PaO_2 水平比较差异无统计学意义(P>0.05)；治疗后，两组 $PaCO_2$ 均较治疗前降低，观察组下降更明显，两组 PaO_2 均较治疗前上升，观察组高于对照组(P<0.05)，见表 4。

表 4 两组治疗前后 $PaCO_2$、PaO_2 的比较($\bar{x}\pm s$,n=56)

Table 4 Comparison of the $PaCO_2$, PaO_2 between two groups before and after the treatment ($\bar{x}\pm s$, n=56)

Items	Time	Control group	Observation group
$PaCO_2$(mmHg)	Before treatment	56.87± 7.11	55.92± 6.98
	After treatment	46.93± 5.86#	43.20± 5.40△ #
PaO_2(mmHg)	Before treatment	57.60± 7.20	56.21± 7.03
	After treatment	79.58± 9.94#	84.25± 10.51△ #

Note: compared with control group △ P<0.05; compared with before treatment #P<0.05.

2.5 两组治疗前后血清 MDA、SOD 水平的比较

治疗前，两组血清 MDA、SOD 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 MDA 水平均较治疗前降低，观察组低于对照组，两组血清 SOD 水平均较治疗前上升，观察组高于对照组(P<0.05)，见表 5。

表 5 两组治疗前后血清 MDA、SOD 水平的比较($\bar{x}\pm s$,n=56)

Table 5 Comparison of the serum MDA and SOD levels between two groups before and after the treatment ($\bar{x}\pm s$, n=56)

Items	Time	Control group	Observation group
MDA(mmol/ml)	Before treatment	9.55± 1.18	9.40± 1.16
	After treatment	8.51± 1.06#	7.93± 0.99△ #
SOD(mU/ml)	Before treatment	59.11± 7.35	60.23± 7.50
	After treatment	74.10± 9.21#	78.60± 9.82△ #

Note: compared with control group △ P<0.05; compared with before treatment #P<0.05.

2.6 两组治疗前后 T 淋巴细胞亚群的比较

治疗前，两组 T 淋巴细胞亚群水平比较差异无统计学意义(P>0.05)；治疗后，两组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均较治疗前上升，观察组高于对照组，两组 $CD8^+$ 均较治疗前降低，观察组低

于对照组(P<0.05),见表 6。

表 6 两组治疗前后 T 淋巴细胞亚群的比较($\bar{x}\pm s$,n=56)

Table 6 Comparison of the T lymphocyte subsets between two groups before and after the treatment ($\bar{x}\pm s$, n=56)

Items	Time	Control group	Observation group
$CD3^+$(%)	Before treatment	52.35± 6.51	51.78± 6.42
	After treatment	57.40± 7.17#	62.33± 7.78△ #
$CD4^+$(%)	Before treatment	32.11± 4.06	32.89± 4.11
	After treatment	35.32± 4.40#	38.70± 4.85△ #
$CD8^+$(%)	Before treatment	30.24± 3.79	30.90± 3.85
	After treatment	28.18± 3.51#	26.05± 3.25△ #
$CD4^+/CD8^+$	Before treatment	1.08± 0.13	1.09± 0.13
	After treatment	1.31± 0.16#	1.50± 0.19△ #

Note: compared with control group △ P<0.05; compared with before treatment #P<0.05.

2.7 两组不良反应发生情况的比较

用药期间,两组均未见明显不良反应(P>0.05)。

3 讨论

COPD 是肺部常见疾病,其致病因素尚未明确,临床研究证实与吸烟、空气污染、感染等因素有关,可引起咳嗽、咯痰、呼吸困难、气短等临床表现,可对全身系统造成不同程度的影响[9]。其中,COPD 急性加重期的住院率及病死率较高,患者生活质量显著降低,临床以控制病情、改善生活质量、减少病死率为治疗原则[10]。研究表明糖皮质激素可引起嗜酸性细胞的合成及增殖产生抑制,介导炎性因子的分泌,缓解气道炎症[11]。布地奈德是糖皮质激素的代表药物,经雾化吸入后可结合糖皮质激素受体,提高溶酶体膜、平滑肌细胞、内皮细胞的稳定性,调节机体免疫反应,减少组胺等物质的分泌,减轻酶促反应,使平滑肌收缩受到抑制[12]。但国外研究指出 COPD 急性加重期患者单用布地奈德治疗后临床表现改善并不明显,本研究也发现采用布地奈德治疗后总有效率相对较低[13]。

COPD 属中医学 " 喘证、痰饮、肺胀 " 等范畴,与脾、肾、肺等亏虚相关,痰浊、淤血内停是主要病机,身感外邪可致疾病加重,引咳嗽、气促、胸闷等表现,治疗应以祛瘀化痰之法[14]。舒血宁中银杏叶入肺、心经,性味苦、甘、涩,可畅通静脉,活血化瘀,平喘止咳,滋阴敛肺[15]。舒血宁注射液含黄酮成分,可促进氧自由基的清除,抗氧化,调节微循环[16]。本研究结果显示加用舒血宁注射液治疗组总有效率高于单用布地奈德组,说明两者联合治疗可利于病情的控制,促进疗效的提高,减轻患者痛苦。

MMP-9 可介导细胞外基质的降解与重建, 诱导肺泡的基质成分受到破坏,破坏肺泡结构,导致肺部肿胀,并调节气道重塑,造成气流受限[17,18]。炎症反应可使系列肺结构细胞和相关炎症细胞激活,于 COPD 发生期间起到关键作用[19]。IL-6 可参与机体的炎症反应与病理生理过程,诱导阻胺释放,加剧机体的炎症反应,导致病情加重[20]。IL-8 可结合中性粒细胞的特定受体,诱导其趋化并变形,导致组织受损,引起气道壁产生增厚,造成气流阻塞[21]。TNF-α 可利于炎症介质的浸润和游离,导致肺功能受损,同时也可促进中性粒细胞的分解能力,导致炎症反应加剧,诱导组织产生纤维化[22]。本研究结果显示加用舒血宁注射液治疗后 MMP-9、IL-6、IL-8、TNF-α 显著下降, 说明两者联合治疗可利于机体炎症反应的改善, 缓解气道的高反应性,减轻症状。相关研究指出 COPD 急性加重期患者由于痰液难以咯出、呼吸比较急促,同时气道黏液分泌物增加可导致气道感染加剧,导致肺功能减弱,诱导肺部换气及通气功能受阻,对氧供造成影响,引起血气分析产生异常变化[23]。本研究结果显示加用舒血宁注射液治疗后肺功能及血气分析指标改善较单用布地奈德组更明显,说明两者联合治疗可利于肺功能的恢复,改善动脉血气,恢复机体氧供。

临床研究显示 COPD 急性加重期患者多存在氧化 - 抗氧化失衡, 机体对氧自由基的清除能力减弱可促进 MDA 的产生,导致 SOD 活性下降,加重患者呼吸道症状[24]。同时,免疫功能减弱是 COPD 急性加重的重要诱因,机体正常免疫功能状态的维持需要 T 细胞亚群的互相作用,$CD3^+$、$CD4^+$ 降低,$CD8^+$ 上升可引起免疫抑制[25,26]。本研究结果显示加用舒血宁注射液治疗后氧化应激及 T 淋巴细胞亚群改善比较明显,说明两者联合治疗更有利于氧化应激损伤的缓解, 纠正机体的免疫功能紊乱,提高免疫能力。此外,本研究结果显示两组安全性均较高,用药期间未出现明显不良反应。

综上所述,舒血宁注射液联合布地奈德治疗 COPD 急性加重期患者的疗效确切, 可降低血清 MMP-9、IL-6、IL-8、TNF-α 水平,改善肺功能,减轻氧化应激并改善动脉血气及免疫功能。

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