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不同剂量乌司他丁联合微量推注泵美罗培南对重症肺炎患者的疗效及血管生成素 2 的影响 *

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摘要 目的：探讨与分析不同剂量乌司他丁联合微量推注泵美罗培南对重症肺炎患者的疗效及血管生成素 -2 的影响。**方法：**2019 年 1 月到 2022 年 2 月选择在本院诊治的重症肺炎患者 78 例作为研究对象，将其分为研究组与对照组各 39 例，两组都给予美罗培南微量推注治疗，研究组与对照组分别给予高剂量与低剂量的乌司他丁治疗，连续应用 7 d，观察患者的疗效及血清血管生成素 2 表达变化情况。**结果：**研究组的 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间较对照组少（*P*<0.05）。研究组的治疗总有效率较对照组高（*P*<0.05）。两组治疗后的血清白细胞介素 -6（IL-6）、白细胞介素 -17（IL-17）含量明显低于治疗前（*P*<0.05），研究组治疗后的血清 IL-6、IL-17 含量也明显低于对照组（*P*<0.05）。两组治疗后的血清血管生成素 -2 含量低于治疗前，治疗后研究组血清血管生成素 -2 含量低于对照组（*P*<0.05）。**结论：**高剂量乌司他丁联合微量推注泵美罗培南在重症肺炎患者的应用能抑制血清血管生成素 -2 的表达，也可抑制血清 IL-6、IL-17 的表达，从而能提高治疗效果，促进改善患者的临床症状，有利于患者康复。

关键词：剂量；乌司他丁；美罗培南；重症肺炎；血管生成素 2

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Efficacy of Different Doses of Ulinastatin Combined with Microbolus Meropenem in Patients with Severe Pneumonia and the Effect of Angiopoietin 2*

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ABSTRACT Objective: To investigate and analysis the efficacy of different doses of ulinastatin combined with microbolus meropenem in patients with severe pneumonia and the effect of angiopoietin-2. **Methods:** From January 2019 to February 2022, 78 cases of patients with severe pneumonia who were diagnosed and treated in our hospital were selected as the research subjects. Accorded to the simple 1:1 allocation principle, the patients were divided into the study group and the matched group of each groups with 39 cases. For example, both groups were given meropenem micro-bolus injection, and the study group and matched group were given high-dose and low-dose ulinastatin treatment, respectively for 7 days. **Results:** The ICU stay time, fever reduction time, inflammation absorption time and sputum color change time in the study group were shorter than those in the matched group (*P*<0.05). The total effective rates of the study group was higher than matched group (*P*<0.05). The serum interleukin-6 (IL-6) and interleukin-17 (IL-17) levels in the two groups after treatment were lower than those before treatment, and the study group were also significantly lower than those in the matched group (*P*<0.05). The levels of serum angiopoietin-2 in the two groups after treatment were lower than those before treatment, and the levels of serum angiopoietin-2 in the study group after treatment were lower than those in the matched group (*P*<0.05). **Conclusion:** The application of high-dose ulinastatin combined with micro-bolus pump meropenem in patients with severe pneumonia can inhibit the expression of serum angiopoietin-2, and also inhibit the expression of serum IL-6 and IL-17, thereby improving the treatment effect. It can improve the clinical symptoms of patients and help patients recover.

Key words: Dose; Ulinastatin; Meropenem; Severe pneumonia; Angiopoietin-2

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前言

重症肺炎是临床上的危重疾病，可导致患者发生多器官功能障碍综合征，死亡率一直居高不下[1]。重症肺炎的具体发病机制还不明确，但是病因比较多，包括细菌性感染与病毒性感染，且发现体内炎症介质可参与器官及组织功能损伤的过程[2]。重症肺炎患者的重要环节是抗感染治疗，美罗培南是一种β 内酰胺类抗生素，具有广泛抗菌效果[3]。乌司他丁是一种蛋白酶抑制剂，通过减轻肺氧化性损伤，可以抑制氧化物阴离子及过氧化氢的生成，达到肺保护的作用[4]。但是当前临床上对于乌司他丁的使用剂量还无相关探讨，剂量使用过大具有一定的不良反应，剂量使用过小可能不能有效发挥治疗作用[5]。血管生成素 -2 是血管生成素家族一员，可导致血管内皮细胞功能障碍、血管通透性增加，能抑制血管生成，促进血管细胞凋亡，与危重患者的病情存在相关性[6]。本文具体探讨了不同剂量乌司他丁联合微量推注泵美罗培南应用于重症肺炎患者的疗效及对血管生成素 2 的影响，进而对乌司他丁的最佳使用剂量与作用机制有初步了解。

1 资料与方法

1.1 研究对象

2019 年 1 月到 2022 年 2 月选择在中国人民解放军空军第九八六医院诊治的重症肺炎患者 78 例作为研究对象。医院伦理委员会批准此次研究。

纳入标准：符合重症肺炎的诊断标准；年龄 18-70 岁；治疗期间无发生死亡情况；知情并签署同意书；临床资料完整。

排除标准：正在参加其他药物临床试验者；脑死亡状态者；合并高危传染性疾病者；免疫缺陷性疾病者；心理精神障碍者。

根据简单 1:1 分配原则把患者分为研究组与对照组各 39 例，两组患者的年龄、性别、APACHEⅡ评分、SOFA 评分、发病到入院时间等对比无明显差异（P>0.05）。见表 1。

表 1 一般资料对比

Table 1 The comparison of the general data

Groups	n	APACHEⅡ score (score)	SOFA Score (score)	Age (year)	Gender (male / female)	Time from onset to admission (h)
Research group	39	21.10± 2.24	8.52± 0.45	56.23± 1.20	20/19	14.33± 1.98
Matched group	39	21.83± 2.43	8.49± 0.34	56.11± 1.19	21/18	14.32± 1.11

1.2 治疗方法

两组都给予美罗培南微量推注治疗，注射用美罗培南（美平）（国药准字 H20140702，Sumitomo Dainippon Pharma Co., Ltd.）0.5 g 加入 0.9 %氯化钠溶液（国药准字 H44025125，广州珠江制药厂）100 mL 中静脉滴注，每 8 h 给药 1 次。

研究组与对照组分别给予高剂量与低剂量的乌司他丁治疗，选择乌司他丁（国药准字 H20142442，广东天普生化公司）100 万 U、50 万 U 加入 0.9 %氯化钠中配置成 50 mL，持续静脉泵入，连续应用 7 d。

所有患者也都对症性给予吸氧、营养支持、祛痰平喘、补液等支持治疗。

1.3 观察指标

（1）记录两组患者的 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间。

（2）在治疗后进行总体疗效评价，显效：症状、体征被发现全部消失，肺部未发生炎性反应；有效：症状、体征有所改善，肺部基本无炎性情况；无效：无达到上述标准甚或恶化。总有效率 = 显效率 + 有效率。

（3）所有患者在治疗前后抽取患者的空腹外周静脉血 2-3 mL，分离上层血清后，采用化学发光法检测白细胞介素 -6（Interleukin-6, IL-6）、白细胞介素 -17（Interleukin-17, IL-17）含量，检测试剂盒购自深圳华大基因公司。

（4）取上述的血清学标本，采用酶联免疫法检测血清血管生成素 -2 含量，检测试剂盒购自武汉三鹰公司。

1.4 统计方法

统计分析过程中应用的软件是 SPSS20.00，通过百分率和均数± 标准差来表示计量结果与计数结果，计数数据对比进行 x^2 检验，计量数据对比为 t 检验，检验水准α=0.05，P<0.05 表示统计学差异显著。

2 结果

2.1 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间对比

研究组的 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间都显著少于对照组（P<0.05）。见表 2。

表 2 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间对比(d，均数± 标准差)

Table 2 Comparison of the two groups' ICU hospitalization time, antipyretic time, inflammation absorption time and sputum color change time (d, mean ± standard deviation)

Groups	n	ICU length of stay	The antipyretic time	Inflammatory absorption time	Sputum color change in time
Research group	39	7.21± 0.45#	2.45± 0.33#	4.25± 0.29#	5.02± 0.34#
Matched group	39	10.63± 1.48	4.56± 0.57	6.28± 0.54	6.87± 0.67

Note: Compared with the Matched group, #P<0.05, the same below.

2.2 总有效率对比

研究组的治疗总有效率较对照组高(P<0.05)。见表 3。

2.3 血清 IL-6、IL-17 含量变化对比

两组治疗后的血清 IL-6、IL-17 含量明显低于治疗前，研究组治疗后的血清 IL-6、IL-17 含量也明显低于对照组(P<0.05)。见表 4。

表 3 治疗总有效率对比(n)

Table 3 Total response efficiency comparison (n)

Groups	n	Excellence	Valid	Invalid	Total effective rate
Research group	39	35	3	1	38(97.4%)#
Matched group	39	20	13	6	33(84.6%)

表 4 治疗前后血清 IL-6、IL-17 含量变化对比(pg/mL，均数± 标准差)

Table 4 Comparison of serum IL-6 and IL-17 content before and after treatment (pg/mL, mean ± standard deviation)

Groups	n	IL-6		IL-17	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Research group	39	123.33± 15.02	23.01± 1.11*#	78.98± 8.22	17.22± 1.11*#
Matched group	39	123.98± 14.29	49.87± 2.84*	78.99± 5.20	25.09± 2.68*

Note: Compared with the Pretherapy, *P<0.05, the same below.

2.4 血清血管生成素 -2 含量变化对比

两组治疗后的血清血管生成素 -2 含量明显低于治疗前，治疗后研究组较对照组低(P<0.05)。见表 5。

表 5 治疗前后血清血管生成素 -2 含量变化对比(mg/mL，均数± 标准差)

Table 5 Comparison of serum angiopoietin-2 content before and after treatment (mg/mL, mean ± standard deviation)

Groups	n	Pretherapy	Post-treatment
Research group	39	1.98± 0.13	1.22± 0.15*#
Matched group	39	1.99± 0.22	1.67± 0.29*

3 讨论

重症肺炎是呼吸道系统的危重疾病，大量患者伴随有各种基础疾病，对于临床治疗带来一定的不足[7,8]。同时一些患者在 ICU 的治疗过程中，全身会发生炎症、肺部通气产生障碍等，也会增加治疗难度[9]。本研究显示研究组的 ICU 住院时间、退热时间、炎症吸收时间与痰液颜色改变时间都显著少于对照组；研究组的治疗总有效率为 97.4 %，显著高于对照组的 84.6 %，表明高剂量乌司他丁联合微量推注泵美罗培南应用于重症肺炎患者，可提高疗效，改善临床症状。分析可知：美罗培南为一种广谱抗菌药物，药物进入体内后能有效抑制肺炎链球菌，大肠埃希菌，鲍曼不动杆菌等的细胞壁繁殖与合成、复制，可发挥杀菌消毒作用，但也对部分有害菌的抑制效果比较低，会减少药物的稳定性[10,11]。乌司他丁是一种糖蛋白，具有广谱抑酶作用，可对微循环、组织灌注起作用。此外，该药物可有效结合毒性蛋白酶，从而保护细胞和组织[12-14]。

本研究显示两组治疗后的血清 IL-6、IL-17 含量明显低于治疗前，研究组治疗后的血清 IL-6、IL-17 含量也较对照组低，表明高剂量乌司他丁联合微量推注泵美罗培南在重症肺炎患者的应用能抑制血清 IL-6、IL-17 的表达。分析可知：血清 IL-6、IL-17 具有检测便捷、快速等优势。其作为炎症急性时相反应指标，在机体内呈组成性表达。当机体在外在炎症因子刺激后，机体血液中的 IL-6、IL-17 水平持续升高，可能放大和加重病情。且 IL-6、IL-17 的变化情况比体温、白细胞计数的变化更早[15-17]。美罗培南是重症肺炎患者的常用抗菌药物，不易被β- 内酰胺酶所催化水解，可通过对细胞壁的合成产生干扰作用，可较好的抑制多重耐药菌，从而发挥抗菌效果产生抑制作用作用。乌司他丁半衰期较短，治疗效果和给药剂量存在密切相关，适当增加药物治疗能取得更好的效果[20,21]。

很多重症肺炎患者在发病早期的症状比较隐匿，若病情恶化会使其发生感染性休克、呼吸衰竭，为此要给予患者积极性的对症治疗[22]。血清血管生成素 -2 水平在正常人中很低，在缺氧、缺血等因素的刺激下，血管生成素 -2 水平可明显增高[23]。乌司他丁对组织和器官缺血再灌注损伤产生缓解作用，并对患者休克时的微循环缺血、缺氧状态进行改善，进而保护机体主要脏器功能。同时该药物也可对氧自由基等产生抑制作用，并降低内源性休克因子表达，减少中性粒细胞的聚集，改善免疫功能[24,25]。本研究显示两组治疗后的血清血管生成素 -2 含量较治疗前低，研究组治疗后较对照组低，表明高剂量乌司他丁联合微量推注泵美罗培南在重症肺炎患者的应用能抑制血清血管生成素 -2 的表达。分析可知，血管生成素 -2 可结合于血管内皮特异性受体酪氨酸激酶，对血管通透性具有提高作用，增强血

管内皮细胞基底层降解，诱发血管内皮细胞的分裂、凋亡，导致患者病情恶化[26,27]。乌司他丁属于胰蛋白酶的抑制剂，可阻碍溶酶体释放的水解酶，也可防止过度释放炎症介质，还能阻碍中性粒细胞对肺组织的浸润，从而促进改善患者的肺功能。乌司他丁也可改善机体低灌注时的循环状态，对花生四烯酸代谢具有改善作用，作用于抑制血小板释放活性物质、维护血小板正常聚集功能机内皮细胞整性，有助于缓解炎症刺激所致的肺功能损伤，也可维持生理功能平衡，改善患者体内水电解质紊乱，从而促进持续改善患者的预后[28-30]。本研究存在一定不足，存在样本量过少、单中心研究等缺点，将在后续研究中探讨。

总之，高剂量乌司他丁联合微量推注泵美罗培南在重症肺炎患者的应用能抑制血清血管生成素 -2 的表达，也可抑制血清 IL-6、IL-17 的表达，从而能提高治疗效果，促进改善患者的临床症状，有利于患者康复。

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