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哌拉西林他唑巴坦与头孢哌酮钠舒巴坦治疗 COPD 合并铜绿假单胞菌感染的疗效和安全性对比 *

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摘要 目的:对比哌拉西林他唑巴坦与头孢哌酮钠舒巴坦治疗慢性阻塞性肺疾病(COPD)合并铜绿假单胞菌感染的疗效和安全性。**方法:**选择2017年1月至2020年1月我院呼吸科住院治疗的60例COPD合并铜绿假单胞菌感染患者纳入研究,通过抽签法分为A组和B组,各30例。A组在常规治疗基础上给予哌拉西林他唑巴坦,B组在常规治疗基础上给予头孢哌酮钠舒巴坦,均持续治疗7d。比较A组和B组患者的临床疗效、一般治疗情况、血清实验室指标、血气指标的变化及不良反应。**结果:**治疗后7d,A组患者的临床疗效、细菌清除率结果分别为93.33%、83.33%,B组为90.00%、76.67%,差异无统计学意义($P>0.05$);A组体温正常时间、白细胞计数(WBC)正常时间、肺部炎症病灶消失时间、住院时间分别为 (2.68 ± 0.47) d、 (5.05 ± 0.53) d、 (9.21 ± 1.30) d、 (10.02 ± 1.94) d,均明显短于B组的 (3.31 ± 0.51) d、 (6.52 ± 0.60) d、 (10.37 ± 1.88) d、 (11.69 ± 1.61) d,差异均有统计学意义($P<0.05$);治疗后3d时,A组患者的WBC、C反应蛋白(CRP)、降钙素原(PCT)分别为 $(10.38\pm 1.75)\times 10^9/L$ 、 $(9.75\pm 1.55)mg/L$ 、 $(1.94\pm 0.31)\mu g/L$,均明显低于B组的 $(12.10\pm 2.18)\times 10^9/L$ 、 $(11.18\pm 1.64)mg/L$ 、 $(2.26\pm 0.29)\mu g/L$,治疗后7d时,A组患者的WBC、CRP、PCT分别为 $(6.29\pm 1.40)\times 10^9/L$ 、 $(5.91\pm 0.77)mg/L$ 、 $(0.86\pm 0.20)\mu g/L$,均明显低于B组的 $(7.55\pm 1.37)\times 10^9/L$ 、 $(7.04\pm 1.29)mg/L$ 、 $(1.17\pm 0.34)\mu g/L$,差异均有统计学意义($P<0.05$);A组患者的动脉血氧饱和度(SpO_2)、血氧分压(PaO_2)分别为 $(92.11\pm 3.06)\%$ 、 $(68.37\pm 5.13)mmHg$,均明显高于B组的 $(88.64\pm 3.18)\%$ 、 $(62.84\pm 3.20)mmHg$,二氧化碳分压($PaCO_2$)为 $(44.12\pm 3.03)mmHg$,明显低于B组的 $(48.49\pm 4.21)mmHg$,差异均有统计学意义($P<0.05$)。**结论:**哌拉西林他唑巴坦与头孢哌酮钠舒巴坦对COPD合并铜绿假单胞菌感染患者均具有较好的抗菌效果及安全性,但哌拉西林他唑巴坦可缩短恢复时间,临床应用价值更高。

关键词:慢性阻塞性肺疾病;铜绿假单胞菌感染;哌拉西林他唑巴坦;头孢哌酮钠舒巴坦;细菌清除率

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Comparison of Efficacy and Safety of Piperacillin Tazobactam and Cefoperazone Sodium Sulbactam in the Treatment of COPD Complicated with *Pseudomonas Aeruginosa* Infection*

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ABSTRACT Objective: To study the comparison of efficacy and safety of piperacillin tazobactam and cefoperazone sodium sulbactam in the treatment of chronic obstructive pulmonary disease(COPD) complicated with *Pseudomonas aeruginosa* infection. **Methods:** 60 cases COPD patients complicated with *Pseudomonas aeruginosa* infection in respiratory department of our hospital from January 2017 to January 2020 were enrolled in the study, the method of drawing lots was divided into A group and B group, 30 cases respectively. The A group was given piperacillin tazobactam on the basis of conventional treatment, and B group was given cefoperazone sodium sulbactam on the basis of conventional treatment, both of which lasted for 7 days. The clinical efficacy, general treatment, changes of serum laboratory indexes, blood gas index and adverse reactions were compared between A group and B group. **Results:** After treatment 7 days, the clinical efficacy and bacterial clearance rate of A group patients were 93.33% and 83.33%, respectively, while those of group B were 90.00% and 76.67%, with no significant difference ($P>0.05$); the body temperature normal time, white blood cell count (WBC) normal time, pulmonary inflammatory lesions Disappearance time and the length of hospital stay in A group patients were (2.68 ± 0.47) d, (5.05 ± 0.53) d, (9.21 ± 1.30) d, (10.02 ± 1.94) d, which were significantly shorter than those of B group (3.31 ± 0.51) d, (6.52 ± 0.60) d, (10.37 ± 1.88) d, (11.69 ± 1.61) d, with significant difference($P<0.05$); at after treatment 3 days, the WBC, C reactive protein (CRP) and procalcitonin (PCT) in A group patients were $(10.38\pm 1.75)\times 10^9/L$, $(9.75\pm 1.55)mg/L$, $(1.94\pm 0.31)\mu g/L$, which were significantly lower than

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those of B group (12.10 ± 2.18) $\times 10^9/L$, (11.18 ± 1.64) mg/L , (2.26 ± 0.29) $\mu g/L$, at after treatment 7 days, the WBC, CRP and PCT in A group patients were (6.29 ± 1.40) $\times 10^9/L$, (5.91 ± 0.77) mg/L , (0.86 ± 0.20) $\mu g/L$, which were significantly lower than those of B group (7.55 ± 1.37) $\times 10^9/L$, (7.04 ± 1.29) mg/L , (1.17 ± 0.34) $\mu g/L$, with significant difference ($P < 0.05$); the arterial blood oxygen saturation (SO_2), partial pressure of oxygen (PaO_2) in A group patients were (92.11 ± 3.06)%, (68.37 ± 5.13) $mmHg$, which were significantly higher than those of B group (88.64 ± 3.18)%, (62.84 ± 3.20) $mmHg$, the carbon dioxide partial pressure ($PaCO_2$) was (44.12 ± 3.03) $mmHg$, which was significantly lower than those of B group (48.49 ± 4.21) $mmHg$, with significant difference ($P < 0.05$); the total incidence of adverse reactions in the two groups were 13.33% and 16.67%, respectively, with no significant difference ($P > 0.05$). **Conclusion:** Piperacillin tazobactam and cefoperazone sodium sulbactam have good antibacterial effect and safety on COPD complicated with *Pseudomonas aeruginosa* infection patients, but piperacillin tazobactam can shorten the recovery time and has higher clinical application value.

Key words: Chronic obstructive pulmonary disease; *Pseudomonas aeruginosa* infection; Piperacillin tazobactam; Cefoperazone sodium sulbactam; Bacterial clearance rate

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前言

慢性阻塞性肺疾病(COPD)是我国临床上常见的呼吸系统疾病,具有病程长、易反复发作的特点^[1,2]。相关数据显示,有50%~70%的COPD患者会合并呼吸道感染,也是导致病情加重的重要原因之一^[3,4]。铜绿假单胞菌是COPD患者呼吸道感染的常见病原菌之一,且目前的研究指出,我国铜绿假单胞菌对抗菌药物的耐药情况十分严峻,多种耐药性的情况也较为多见,给COPD患者的临床治疗带来了较多困难^[5,6]。如何合理的选择抗生素、有效控制感染症状、促进病情改善显得极为重要。哌拉西林他唑巴坦、头孢哌酮钠舒巴坦均是临床控制铜绿假单胞菌感染的常用药物,具有较好的抑菌作用,各自具有优势^[7,8]。因此,本研究将哌拉西林他唑巴坦与头孢哌酮钠舒巴坦分别用于COPD合并铜绿假单胞菌感染的治疗,旨在对比两者的疗效和安全性。

1 资料与方法

表1 A组和B组患者一般资料情况对比($\bar{x} \pm s, n(\%)$)

Table 1 Comparison of the general information in A group and B group patients ($\bar{x} \pm s, n(\%)$)

Groups	Gender		Age (years)	BMI (kg/m ²)	Course of COPD disease (years)	Pulmonary function classification	
	Male	Female				II	III
A group (n=30)	18 (60.00)	12 (40.00)	58.71 $\pm$ 8.13	23.49 $\pm$ 3.16	6.96 $\pm$ 1.57	14 (46.67)	16 (53.33)
B group (n=30)	20 (66.67)	10 (33.33)	58.30 $\pm$ 9.28	23.57 $\pm$ 2.70	7.11 $\pm$ 1.26	15 (50.00)	15 (50.00)

1.2 治疗方法

两组均给予COPD的常规治疗,包括维持水电解质及酸碱平衡、补液、氧疗、支气管舒张剂等。A组:在常规治疗基础上给予哌拉西林他唑巴坦(规格1.125 g,厂家:齐鲁制药集团,国药准字H19990182)治疗,剂量4.5 g加入100 mL生理盐水,tid。B组:在常规治疗基础上给予头孢哌酮钠舒巴坦(规格1.5 g,厂家:辉瑞制药有限公司,国药准字H20020597)治疗,剂量3 g加入100 mL生理盐水中,q 12 h/次。均持续治疗7 d。

1.3 观察指标

1.3.1 临床疗效 于治疗7 d后参照《抗菌药物临床试验技术指导原则》^[10]进行评价,显效:患者体温、血象等检查均呈正常,

1.1 一般资料

选择2017年1月至2020年1月我院呼吸科住院治疗的60例COPD合并铜绿假单胞菌感染患者纳入研究,本研究已经由本院伦理委员会批准实施。纳入标准:①参照《慢性阻塞性肺疾病诊治指南》^[9]中相关标准,符合COPD诊断,并通过临床症状、胸部X线、实验室检查等手段确诊,处于急性加重期;②经过呼吸道分泌物检查显示合并呼吸道感染,且致病菌为铜绿假单胞菌单一感染;③年龄40~80岁;④签署研究知情同意书。排除标准:①近期接受过相关抗菌治疗;②呼吸道分泌物检查显示为其余类型感染;③合并其他COPD严重并发症;④同时合并其余部位感染;⑤合并自身免疫性疾病或者近期使用过免疫抑制剂;⑥精神异常或认知异常;⑦合并其余严重躯体疾病;⑧妊娠期哺乳期;⑨对研究所使用药物过敏。通过抽签法分为A组和B组,各30例,A组和B组的一般资料组间比较差异无统计学意义($P > 0.05$),见表1。

呼吸道内检查无脓性分泌物,肺部CT检查正常,无炎症表现;有效:患者体温、血象等检查均呈正常,呼吸道内检查基本无脓性分泌物,肺部CT检查显示炎症表现较治疗前有改善;无效:未满足上述标准,甚至有加重表现。总有效率=显效率+有效率。

1.3.2 一般治疗情况 记录两组治疗7 d后的铜绿假单胞菌清除率(通过痰培养检查显示无病原菌),以及体温正常时间、白细胞计数(WBC)正常时间[(4~10) $\times 10^9/L$]、肺部炎症病灶消失时间及住院时间。

1.3.3 血清实验室指标 采集两组患者治疗前、治疗后3 d及7 d时的空腹静脉血5 mL,室温下静置30 min后,上离心机处理(转速3000 r/min,时间15 min),收集血清液待检测,WBC的

检测选择迈瑞 5180c 血细胞分析仪,C 反应蛋白(CRP)的检测采用免疫散射比浊法,降钙素原(PCT)的检测采用酶联荧光分析法,试剂盒均购于深圳迈瑞生物有限公司。

1.3.4 血气指标 于治疗前、治疗后 7 d 时进行检查,仪器选择美中互利工业公司生产的 NOVA pHox plus 血气分析仪,指标包括动脉血氧饱和度(SaO₂)、血氧分压(PaO₂)二氧化碳分压(PaCO₂)。

1.3.5 安全性 记录用药过程中的相关不良反应。

1.4 统计学分析

以 spss18.0 软件包处理实验数据,计量资料用均数± 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验,计数资料组间比较采用 χ^2 检验,以 $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 A 组和 B 组患者临床疗效结果对比

通过对比治疗后 7d 的结果显示,A 组和 B 组患者的临床疗效分别为 93.33%和 90.00%,差异无统计学意义($P > 0.05$),见表 2。

表 2 A 组和 B 组患者临床疗效结果对比[n(%)]

Table 2 Comparison of the clinical efficacy in A group and B group patients [n(%)]

Groups	Remarkable effect	Effective	Invalid	Total effective rate
A group(n=30)	18(60.00)	10(33.33)	2(6.67)	28(93.33)
B group(n=30)	15(50.00)	12(40.00)	3(10.00)	27(90.00)

2.2 A 组和 B 组患者一般治疗情况对比

通过比较两组治疗 7 d 后的细菌清除率结果显示,差异无统计学意义($P > 0.05$),但 A 组在体温正常时间、WBC 正常时

间、咳嗽消失时间、肺部炎症病灶消失时间和 B 组比较,均明显更短($P < 0.05$),见表 3。

表 3 A 组和 B 组患者一般治疗情况对比[$\bar{x} \pm s$,n(%)]

Table 3 Comparison of the general treatment in A group and B group patients[$\bar{x} \pm s$, n(%)]

Groups	Bacterial clearance rate		Pulmonary inflammatory lesions	Disappearance time(d)	Length of stay(d)
	Body temperature normal time(d)	WBC normal time(d)			
A group(n=30)	25(83.33)	2.68± 0.47 ^a	5.05± 0.53 ^a	9.21± 1.30 ^a	10.02± 1.94 ^a
B group(n=30)	23(76.67)	3.31± 0.51	6.52± 0.60	10.37± 1.88	11.69± 1.61

Note: Vs the B group, ^a $P < 0.05$.

2.3 A 组和 B 组患者不同时间点血清实验室指标结果对比

通过比较发现,A 组和 B 组患者治疗后 3 d、7 d 时血清 WBC、CRP、PCT 实验室指标结果均低于治疗前,且在治疗后 3 d、

7 d 时,A 组患者血清 WBC、CRP、PCT 实验室指标结果和对照组相比,均明显更低($P < 0.05$),见表 4。

表 4 A 组和 B 组患者不同时间点血清实验室指标结果对比($\bar{x} \pm s$)

Table 4 Comparison of the serum laboratory indicators in A group and B group patients at different time points($\bar{x} \pm s$)

Groups		WBC($\times 10^9/L$)	CRP(mg/L)	PCT($\mu g/L$)
A group(n=30)	Before treatment	14.74± 2.63	13.16± 2.40	3.08± 0.62
	After treatment 3 d	10.38± 1.75 ^{ab}	9.75± 1.55 ^{ab}	1.94± 0.31 ^{ab}
	After treatment 7 d	6.29± 1.40 ^{ab}	5.91± 0.77 ^{ab}	0.86± 0.20 ^{ab}
B group(n=30)	Before treatment	14.68± 2.77	13.09± 2.56	3.11± 0.57
	After treatment 3 d	12.10± 2.18 ^a	11.18± 1.64 ^a	2.26± 0.29 ^a
	After treatment 7 d	7.55± 1.37 ^a	7.04± 1.29 ^a	1.17± 0.34 ^a

Note: Vs the before treatment, ^a $P < 0.05$; vs the B group at the same time, ^b $P < 0.05$.

2.4 A 组和 B 组患者血气分析指标结果对比

通过比较发现,A 组和 B 组患者治疗后 SaO₂、PaO₂、PaCO₂ 指标结果和治疗前相比,均得到明显改善,且 A 组患者 SaO₂、PaO₂ 指标结果和对照组相比,均明显高,PaCO₂ 的结果明显更低($P < 0.05$),见表 5。

2.5 安全性评价

两组患者的胃肠道反应、皮疹、血液系统异常、肝功能异常总发生率结果比较,差异无统计学意义($P > 0.05$),见表 6。

3 讨论

COPD 是临床上常见的慢性气道炎症反应性疾病,随着我国人口的老齡化,该病的发生率也呈现着逐年增长的趋势,COPD 患者在发病后不仅会对呼吸系统产生影响,且同时会累及到肺脏等其余器官,造成组织发生反复性损伤,对生活质量及生命安全均有着严重威胁^[11,12]。目前的研究发现,在大多数 COPD 患者的呼吸道中均可见不同程度的细菌数定植,当机体

表 5 A 组和 B 组患者血气分析指标结果对比($\bar{x} \pm s$)Table 5 Comparison of the blood gas analysis index result A group and B group patients($\bar{x} \pm s$)

Groups		SaO ₂ (%)	PaO ₂ (mmHg)	PaCO ₂ (mmHg)
A group(n=30)	Before treatment	83.23± 3.71	56.17± 5.29	56.31± 4.18
	After treatment	92.11± 3.06 ^{ab}	68.37± 5.13 ^{ab}	44.12± 3.03 ^{ab}
B group(n=30)	Before treatment	83.17± 4.04	56.40± 4.71	56.18± 5.22
	After treatment	88.64± 3.18 ^a	62.84± 3.20 ^a	48.49± 4.21 ^a

Note: Vs the before treatment, ^a $P < 0.05$; vs the B group, ^b $P < 0.05$.

表 6 A 组和 B 组患者不良反应结果对比[n(%)]

Table 6 Comparison of the adverse reactions results A group and B group patients [n(%)]

Groups	Gastrointestinal reactions	Rash	Abnormal blood system	Abnormal liver function	Total incidence
A group(n=30)	1(3.33)	1(3.33)	2(6.67)	0(0.00)	4(13.33)
B group(n=30)	2(6.67)	1(3.33)	1(3.33)	1(3.33)	5(16.67)

受到内部或者外界的刺激下,细菌株会发生持续性的繁殖,当数量达到一定的阈值时,可致使患者病情处于急性加重期,可明显增加患者住院率,感染严重者甚至会加剧死亡率,给预后带来诸多不良影响^[13,14]。

在 COPD 合并呼吸道感染的患者中,主要病原菌类型包括革兰阴性菌和革兰阳性,既往检出类型多见于肺炎链球菌、流感嗜血杆菌等^[15,16]。然而随着近年来不合理抗菌药物使用现象的加剧,加上人口老龄化、免疫抑制剂使用增加等因素,铜绿假单胞菌在 COPD 患者气道分泌物中的检出率也呈现着越来越高的趋势,目前已成为 COPD 急性发作的主要病原菌^[17,18]。李宗平等^[19]一项研究显示,在急性期 COPD 患者中,铜绿假单胞菌的检出率高达 61.67%,明显高于疾病稳定期的患者。铜绿假单胞菌属于非发酵革兰阴性菌,是一种大量使用广谱抗生素后所激发的一类病原菌,广泛分布于人体的呼吸道中^[20,21]。现今临床上铜绿假单胞菌的耐药情况已十分严峻,甚至有较多患者出现多重耐药、泛耐药的现象,给临床的抗菌增加了不少难度^[22,23]。其耐药机制主要是由于以下几点,① 其可生成 β -内酰胺酶,对 β -内酰胺类抗菌药物中的 β -内酰胺结构产生水解效果,从而降低的药物的敏感性,② 菌体蛋白结构及功能呈异常改变,③ 可形成生物保护膜,令抗菌药物的抑菌作用降低^[24,25]。选择合理有效的方案治疗 COPD 合并铜绿假单胞菌感染患者显得极为重要。

β -内酰胺类抗生素仍是目前治疗铜绿假单胞菌感染的常用药物之一^[26,27]。哌拉西林他唑巴坦属于一种广谱的 β -内酰胺酶抑制剂药物,也是一种半合成的青霉素,临床研究已证实,其在大多数革兰阴性菌、革兰阳性菌中均可起到良好的抗菌活性^[28,29]。其主要成分中哌拉西林对铜绿假单胞菌具有有效的清除作用,但容易被 β -内酰胺酶所水解,产生耐药,但他唑巴坦属于一种不可逆的竞争性的 β -内酰胺酶抑制剂,两者联合会减少哌拉西林的水解程度,并对哌拉西林的抗菌谱起到补充作用,从而提高抗菌效果^[30,31]。头孢哌酮钠舒巴坦是由头孢哌酮钠和舒巴坦所组成的复方制剂,临床上多用于呼吸系统、生殖系统、泌尿系统等感染的治疗。主要抗菌活性成分为头孢哌酮,但其对 β -内酰胺酶的稳定性较差也容易被水解,但联合舒巴坦后可明显提高头孢哌酮钠的稳定性,加强抗菌效果^[32]。

本研究通过观察显示,两组患者在治疗后 7 d 时,使用哌

拉西林他唑巴坦治疗的患者临床疗效总有效率和细菌清楚率分别为 93.33%、83.33%,使用头孢哌酮钠舒巴坦治疗的患者分别为 90.00%、76.67%,差异无统计学意义,显示出两种药物均可获得满意的抗菌疗效,且疗效相似。但本研究进一步分析也发现,使用哌拉西林他唑巴坦治疗的患者体温正常时间、WBC 正常时间、咳嗽消失时间、肺部炎症病灶消失时间均明显更短,且在治疗后 3 d、7 d 时的血清 WBC、CRP、PCT 实验室指标也明显比使用头孢哌酮钠舒巴坦的患者更低,显示出哌拉西林他唑巴坦可更早期的控制感染、明显缩短恢复时间,通过分析是由于他唑巴坦属于舒巴坦的衍生物,对超广谱的 β -内酰胺酶的抑制效果更强,且哌拉西林他唑巴坦的脂溶性较好,所获得的抗菌疗效也更加满意。在 Hall RG 等^[33]研究中也显示,和头孢哌酮钠舒巴坦相比,哌拉西林他唑巴坦的药物配比更加均匀,稳定性也更好,所得到的抗菌效果也更强。祝明伟的^[34]一项研究中也显示,哌拉西林-他唑巴坦在治疗老年冠心病患者中的抗感染效果明显优于头孢哌酮钠舒巴坦,效果更加明显。

且本研究通过对治疗后 7 d 时的血气指标观察中也显示,使用哌拉西林他唑巴坦治疗的患者改善程度更明显,分析是由于在早期有效的控制感染后,也有助于促进患者病情的恢复。本研究在通过对用药安全性的分析中显示,两组患者胃肠道反应、皮疹、血液系统异常、肝功能异常的总发生率分别为 13.33%和 16.67%,差异无统计学意义,显示出两组抗菌药物均具有较好的安全性。但在 Beaulieu CI 等^[35]研究中显示,哌拉西林他唑巴坦在使用过程中容易发生血液系统异常表现。但本研究中也未出现明显的差异性,考虑和本研究样本量较少、使用时间较短相关,抗菌药物使用时间的减少也会降低相应不良反应的发生率。然而本研究也存在着不足之处,例如所纳入较少、单中心研究等,此后也有待进一步的扩大研究来验证本结论。

综上所述,哌拉西林他唑巴坦与头孢哌酮钠舒巴坦对 COPD 合并铜绿假单胞菌感染患者均具有较好的抗菌效果及安全性,但哌拉西林他唑巴坦可缩短恢复时间,临床应用价值更高。

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