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噻托溴铵联合布地奈德福莫特罗对慢性阻塞性肺疾病的疗效及对 TGF-β、TIMP-1、IL-6 水平的影响 *

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摘要 目的:探讨噻托溴铵联合布地奈德福莫特罗治疗慢性阻塞性肺疾病(COPD)患者的临床疗效及对转化生长因子 -β(TGF-β)、基质金属蛋白酶抑制因子 -1(TIMP-1)及白细胞介素 -6(IL-6) 水平的影响。**方法:**选取我院于 2016 年 1 月至 2016 年 12 月期间收治的 80 例稳定期的 COPD 患者,按乱数表法分为对照组和观察组,两组均为 40 例。两组患者均进行常规治疗和布地奈德福莫特罗吸入治疗,观察组在此基础上加用噻托溴铵吸入剂。连续治疗 12 周后对两组患者的临床疗效、肺功能、血气指标、细胞因子水平进行评价。**结果:**观察组患者总有效率高于对照组(*P<0.05*)。治疗后,观察组肺功能指标用力肺活量(FVC)、一秒用力呼气容积(FEV1)、第一秒用力呼气容积占用力肺活量比值(FEV1/FVC)、动脉血氧分压(PaO_2)和动脉血二氧化碳分压($PaCO_2$)改善程度均优于对照组(*P<0.05*)。治疗后观察组患者血清中 IL-6、TIMP-1 及 TGF-β 水平均低于对照组(*P<0.05*)。**结论:**噻托溴铵与布地奈德福莫特罗的联合治疗稳定期的 COPD 患者疗效显著，并且能够有效改善患者肺功能和血气指标，降低血清 TGF-β、TIMP-1 及 IL-6 水平,值得临床推广使用。

关键词:噻托溴铵;布地奈德福莫特罗;慢性阻塞性肺疾病;肺功能;血气指标

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Clinical Efficacy of Tiotropium Bromide Combine With Budesonide and Formoterol in the Treatment of Chronic Obstructive Pulmonary Disease and its Effects on Levels of TGF-β, TIMP-1 and IL-6*

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ABSTRACT Objective: To observe the clinical efficacy of tiotropium bromide combine with budesonide and formoterol in the treatment of chronic obstructive pulmonary disease (COPD) and its effects on levels of Transforming growth factor-β (TGF-β), Matrix metalloproteinase inhibitor -1(TIMP-1) and Interleukin -6(IL-6). **Methods:** 80 patients with stable COPD who were treated in our hospital from January 2016 to December 2016 were selected, the patients were divided into observation group and control group according to the random number table method, 40 cases in each group. Both groups were treated with conventional treatment and budesonide and formoterol inhalation therapy. On the basis of conventional treatment, the observation group were treated combine of tiotropium bromide. After 12 weeks of continuous treatment, the clinical efficacy, pulmonary function, blood gas index and cytokine levels of the two groups were evaluated. **Results:** The total effective rate in the observation group was significantly higher than that in the control group (*P<0.05*). After treatment, the lung function index of forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), the forced expiratory volume in the first second accounted for the ratio of forced vital capacity (FEV1 / FVC), arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure ($PaCO_2$) in the observation group were better than those in the control group (*P<0.05*). The serum levels of TGF-β, TIMP-1 and IL-6 after treatment in the observation group were lower than those in the control group (*P<0.05*). **Conclusion:** Tiotropium bromide combine with budesonide and formoterol is effective in the treatment of COPD, which can effectively improve the pulmonary function and blood gas in patients, serum TGF-β, TIMP-1 and IL-6 levels are decreased, it is worthy of clinical application.

Key words: Tiotropium bromide; Budesonide and formoterol; Chronic obstructive pulmonary disease; Pulmonary function; Blood gas index

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前言

慢性阻塞性肺疾病(Chronic obstructive pulmonary disease，COPD)是一种以慢性炎症和持续气流受限为主要病理特征的、

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可以防治的慢性呼吸系统常见疾病[1-3]。COPD 的临床症状主要有慢性咳嗽、咳痰、呼吸困难和胸闷等[4]。由于 COPD 影响因素较多，易反复发作，如不及时治疗会造成患者生活质量急剧下降，甚至可进展为呼吸衰竭，危及患者的生命，因此寻找有效的 COPD 的治疗手段成为亟待解决的问题[5,6]。布地奈德福莫特罗能起到抗炎以及扩张支气管的作用，在临床上主要作为 COPD 的维持和缓解性治疗药物，也是临床用于治疗 COPD 的常见药物 [7-9]。噻托溴铵为抗胆碱能支气管扩张药，临床上主要用于 COPD 的维持治疗，并且能够改善患者肺功能和呼吸不畅等症状[10-12]。本研究旨在探讨噻托溴铵与布地奈德福莫特罗联合使用对稳定期的 COPD 的疗效和对患者血清中转化生长因子 -β（Transforming growth factor-β, TGF-β）、基质金属蛋白酶抑制因子 -1（Tissue inhibitor of metalloproteinase-1, TIMP-1）及白细胞介素 -6（Interleukin-6, IL-6）水平的影响。

1 资料与方法

1.1 临床资料

选取我院于 2016 年 1 月至 2016 年 12 月期间收治的 80 例处于稳定期的 COPD 患者，所有患者按乱数表法分为对照组和观察组，两组均为 40 例。对照组：男 24 例，女 16 例；年龄 56~81 岁，平均（64.14± 5.19）岁；病程 5~12 年，平均（8.13± 2.68）年；COPD 全球倡议（GOLD）分级标准：III 级 30 例，IV 级 10 例。观察组：男 23 例，女 17 例；年龄 61~79 岁，平均（63.76± 5.51）岁；病程 4~12 年，平均（7.84± 3.07）年；GOLD 分级标准：III 级 28 例，IV 级 12 例。两组的一般资料无明显差异（*P*> *0.05*），具有可比性。本研究内容符合医院伦理委员会制定的相关规定，并已通过委员会的审批。

1.2 纳入排除标准

纳入标准：诊断标准参照《慢性阻塞性肺疾病诊治指南》中相关的内容，所有患者均被确诊为稳定期的 COPD[13]。患者及其家属对本研究知情同意。排除标准：（1）心、肝、肾等器官功能不全者以及免疫系统功能异常者；（2）对研究所用药物有禁忌者；（3）长期或近一个月内使用过激素类药物；（4）存在意识障碍或精神疾患，不能配合治疗者；（5）有活动性结核、肺癌等其他肺部疾病者。

1.3 治疗方法

两组患者均给予止咳化痰、吸氧、调节体内电解质紊乱等常规治疗，同时给予患者布地奈德福莫特罗粉吸入剂（AstraZeneca AB，国药准字 H20140458，规格：160 微克 /4.5 微克 / 吸，60 吸 / 支），2 吸 / 次，2 次 /d；观察组在对照组的基础上同时按照 18 μg/ 次加用噻托溴铵粉吸入剂（Boehringer Ingelheim Pharma GmbH & Co.KG，国药准字 H20140933，规格：18 μg× 10 s），1 次 /d，两组患者均连续治疗 12 周。

1.4 评价指标

1.4.1 疗效 参照曾林森等[14]的论述，结合本治疗方案确定疗效判定标准：（1）治愈：临床症状完全消失；（2）显效：临床症状明显好转，痰液少且稀薄，肺部啰音明显减少；（3）有效：临床症状有所缓解，痰液量多但稀薄，肺部啰音减少；（4）无效：临床症状无好转或加重。总有效率 = 治愈率 + 显效率 + 有效率。

1.4.2 检测指标 在治疗前后，应用肺功能仪于测定两组的第一秒用力呼气容积（FEV1）、用力肺活量（FVC）、第一秒用力呼气容积占用力肺活量比值（FEV1/FVC），两组的动脉血氧分压（PaO_2）、二氧化碳分压（$PaCO_2$）应用血气分析仪进行测定。于治疗前、治疗后采集两组患者空腹静脉血 3~5 mL，于 4℃离心机中 5000 rpm 离心 10 min 后，取上清，采用 ELISA 检测 TGF-β（试剂盒购于 BD Biosciences, San Diego, CA, USA）、TIMP-1（试剂盒购于 R&D Systems, Minneapolis, USA）和 IL-6（试剂盒购于 BD Biosciences, San Diego, CA, USA），所有操作参考试剂盒操作指南进行。

1.5 统计学方法

运用 SPSS 19.0 进行分析，临床疗效、GOLD 分级等计数资料采用（%）表示，比较采用 x^2 检验，肺功能指标、血气指标等计量资料以（$\bar{x}\pm s$）表示，采用 t 检验，将α=0.05 作为检验标准。

2 结果

2.1 两组患者临床疗效比较

对照组总有效率为 75.00%，观察组为 97.50%，两组比较差异有统计学意义（*P<0.05*）。见表 1。

表 1 两组治疗效果比较[n(%)]

Table 1 Comparison of clinical results of two groups [n (%)]

Groups	Cure	Effective	Valid	Invalid	Total efficiency
Control group（n=40）	2（5.00）	18（45.00）	10（25.00）	10（25.00）	30（75.00）
Observation group（n=40）	6（15.00）	28（70.00）	5（12.50）	1（2.50）	39（97.50）*

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

2.2 两组患者肺功能比较

治疗前两组患者 FVC、FEV1 和 FEV1/FVC 比较无统计学差异（*P>0.05*）；两组患者治疗后 FVC、FEV1 和 FEV1/FVC 水平均明显高于治疗前，且观察组的各项指标均高于对照组（*P< 0.05*），结果如表 2 所示。

2.3 两组患者血气指标比较

两组患者治疗前血气指标无统计学差异（*P>0.05*）；治疗后两组患者的 PaO_2 明显升高，$PaCO_2$ 水平明显降低（*P<0.05*）；治疗后观察组的 PaO_2 高于对照组，$PaCO_2$ 低于对照组（*P<0.05*），结果如表 3 所示。

2.4 两组患者细胞因子水平比较

两组患者治疗前 TGF-β、TIMP-1 及 IL-6 水平无统计学差异（*P>0.05*）；治疗后两组患者 TGF-β、TIMP-1 及 IL-6 水平明显降低（*P<0.05*），治疗后观察组 IL-6、TIMP-1 及 TGF-β 水平均低于对照组（*P<0.05*），结果如表 4 所示。

3 讨论

COPD 患者存在明显的气流受限[15]，我国流行病学调查结

表 2 两组患者肺功能比较($\bar{x}\pm s$)

Table 2 Comparison of pulmonary function of two groups ($\bar{x}\pm s$)

Groups	Time	FVC(ml)	FEV1(ml)	FEV1/FVC(%)
Control group(n=40)	Before treatment	2.19± 0.37	1.87± 0.39	57.48± 8.14
	After treatment	2.51± 0.28*	2.27± 0.42*	61.87± 7.34*
Observation group(n=40)	Before treatment	2.23± 0.46	1.85± 0.36	56.21± 7.66*
	After treatment	3.01± 0.51*#	2.61± 0.35*#	72.83± 6.39*#

Note: compared with the same group before treatment, *$P<0.05$; compared with the control group over the same period, #$P<0.05$.

表 3 两组患者血气指标比较($\bar{x}\pm s$)

Table 3 Comparison of blood gas index of two groups ($\bar{x}\pm s$)

Groups	Time	PaO_2(mm Hg)	$PaCO_2$ (mm Hg)
Control group(n=40)	Before treatment	55.92± 6.43	48.87± 4.39
	After treatment	66.87± 5.46*	38.27± 6.42*
Observation group(n=40)	Before treatment	53.23± 6.46	49.85± 7.36
	After treatment	78.01± 5.51*#	31.61± 4.35*#

Note: compared with the same group before treatment,*$P<0.05$; compared with the control group over the same period,#$P<0.05$.

表 4 两组患者细胞因子水平比较($\bar{x}\pm s$)

Table 4 Comparison of cell factor levels of two groups ($\bar{x}\pm s$)

Groups	Time	TGF-β (ng/L)	TIMP-1 (ng/mL)	IL-6 (ng/mL)
Control group(n=40)	Before treatment	97.92± 11.43	170.87± 45.39	30.17± 8.24
	After treatment	89.87± 9.46*	142.27± 32.42*	21.87± 7.39*
Observation group(n=40)	Before treatment	98.23± 12.46	168.85± 53.36	29.71± 11.05
	After treatment	78.01± 9.51*#	121.61± 34.35*#	15.23± 6.79*#

Note: compared with the same group before treatment,*$P<0.05$; compared with the control group over the same period, #$P<0.05$.

果显示[16,17],在大于 40 岁的人群中约有 8.2%的人患有 COPD,由此可见 COPD 已成为威胁中老年人群生命健康的主要慢性疾病之一。COPD 的病因及发病机制复杂,至今尚不明确,普遍认为与吸烟、环境污染、职业性粉尘、化学物质接触、感染、遗传因素等有密切关系[18-20]。由于其发病机理的复杂性,且各个阶段相互促进,而目前的药物多针对某一个环节,故疗效一般,因此应结合 COPD 的可能发病机制,探讨针对多环节的治疗方案。相关研究已证实[21],气道炎性症状的持续存在、肺组织结构破坏、气道重塑以及肺功能下降均与炎症细胞及其所释放的多种细胞因子有关,这可能是 COPD 的重要发生机制。因此,减轻 COPD 患者气道炎症反应,改善肺通气功能,是治疗 COPD 的关键。

布地奈德福莫特罗是由布地奈德和福莫特罗两种成份组成。布地奈德作为糖皮质激素,能够对免疫反应起到抑制作用,同时可以降低抗体合成,从而减少组胺等过敏活性介质的释放。另一方面,布地奈德可减少支气管合成、收缩物质的生成,减轻平滑肌的收缩反应,进而达到对 COPD 引起气道炎症的改善作用[22,23]。福莫特罗是一种长效的选择性肾上腺素β2 受体激动剂,能够改善 COPD 患者支气管痉挛症状,同时可舒张支气管平滑肌,并且福莫特罗能使 FEV1 和 FVC 增加[24]。由于糖皮质激素与β2 受体之间具有协同作用,所以布地奈德和福莫特罗的联用可以起到抗炎、舒张支气管平滑肌等作用[25,26]。噻托溴铵为抗胆碱能支气管扩张药,可以显著改善患者呼吸困难等症状。临床研究表明,首次给药 30 min 内便能使肺功能得到显著改善,并且在给药期内一直保持其支气管扩张作用,而无耐受现象发生。因此,布地奈德福莫特罗联合噻托溴铵治疗 COPD,可显著减轻患者气道炎症反应,改善肺通气功能。

本次研究结果显示,观察组患者总有效率为 97.50%,显著高于对照组的 75.00%($P<0.05$),表明噻托溴铵与布地奈德福莫特罗的联合用药治疗效果优于布地奈德福莫特罗单独使用的治疗效果。治疗后两组肺功能指标 FVC、FEV1、FEV1/FVC 和血气指标 PaO_2 和 $PaCO_2$ 的均优于治疗前($P<0.05$),同时治疗后的观察组各项指标均优于对照组,可能主要是由于联合使用的药物均具有各自的作用靶点,通过这些靶点发挥不同的功能,从而达到对 COPD 疾病的整体改善,同时也进一步说明噻托溴铵与布地奈德福莫特罗的联合使用对 COPD 患者的血气指标和肺功能具有较好的改善作用,较单独用药更加有效,这与吴笑驰等[27]报道相一致。TGF-β 作为一种转化生长因子能够影响 MMPs 与 TIMP-1 之间的平衡,而 TIMP-1 作为 MMPs 的抑制因子,主要通过抑制 MMPs 减少其对细胞外基质(ECM)的裂解,使得 ECM 的降解与合成达到平衡状态,而 TGF-β 的变化会改变这种平衡导致 ECM 的减少,导致气管重塑,造成

COPD 的发生[28-30]。IL-6 作为炎症因子主要起到促炎的作用，当 COPD 发生时会产生大量的炎症因子，而这些炎症因子会进一步对肺部造成损伤加重 COPD，因此 COPD 的治疗对于炎症的控制是十分重要的。本次研究结果也显示，治疗后两组患者血清 IL-6、TIMP-1 及 TGF-β 水平均明显降低，且观察组患者上述指标水平均明显低于对照组（*P<0.05*），提示联合用药能够显著改善 COPD 患者气道炎性反应。

综上所述，噻托溴铵与布地奈德福莫特罗的联合治疗稳定期的 COPD 患者疗效显著，并且能够有效改善患者肺功能和血气指标，同时对炎性反应也有显著的控制作用，值得临床推广使用。

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