

doi: 10.13241/j.cnki.pmb.2017.15.041

噻托溴铵联合沙美特罗治疗慢性阻塞性肺疾病的临床效果

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摘要 目的:探讨噻托溴铵联合沙美特罗治疗慢性阻塞性肺疾病的临床效果。**方法:**选取我院 2008 年 8 月~2016 年 8 月期间收治的 68 例慢性阻塞性肺疾病患者,由电脑随机均分为两组,每组 34 例,其中对照组给予沙美特罗进行治疗,而观察组在此基础上施加噻托溴铵治疗。对比观察两组患者治疗前后肺功能指标的变化、运动能力、生活质量、预后及不良事件发生率。**结果:**治疗前,两组患者的肺功能各项指标、6 分钟步行距离(6MWD)和圣乔治呼吸问卷(SGRQ)评分均无明显差异($P>0.05$)。治疗后均较治疗前有明显改善,且观察组同期改善程度均显著高于对照组($P<0.05$)。观察组在治疗后 12 个月内发生急性加重的例数明显少于对照组($P<0.05$),且不良事件发生率明显低于对照组($P<0.05$)。**结论:**联合使用噻托溴铵与沙美特罗治疗慢性阻塞性肺疾病,可更好地改善患者的肺功能、运动能力及生活质量,且急性加重率和不良事件发生率更低,值得进一步推广与应用。

关键词:噻托溴铵;沙美特罗;慢性阻塞性肺疾病;临床效果

中图分类号:R563 **文献标识码:**A **文章编号:**1673-6273(2017)15-2957-04

Effect of Tiotropium Combined with Salmeterol in the Treatment of Chronic Obstructive Pulmonary Disease

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ABSTRACT Objective: To investigate the effects of combining tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease. **Methods:** 68 cases of chronic obstructive pulmonary disease in our hospital were selected from August 2008 to August 2016. All the patients were randomly divided into two groups, 34 cases in each group. The control group was treated with Salmeterol, while the observation group was treated with the Tiotropium based on the control group. The changes of pulmonary function, exercise capacity, quality of life, prognosis and adverse events were compared between the two groups before and after treatment. **Results:** Before treatment, there were no significant differences in lung function indexes, 6 minutes walk distance (6MWD) and St. George's Respiratory Questionnaire (SGRQ) scores in the two groups ($P>0.05$). After treatment, the pulmonary function index, 6MWD and SGRQ score of the two groups were significantly improved. And the improvement degree of lung function indexes, 6MWD and SGRQ scores in the same period of observation group was significantly higher than that in control group ($P<0.05$). In addition, the patients with acute exacerbation in the observation group were significantly less than the control group ($P<0.05$) within 12 months after treatment, and the incidence of adverse events was significantly lower than that of the control group ($P<0.05$). **Conclusions:** Tiotropium combined with Salmeterol can significantly improve the pulmonary function, exercise capacity, quality of life of patients in the treatment of chronic obstructive pulmonary disease, and the combined curative effect is superior to Salmeterol monotherapy with less adverse events, so it is worthy of further promotion and application.

Key words: Tiotropium; Salmeterol; Chronic obstructive pulmonary disease; Clinical effect

Chinese Library Classification(CLC): R563 **Document code:** A

Article ID: 1673-6273(2017)15-2957-04

前言

慢性阻塞性肺疾病(Chronic obstructive pulmonary disease, COPD)是一种气道慢性炎症引起的持续气流受限性疾病,是呼吸系统的常见疾病、多发病^[1],可进一步发展为肺心病和呼吸衰

竭,致残率和病死率很高^[2]。目前,噻托溴铵和沙美特罗是治疗慢性阻塞性肺疾病的重要药物,其疗效均已通过大量的临床试验得到认可^[3-5],关于二者联合用药的治疗效果也得到了部分研究的肯定。但是,关于二者联合治疗的安全性及生活质量的研究尚不多见,仍需进一步证实。为此,本次选取近年来我院收治的 68 例慢性阻塞性肺疾病患者作为研究对象,对比观察采用噻托溴铵联合沙美特罗与单独采用沙美特罗治疗的临床效果。

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(收稿日期:2016-09-22 接受日期:2016-10-21)

1 资料与方法

1.1 研究对象

68 例 COPD 患者, 收治时间为 2008 年 8 月~2016 年 8 月, 由电脑随机均为观察组和对照组, 其中对照组 34 例, 男 24 例, 女 10 例, 年龄分布范围为 53 岁~76 岁, 病程 4 年~15 年; 观察组 34 例, 男 22 例, 女 12 例, 年龄分布范围为 55 岁~74

岁, 病程 2 年~13 年。所有患者经诊断均符合 "慢性阻塞性肺疾病诊治指南(2013 年修订版)"^[6], 并排除以下情况: ① 支气管哮喘患者; ② 变应性鼻炎患者; ③ 心、肝、肾等重要器官功能严重不全的患者; ④ 窄角型青光眼患者; ⑤ 前列腺增生、膀胱颈狭窄患者; ⑥ 对抗胆碱药物、乳糖等吸入过敏者; ⑦ 肺结核活动期患者; ⑧ 不同意接受本次治疗。两组患者在性别、年龄、病情等方面比较, 具有可比性($P>0.05$)。

表 1 两组患者的一般情况比较(n,%)
Table 1 Comparison of the general data in the two groups (n,%)

General data	Control group(n=34)	Observation group(n=34)	P
Male/female	24/10	22/12	>0.05
Average age(years)	57.5± 12.3	58.2± 13.1	>0.05
Average course(years)	7.5± 4.1	7.7± 3.4	>0.05
Medium classification(n,%)	25(73.5%)	24(70.6%)	>0.05
Severe classification(n,%)	9(26.5%)	10(29.4%)	>0.05

1.2 方法

患者均接受包括止咳化痰、防治感染、吸氧、增强免疫力等常规治疗。对照组患者给予沙美特罗(沙美特罗替卡松粉吸入剂, Glaxo Wellcome Production, 批准文号 H20150324)50/250 μg 吸入治疗, 每日早晚各 1 次。观察组患者在给予沙美特罗吸入治疗的基础上(用量同上)施加噻托溴铵(正大天晴药业集团股份有限公司, 国药准字 H20060454)18 μg/10 s 吸入治疗, 每日睡前 1 次。两组患者的疗程均为 12 周, 并在治疗后 1、3、6、12 个月进行定期随访。

1.3 观察指标

(1) 肺功能指标: 用力肺活量(FVC)、第 1 秒用力呼气容积(FEV1)、第 1 秒用力呼气容积与预计值的比值(FEV1/pred)、第 1 秒用力呼气容积与用力肺活量的比值(FEV1/FVC); (2) 运动能力: 6 分钟步行试验(6MWD); (3) 生活质量评价: 应用 SGRQ 生活质量问卷, 总分值为 100 分, 健康状况与总得分呈负相关,

且单项得分或总和得分的分值波动在 4 分以上均具有临床意义; (4) 安全性观察指标: 根据急性发作次数、死亡例数、不良事件(头痛、咽部刺痛、恶心、声音嘶哑、心动过速、轻度手抖等)发生率进行评估。

1.4 统计学处理

SPSS13.0 软件, 计量资料的假设性检验组内采用 t 检验, 组间比较采用方差分析; 计数资料的假设性检验采用 χ^2 检验, 检验水准取 $\alpha=0.05$ 。

2 结果

2.1 肺功能指标

治疗前两组患者的肺功能各项指标均无明显差异($P>0.05$)。治疗后两组各期均改善明显, 且同期观察组改善程度高于对照组, 均 $P<0.05$ 。详见表 2。

表 2 两组患者肺功能指标对比($\bar{x} \pm s$)
Table 2 Comparison of pulmonary function indexes in the two groups($\bar{x} \pm s$)

Indexes	Groups	Before treatment	1 month	3 months	6 months	12 months
FVC(L)	Control group	2.18± 0.05	2.25± 0.46*	2.27± 0.42*	2.30± 0.43*	2.32± 0.28*
	Observation group	2.17± 0.12	2.37± 0.15* [△]	2.41± 0.17* [△]	2.43± 0.13* [△]	2.44± 0.16* [△]
FEV1(L)	Control group	0.97± 0.11	1.15± 0.11*	1.16± 0.13*	1.17± 0.11*	1.19± 0.12*
	Observation group	1.01± 0.12	1.21± 0.12* [△]	1.27± 0.14* [△]	1.34± 0.13* [△]	1.36± 0.12* [△]
FEV1/pred (%)	Control group	42.4± 5.12	44.5± 7.46*	47.6± 7.15*	49.4± 7.13*	51.2± 8.11*
	Observation group	42.5± 6.11	46.6± 7.54* [△]	49.4± 7.82* [△]	51.2± 8.21* [△]	55.3± 9.01* [△]
FEV1/FVC (%)	Control group	52.6± 9.14	52.8± 9.42*	53.1± 9.56*	53.7± 9.32*	54.2± 9.36*
	Observation group	52.9± 8.71	53.7± 9.25* [△]	54.3± 9.44* [△]	55.2± 9.61* [△]	56.1± 9.28* [△]

Note: * indicates that compared with before treatment in the same group, $P<0.05$; [△] indicates that compared with control group, $P<0.05$.

2.2 运动能力与生活质量评分

治疗前两组患者的 6MWD 和 SGRQ 评分均无明显差异($P>0.05$)。治疗后, 两组患者的各期 6MWD 和 SGRQ 评分均较

治疗前有明显改善, 且同期观察组改善程度与对照组相比比较高, $P<0.05$ 。详见表 3。

表 3 两组患者 6MWD 和 SGRQ 评分的比较($\bar{x} \pm s$)Table 3 Comparison of the exercise capacity and quality of life in two groups after treatment($\bar{x} \pm s$)

Indexes	Groups	Before treatment	1 month	3 months	6 months	12 months
6MWD(m)	Control group	252.3± 8.72	278.2± 11.34*	279.5± 7.43*	281.4± 6.25*	282.2± 7.57*
	Observation group	251.5± 11.21	283.7± 10.56* ^Δ	311.3± 9.67* ^Δ	314.5± 8.14* ^Δ	318.7± 8.38* ^Δ
SGRQ scores	Control group	59.8± 2.11	56.3± 2.12*	54.4± 2.26*	53.7± 2.46*	53.3± 2.21*
	Observation group	60.0± 2.09	54.8± 2.31* ^Δ	50.3± 2.21* ^Δ	49.5± 1.98* ^Δ	48.6± 2.01* ^Δ

Note: * indicates that compared with before treatment in the same group, $P < 0.05$; ^Δ indicates that compared with control group, $P < 0.05$.

2.3 预后和不良事件发生率

观察组患者在治疗后 12 个月内发生急性加重的例数有 4 例(11.8 %),对照组为 11 例(32.4 %),观察组明显少于对照组($P < 0.05$)。两组均有部分患者发生不良反应,以口感、心悸、声

嘶较常见,但两组不良反应症状均较轻,经对症治疗或休息后缓解,未产生严重影响。观察组不良事件发生率、死亡率也都低于对照组,但差异不具有统计学意义($P > 0.05$)。详见表 4。

表 4 两组患者预后和不良事件发生率的比较(n,%)

Table 4 Comparison of prognosis and incidence of adverse events in two groups(n,%)

Indexes		Control group(n=34)	Observation group(n=34)
	Total	11(32.4%)	4(11.8%)*
Acute exacerbation within 12 months(n,%)	Within 3 months(n,%)	3(8.8%)	0(0)*
	Within 3 to 6 months(n,%)	5(14.7%)	2(5.9%)*
	Within 6 to 12 months(n,%)	3(8.8%)	2(5.9%)
Adverse reactions(n,%)		7(20.6%)	3(8.8%)
mortality(n,%)		3(8.8%)	1(2.9%)

Note: * indicates that compared with control group, $P < 0.05$.

3 讨论

慢性阻塞性肺疾病的确切病因尚不清楚,大多认为慢性支气管炎和阻塞性肺气肿的发病因素都可能参与慢性阻塞性肺病的发病^[7-9],目前临床治疗办法是给予药物治疗,从而减缓患者的症状,阻止或缓解肺功能下降,改善患者的生活质量。

抗炎治疗在慢性阻塞性肺疾病的治疗过程中具有重要的作用。沙美特罗是一种选择性长效 β_2 受体激动剂,它通过选择性激动气道平滑肌上的 β_2 受体发挥长效支气管扩张的作用,以及抑制过敏介质释放、增殖肥大细胞^[10],另外它可使 β_2 受体的数量增加,敏感性增强,从而减轻气道炎症反应^[11]。本组研究结果显示,对照组单纯采用沙美特罗吸入治疗,治疗后患者的肺功能指标、运动能力及生活质量均有一定的改善,证实了沙美特罗对于治疗慢性阻塞性肺疾病具有较好的临床效果,与文献报道的结论基本一致^[12,13]。

抗胆碱能药物能够抑制副交感神经活性,降低支气管平滑肌张力和黏液的高分泌,扩张支气管,缓解气流受阻,也能起到抗炎作用^[14]。噻托溴铵可以拮抗气道中胆碱能受体,尤其是对 M1、M3 的拮抗时间较 M2 要长将近 100 倍之多^[15],因此可以持久地阻碍支气管的收缩以及腺体的分泌,使气道保持 24 h 畅通,减少炎症的发生^[16]。因此,噻托溴铵联合沙美特罗可以发挥不同药物成分的作用机制,起到协同增效的作用^[17,18]。吴海洪等^[19]认为,高度脂溶性沙美特罗可选择性与 β_2 受体结合,能够增加细胞内环磷酸腺苷的浓度,起到长效扩张支气管平滑肌和抗炎的作用,同时还能降低血管的通透性,减轻气道肿胀,促进

支气管黏液分泌,改善肺功能,二者联合的临床疗效要优于单纯采用沙美特罗,且未增加不良事件发生率。熊雪芳^[20]等治疗老年 COPD 时运用了沙美特罗 / 丙酸氟替卡松和噻托溴铵联合治疗,结果表明噻托溴铵具有长效扩张支气管平滑肌的作用,在达到治疗效果的同时不会产生全身性抗胆碱能作用。本文中观察组患者的肺功能、运动能力、生活质量均有明显改善,且改善优于对照组,治疗后 12 个月内发生急性加重的例数也明显少于对照组,证实了二者联合的治疗效果优于单纯使用沙美特罗。然而,尽管观察组不良反应发生率及病死率均低于对照组,但差异不具有统计学意义,这可能与本文收集例数较少有一定关系,我们也将在今后的研究中扩大样本量进行研究。

总之,联合使用噻托溴铵和沙美特罗治疗 COPD,可明显改善肺功能、运动能力,提高生活质量,改善预后和降低不良事件发生率,联合使用的疗效优于沙美特罗单药治疗,值得进一步推广与应用。

参考文献(References)

- [1] Saraiva C, Abreu T, Neves D, et al. Mortality Predictive Factors in Subjects With COPD After a Pulmonary Rehabilitation Program: A 3-Year Study[J]. Respiratory Care, 2016, 61(9): 1179-1185
- [2] Stach A, Emberlin J, Smith M, et al. The Effect of Incidental Consolidation on Management and Outcomes in COPD Exacerbations: Data from the European COPD Audit[J]. PLoS One, 2015, 10(7): 311-321
- [3] Pelaia G, Vatrella A, Busceti M T, et al. Pharmacologic rationale underlying the therapeutic effects of tiotropium/olodaterol in COPD[J]. Therapeutics & Clinical Risk Management, 2015, 11: 1563-1572
- [4] Vogelmeier C F, Asijee G M, Kupas K, et al. Tiotropium and Salme-

- terol in COPD Patients at Risk of Exacerbations: A Post Hoc Analysis from POET-COPD[J]. *Advances in Therapy*, 2015, 32(6): 1-11
- [5] Trudo F, Kern D M, Davis J R, et al. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments [J]. *International Journal of Copd*, 2015, 10: 2055-2066
- [6] 中华医学会呼吸病学分会慢性阻塞性肺疾病学组.慢性阻塞性肺疾病诊治指南(2013年修订版)[J]. *中华结核和呼吸杂志*, 2013, 36(4): 255-264
- Chronic Obstructive Pulmonary Disease Committee, Respiratory Society, Chinese Medical Association. The guideline for diagnosis and management of chronic obstructive pulmonary disease (2013 revised edition)[J]. *Chinese Journal of Tuberculosis and Respiratory Diseases*, 2013, 36(4): 255-264
- [7] Tashkin D P. Dual anti-inflammatory agents prevent COPD exacerbations[J]. *Lancet*, 2015, 385(9971): 832-834
- [8] James A J, Reinius L E, Verhoek M, et al. The Chitinase Proteins YKL-40 and Chitotriosidase are Increased in Both Asthma and COPD [J]. *Am J Respir Crit Care Med*, 2015, 193(2): 131-142
- [9] Roberts M H, Clerisme-Beaty E, Kozma C M, et al. A retrospective analysis to identify predictors of COPD-related rehospitalization[J]. *BMC Pulmonary Medicine*, 2016, 16(1): 1-13
- [10] Alvaradogonzalez A, Arce I. Tiotropium Bromide in Chronic Obstructive Pulmonary Disease and Bronchial Asthma [J]. *Journal of Clinical Medicine Research*, 2015, 7(11): 831-839
- [11] Singh D, Worsley S, Zhu C Q, et al. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial [J]. *Bmc Pulmonary Medicine*, 2015, 15(1): 1-12
- [12] Wedzicha J A, Banerji D, Chapman K R, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD [J]. *New England Journal of Medicine*, 2016, 374(23): 2222-2234
- [13] Bender BG, Hernandez Vecino RA, McGrath K, et al. Comparative Analysis of Persistence to Treatment among Patients with Asthma or COPD Receiving AirFluSal Forspiro or Seretide Diskus Salmeterol/Fluticasone Propionate Combination Therapy [J]. *J Allergy Clin Immunol Pract*, 2016, 4(5): 884-889
- [14] Collamati A, Martone A M, Poscia A, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence [J]. *Aging Clinical and Experimental Research*, 2015, 28(1): 25-35
- [15] Matsuse H, Yamagishi T, Kodaka N, et al. Tiotropium bromide as add-on therapy to inhaled corticosteroids for treating asthma [J]. *Expert Opinion on Pharmacotherapy*, 2015, 16(9): 1403-1409
- [16] Sharma A, Weber B, Wein M, et al. Essential criteria for pharmacokinetic studies supporting bioequivalence of inhaled tiotropium bromide products[J]. *Clin Pharmacol Drug Dev*, 2016, 5(1): 52-56
- [17] Alvaradogonzalez A, Arce I. Tiotropium Bromide in Chronic Obstructive Pulmonary Disease and Bronchial Asthma [J]. *Journal of Clinical Medicine Research*, 2015, 7(11): 831-839
- [18] Shohrati M, Jalili M, Afshar H, et al. Efficacy of Tiotropium Bromide and Rehabilitation Treatment on Pulmonary Function of Patients With Sulfur Mustard Lung Injury [J]. *Journal for the Theory of Social Behaviour*, 2015, 17(12): 393-407
- [19] 吴海洪, 高芳蝶, 詹洁坚. 噻托溴铵联合沙美特罗/氟替卡松治疗慢性阻塞性肺疾病的临床研究[J]. *中国临床药理学杂志*, 2015, 31(6): 412-414
- Wu Hai-hong, Gao Fang-die, Zhan Jie-jian. Clinical efficacy of the treatment of tiotropium bromide combined salmeterol/fluticasone on chronic obstructive pulmonary disease [J]. *The Chinese Journal of Clinical Pharmacology*, 2015, 31(6): 412-414
- [20] 熊雪芳, 孙蕾. 沙美特罗/丙酸氟替卡松联合噻托溴铵治疗老年慢性阻塞性肺疾病的临床研究[J]. *中国临床药理学杂志*, 2014, 30(4): 291-293
- Xiong Xue-fang, Sun Lei. Efficacy of salmeterol/fluticasone propionate combined with tiotropium in elderly patients with chronic obstructive pulmonary disease[J]. *The Chinese Journal of Clinical Pharmacology*, 2014, 30(4): 291-293