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沙丁胺醇联合福多司坦治疗慢性阻塞性肺疾病稳定期的疗效及对患者血清 IL-6、TNF-α、hs-CRP 水平的影响 *

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摘要 目的:探讨沙丁胺醇联合福多司坦治疗慢性阻塞性肺疾病稳定期的临床疗效及对患者血清白细胞介素 -6(IL-6)、肿瘤坏死因子α(TNF-α)、超敏 c 反应蛋白(hs-CRP)水平的影响。**方法:**选择 2016 年 1 月到 2017 年 1 月我院接诊的稳定期慢性阻塞性肺病患者 100 例作为研究对象,按照随机数表法分为观察组(n=51)和对照组(n=49)。对照组使用沙丁胺醇治疗,观察组采用沙丁胺醇联合福多司坦治疗。比较两组治疗后的疗效、治疗前后血清 IL-6、TNF-α、hs-CRP、肺功能的变化及不良反应的发生情况。**结果:**治疗后,观察组临床疗效总有效率(94.12%)显著高于对照组(75.51%,$P<0.05$)。两组患者治疗后血清 IL-6、TNF-α、hs-CRP 水平均治疗前均明显下降，且观察组患者血清 IL-6、TNF-α、hs-CRP 水平均明显低于对照组 ($P<0.05$)；两组治疗后各第 1 秒用力呼气容积(FEV1)、用力肺活量(FVC)、最大呼气流量(PEF)较治疗前均显著升高($P<0.05$),且观察组 FEV1、FVC、PEF 均明显高于对照组($P<0.05$);两组患者不良反应总发生率分别 19.61%、38.78%,观察组显著低于对照组($P<0.05$)。**结论:**沙丁胺醇联合福多司坦治疗慢性阻塞性肺疾病稳定期的临床疗效和安全性均显著优于单用沙丁胺醇治疗,可能与其有效改善患者血清 IL-6、TNF-α、hs-CRP 水平有关。

关键词:沙丁胺醇;福多司坦;慢性阻塞性肺疾病;白细胞介素 -6;肿瘤坏死因子 α;超敏 c 反应蛋白

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Curative Efficacy of Salbutamol Combined with Fordostatin in the Treatment of Chronic Obstructive Pulmonary Disease at the Stable Stage and Its Effects on the Serum IL-6, TNF-α, and hs-CRP Levels*

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ABSTRACT Objective: To study the curative efficacy of Salbutamol combined with fordostatin in the treatment of chronic obstructive pulmonary disease(COPD) at stable stage and its effects on the serum interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), hypersensitive c-reactive protein (hs-CRP). **Methods:** 100 patients with COPD at stable stage who were treated in our hospital from January 2016 to January 2017 were selected as the subjects, they were divided into the observation group (n=51) and the control group (n=49) according to the randomized table. The control group was treated with salbutamol, and the observation group was treated with salbutamol combined with fordostatin. The efficacy, changes of serum IL-6, TNF-α, hs-CRP, pulmonary function before and after treatment and the incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate (94.12%) in the observation group was significantly higher than that in the control group (75.51%, P<0.05). The serum IL-6, TNF-α, and hs-crp levels in both groups were significantly decreased after treatment, and serum il-6, TNF-α, and hs-CRP levels in the observation group were significantly lower than those in the control group ($P<0.05$). After treatment, the forced expiratory volume (FEV1), forced vital capacity (FVC), and maximum expiratory flow (PEF) in both groups were significantly increased ($P<0.05$), and the FEV1, FVC, and PEF in the observation group were significantly higher than those in the control group ($P<0.05$). The total incidence of adverse reactions in the two groups was 19.61% and 38.78%, respectively, which was significantly lower in the observation group than that of the control group ($P<0.05$). **Conclusion:** The clinical efficacy and safety of salbutamol combined with fodostam in the treatment of COPD at stable stage is significantly better than that of salbutamol alone, which may be related to the effective improvement of serum IL-6, TNF-α, hs-CRP levels.

Key words: Salbutamol; Fordostein; Chronic obstructive pulmonary disease; Interleukin-6; Tumor necrosis factor; Hypersensitive c-reactive protein

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前言

慢性阻塞性肺疾病(COPD)呈进行性发展,气道的慢性炎症反应与发生发展密切相关，以 40 岁左右中老年人为多发人群,临床表现为咳嗽咳痰、气促等症状,且具有反复发作的特点,严重影响患者的生活质量[1,2]。COPD 若不及时治疗可发生肺源性心脏病、呼吸衰竭,在治疗上以控制炎症反应为主。

沙丁胺醇是β2 受体激动剂,具有扩张支气管,缓解气促、呼吸困难等症状,但是单用沙丁胺醇治疗慢性阻塞性肺疾病的效果并不显著,且部分患者会出现耐药现象[3,4]。福多司坦是日 S.S. 制药公司 1988 年开发的一种具有祛痰作用的半胱氨酸衍生物,能够抑制呼吸道上皮细胞增生,并有抗炎作用,其药效强,副作用小,被临床广泛运用于治疗慢性呼吸系统疾病[5,6]。本研究旨在探讨沙丁胺醇联合福多司坦治疗慢性阻塞性肺疾病稳定期的临床疗效,并观察其对患者血清 IL-6、TNF-α、hs-CRP 水平的影响,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月到 2017 年 1 月我院接诊的 100 例 COPD 患者进行研究。采用简单随机分组法分为观察组,男 30 例,女 21 例;55-79 岁,平均(64.25± 9.89)岁,病程 3~15 年,平均(7.87± 3.25)年。对照组 49 例,男 27 例,女 22 例;年龄 54~80 岁,平均(65.19± 9.68)岁,病程 2~16 年 ,平均(7.89± 3.26)年。两组患者一般资料均无显著性差异,具有可比性。

纳入标准:(1)未合并严重心脑血管疾病者;(2)配合研究;(3)符合《慢性阻塞性肺疾病诊治指南》[7]诊断标准。排除标准:(1)哺乳期患者;(2)呼吸衰竭需要机械通气者;(3)肺癌合并阻塞性肺炎者。

1.2 方法

对照组给予沙丁胺醇(规格 2 mg,厂家:金花企业(集团)股份有限公司西安金花制药厂,国药准字 H20010648)50 μg 吸入治疗,1 d 2 次。观察组在对照组的基础上加用福多司坦 (规格 0.2 g,厂家:江苏正大丰海制药有限公司,国药准字H20090216) 400 mg 口服,1 d 3 次。

1.3 观察指标

采集所有受试者入组后第 2 d 清晨空腹静脉血 5 mL,EDTA 抗凝后离心 15 min,速度为 2500 r/min,提取上层血清液,储存于冷冻箱内备检,血清 IL-6、TNF-α、hs-CRP 的测定采用双抗体夹心酶联免疫吸附法(ELISA);肺功能采用 HI-101 肺功能检测仪测定第 1 秒用力呼气容积 (FEV1)、用力肺活量(FVC)、最大呼气流量(PEF)水平。

疗效评定标准[8]:显效:与治疗前比较,主要症状消失;有效:咳嗽、气促等较治疗前显著改善;无效:临床症状无明显改善甚至加重。以显效人数加有效人数为总有效率。

1.4 统计学分析

采用 SPSS22.0 软件包处理数据，计量资料用均数± 标准差($\bar{x}$± s)表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较采用 x^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后，观察组和对照组患者总有效率分别为 94.12%、75.51%,观察组显著高于对照组,差异具有统计学意义(P<0.05),见表 1。

表 1 两组患者疗效的比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	51	29(56.86)	19(37.25)	3(5.88)	48(94.12)
Control group	49	24(48.98)	13(26.53)	12(24.49)	37(75.51)
x^2 value					6.786
P value					0.009q

2.2 两组患者治疗前后血清 IL-6、TNF-α、hs-CRP 水平的比较

治疗后,两组患者血清 IL-6、TNF-α、hs-CRP 水平均较治疗前显著改善,且观察组患者同期血清 IL-6、TNF-α、hs-CRP 水平均明显低于对照组(P<0.05),见表 2。

表 2 两组患者治疗前后血清 IL-6、TNF-α、hs-CRP 水平的比较($\bar{x}$± s,ng/L)

Table 2 Comparison of the serum IL-6, TNF-α and hs-CRP levels between the two groups before and after treatment($\bar{x}$± s,ng/L)

Groups	n	IL-6		TNF-α		hs-CRP	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group	51	481.23± 76.16	50.34± 8.39	533.07± 134.55	61.11± 18.72	109.16± 14.24	11.23± 2.75
Control group	49	479.89± 77.66	201.15± 45.16	531.28± 138.43	240.75± 52.08	109.34± 14.56	19.89± 3.72
t value		0.087	23.436	0.066	23.131	0.063	13.274
P value		0.931	0.000	0.948	0.000	0.950	0.000

2.3 两组患者治疗前后肺功能的比较

治疗后，两组 FEV1、FEV1 /FVC 及 PEF 较治疗前均显著升高($P<0.05$)，且观察组以上指标均明显高于对照组($P<0.05$)，见表 3。

表 3 两组患者治疗前后肺功能的比较($\bar{x}\pm s$)

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

Groups	n	FEV1(L)		FEV1 /FVC(%)		PEF(L/s)	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group	51	1.61± 0.28	1.91± 0.57	52.18± 5.36	65.83± 6.11	2.66± 0.59	3.99± 0.43
Control group	49	1.59± 0.25	1.62± 0.59	51.91± 4.78	56.17± 5.28	2.67± 0.49	3.06± 0.45
t value		0.376	2.500	0.266	8.445	0.092	10.568
P value		0.708	0.014	0.791	0.000	0.927	0.000

2.4 两组患者并发症发生情况的比较

两组患者并发症总发生率分别 19.61%、38.78%，观察组显著低于对照组($P<0.05$)，见表 4。

表 4 两组患者不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions between the two groups[n(%)]

Groups	n	Nausea	Heart palpitations	Have a headache	Gastrointestinal reaction	The total incidence of
Observation group	51	2	3	3	2	10(19.61)
The control group	49	4	5	6	4	19(38.78)
x^2 value						4.459
P value						0.035

3 讨论

COPD 是一种常见的慢性疾病，其可导致肺功能进行性下降，引起肺心病，甚至呼吸衰竭及全身不良效应[9,10]。COPD 的致残率及死亡率较高，预后差，使患者的劳动力和生活质量明显下降。慢性阻塞性肺疾病患者咳嗽咳痰会导致呼吸道感染，因为其在咳嗽咳痰时，刺激气道黏膜，当黏液黏度过高时，气道阻塞，导致窒息和生命危险[11,12]。

沙丁胺醇是临床上治疗慢性阻塞性肺病的常用药物，可舒张支气管，迅速缓解临床症状，通过松弛支气管平滑肌来达到缓解支气管痉挛的目的。但其单一用药起效慢，效果并不特别显著，因此较多学者提出在此基础上联合治疗[13,14]。福多司坦是一种新型祛痰剂，是半胱氨酸的衍生物，具有降低痰黏度的作用，促进气管浆液分泌作用，能有效改善慢性阻塞性肺疾病咳嗽咳痰情况，在治疗呼吸道感染性疾病有较高的疗效[15,16]，可用于治疗慢阻肺等呼吸系统疾病[17,18]。

本研究结果显示联合福多司坦治疗的患者的临床总有效率高达 94.12%，明显高于单独使用沙丁胺醇治疗，且患者的不良反应发生率明显低于使用沙丁胺醇治疗，说明联合沙丁胺醇治疗慢性阻塞性肺疾病安全有效，能有效提高患者的临床疗效，且不会增加并发症的发生。许多研究证实福多司坦可以改善肺功能，扩张支气管[19,20]。本研究结果显示患者治疗后的肺功能各项指标明显改善，且联合用药的患者的肺功能均明显高于单一治疗的患者。福多斯坦可能通过改善痰液体积和痰液粘度促进痰液排出，从而改善 COPD 患者的气流受限，与上述观点基本一致[21-23]。分析是原因可能因为福多司坦能有效的抑制呼吸道细胞过多增值，改善黏液纤毛的清除功能，从而抑制黏液的过多分泌，最终改善患者的肺功能[24-26]。

IL-6 是一种由纤维母细胞、巨噬细胞等多种细胞产生的细胞因子，能够刺激参与免疫反应的细胞增殖、分化；TNF-α 是最早发现的细胞因子，由活化的单核 - 巨噬细胞及其他多种细胞产生，能使肿瘤组织细胞发生出血性坏死[27,28]；hs-CRP 是血浆中的一种 C 反应蛋白，当机体受到微生物的入侵时或者组织损伤刺激肝细胞得来的一种蛋白质，作为急性全身炎症反应的非特异性标记物[29,30]。本研究结果显示联合用药患者的血清 IL-6、TNF-α、hs-CRP 水平明显低于使用沙丁胺醇治疗的患者，说明福多司坦可能通过减轻慢阻肺患者轻体内炎症反应改善其肺功能。

综上所述，沙丁胺醇联合福多司坦治疗慢性阻塞性肺疾病稳定期的临床疗效和安全性均显著优于单用沙丁胺醇治疗，可能与其有效改善患者血清 IL-6、TNF-α、hs-CRP 水平有关。

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