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布地奈德福莫特罗联合异丙托溴胺治疗慢性阻塞性肺疾病急性加重期的疗效及对 FeNO、cTnI 的影响 *

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摘要 目的：探讨布地奈德福莫特罗联合异丙托溴胺治疗 慢性阻塞性肺疾病急性加重期的疗效及对呼出气一氧化氮（FeNO）、心肌肌钙蛋白（cTnI）的影响 。**方法：**选择 2020 年 7 月 -2021 年 5 月在我院接受治疗的 80 例慢性阻塞性肺疾病急性加重期患者，采用随机数表法分为试验组（n=41）和对照组（n=39）。对照组给予异丙托溴胺治疗，试验组在对照组的基础上联合布地奈德福莫特罗治疗。比较两组临床疗效、FeNO、cTnI、白细胞介素 6（IL-6）、超敏 C 反应蛋白（CRP）、临床症状改善情况及不良反应发生情况。**结果：**治疗后，两组总有效率比较差异显著（P<0.05）；治疗前，试验组和对照组 FeNO、cTnI 比较无显著差异；治疗后，试验组和对照组 FeNO、cTnI 均随着时间的推移而降低，且试验组均低于对照组，差异显著（P<0.05）；治疗前，试验组和对照组血清 IL-6 及 CRP 比较无显著差异；治疗后，试验组和对照组血清 IL-6 及 CRP 均随着时间的推移而降低，且试验组均低于对照组，差异显著（P<0.05）；试验组憋喘、咳嗽、哮鸣音及湿啰音消失需要的时间均显著低于对照组，差异显著（P<0.05）；两组不良反应总发生率为 9.76%、17.95%，无显著差异（P>0.05）。**结论：**在慢性阻塞性肺疾病急性加重期中应用布地奈德福莫特罗联合异丙托溴胺治疗疗效显著，可有效改善患者 FeNO、cTnI 水平，且不会增加并发症。

关键词：布地奈德福莫特罗；异丙托溴胺；慢性阻塞性肺疾病；急性加重期；呼出气一氧化氮；心肌肌钙蛋白

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Efficacy of Budesonide Formoterol Combined with Ipratropium Bromide in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Its Effect on FeNO and cTnI*

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ABSTRACT Objective: To study Efficacy of budesonide formoterol combined with ipratropium bromide in the treatment of acute exacerbation of chronic obstructive pulmonary disease and its effect on Expiratory nitric oxide (FeNO), cardiac troponin (cTnI). **Methods:** 80 patients with acute exacerbation of CHRONIC obstructive pulmonary disease treated in our hospital from July 2020 to May 2021 were selected and divided into experimental group (n=41) and control group (n=39) by random number table method. The control group was given ipratropium bromide treatment, the experimental group was combined with budesonide formoterol treatment on the basis of the control group. Clinical efficacy, FeNO, cTnI, INTERleukin-6 (IL-6), hypersensitive C-reactive protein (CRP), improvement of clinical symptoms and occurrence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of the two groups was significantly different (P<0.05); Before treatment, there was no significant difference in FeNO and cTnI between the experimental group and the control group. After treatment, FeNO and cTnI in experimental group and control group decreased over time, and experimental group was lower than control group, the difference was significant (P<0.05); Before treatment, there were no significant differences in serum IL-6 and CRP between experimental group and control group. After treatment, serum IL-6 and CRP in experimental group and control group decreased over time, and the experimental group was lower than the control group, the difference was significant (P<0.05); The time required for the disappearance of dyspnea, cough, wheezing and wet rales in experimental group was significantly lower than that in control group (P<0.05); The total incidence of adverse reactions between the two groups was 9.76% and 17.95%, with no significant difference (P>0.05). **Conclusion:** In the acute exacerbation of chronic obstructive pulmonary disease, budesonide formoterol combined with ipratropium bromide has a significant therapeutic effect, which can effectively improve the levels of FeNO and cTnI in patients without increasing complications.

Key words: Budesonide Formoterol; Ipratropium bromide; Chronic obstructive pulmonary disease; Acute exacerbation; Exhaled

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前言

慢性阻塞性肺疾病是呼吸科常见疾病,临床表现为呼吸困难、咳嗽等症状,已成为全球患病导致死亡的重要疾病之一,根据病情可分为稳定期和急性加重期,其中稳定期病情相对较轻,若不及时治疗则会演变成急性加重期,增加肺心病、心衰、呼吸衰竭等严重并发症,严重时还可导致患者死亡,严重威胁人们的生命[1-3]。支气管舒张剂是治疗慢性阻塞性肺疾病的一线药物,其中异丙托溴胺是一种选择性较高的受体阻断药,能直接作用在患者支气管平滑肌 M 受体上,对乙酰胆碱产生竞争性阻断之效,扩张支气管,缓解临床症状[4,5]。布地奈德福莫特罗为多剂量粉吸入剂,含有福莫特罗和布地奈德两种成分,在减轻哮喘的加重方面有协同作用[6]。有研究显示,慢性阻塞性肺疾病的发生与多种生物活性因子有关,如 FeNO、cTnI[7]。FeNO 是一项广泛适用的气道炎症检测技术,能有效评估气道炎症反应严重程度;cTnI 是心肌肌肉收缩的调节蛋白,仅存在于心肌中,在发生心肌梗死时其水平发生异常[8,9]。但布地奈德福莫特罗联合异丙托溴胺对慢性阻塞性肺疾病急性加重期患者 FeNO、cTnI 的影响需进一步探讨,本研究旨在探讨布地奈德福莫特罗联合异丙托溴胺治疗慢性阻塞性肺疾病急性加重期的疗效,并分析其对 FeNO、cTnI 的影响。

1 资料与方法

1.1 一般资料

选择 2020 年 7 月 -2021 年 5 月在我院接受治疗的 80 例慢性阻塞性肺疾病急性加重期患者,采用随机数表法分为 2 组,试验组 41 例,男 28 例,女 13 例,年龄 50~89 岁,平均(71.9±9.1)岁;对照组 39 例,男 27 例,女 12 例,年龄 51~88 岁,平均(71.6±8.8)岁;两组间一般资料及患者病程年数无明显统计学差异 (P>0.05),可比较。

参照《慢性阻塞性肺疾病诊治指南(2021 年修订版)》[10]中的诊断标准;临床症状伴有咳痰、慢性咳嗽;脓性痰且痰量变多;连续性气流受限。

纳入标准:(1)符合相关标准;(2)肝肾功能正常;(3)无胰岛素治疗史;(4)相关指标数据完整;(5)知情同意。排除标准:(1)精神障碍者;(2)近 3 个月有抗生素治疗者;(3)严重自身免疫性疾病;(4)恶性肿瘤者;(5)对本研究药物过敏者;(6)哮喘疾病史者。

1.2 方法

对照组给予异丙托溴胺(规格 2 毫升:500 微克,厂家:英国勃林格殷格翰药业有限公司,进口药品注册证号 H20040454)雾化吸入治疗,每日 3 次,1 次 500 微克。试验组在对照组的基础上给予布地奈德福莫特罗:(规格:320 微克 / 9.0 微克 / 吸;生产厂家:AstraZeneca AB;进口药品注册证号:H20160447)每日 2 次,1 次 1 吸。

1.3 观察指标

采集肘静脉血 4 mL,采用化学免疫法检测 cTnI;用免疫速率法检测 CRP;采用电化学发光检测 IL-6;记录患者临床症状改善情况;记录不良反应。

疗效评定标准:显效:临床症状消失,肺部啰音、痰液量显著改善;有效:症状消失,肺部啰音、痰液量有所改善;无效:无明显改善或加重。

1.4 统计学分析

以 spss22.0 软件包处理,符合正态分布计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,χ^2 检验,P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床治疗效果评价

治疗后,两组总有效率比较差异显著(P<0.05)见表 1。

表 1 两组临床治疗效果评价[n(%)]

Table 1 Clinical therapeutic effect evaluation of the two groups[n(%)]

Groups	n	Excellent	valid	Invalid	Total effective rate
Experimental group	41	24(58.54)	14(34.15)	3(7.32)	38(92.68)
Control group	39	16(41.03)	12 (30.77)	11(28.21)	28(71.79)
χ^2 value			6.040		
P value			0.014		

2.2 两组 FeNO、cTnI 检查结果比较

治疗前,试验组和对照组 FeNO、cTnI 比较无显著差异;治疗后,试验组和对照组 FeNO、cTnI 均随着时间的推移而降低,且试验组均低于对照组,差异显著(P<0.05),见表 2。

2.3 两组 IL-6 及 CRP 检查结果比较

治疗前,试验组和对照组血清 IL-6 及 CRP 比较无显著差异;治疗后,试验组和对照组血清 IL-6 及 CRP 均随着时间的推移而降低,且试验组均低于对照组,差异显著(P<0.05),见表 3。

2.4 两组临床症状改善情况比较

试验组憋喘、咳嗽、哮鸣音及湿啰音消失需要的时间均显著低于对照组,差异显著(P<0.05),见表 4。

2.5 两组用药安全性评价

两组不良反应总发生率为 9.76%、17.95%,无显著差异(P>0.05),见表 5。

表 2 两组 FeNO、cTnI 检查结果比较($\bar{x}\pm s$)

Table 2 Comparison of FeNO and cTnI test results between the two groups($\bar{x}\pm s$)

Groups	n	FeNO(ppb)		cTnI(ng/mL)	
		Before the intervention	After the intervention	Before the intervention	After the intervention
Experimental group	41	31.21±10.01	17.25±5.32	0.092±0.011	0.031±0.010
Control group	39	31.18±10.05	24.52±5.26	0.095±0.015	0.065±0.025
t value		0.013	6.143	1.024	8.059
P value		0.989	0.000	0.309	0.000

表 3 两组 TIL-6 及 CRP 检查结果比较($\bar{x}\pm s$)

Table 3 Comparison of IL-6 and CRP test results between the two groups($\bar{x}\pm s$)

Groups	n	IL-6(pg/mL)		CRP(mg/L)	
		Before the intervention	After the intervention	Before the intervention	After the intervention
Experimental group	41	37.15±10.62	11.21±5.02	22.66±6.35	10.17±1.04
Control group	39	37.70±10.49	18.79±5.37	22.71±6.42	15.20±1.15
t value		0.233	6.525	0.035	18.333
P value		0.816	0.000	0.972	0.000

表 4 两组临床症状改善情况比较($\bar{x}\pm s$,d)

Table 4 Comparison of improvement of clinical symptoms between the two groups($\bar{x}\pm s$, d)

Groups	n	Hold back breath	cough	The wheezing disappeared	Wet rales disappear
Experimental group	41	2.59±0.51	4.18±0.81	4.79±0.89	2.78±0.34
Control group	39	4.35±0.97	5.56±1.05	6.38±1.35	5.57±0.87
χ^2 value		10.229	6.601	6.249	19.065
P value		0.000	0.000	0.000	0.000

表 5 两组用药安全性评价[n(%)]

Table 5 Drug safety evaluation of the two groups[n(%)]

Groups	n	Digestive tract reaction	nausea	Dry mouth	The total incidence of
Experimental group	41	1	2	1	4(9.76)
Control group	39	3	2	2	7(17.95)
χ^2 value					1.131
P value					0.288

3 讨论

慢性阻塞性肺疾病是由于气道炎症所造成气道损伤及结构重塑的疾病,多发生于中老年人群,长期危害人民群众身体健康,据调查显示,我国 40 岁以上人群中慢性阻塞性肺疾病发病率高达 8.2%,其患病人数逐年增多,已成为重要的公共卫生问题[11-13]。该病发病机制较为复杂,有研究显示[14]可能与以下方面有关:(1)细胞因子学说;(2)抗氧化失调;(3)气道炎症;(4)抗蛋白酶失衡。根本病情可分为稳定期和急性加重期,在急性加重期时患者脓痰量增加,呼吸困难,容易导致呼吸道阻塞,引发心力衰竭、呼吸衰竭等并发症,有研究对慢性阻塞性肺疾病患者进行随访发现约 25%患者可发展成慢性肺源性心脏病,严重威胁人们的生命[15]。

慢性阻塞性肺疾病病情复杂,目前多使用联合用药的方式提高临床治疗效果[16]。异丙托溴铵是一种抗胆碱药物,能够阻断 M 型胆碱能受体,增强纤毛运动,清除呼吸道分泌物,有支气管平滑肌松弛、降低气道高反应性和抗炎的作用,有效治疗气道阻塞[17-19]。布地奈德福莫特罗为复方制剂,由布地奈德和富马酸福莫特罗组成,其中布地奈德具有抗炎作用,福莫特罗能舒张患者支气管平滑肌,两种药物具有抗炎、舒张呼吸道平滑肌的作用,可改善哮喘症状和肺功能,减少病情恶化[20-22]。有研究显示,布地奈德福莫特罗能缓解慢性阻塞性肺疾病的临床症状,减轻炎性反应,对减少病情恶化具有重要意义[23,24]。本研究结果显示,布地奈德福莫特罗联合异丙托溴胺治疗的患者总有效率较单独使用异丙托溴胺的患者高,且治疗期间未发生明显不良反应,结果提示,布地奈德福莫特罗联合异丙托溴胺能提高慢性阻塞性肺疾病急性加重期的临床疗效,且不会增加药物不良反应的发生。本研究还显示,治疗后患者血清 IL-6 及 CRP

明显降低，且布地奈德福莫特罗联合异丙托溴胺治疗的患者低于对照组，试验组憋喘、咳嗽、哮鸣音及湿啰音消失需要的时间也显著低于对照组，结果提示，布地奈德福莫特罗联合异丙托溴胺能降低慢性阻塞性肺疾病患者的炎症反应，缓解憋喘、咳嗽等临床症状，Goto T [25]等研究也显示，布地奈德福莫特罗联合其他药物能缓解慢性阻塞性肺疾病的喘息症状，改善患通气功能，与本研究结果相似。分析其原因可能是因为异丙托溴铵属于一种具有抗胆碱能特性药物，可松弛患者支气管，改善痰液堵塞症状；布地奈德福莫特罗中布地奈德有抗气道炎症的作用，可抑制炎症细胞的活化，而福莫特罗是一种长效的高度选择性支气管 β2 受体激动剂，具有促进呼吸道纤毛运动的能力，达到舒张支气管扩张的作用，布地奈德福莫特罗联合异丙托溴胺可发挥抑制机体炎症反应的作用，最终起到促进患者疾病恢复的目的。

有研究显示，多种生物活性因子在慢性阻塞性肺疾病急性加重期中表达异常，可能参与了疾病的发生[26,27]。FeNO 主要来源于呼吸道上皮细胞在炎症细胞因子诱导下表达一氧化氮合酶，与气道高反应有紧密关系，当气道内发生炎症时，支气管黏膜上皮细胞出现通透性变化，导致机体细胞功能发生障碍，气道平滑肌功能受损，最终导致其水平升高[28-31]。cTnI 是近年新发现的反映心肌损伤的指标，仅存在于心肌收缩蛋白的细肌丝上，当心肌细胞受损后 cTnI 迅速进入血液循环，18h~20h 后达到顶峰[32,33]。有研究显示，当肺部重要器官出现病变后呼吸功能受到抑制，导致心肌缺血缺氧，从而导致 cTnI 升高，因此被证实与慢性阻塞性肺疾病关系密切[34]。本研究将 FeNO、cTnI 作为参与慢性阻塞性肺疾病急性加重期的重要指标，观察在不同治疗方案中其水平变化，结果显示，治疗后患者 FeNO、cTnI 均明显降低，且布地奈德福莫特罗联合异丙托溴胺治疗的患者低于单独使用异丙托溴胺的患者，提示，布地奈德福莫特罗联合异丙托溴胺可降低慢性阻塞性肺疾病急性加重期患者 FeNO、cTnI 水平，分析其原因可能是因为布地奈德福莫特罗中福莫特罗可激活腺苷酸环化酶，达到舒张支气管扩张的作用，有效预防气道重塑，从而改善 FeNO、cTnI 水平。

综上所述，在慢性阻塞性肺疾病急性加重期中应用布地奈德福莫特罗联合异丙托溴胺治疗疗效显著，可有效改善患者 FeNO、cTnI 水平，且不会增加并发症。

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