doi: 10.13241/j.cnki.pmb.2017.24.030

布地奈德福莫特罗治疗支气管哮喘患者的临床疗效及对患者血清炎性因子水平的影响

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摘要 目的:探讨布地奈德福莫特罗吸入治疗对慢性支气管哮喘患者的临床疗效及其对患者血清炎性因子水平、肺功能和生活质量的影响。**方法:**选择 2014 年 2 月至 2016 年 2 月于我院呼吸内科就诊并确诊为慢性支气管哮喘患者 123 例,根据随机数字表法分为观察组 65 例和对照组 58 例。比较两组患者治疗前后血清白介素 17(IL-17)、白介素 33(IL-33)、基质金属蛋白酶 9(MMP-9)、肺功能、生活质量评分的变化、临床疗效有效率及不良反应的发生情况。**结果:**观察组的总有效率为 92.3%(60/65),显著高于对照组(81.03%,P<0.05)。治疗后,两组患者的血清 IL-17、IL-33 水平与治疗前相比均显著降低(P<0.05),且观察组显著低于对照组(P<0.05);两组血清 MMP-9 水平与治疗前相比差异均无统计学意义(P>0.05);观察组患者的第一秒用力呼吸容积(FEV1)、峰值呼气流速(PEF)与第一秒用力呼气容积与用力肺活量比值(FEV1/FVC)水平均明显增加,且观察组上述指标明显高于对照组(P<0.05);圣. 乔治呼吸问卷(SGRQ)评分结果显示观察组患者的生活质量显著高于对照组患者。**结论:**布地奈德福莫特罗吸入治疗对慢性支气管哮喘临床效果显著,可显著控制炎症反应,改善肺功能,显著提升患者生活质量。

关键词:慢性支气管哮喘;布地奈德福莫特罗;肺功能;IL-33;MMP-9;SGRQ 评分

中图分类号:R562.25 **文献标识码:**A **文章编号:**1673-6273(2017)24-4723-04

Clinical Efficacy of Budesonide and Formoterol Fumarate Powder in the Treatment of Patients with Bronchial Asthma and Its Effect on the Serum Levels of Inflammatory Factors

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ABSTRACT Objective: To explore the clinical efficacy of Budesonide and Formoterol Fumarate Powder in the treatment of patients with bronchial asthma and its effect on the serum levels of inflammatory factors. **Methods:** 123 cases treated and diagnosed as bronchial asthma in our hospital from February, 2014 to February, 2016 were randomly divided into the observation group (65 cases) and control group (58 cases). The serum levels of IL-17, IL-33, MMP-9, pulmonaryfunction,quality of life, total effective rate and incidence of adverse reactions were compared between the two groups. **Results:** The total effective rate of observation group was 92.3%, which was significantly higher than that of the control group (81.03%, P<0.05). After therapy, the serum level of IL-17, IL-33 in both groups were largely decreased compared with those before therapy (p<0.05), and those of observation group were significantly lower than the control group (p<0.05); the serum level of MMP-9 in both groups showed no statistical difference compared with that of before therapy. Similarly, the level of FEV1, PEF and FEV1/FVC of observation group were obviously increased compared with those before therapy (p<0.05) and were significantly higher than those of the control group (p<0.05); the quality of life in the observation group was better than that of the control group based on the SGRQ score (p<0.05). **Conclusion:** Budesonide and Formoterol Fumarate Powder was effective on the patients with chronic bronchial asthma, which could control the inflammatory reactions, improve the pulmonary function as well as the quality of life.

Key words: Chronic bronchial asthma; Budesonide and Formoterol Fumarate Powder; Pulmonary function; IL-33; MMP-9; SGRQ score

Chinese Library Classification(CLC): R562.25 Document code: A

Article ID: 1673-6273(2017)24-4723-04

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(收稿日期:2017-01-05 接受日期:2017-01-31)

前言

支气管哮喘是一种由多种细胞(肥大细胞、嗜酸性粒细胞和 T 淋巴细胞)参与的可急性发作的慢性炎症性疾病,常伴随气道高反应性而导致气喘、胸闷、咳嗽等症状,夜间、凌晨、秋冬寒冷季节多发[1,2]。遗传和环境是哮喘发病的两个危险因素。随着现代生活水平的提升,过敏原的种类激增,近 10 年来世界范围内哮喘发病率增加,其中我国北京、上海两地的哮喘发病率上升 116.5%[3]。哮喘反复发作还可导致慢性阻塞性肺病、肺气肿、肺心病等并发症,严重者可引起多器官功能衰竭,甚至死亡[4,5],严重威胁患者健康,降低生活质量。因此,本研究旨在探究布地奈德福莫特罗针对哮喘治疗的有效性及其对患者肺功能、炎症反应的控制、生活质量改善方面的影响。

1 资料与方法

1.1 一般资料

选择 2014 年 2 月至 2016 年 2 月于我院呼吸内科就诊并确诊为慢性支气管哮喘患者 123 例,根据随机数字表法分为观察组 65 例,对照组 58 例。其中,观察组包含男性 35 例,女性 30 例,平均年龄(47.78± 3.4)岁,平均病程(11.3± 9.4)年;对照组包含男性 32 例,女性 26 例,平均年龄(48.22± 4.03)岁,平均病程 (12.1± 8.6) 年。两组患者基线资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 纳入、排除标准

纳入标准:① 所有患者均符合《支气管哮喘防治指南(支气管哮喘的定义、诊断、治疗和管理方案)》诊断标准。② 近期未使用过糖皮质激素药物。③ 支气管舒张试验、运动试验阳性。④ 病例资料完整,均签署知情同意书。该研究获得我院伦理委员会批准。排除标准:① 合并严重肝肾功能不全;② 恶性肿瘤;③ 对受试药物过敏;④ 依从性差。

1.3 治疗方法

所有患者均给予静卧、吸氧、平喘、抗感染等治疗。对照组患者在此基础上给予多索茶碱类常规治疗药物;在对照组的治疗基础上, 观察组患者给予布地奈德福莫特罗 (瑞典 AstraZenecaAB,进口药品注册证号 H20110556,规格:80 微克 /4.5 微克 / 吸),1-2 吸 / 次,2 次 / 天。两组患者的疗程均为 3 个月。

1.4 临床疗效及检测指标

1.4.1 临床疗效评判 参考文献[6]方法,日间、夜间症状消失;肺功能恢复正常;无需使用硫酸沙丁胺醇等急救药物,上述三项均满足为显效,满足两项为有效,符合一项或者无任何改善或病情加重为无效。总有效率为显效与有效例数总和与受试总例数的比值。

1.4.2 血清炎症水平相关指标检测 所有患者分别于入院 24 小时内,治疗后抽取空腹静脉血 5.0 mL。经离心处理得到血清后,分装于 EP 管中,于 -80 ℃冰箱冻存。采用酶联免疫试剂盒测定血清中白介素 17(IL-17)、白介素 33(IL-33)、基质金属蛋白酶 9(MMP-9)水平。ELISA 试剂盒购买于上海酶联生物有限公司,操作步骤严格按照试剂盒说明书。

1.4.3 肺功能 安排专人分别在治疗前后用肺功能仪(德国耶格肺功能仪,MS-PFT)在早晨(8:30-10:00)进行肺功能检测。记录第一秒用力呼吸容积(FEV1)、峰值呼气流速(PEF)与第一秒用力呼气容积与用力肺活量比值(FEV1/FVC)。

1.4.4 生活质量水平 分别在治疗前、治疗 1、2、3 月采用圣·乔治呼吸问卷(SGRQ)评分来衡量哮喘患者的生活质量改善情况,100 分制,分值高低与患者身体状况呈反比。

1.4.5 不良事件的发生情况 记录两组患者治疗期间不良反应发生情况。

1.5 统计学分析

使用 SPSS17.0 软件,计数资料用卡方检验对比分析,计量资料用 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的对比

观察组的总有效率为 92.3%(60/65),对照组的总有效率为 81.03%(47/58),观察组的总有效率限制高于对照组,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(%)]

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

Groups	Number	Excellent	Effective	Invalid	Total effective rate
Observation group	65	39	21	5	92.3%*
Control group	58	27	20	11	81.03%

Note: compared with control group, *P<0.05;

2.2 两组治疗前后血清 IL-17、IL-33、MMP-9 水平的比较

治疗前,观察组的血清 IL-17、IL-33、MMP-9 水平与对照组比较差异无统计学意义 (P＞0.05)。治疗后, 两组患者的血清 IL-17、IL-33 水平与治疗前相比均显著降低(P＜0.05),且观察组显著低于对照组(P＜0.05);两组 MMP-9 水平与治疗前相比差异无统计学意义(P＞0.05)。

2.3 两组治疗前后肺功能的比较

治疗前, 两组患者的肺功能指标比较差异均无统计学意义,具有可比性(P＞0.05),且均低于正常值范围,说明两组患者均存在一定的通气障碍。治疗后, 两组患者的 FEV1、PEF 与 FEV1/FVC 水平均较治疗前明显增加,且观察组患者显著高于对照组(P＜0.05)。

2.4 两组治疗前后患者生活质量的比较

治疗 2 个月后,两组患者的生活质量评分与治疗前比较均

显著提升，当继续推进治疗 1 个月后，观察组患者的生活质量评分显著高于对照组患者(P＜0.05)。

表 2 两组患者治疗前后血清 IL-17、IL-33、MMP-9 水平的比较[$\bar{x}\pm s$]

Table 2 Comparison of the serum IL-17, IL-33, MMP-9 levels between the two groups before and after the therapy [$\bar{x}\pm s$]

Groups	Number	IL-17(ng/L)		IL-33(ng/L)		MMP-9(μg/L)	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Observation group	65	9.65± 1.25	7.55± 1.29[ab]	15.63± 4.22	12.39± 2.31[ab]	22.72± 2.19	21.74± 1.35
Control group	58	9.63± 1.37	8.49± 1.17[a]	15.84± 3.99	14.09± 2.18[a]	22.59± 1.97	22.16± 1.22

Note: compared with before therapy, [a]P<0.05; after therapy, compared with control group, [b]P<0.05.

表 3 两组患者治疗前后肺功能比较[$\bar{x}\pm s$]

Table 3 Comparison of the pulmonary function between the two groups before and after the therapy [$\bar{x}\pm s$]

Groups	Number	FEV1(%)		FEV1/FVC(%)		PEF(L/min)	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Observation group	65	65.4± 4.25	73.15± 3.2[9ab]	55.3± 5.02	68.39± 5.31[ab]	54.22± 7.28	64.74± 4.75[ab]
Control group	58	65.13± 3.37	68.49± 4.17[a]	54.84± 4.99	60.09± 5.18[a]	53.89± 6.81	59.03± 5.14[a]

Note: compared with before therapy, [a]P<0.05; after therapy, compared with control group, [b]P<0.05.

表 4 两组患者治疗前后生活质量改善情况对比[$\bar{x}\pm s$]

Table 4 Comparison of life quality between the two groups before and after the therapy [$\bar{x}\pm s$]

Groups	Number	Before therapy	After therapy		
			1 month	2 month	3 month
Observation group	65	54.62± 17.36	51.84± 15.39	45.47± 16.33[a]	41.29± 15.71[bc]
Control group	58	54.47± 16.11	52.79± 15.38	48.19± 15.69[a]	44.77± 15.12[a]

Note: compared with before therapy, [a]P<0.05; before therapy, compared with control group, [b]P<0.05; after therapy, compared with control group, [c]P<0.05.

2.5 两组安全性评价

治疗期间，两组均未出现严重不良反应。

3 讨论

哮喘为一种慢性呼吸道疾病，其反复发作不但直接威胁患者的健康而且长期以来还会给患者造成沉重的经济负担。哮喘病的病因复杂，国内外研究尚无统一定论。气道炎症损伤及肺功能障碍是目前而言较为公认的致哮喘发病原因[7-10]。因此针对哮喘的积极防治应主要集中在抗炎及改善肺功能两个方面。IL-17 是由辅助性 T 细胞 17 主导分泌的细胞因子，可大量聚集气道炎症因子，增多气道分泌物，与高气道炎症，高气道反应性密切相关[11-13]。IL-17 还可以激活气道上皮细胞促使其分泌更多的炎性因子(IL-6、IL-11)。IL-33 是新近发现的一类由辅助性 T 细胞 2 主导分泌的多向促炎因子，可作用于嗜酸性粒细胞，并参与到体液免疫与细胞免疫机制[14-16]。本研究结果显示观察组患者治疗后的血清 IL-17、IL-33 水平与治疗前相比显著降低，表明其炎症控制效果明显较对照组更好。MMP-9 是一种可高效降解细胞外基质(ECM)的一类内肽酶，当其作用于呼吸道时，促使呼吸道细胞外基质水解释放炎性因子，扩大炎症反应。研究显示正常肺部组织中无 MMP 蛋白表达，而在炎性环境下诱导产生[17,18]。本研究结果显示所有患者治疗前后 MMP-9 水平无显著变化，分析原因可能是由于患者病程长，长期炎症反应产生大量 MMP-9，为期 3 个月的治疗还不足以改善患者高 MMP-9 的状态，或者是患者机体在进行 MMP-9 的合成作用，具体的机制还需长期治疗监测。

布地奈德福莫特罗是布地奈德与福莫特罗两者的复合制剂，前者是一种具有高效局部抗炎作用的糖皮质激素，可增强内皮细胞，平滑肌细胞的稳定性，抑制机体过免疫反应，减少组胺等过敏介质的释放，福莫特罗是一种长效选择性肾上腺素 β2 受体激动药，具有扩张血管，显著改善肺功能的作用，此外其还具有与布地奈德类似的抗组胺功效[19,20]。大量的研究也表明两者并存具有明显的协同作用。本研究采用布地奈德福莫特罗吸入治疗慢性支气管哮喘，研究结果显示观察组(布地奈德福莫特罗)的总有效率为 92.3%，显著高于对照组(常规治疗)的总有效率(81.03%)，提示布地奈德福莫特罗吸入治疗慢性支气管哮喘的疗效较好。另外，本研究结果显示观察组与对照组患者通气障碍正在一步步缓解，肺功能较治疗前有较大改善，且观察组患者的肺功能改善明显，生活质量更优。

综上所述，布地奈德福莫特罗吸入治疗对慢性支气管哮喘临床效果显著，可显著控制炎症反应，改善肺功能，显著提升患

者生活质量。

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