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乌司他丁联合利奈唑胺对重症肺炎患者血清 PCT、CRP、TNF- α 及白细胞计数的影响 *

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摘要 目的:探讨乌司他丁联合利奈唑胺对重症肺炎患者血清降钙素原(PCT)、C-反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)及白细胞计数的影响。**方法:**选择2014年2月-2018年2月在我院住院诊治的重症肺炎患者128例,根据治疗方法的不同分为观察组68例与对照组60例,对照组给予利奈唑胺治疗,观察组在对照组治疗的基础上给予乌司他丁治疗,两组都治疗观察2周,检测和比较两组治疗后临床疗效,治疗前后1秒钟用力呼气量占用力肺活量比值(FEV1/FVC)、血清PCT、CRP、TNF- α 水平及白细胞计数的变化情况。**结果:**观察组与对照组的总有效率分别为94.1%和76.7%,观察组的总有效率显著高于对照组($P<0.05$)。观察组与对照组治疗后的FEV1/FVC值、白细胞计数均显著高于治疗前($P<0.05$),且观察组以上指标明显高于对照组($P<0.05$)。观察组与对照组治疗后的血清PCT、CRP、TNF- α 水平都显著低于治疗前($P<0.05$),且观察组以上指标均显著低于对照组($P<0.05$)。**结论:**乌司他丁联合利奈唑胺治疗重症肺炎患者能显著提高临床疗效,改善患者肺功能,可能与其降低血清PCT、CRP、TNF- α 水平,提高白细胞计数有关。

关键词:乌司他丁;利奈唑胺;重症肺炎;降钙素原;白细胞计数

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Effects of Ulinastatin Combined with Linezolid on the Serum PCT, CRP, TNF- α Levels and White Blood Cell Counts of Severe Pneumonia Patients*

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ABSTRACT Objective: To investigate the effect of ulinastatin and linezolid on the serum calcitonin (PCT), C- reactive protein (CRP), tumor necrosis factor - α (TNF- α) levels and leukocyte count of patients with severe pneumonia. **Methods:** 128 cases of patients with severe pneumonia in our hospital from February 2014 to February 2018 were selected. According to different treatment methods, they were divided into the observation group (68 cases) and the control group (60 cases), the control group was treated with linezolid, while the observation group was treated with ulinastatin on the basis of control group, and the patients in both groups were treated for 2 weeks. The clinical efficacy after treatment, changes of forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC), serum PCT, CRP, TNF- α levels and white blood cell count before and after treatment were measured and compared between two groups. **Results:** The total effective rate of observation group and control group were 94.1% and 76.7% respectively, which was significantly higher in the observation group than that of the control group ($P<0.05$). The FEV1/FVC value and white blood cell count of both groups were significantly higher than those before treatment ($P<0.05$), which were significantly higher in the observation group than those of the control group ($P<0.05$). The levels of serum PCT, CRP and TNF- α levels in both groups were significantly lower than those before treatment ($P<0.05$), which were significantly lower in the observation group than those in the control group ($P<0.05$). **Conclusion:** Ulinastatin combined with linezolid can significantly improve the clinical efficacy and the lung function in the treatment of patients with severe pneumonia. It may be related to reduce the levels of serum PCT, CRP, TNF- α and increase the white blood cell count.

Key words: Ulinastatin; Linezolid; Severe pneumonia; Procalcitonin; White blood cell count

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前言

重症肺炎是重症监护病房(ICU)中最常见的危重症之一,其病情的进展可导致左室充盈压持续升高,肺血管内膜重塑,

临床表现为持续呼吸道恶化症状,如咳痰量增多,伴发热等症状^[1,2]。该病具有较高的死亡率,其病原菌多耐药,早期诊治可有效降低患者的死亡率^[3]。目前,临床常采用利奈唑胺治疗重症肺炎,虽然其有一定的效果,但存在肾毒性,长期服用会加重肺炎

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的耐药性^[4]。中医认为重症肺炎的病机为气机郁滞、肺失宣降,治疗以清热解毒、祛痰润肺为主^[5]。

乌司他丁(ulinastatin)来自于人类尿液,是一种广谱蛋白酶抑制剂,对多种水解酶、蛋白酶都有一定的抑制作用,可有效抑制炎症介质释放^[6,7]。血清降钙素原(PCT)是一种新的感染性炎症标记物,血清 PCT 的检测有助于重症肺炎的早期诊断与病情判断^[8,9]。C-反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)作为生物学指标已经被广泛应用于炎症感染的诊断^[10]。现代研究表明重症肺炎患者普遍存在炎症反应,表现为炎症介质以各种方式进行相互调控,呈瀑布样激活放大,导致机体出现剧烈的炎症反应^[11,12]。且重症肺炎患者也会发生白细胞计数异常,引起心血

管、肾脏等并发症,甚至导致患者死亡^[13,14]。本研究主要探讨了乌司他丁联合利奈唑胺对重症肺炎患者血清 PCT、CRP、TNF- α 水平及白细胞计数的影响,现总结报道如下。

1 资料与方法

1.1 研究对象

2014 年 2 月-2018 年 2 月,采用回顾性、总结研究方法,选择在我院住院诊治的重症肺炎患者 128 例,根据治疗方法的不同分为观察组 68 例与对照组 60 例,两组一般资料比较差异均无统计学意义($P>0.05$),具有可比性。

表 1 两组一般资料的对比

Table 1 Comparison of the general data between two groups

Groups	n	Gender (Male /female)	Age (year)	Body mass index (kg/m ²)	Emergency admission time (h)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Observation group	68	38/30	56.23 $\pm$ 1.20	21.89 $\pm$ 2.89	14.33 $\pm$ 2.98d	134.20 $\pm$ 18.22	81.44 $\pm$ 9.14
Control group	60	32/28	56.11 $\pm$ 2.19	22.39 $\pm$ 1.04	14.32 $\pm$ 3.11	132.11 $\pm$ 19.42	80.99 $\pm$ 8.42
<i>P</i>		0.772	0.814	0.655	0.913	0.184	0.578

1.2 纳入与排除标准

纳入标准:1) 年龄 ≥ 18 岁;符合重症肺炎的诊断标准,经三代头孢菌素、碳氢酶烯类、喹诺酮类抗生素治疗无效或效果较差;2) 临床资料完整;3) 医院伦理委员会批准了此次研究;4) 肺功能 FEV1/FVC $<70\%$;5) 患者在自愿条件下签署了知情同意书。

排除标准:1) 临床资料缺项者;2) 精神疾病患者;3) 过敏体质或对本研究所用药物过敏者;4) 伴有肺炎以外的其他肺部疾病者;5) 妊娠与哺乳期妇女。

1.3 治疗方法

对照组:给予利奈唑胺治疗,静脉滴注利奈唑胺(注册证号 H20110312, Fresenius kabi AB) 30 mL, 2 次/d, 连续治疗观察 2 周。

观察组:在利奈唑胺治疗的基础上给予乌司他丁治疗,乌司他丁(国药准字 H20142442, 广东天普生化医药股份有限公司) 10 万 U 用生理盐水稀释后进行静脉滴注, 1 次/d, 连续观察治疗 2 周。

两组在治疗期间都给予止咳、补液、雾化吸入、去痰、营养支持等治疗。

1.4 观察指标

(1) 疗效评价标准:临床症状和体征消失或基本消失,病原学检查及实验室检查结果均恢复正常判定为治愈;临床症状和体征显著缓解,病原学检查及实验室检查结果均恢复正常判定为显效;临床症状和体征好转,病原学检查及实验室检查结果均

有所改善判定为好转;未达到上述标准甚或恶化判定为无效。

(2) 肺功能测定:采用德国 Jeager 公司生产的 Masterscreen-Diff) 肺功能测定仪,所有患者在接受检查前均安静休息 15 min 以上,测定 1 秒钟用力呼气量占用力肺活量比值(FEV1/FVC),取测定三次的平均值。(3) 两组在治疗前后进行血液学测定,在治疗前后抽取空腹静脉血 3-5 mL,提取血清后低温保存,采用酶联免疫法测定血清 PCT、CRP、TNF- α 水平,外周血白细胞计数由我院检验科完成。

1.5 统计学方法

选择 SPSS22.00 统计学软件对计量数据与计数数据进行分析,分别以均数 $\pm$ 标准差($\bar{x}\pm s$)、百分比、率、%表示,组间比较分别采用 t 检验、卡方检验等,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组总有效率的对比

观察组与对照组的总有效率分别为 94.1%和 76.7%,观察组的总有效率显著高于对照组,差异有统计学意义 ($P<0.05$),见表 2。

2.2 两组治疗前后肺功能指标对比

观察组与对照组治疗后的 FEV1/FVC 值均显著高于治疗前($P<0.05$),且观察组明显高于对照组($P<0.05$)。见表 3。

表 2 两组治疗总有效率对比

Table 2 Comparison of the total efficiency between two groups

Groups	n	Cure	Obvious effect	Improved	No effect	Total effective rate
Observation group	68	54	10	4	0	64(94.1%)
Control group	60	26	20	8	6	46(76.7%)
<i>P</i>						0.002

表 3 两组治疗前后 FEV1/FVC 值变化的对比(%)

Table 3 Comparison of the FEV1/FVC values before and after treatment between two groups (%)

Groups	n	Before treatment	After treatment
Observation group	68	40.55± 4.85	63.22± 5.11* [#]
Control group	60	40.11± 3.11	53.22± 4.29*

Note: compared with the before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$.

2.3 两组治疗前后白细胞计数变化对比

显著高于对照组($P<0.05$),见表 4。

治疗后,观察组的白细胞计数显著高于治疗前($P<0.05$),且

表 4 两组治疗前后白细胞计数变化的对比($\times 10^9/L$)

Table 4 Comparison of the white blood cell count before and after treatment between two groups ($\times 10^9/L$)

Groups	n	Before treatment	After treatment
Observation group	68	13.30± 2.48	18.87± 4.00* [#]
Control group	60	13.22± 3.19	13.98± 2.88*

Note: compared with the before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$.

2.4 两组治疗前后血清 PCT、CRP、TNF- α 水平变化对比

疗前($P<0.05$),且观察组以上指标均显著低于对照组($P<0.05$)。

治疗后,两组的血清 PCT、CRP、TNF- α 水平都显著低于治 见表 5。

表 5 两组治疗前后血清 PCT、CRP、TNF- α 水平变化对比

Table 5 Comparison of the changes of serum PCT, CRP and TNF- α levels between the two groups before and after treatment

Groups	n	PCT(ng/L)		CRP(mg/L)		TNF- α (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	68	783.22± 114.29	341.44± 187.20* [#]	60.33± 15.39	10.11± 3.19* [#]	40.10± 8.19	10.77± 8.14* [#]
Control group	60	771.40± 193.55	511.40± 193.55*	60.00± 5.01	27.49± 5.32*	40.01± 9.14	19.38± 8.11*

Note: compared with the before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$.

3 讨论

重症肺炎的病情危重,病死率高,发病原因及机制目前仍不完全明确,研究认为与吸烟、环境污染、细菌感染等多种因素有关^[15]。利奈唑胺属小分子唑烷酮类抗菌药物,具有肺组织穿透力强、抗菌活性高等优点,能特异性结合 23s RNA 位点并抑制核糖体起始复合物的产生,且对肝肾功能影响较小^[16]。但是该药的长期使用可导致机体产生交叉耐药性,导致治疗效果下降。乌司他丁是从健康男性尿液中分离纯化出来的一种糖蛋白,由 143 个氨基酸组成,具有广谱抑酶作用,能改善微循环和组织灌注^[17]。本研究显示观察组的总有效率更高,表明乌司他丁的应用能提高治疗效果。相关研究也表明在乌司他丁可增强垂体-肾上腺系统活动,提高循环中的皮质醇含量,从而改善患者的预后^[18]。

重症肺炎患者的主要症状是气促、咳嗽加剧、痰量增加、喘息、胸闷加重,痰量呈脓性或粘液脓性,此外也可出现嗜睡、疲乏、全身不适、失眠和精神紊乱等症状^[19]。重症肺炎是诱发脓毒性休克、导致多器官功能障碍综合征的重要原因,发病机制与机体免疫功能紊乱或低下、诱导多种炎性因子释放有关,可导致肺功能下降^[20]。相关研究表明乌司他丁具有稳定溶酶体膜、清除氧自由基、抑制心肌抑制因子产生的作用,可改善外在因素刺激引起的对内脏器官与细胞的损伤以及改善低灌注时的

循环状态,从而改善患者的肺功能^[21]。本研究结果也显示观察组治疗后 FEV1/FVC 值显著高于对照组,表明联合应用乌司他丁有助于改善重症肺炎患者的肺功能。

正常情况下,机体的促炎和抗炎反应处于动态平衡状态,过度反应都会引起两者的平衡失调,导致机体免疫内稳机制被完全打破。重症肺炎的发生、发展不一定依赖细菌毒素、细菌的持续存在、作用,炎症介质瀑布式级联反应导致炎症反应紊乱是其发病的主要原因。PCT 是一种应激性急性期反应蛋白,属于前肽糖类蛋白,在人体中呈现组成性表达,特别在肝、小肠、睾丸、肺、前列腺、肾中水平最高。外在炎症因子刺激后,机体血液中的 PCT 水平持续升高,PCT 虽然刺激炎症因子的表达,但却可能放大和加重病情^[22]。TNF- α 可被多种刺激物质等诱导产生,是一种具有广谱效应的细胞因子,与肝细胞炎症、坏死及病情发展密切相关。有研究显示 PCT、CRP 与 TNF- α 可以各种方式进行相互调控,呈瀑布样激活放大,导致机体出现剧烈的炎症反应^[23-25]。本研究显示两组患者治疗后的血清 PCT、CRP、TNF- α 值都显著低于治疗前,且观察组显著低于对照组,表明乌司他丁的应用能更有效抑制机体的炎症反应,也可通过神经内分泌系统对免疫系统发生影响,使患者达到“阴平阳秘”而病愈^[26]。

有研究显示白细胞计数是重症肺炎患者死亡率的一个独立预测因子,特别是入 ICU 后持续 4d 以上的白细胞计数下降

时,患者的死亡率增加5倍左右^[23]。随着重症肺炎病情的发展,凝血酶、花生四烯酸代谢产物可激活血小板并形成聚集,导致白细胞计数减少^[27]。有研究显示乌司他丁也能抑制氧自由基的产生,抑制内源性休克因子的表达,减少中性粒细胞的聚集,从而提高机体白细胞计数^[28,29];且乌司他丁可改善花生四烯酸的代谢,对抑制血小板释放活性物质、维护血小板正常聚集功能和内皮细胞完整性具有重要意义^[30]。本研究显示观察组治疗后的白细胞计数显著高于对照组,也进一步说明乌司他丁有助于控制重症肺炎患者的病情。

总之,乌司他丁联合利奈唑胺治疗重症肺炎患者能显著提高临床疗效,改善患者肺功能,可能与其降低血清PCT、CRP、TNF- α 水平,提高白细胞计数有关。

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