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沙美特罗联合噻托溴铵对慢性阻塞性肺疾病患者血清 MMP-2, MMP-9 及 IL-8 水平的影响 *

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摘要 目的：探讨沙美特罗联合噻托溴铵对慢性阻塞性肺疾病患者血清炎症因子水平及肺功能的影响。**方法：**选择 2014 年 5 月-2016 年 5 月我院收治的慢性阻塞性肺病患者 83 例作为研究对象，根据治疗方法不同，将所选患者分为研究组（45 例）和对照组（38 例）。研究组患者采用沙美特罗联合噻托溴铵吸入治疗，对照组患者采用沙美特罗治疗。观察并比较两组患者治疗前后血清 MMP-2，MMP-9 及 IL-8 水平及肺功能指标的变化情况。**结果：**治疗前两组患者血清 MMP-2，MMP-9 及 IL-8 水平比较，差异无统计学意义（P>0.05）；治疗后两组患者血清 MMP-2，MMP-9 及 IL-8 水平均低于治疗前，且研究组低于对照组，差异均具有统计学意义（P<0.05）。与治疗前比较，两组患者治疗后 FEV1/FVC，FEV1 及 MVV 均升高，差异具有统计学意义（P<0.05）；与对照组比较，研究组患者治疗后 FEV1/FVC，FEV1 及 MVV 较高，差异具有统计学意义（P<0.05）。**结论：**沙美特罗联合噻托溴铵治疗慢性阻塞性肺疾病的临床效果显著，不仅能够降低患者血清炎症因子水平，还可改善患者肺功能，值得临床推广应用。

关键词：慢性阻塞性肺疾病；炎症因子；肺功能；沙美特罗；噻托溴铵

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Effects of Salmeterol and Tiotropium Bromide on Serum Levels of MMP-2, MMP-9 and IL-8 in Patients with COPD*

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ABSTRACT Objective: To investigate the effect of salmeterol combined with tiotropium bromide on serum levels of inflammatory factors and pulmonary function in patients with chronic obstructive pulmonary disease. **Methods:** 83 cases with chronic obstructive pulmonary disease who were treated in our hospital from May 2014 to May 2016 were selected, and according to the different treatment methods, the selected patients were divided into the study group (45 cases) and the control group (38 cases). The patients in the study group were treated with salmeterol combined with the tiotropium bromide, and the control group were treated with salmeterol. Then the serum levels of MMP-2, MMP-9 and IL-8 and the pulmonary function indexes of patients in the two groups were observed and compared before and after the treatment. **Results:** There was no statistically significant difference about the serum levels of MMP-2, MMP-9 and IL-8 in the two groups before the treatment (P>0.05); After treatment, the serum levels of MMP-2, MMP-9 and IL-8 in the two groups decreased, and the study group was lower than that of the control group, and the differences were statistically significant (P<0.05). Compared with before treatment, the FEV1 / FVC, FEV1 and MVV in the two groups increased after the treatment, and the differences were statistically significant (P<0.05); Compared with the control group, the FEV1 / FVC, FEV1 and MVV in the study groups after treatment were higher, and the differences were statistically significant (P<0.05). **Conclusion:** Salmeterol combined with tiotropium bromide have significant clinical effect on the treatment of chronic obstructive pulmonary disease, which can reduce the level of serum inflammatory factors and improve the pulmonary function of patients with COPD, and it is worthy of clinical application.

Key words: COPD; Inflammatory factors; Pulmonary function; Tiotropium bromide; Salmeterol

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前言

慢性阻塞性肺疾病（chronic obstructive pulmonary disease）是由多种因素引起的肺部气流受限不完全可逆并呈进行性进

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展的临床综合症状,主要表现为慢性咳嗽、咳少量粘液性痰、气短及呼吸困难、喘息等全身性症状,严重者可发展为呼吸衰竭[1-3]。目前临床主要以保守治疗为主,但常规治疗用药时间长、副作用大,临床疗效并不理想,无法快速改善患者肺功能[4,5]。沙美特罗是新型选择性长效 β2 受体激动剂, 噻托溴铵为特异选择性抗胆碱药物[6]。近年来研究显示,沙美特罗联合噻托溴铵可以通过抑制慢性阻塞性肺疾病患者血清炎症因子的释放及炎症细胞的迁移活化,在疾病进展过程中起到明显的抗炎作用[7]。因此,本研究通过观察沙美特罗联合噻托溴铵对慢性阻塞性肺疾病患者血清炎症因子水平的影响,探讨两种药物的临床疗效及机制。

1 资料与方法

1.1 临床资料

选择 2014 年 5 月 -2016 年 5 月我院收治的慢性阻塞性肺病患者 83 例,其中男 47 例,女 36 例;年龄 57-66 岁,平均年龄(61.57± 5.73)岁。根据治疗方法不同,将所选患者分为研究组(45 例)和对照组(38 例)。其中,研究组(45 例)包括男 22 例,女 23 例;平均年龄(60.82± 5.68)岁;对照组(38 例)包括男 16 例,女 22 例;平均年龄(59.58± 5.03)岁。两组差异无统计学意义(P>0.05)。

1.2 纳入及排除标准

符合《慢性阻塞性肺疾病诊疗规范(2011 年版)》[8]关于慢性阻塞性肺疾病的诊断标准:伴有慢性持续性咳嗽、咳痰,晨间咳嗽明显,夜间出现阵咳嗽或排痰,气喘、胸闷以及呼吸困难等症状;伴有体重下降,食欲减退等症状和体征;胸廓前后径增大;呼吸变浅,频率加快;触觉语颤减弱;肺下界和肝下界下移;双肺呼吸音减弱,可闻及干性或湿性啰音。排除严重的心、肾功能异常患者;恶性肿瘤患者;有明显的认知功能障碍患者;严重的代谢性疾病患者。所有患者均知情并签署知情同意书,并经医院伦理委员会批准。

1.3 治疗方法

所有患者均给予控制感染、治疗原发性疾病、化痰、镇静解痉平喘、减轻肺部水肿、改善水电解质紊乱、小剂量兴奋剂、调节酸碱平衡、改善肺顺应性、预防并发症等常规治疗,对照组在常规治疗基础上给予沙美特罗丙酸氟替卡松 50/500 μg,2 次 /d, 研究组在对照组基础上联合给予噻托溴铵干粉吸入剂 18 μg,1 次 /d。两组患者均治疗 3 个月。

1.4 观察指标及检测方法

抽取所有研究对象空腹静脉血 3 mL,3000 r/min 离心 10 min(离心半径 3 cm)取血清置于 -20 ℃冰箱保存待检。采用酶联免疫吸附实验法检测 MMP-2,MMP-9 及 IL-8 含量, 实验步骤均严格按照试剂盒说明书操作。

1.5 肺功能指标

分别于治疗前和治疗后 3 个月进行动脉血气分析、肺功能。采用血气生化分析仪(南京普朗医疗公司,PL2000PLUS)检测患者二氧化碳分压($PaCO_2$)、血氧分压(PaO_2)、酸碱度(pH)等动脉血气指标; 肺功能指标包括 1 s 用力呼气容积 / 用力肺活量[(FEV1/FVC)%]、1 s 用力呼气容积(FEV1%) 及每分钟最大通气量(MVV)。

1.6 统计学处理

计量资料以(均数± 标准差)表示,采用 t 检验,计数资料以百分数表示,应用卡方检验,P<0.05 为差异有统计学意义。

2 结果

2.1 患者治疗前后血清 MMP-2 水平比较

治疗前, 对照组患者血清 MMP-2 水平为 (0.55± 0.11) ng/mL,研究组患者血清 MMP-2 水平为(0.56± 0.12)ng/mL;治疗前, 两组患者血清 MMP-2 水平比较, 差异无统计学意义(P>0.05); 治疗后, 对照组患者血清 MMP-2 水平为 (0.43± 0.13)ng/mL, 研究组患者血清 MMP-2 水平为 (0.33± 0.10) ng/mL。治疗后,两组患者血清 MMP-2 水平均低于治疗前,且研究组低于对照组,差异均具有统计学意义(P<0.05)。见表 1。

表 1 两组患者治疗前后血清 MMP-2 水平比较(ng/mL, $\bar{x}$± s)

Table 1 Comparison of the serum levels of MMP-2 between two groups before and after treatment (pg/mL, $\bar{x}$± s)

Groups	Before treatment	After treatment
Control group	0.55± 0.11	0.43± 0.13*#
Study group	0.56± 0.12	0.33± 0.10*

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

2.2 患者治疗前后血清 MMP-9 水平比较

治疗前, 对照组患者血清 MMP-9 水平为 (0.56± 0.14) ng/mL,研究组患者血清 MMP-9 水平为(0.58± 0.11)ng/mL;治疗前, 两组患者血清 MMP-9 水平比较, 差异无统计学意义(P>0.05); 治疗后, 对照组患者血清 MMP-9 水平为 (0.47± 0.15)ng/mL, 研究组患者血清 MMP-9 水平为 (0.39± 0.12) ng/mL。治疗后,两组患者血清 MMP-9 水平均低于治疗前,且研究组低于对照组,差异均具有统计学意义(P<0.05)。见表 2。

表 2 两组患者治疗前后血清 MMP-9 水平比较(ng/mL, $\bar{x}$± s)

Table 2 Comparison of the serum levels of MMP-9 between two groups before and after treatment(pg/mL, $\bar{x}$± s)

Groups	Before treatment	After treatment
Control group	0.56± 0.14	0.47± 0.15*#
Study group	0.58± 0.11	0.39± 0.12*

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

2.3 患者治疗前后血清 IL-8 水平比较

治疗前,对照组患者血清 IL-8 水平为(0.52± 0.16)ng/mL,研究组患者血清 IL-8 水平为(0.58± 0.14)ng/mL;治疗前,两组患者血清 IL-8 水平比较,差异无统计学意义(P>0.05);治疗后,对照组患者血清 IL-8 水平为(0.47± 0.12)ng/mL,研究组患者血清 IL-8 水平为(0.38± 0.19)ng/mL。治疗后,两组患者血清 IL-8 水平均低于治疗前,且研究组低于对照组,差异均具有统计学意义(P<0.05)。见表 3。

2.4 患者治疗前后肺功能比较

两组患者治疗后 FEV1/FVC,FEV1 及 MVV 均高于治疗

前，差异具有统计学意义（P<0.05）；研究组患者治疗后FEV1/FVC,FEV1 及 MVV 高于对照组，差异具有统计学意义（P<0.05）。见表 4。

表 3 两组患者治疗前后血清 IL-8 水平比较(ng/mL，$\bar{x}\pm s$)

Table 3 Comparison of the serum levels of IL-8 level between two groups before and after treatment(pg/mL, $\bar{x}\pm s$)

Groups	Before treatment	After treatment
Control group	0.52± 0.16	0.47± 0.12*#
Study group	0.58± 0.14	0.38± 0.19*

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

3 讨论

沙美特罗具有高度脂溶性,能够到达受体部位并选择性地与 β2 受体结合,维持支气管平滑肌的舒张功能,降低血管通透性,减轻气道肿胀,进而改善 COPD 患者的肺功能[9]。相关研究表明，沙美特罗能够促进糖皮质激素受体向细胞核的移位,增加敏感基因转录,从而增强抗炎活性[10]。噻托溴铵属于长效、特异性的抗胆碱能药物,具有扩张支气管、改善呼吸困难的作用[11]。有研究表明,噻托溴铵具有抗炎作用,能够减少气道分泌物,还能抑制肺泡巨噬细胞释放中性粒细胞和嗜酸粒细胞趋化活性物质[12]。

表 4 两组患者治疗前后肺功能的分析比较

Table 4 Comparison of pulmonary function between the two groups before and after the treatment

Groups	FEV1/FVC(%)		FEV1(%)		MVV(L/min)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	43.84± 0.51	65.46± 0.80*#	60.56± 1.02	69.68± 1.31*#	64.48± 1.24	75.54± 1.12*#
Control group	45.39± 0.42	58.74± 0.73*	60.38± 1.03	63.44± 1.05*	63.92± 1.51	69.88± 1.07*

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

基质金属蛋白酶 2(MMP-2)基因位于人类染色体 16q21,由 13 个外显子和 12 个内含子所组成，结构基因总长度为 27 kb[13]。目前研究证实,MMP2 在慢性阻塞性肺疾病的发生及发展过程中具有重要作用[14]。基质金属蛋白酶 9(MMP-9)作用于呼吸道的细胞外基质和基底膜,是调节细胞外基质降解合成的主要酶类[15]。有研究证实,MMP-9/TIMP-1 比值失衡在慢性阻塞性肺疾病(COPD)的发生、发展中起重要作用[16]。因此,临床可通过检测患者血清 MMP-9 水平判断慢性阻塞性肺疾病的病情进展。IL-8 是炎症性疾病的重要介质,对特异性和非特异性的免疫细胞具有强烈的趋化作用[17]。相关研究表明,IL-8 水平在感染及自身免疫性疾病患者血清中显著增加[18]。因此,临床可通过测定 IL-8 水平对炎症进行鉴别诊断。

本研究结果显示，治疗前两组患者血清 MMP-2,MMP-9 及 IL-8 水平比较,差异无统计学意义(P>0.05);治疗后两组患者血清 MMP-2,MMP-9 及 IL-8 水平均低于治疗前，且研究组低于对照组,差异均具有统计学意义(P<0.05)。这与相关研究结果一致[19,20],说明沙美特罗联合噻托溴铵治疗慢性阻塞性肺疾病的临床显著，能够有效抑制气道的胆碱能神经递质的传递,降低细胞炎性因子水平。本研究还发现,与治疗前比较,两组患者治疗后 FEV1/FVC,FEV1 及 MVV 均升高,且研究组高于对照组,差异均具有统计学意义(P<0.05)。结果说明,沙美特罗联合噻托溴铵能够减轻慢性阻塞性肺疾病患者的气道肿胀情况,改善患者肺功能。

综上所述,沙美特罗联合噻托溴铵治疗慢性阻塞性肺疾病的临床效果显著,能够降低患者血清炎症因子水平,改善肺功能,值得临床推广应用。

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