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乌司他丁联合布地奈德治疗支气管哮喘急性发作期的临床疗效 及对患者血清 PDCD5、S1P、OPN 水平的影响 *

李 莉¹ 白晓兵¹ 王景阳² 王二雄³ 贾 娟^{4△}

(1 榆林市第一医院呼吸内科 陕西 榆林 719000; 2 西安交通大学医学院 陕西 西安 710049;

3 延安大学第二附属医院呼吸内科 陕西 榆林 719002; 4 榆林市第二医院呼吸内科 陕西 榆林 719000)

摘要 目的: 探讨乌司他丁联合布地奈德治疗支气管哮喘急性发作期的临床疗效及对患者血清程序化细胞死亡因子 5(PDCD5)、1-磷酸鞘氨醇(S1P)、骨桥蛋白(OPN)水平的影响。**方法:** 选择 2014 年 3 月到 2017 年 3 月于我院进行治疗的 170 例支气管哮喘急性发作期患者作为研究对象,按照随机数表法分为观察组(n=90)和对照组(n=80)。对照组使用布地奈德治疗,观察组在对照组的基础上使用乌司他丁进行治疗。比较两组的临床疗效,治疗前后血清 PDCD5、S1P、OPN 水平、第 1 秒用力呼气容积(FEV1)、用力肺活量(FVC)、FEV1/FVC 水平的变化、临床症状改善情况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为 95.56%,明显高于对照组(71.25%, $P < 0.05$);两组血清 PDCD5、S1P、OPN 水平较治疗前均显著降低($P < 0.05$),且观察组血清以上指标均明显低于对照组($P < 0.05$);两组 FEV1、FVC、FEV1/FVC 水平较治疗前均显著升高($P < 0.05$),观察组以上指标均明显高于对照组($P < 0.05$);观察组患者咳嗽、哮鸣音及胸闷气短消失时间均明显短于对照组($P < 0.05$);观察组不良反应总发生率为 6.67%,显著低于对照组(18.75%, $P < 0.05$)。**结论:** 乌司他丁联合布地奈德治疗支气管哮喘急性发作期患者的临床效果显著优于单用布地奈德治疗,可能与其有效改善患者血清 PDCD5、S1P、OPN 水平有关。

关键词: 乌司他丁;布地奈德;支气管哮喘急性发作期;程序化细胞死亡因子 5;1-磷酸鞘氨醇;骨桥蛋白

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Curative Efficacy of Ustardine and Budesonide in the Treatment of Acute Attack of Bronchial Asthma and Its Effects the Serum PDCD5, S1P and OPN Levels*

LI Li¹, BAI Xiao-bing¹, WANG Jing-yang², WANG Er-xiong³, JIA Juan^{4△}

(1 Department of Respiratory Medicine, first Hospital of Yulin, Yulin, Shaanxi, 719000, China;

2 Xi'an Jiaotong University Medical School, Xi'an, Shaanxi, 710049, China;

3 Department of Respiratory Medicine, The second affiliated Hospital of Yan'an University, Yulin, Shaanxi 719002, China;

4 Department of Respiratory Medicine, The second Hospital of Yulin City, Yulin, Shaanxi, 719000, China)

ABSTRACT Objective: To study the curative efficacy of ustardine and budesonide in the treatment of acute attack of bronchial asthma and its effects on the serum programmed cell death factor 5 (PDCD5), 1-sphingosine (S1P), osteopontin (OPN) levels. **Methods:** 170 cases of patients with acute episodes of bronchial asthma treated in our hospital from March 2014 to March 2017 were selected as the research objects, the patients were divided into the observation group (n=90) and the control group (n=80) according to the random number table method. The control group was treated with budesonide, and the observation group was treated with ulinastatin on the basis of control group. The clinical effects, changes of serum PDCD5, S1P, OPN levels, forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC levels before and after treatment, as well as the improvement of clinical symptoms and the occurrence of adverse reactions of the two groups were compared. **Results:** After treatment, the total effective rate of the observation group was 95.56%, which was significantly higher than that of the control group (71.25%, $P < 0.05$). The levels of PDCD5, S1P and OPN in the two groups were significantly lower than those before treatment ($P < 0.05$), and the above serum indexes in the observation group were significantly lower than those in the control group ($P < 0.05$). The levels of FEV1, FVC and FEV1/FVC in the two groups were significantly higher than those before treatment ($P < 0.05$), and the above indicators in the observation group were significantly higher than those in the control group ($P < 0.05$). The cough, asthma and short disappearance time in the observation group were significantly shorter than those in the control group

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作者简介:李莉(1979-),女,博士,副主任医师,研究方向:主要从事临床呼吸内科方面研究,电话:18092565671,

E-mail:suwenli022@163.com

△ 通讯作者:贾娟(1979-),女,本科,副主任医师,研究方向:呼吸内科常见病,慢性阻塞性肺疾病,肺栓塞等的诊断与治疗,

E-mail:suwenli022@163.com

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($P<0.05$). The total incidence of adverse reactions in the observation group was 6.67%, which was significantly lower than that in the control group (18.75%, $P<0.05$). **Conclusion:** The clinical effect of ulinastatin combined with budesonide is significantly better than that of single budesonide treatment in the treatment of patients with acute bronchial asthma attack, which may be related to the effective improvement of patients' serum PDCD5, S1P and OPN levels.

Key words: Ulinastatin; Budesonide; Acute attack of bronchial asthma; Programmed cell death factor 5; 1- phosphosphingamine; osteopontin

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前言

支气管哮喘是一种呼吸系统的常见病,是由多种细胞参与的气道慢性炎症性疾病,以气道反应高、气道炎症为主要特征,临床表现为发作性喘息、气急、胸闷或咳嗽、呼吸困难等症状,严重影响患者的生活质量^[1,2]。近年来,支气管哮喘的发病率不断上升,目前对于该病有抗炎、改善通气、雾化吸入等方式,以雾化吸入为其主要治疗方式,具有见效快、直接达到局部等优点^[3,4]。

布地奈德是一种具有高效局部抗炎作用的糖皮质激素,可修复气道,降低气道阻塞,改善肺功能,但是其单一用药效果不佳^[5,6]。乌司他丁作为广谱的蛋白酶抑制剂,是从新鲜人尿中提取的一种蛋白水解酶活力的糖蛋白,由143个氨基酸组成,对多种炎症因子有显著的拮抗作用^[7,8]。本研究主要探讨了乌司他丁联合布地奈德治疗支气管哮喘急性发作期的临床疗效,并观察了其对患者血清 PDCD5、S1P、OPN 水平的影响,结果报道如下。

1 资料与方法

1.1 一般资料

选择2014年3月到2017年3月于我院进行治疗的170例支气管哮喘急性发作期患者进行研究,研究已获得我院伦理会批准实施,将患者通过随机数表法分为两组。观察组男59例,女31例;年龄19~71岁,平均(47.85±8.62)岁;病程1~6年,平均(3.72±0.85)年。对照组男48例,女32例;年龄20~69岁,平均(46.13±7.95)岁;病程1.5~6年,平均(3.72±0.95)年。两组性别($\chi^2=0.560$, $P=0.454$)、年龄($t=1.347$, $P=0.180$)等一般临床资料比较差异不显著($P>0.05$),具有可比性。

纳入标准^[9]: (1)符合《临床疾病诊断与疗效判断标准》诊断标准; (2)入院前1月内未使用介质阻滞剂者; (3)未合并肾、肺、肝等脏器重大疾病者。排除标准: (1)对本文药物过敏者; (2)存在精神疾病、沟通障碍者; (3)不配合本次研究,依从性差者。

1.2 治疗方法

两组患者入院后均使用常规吸氧、补液、抗感染、纠正电解质紊乱等基础治疗。对照组采用布地奈德(规格:64 μg;生产厂家:AstraZeneca AB; 国药准字 H20090402)1 mg+2.5 mL 0.9% 氯化钠溶液雾化吸入治疗,每次15分钟,一天3次。观察组在对照组的基础上加用乌司他丁治疗,乌司他丁(规格:2 mL:10万单位;生产厂家:广东天普生化医药股份有限公司; 国药准字 H19990134)10万U静脉滴注,一天3次。两组均治疗7d。

1.3 观察指标

所有患者抽取空腹静脉血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, 使用酶联免疫吸附法对血清 PDCD5、S1P、OPN 进行检测; 肺功能采用 HI-101 肺功能检测仪测定 FEV1、FVC、FEV1/FVC 水平, 仪器购于北京裕天医疗技术有限公司; 记录临床症状改善时间及不良反应的发生情况。

疗效评定标准: 显效: 治疗后, 肺部哮鸣音及临床症状消失; 有效: 治疗后, 肺部哮鸣音及临床症状均明显减轻; 无效: 临床症状无明显改善甚至加重, 总有效率 = (显效 + 有效) / 总例数 × 100%。

1.4 统计学分析

用 SPSS 18.0 软件进行统计学分析。计量资料用表示, 组间比较采用独立样本 t 检验, 计数资料以率表示, 组间比较采用 χ^2 检验, 以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者疗效比较

治疗后, 观察组临床疗效总有效率为 95.56%, 明显高于对照组(71.25%, $P<0.05$), 见表 1。

2.2 两组患者治疗前后血清 PDCD5、S1P、OPN 水平的比较

治疗前, 两组血清 PDCD5、S1P、OPN 水平比较无显著差异($P>0.05$); 治疗后, 两组血清 PDCD5、S1P、OPN 水平较治疗前均显著降低($P<0.05$), 且观察组以上指标明显比对照组低($P<0.05$), 见表 2。

表 1 两组患者临床疗效的比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	90	54(60.00)	32(35.56)	4(4.44)	86(95.56)
Control group	80	31(38.75)	26(32.50)	23(28.75)	57(71.25)
χ^2 value					18.728
P value					0.000

表 2 两组患者治疗前后血清 PDCD5、S1P、OPN 水平的比较($\bar{x} \pm s$)Table 2 Comparison of the serum PDCD5, S1P and OPN levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	PDCD5($\mu\text{g/L}$)		S1P($\mu\text{mol/L}$)		OPN($\mu\text{g/L}$)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	90	68.51 $\pm$ 22.31	16.04 $\pm$ 9.81	1.97 $\pm$ 0.33	1.13 $\pm$ 0.25	64.57 $\pm$ 5.45	31.45 $\pm$ 4.07
Control group	80	68.39 $\pm$ 23.51	22.38 $\pm$ 7.95	1.98 $\pm$ 0.35	1.64 $\pm$ 0.30	65.02 $\pm$ 6.13	48.24 $\pm$ 5.31
t value		0.034	4.593	0.192	12.085	0.507	23.278
P value		0.973	0.000	0.848	0.000	0.613	0.000

2.3 两组患者治疗前后肺功能的比较

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治疗前,两组患者肺功能指标比较均无显著差异($P > 0.05$); 对照组($P < 0.05$),见表 3。

治疗后,两组各肺功能指标如 FEV1、FVC、FEV1/FVC 水平均

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 between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	FEV1(%)		FVC(%)		FEV1/FVC	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	90	68.14 $\pm$ 7.32	79.42 $\pm$ 6.51	52.33 $\pm$ 5.41	66.87 $\pm$ 4.34	61.05 $\pm$ 4.77	73.41 $\pm$ 5.25
Control group	80	67.98 $\pm$ 6.69	69.96 $\pm$ 6.41	52.78 $\pm$ 4.64	53.43 $\pm$ 7.50	60.97 $\pm$ 5.04	63.36 $\pm$ 5.47
t value		0.148	9.526	0.579	14.492	0.106	12.215
P value		0.882	0.000	0.564	0.000	0.916	0.000

2.4 两组患者临床症状改善时间的比较

对照组($P < 0.05$),见表 4。

观察组患者咳嗽、哮鸣音及胸闷气短消失时间均明显短于

表 4 两组患者临床症状改善时间的比较($\bar{x} \pm s, d$)Table 4 Comparison of the improvement time of clinical symptoms between the two groups($\bar{x} \pm s, d$)

Groups	n	Cough	Wheezing sound	Chest condition
Observation group	90	6.11 $\pm$ 1.23	4.18 $\pm$ 1.04	3.15 $\pm$ 0.51
Control group	80	8.67 $\pm$ 1.35	6.39 $\pm$ 1.16	5.56 $\pm$ 1.14
t value		12.937	13.098	18.124
P value		0.000	0.000	0.000

2.5 两组患者不良反应发生情况的比较

(18.75%, $P < 0.05$),见表 4。

观察组不良反应总发生率为 6.67%,显著低于对照组

表 5 两组患者不良反应发生情况的比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between the two groups[n(%)]

Groups	n	Nausea and vomiting	Arrhythmia	Insomnia	The total incidence of
Observation group	90	3(3.33)	2(2.22)	1(1.11)	6(6.67)
Control group	80	6(7.50)	4(5.00)	5(6.25)	15(18.75)
χ^2 value		1.467	10.960	3.285	5.712
P value		0.226	0.327	0.070	0.017

3 讨论

支气管哮喘是一种复杂的气道炎症性疾病,如不及时治疗可能发展为呼吸衰竭^[10,11]。支气管哮喘的发病机制尚不完全明

确,较多学者认为是免疫-炎症反应、气道高反应、神经机制之间的相互作用^[12,13]。因此,治疗主要针对患者慢性气道高反应性炎症,重在抑制其炎症反应,缓解气道痉挛,使其气道通气恢复正常,最终恢复患者的肺功能^[14,15]。

目前,雾化吸入是临床治疗支气管哮喘最有效的途径,可使药物通过呼吸道迅速达到靶器官内发挥作用,同时能减少药物剂量避免全身给药带来的不良反应^[16,17]。布地奈德吸入气道后能够减少腺体分泌,能增强内皮细胞、平滑肌细胞和溶酶体膜的稳定性,能有效抑制气管内收缩物质的合成,减少抗原体结合时的酶促反应,从而有效降低平滑肌的收缩反应,但是其单一用药效果并不特别显著,故较多学者建议在此药物基础上联合用药以控支气管哮喘急性发作期的症状,改善其炎症反应^[18,19]。乌司他丁属蛋白酶抑制剂,具有稳定溶酶体膜的效果,还可清除氧自由基,对炎症介质释放具有抑制作用^[22,23]。有研究显示乌司他丁能阻断炎症因子和白细胞的互相作用,减少炎症对肺功能的损害,改善患者的肺功能^[20,21]。本研究结果显示乌司他丁联合治疗的总临床疗效高达 95.56%,明显高于布地奈德治疗,不良反应总发生率为 6.67%,显著低于使用布地奈德治疗,说明联合乌司他丁治疗支气管哮喘安全性更高。Karani L W^[24]等研究显示乌司他丁能改善患者的肺功能。本研究也显示联合乌司他丁治疗的患者的 FEV1、FVC、FEV1/FVC 水平均明显高于使用布地奈德治疗的患者,咳嗽、哮鸣音及胸闷气短消失时间均明显低于使用布地奈德治疗的患者,与上述观点一致。这说明乌司他丁能改善支气管哮喘患者的肺功能指标及临床症状,分析是因为乌司他丁是从人尿提取精制的糖蛋白,能够抑制胰蛋白酶等各种胰酶,促进临床症状的恢复。

PDCD5 是一个新的凋亡调节基因,其核转位是细胞早期凋亡的信号,能够促进细胞凋亡功能,其高表达在促进细胞凋亡过程中具有重要作用^[25,26]。S1P 是鞘磷脂的一种代谢产物,可作为细胞外介质,参与细胞的生长、增殖、分化等过程^[27,28]。有研究显示 S1P 通过诱导肥大细胞活化脱颗粒,产生多种炎性介质,对支气管平滑肌细胞产生影响,导致气道炎性渗出增加。OPN 存在于体内多种组织和细胞中,主要由活化的巨噬细胞、白细胞分泌,正常人群中其含量较少,在炎症刺激下能诱导其表达增加,刺激相关细胞分泌 OPN^[29,30]。本研究结果显示联合乌司他丁治疗的患者的血清 PDCD5、S1P、OPN 水平明显低于使用布地奈德治疗的患者,分析原因是因为乌司他丁可产生炎性介质拮抗作用,降低血小板聚集状态和粘附力,清除自由基,稳定其溶酶体膜。

综上所述,乌司他丁联合布地奈德治疗支气管哮喘急性发作期患者的临床效果显著优于单用布地奈德治疗,可能与其有效改善患者血清 PDCD5、S1P、OPN 水平有关。

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