

doi: 10.13241/j.cnki.pmb.2018.21.016

乌司他丁对卒中相关性肺炎的疗效及血清炎症因子的影响*

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摘要 目的:研究乌司他丁治疗重症卒中相关性肺炎的疗效及其对患者血清炎症因子的影响。**方法:**选择 2015 年 1 月~2017 年 6 月我院神经内科收治的重症卒中相关性肺炎患者 96 例,将其随机分为三组。对照组采用机械通气、抗感染、化痰、营养支持和补液等常规治疗,观察组 A(低剂量组)在常规治疗基础上给予 0.3 万 U/Kg 体重静脉注射 Q8h,观察组 B(高剂量组)在常规治疗基础上给予 1.2 万 U/kg 体重静脉注射 Q8h,两组均从入院时开始,连续注射 7 天。分别比较各组的住院时间、咳嗽减轻时间、体温复常时间、啰音消失时间,治疗前后血清白介素-6、肿瘤坏死因子- α 以及高迁移率族蛋白-B1(HMGB1)水平的变化。**结果:**观察组 A 和 B 的有效率分别为 91.67% 和 95.84%,均明显高于对照组的 70.83% ($P<0.05$);观察组 A 和 B 的住院时间、咳嗽减轻时间、体温复常时间、啰音消失时间均明显短于对照组 ($P<0.05$),且观察组 B 以上指标均明显短于观察组 A ($P<0.05$)。治疗后,所有患者的血清白介素-6、肿瘤坏死因子- α 以及 HMGB1 水平均较治疗前明显降低 ($P<0.05$),且观察组以上指标明显低于对照组 ($P<0.05$),且观察组 B 以上指标均明显低于观察组 A ($P<0.05$)。**结论:**乌司他丁可加快改善卒中相关性肺炎患者的临床症状,可能与降低患者血清炎症因子 IL-6、TNF- α 和 HMGB-1 水平有关。

关键词:乌司他丁;卒中相关性肺炎;临床疗效;血清炎症因子

中图分类号:R743;R563.1 **文献标识码:**A **文章编号:**1673-6273(2018)21-4077-04

Efficacy of Ulinastatin in the Treatment of Severe Stroke Associated Pneumonia and Its Effect on Serum Inflammatory Factors*

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ABSTRACT Objective: To investigate the clinical efficacy of ulinastatin in the treatment of severe stroke associated pneumonia and its effect on serum inflammatory factors. **Methods:** 96 cases of patients with severe stroke associated pneumonia in our hospital from January 2015 to June 2017 were selected and randomly divided into three groups. The control group was treated with mechanical ventilation, anti infection, expectorant, nutritional support, fluid replacement and other conventional treatment. The observation group A (low-dose group) was given intravenous injection of ulinastatin (0.3 million U/Kg, 8 h) on the basis of routine treatment. The observation group B (high-dose group) was given intravenous injection of ulinastatin (1.2 million U/Kg, 8 h) on the basis of routine treatment. Both groups were treated continuously for 7 days after admission. The hospitalization time, relief time of cough, recovery time of body temperature, rales disappearance time, changes of the serum interleukin-6, tumor necrosis factor- α and high mobility group box-1 (HMGB1) levels before and after treatment were compared among three groups. **Results:** After treatment, the effective rate of observation group A and B were 91.67% and 95.84%, which were significantly higher than that of the control group 70.83% ($P<0.05$). The hospitalization time, relief time of cough, recovery time of body temperature, rales disappearance time of observation group A and B were significantly shorter than those in the control group ($P<0.05$). The levels of interleukin-6, tumor necrosis factor α and interleukin-23 in the observation A and B groups were significantly lower than those in the control group after the treatment ($P<0.05$). The levels of interleukin-6, tumor necrosis factor α and interleukin-23 in the observation group B were significantly lower than those in the observation A after the treatment ($P<0.05$). **Conclusions:** Ulinastatin can accelerate the recovery of patients with stroke-associated pneumonia, which may be related to the decrease of serum inflammatory cytokines IL-6, TNF- α and HMGB-1.

Key words: Ulinastatin; Severe stroke associated pneumonia; Clinical efficacy; Serum inflammatory factors

Chinese Library Classification(CLC): R743; R563.1 **Document code:** A

Article ID: 1673-6273(2018)21-4077-04

* 基金项目:陕西省科技计划科研基金项目(2011K12-05-12);西安市科技计划项目(2016048SF/YX04(2));

西安交通大学第一附属医院院级科研项目(2016QN-18)

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(收稿日期:2018-02-27 接受日期:2018-03-23)

前言

卒中具有高致死率及高致残率,且我国卒中发病率呈逐年上升趋势^[1,2]。原来没有肺部感染的卒中患者罹患感染,引起的肺部实质炎症称之为卒中相关性肺炎 (Stroke associated pneumonia, SAP),是增加卒中死亡率的重要危险因素之一,且导致住院医疗费用显著上升^[3,4]。SAP 不仅是造成脑卒中患者死亡的一个重要原因,而且会严重影响患者神经功能的恢复,故及早有效的预防以及治疗卒中相关性肺炎的相关措施对于提高临床治疗效果,改善脑卒中患者的预后情况具有重要的临床意义。

SAP 的发生与机体吞咽功能障碍以及免疫功能降低等因素紧密相关^[5]。乌司他丁能够治疗由中性粒细胞释放的弹力蛋白酶炎症因子所致的急性免疫损伤,并且已经广泛应用于脓毒血症及其他炎症的治疗之中^[6]。但关于其在重症卒中相关性肺炎患者中的治疗效果的研究较为少见。本研究对我院收治的 48 例重症 SAP 患者给予静脉滴注乌司他丁,探讨其临床疗效及其对患者血清炎症因子的影响,结果如下。

1 资料与方法

1.1 一般资料

选择 2014 年 1 月至 2016 年 12 月我院进行诊治的 96 例重症卒中相关性肺炎患者,均符合相关的诊断标准^[7],随机分为两组。观察组 48 例,男 28 例,女 20 例;年龄 57~86 岁,平均(63.42±12.74)岁;平均发病时间(3.46±1.38) d;肺部感染部位:右肺中叶、右肺上叶、左肺下叶、右肺下叶及两肺感染分别有 18、13、9、6、4 例;合并慢性阻塞性肺疾病患者 12 例,对照组 48 例,男 27 例,女 21 例;年龄 56~87 岁,平均(64.13±12.37)岁;平均发病时间(3.57±1.82) d;肺部感染部位:右肺中叶 17 例,右肺上叶 13 例,左肺下叶 10 例,右肺下叶 6 例,两肺感染 4 例;排除既往史(心房颤动、高血压病、糖尿病、病前 1 周短暂性脑缺血发作病史、高脂血症病史),有吞咽障碍所有患者均登记一般资料、梗死部位、治疗前后 NIHSS 评分、胸部 CT 或胸片、机械通气情况。所有患者已签知情同意书。

1.2 治疗方法

对照组采用抗感染、补液等常规治疗。观察组额外给予乌司他丁静脉注射,并按照剂量分为两个亚组,观察组 A(低剂量组)为 0.3 万 U/Kg 体重静脉注射 Q8h,观察组 B(高剂量组)为 1.2 万 U/kg 体重静脉注射 Q8h,两组均从入院时开始,连续注射 7 天。各组患者的性别、年龄、APACHEII 评分、发病时间比较差异均无统计学意义($P>0.05$),见表 1。

表 1 各组患者的基线资料对比

Table 1 Comparison of the baseline data among different groups

	Observation group A	Observation group B	Control group	P
n	24	24	48	
Sex(male/female)	16/8	12/12	27/21	0.495
Age	62.82±15.32	64.52±13.76	64.13±12.37	0.897
Disease time	3.69±1.67	3.40±1.87	3.57±1.82	0.853
APACHEII	19.33±6.37	18.97±7.01	18.59±7.16	0.912

1.3 观察指标

1.3.1 临床疗效评价标准 所有患者入住 ICU,明确诊断 24 小时内、7 天内、14 天内进行量表评定。根据体温、白细胞计数、气体分泌物 (24 小时吸出物性状数量)、气体交换指数 ($\text{PaO}_2/\text{FiO}_2$, Kpa), X 线胸片浸润影进行临床肺部感染评分(CPIS 评分)。根据年龄、有无严重气管系统功能不全或免疫损害、GCS 评分、体温、平均血压、心率、呼吸频率、 PaO_2 、动脉血 pH、血 Na、血 K、血肌酐、细胞压积及 WBC 等生理指标评分进行急性生理与慢性健康状况 II(APACHEII)评分。

1.3.2 疗效评价指标 治疗 10 天后,评定血常规,白细胞恢复正常($<10 \times 10^9/\text{L}$),体温正常($\leq 37.3^\circ\text{C}$)连续 3 天判定为有效,咳嗽及肺部啰音消失所需指数,记录治疗前后患者呼吸频率、氧合指数($\text{PaO}_2/\text{FiO}_2$)、 PaCO_2 、胸片变化及预后。

1.3.3 观察两组的临床治疗效果 疗效标准^[7]:① 显效:临床症状明显缓解,肺部啰音明显减轻甚至消失,X 线检查显示阴影基本吸收;② 有效:症状有所好转,肺部啰音有所减轻,X 线检查发现阴影明显吸收;③ 无效:症状均未得到改善甚至加重。

1.3.4 血清炎症因子检测 所有和治疗 7 天后采集血清测定

淋巴细胞计数、C 反应蛋白(CRP)及降钙素原(PCT)、乳酸清除率(Lac)。所有患者入院后均在治疗前和治疗后留取血标本,经处理留取血清后,采用 ELISA 方法测定白介素 -6、肿瘤坏死因子 - α 以及高迁移率族蛋白 -B1(HMGB1)水平变化,测定血清炎症因子变化水平,试剂盒均购自上海基免科技有限公司。

1.4 统计学分析

采用 SPSS 15.00 软件,计量资料以 $\bar{x} \pm s$ 表示,组间和组内对比用方差分析和 t 检验,组间率的比较用 χ^2 检验,以 $P<0.05$ 表明差异有统计学意义。

2 结果

2.1 各组患者的临床疗效对比

观察组 A 和 B 的临床总有效率分别为 91.67 % 和 95.84%,均明显高于对照组(70.83 %)($P<0.05$),见表 2。

2.2 两组主要临床症状改善情况的比较

所有观察组的住院时间、咳嗽减轻时间、体温复常时间、啰音消失时间均明显短于对照组($P<0.05$),且观察组 B 以上指标均明显短于观察组 A($P<0.05$),见表 3。

表 2 各组患者的临床疗效比较[例(%)]

Table 2 Comparison of the clinical effect between different groups[n(%)]

Group	n	Effective	Valid	Invalid	Total effective rate
Observation group A	24	9(37.5%)	13(54.16%)	2(8.33%)	91.67%*
Observation group B	24	10(41.66%)	13(54.16%)	1(4.16%)	95.84%*
Control group	48	15(31.25)	19(39.58)	14(29.17)	70.83%

Note: Compared with the control group, *P<0.05.

表 3 各组主要临床症状改善情况的比较(天, $\bar{x} \pm s$)Table 3 Comparison of the improvement of main clinical symptoms between different groups (days, $\bar{x} \pm s$)

Group	n	Hospital stay	Coughing reduces time	Body temperature recovery time	Rale disappearance time
Observation group A	24	9.45 $\pm$ 3.78*	3.19 $\pm$ 1.55*	3.42 $\pm$ 1.43*	5.30 $\pm$ 3.04*
Observation group B	24	8.21 $\pm$ 2.14*	2.64 $\pm$ 1.02**	2.94 $\pm$ 1.25 **	4.53 $\pm$ 1.97**
Control group	48	12.96 $\pm$ 3.57	3.98 $\pm$ 1.83	5.31 $\pm$ 2.74	8.19 $\pm$ 3.37

Note: Compared with the control group, *P<0.05, Compared with the observation group A, **P<0.05.

2.3 各组治疗前后血清炎症因子水平比较

治疗后,所有患者的血清白介素-6、肿瘤坏死因子- α 以及 HMGB1 水平均较治疗前明显降低(P<0.05),且观察组以上指

标均明显低于对照组(P<0.05),同时观察组 B 以上指标均明显低于观察组 A(P<0.05)。见表 4。

表 4 各组治疗前后血清炎症因子水平比较($\bar{x} \pm s$)Table 4 Comparison of the serum inflammatory factor levels between different groups before and after treatment($\bar{x} \pm s$)

Groups	n	IL-6 (ng/mL)		HMGB1 (μ g/mL)		TNF- α (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group A	24	89.04 $\pm$ 5.42	43.24 $\pm$ 4.53**	11.36 $\pm$ 3.17	6.47 $\pm$ 1.26**	152.33 $\pm$ 17.65	59.69 $\pm$ 6.36**
Observation group B	24	89.67 $\pm$ 5.42	33.28 $\pm$ 4.37**	12.03 $\pm$ 3.07	5.26 $\pm$ 1.11**	154.06 $\pm$ 18.31	48.22 $\pm$ 7.41**
Control group	48	89.78 $\pm$ 5.39	57.79 $\pm$ 5.85#	11.34 $\pm$ 3.29	7.59 $\pm$ 1.38#	152.38 $\pm$ 18.57	86.55 $\pm$ 8.49#

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

3 讨论

卒中为神经系统的一种常见病和多发病^[7,8],卒中患者治疗后期死亡的原因主要包括心肌梗死、肺部感染、肺栓塞、消化道出血、心律失常、下肢深静脉血栓形成以及泌尿系统感染等^[9-11]。SAP 指的是原本并未发生肺部感染的卒中患者患上感染性肺炎实质病炎症性疾病^[12,13]。重症卒中患者因病情较为危重,常常伴有吞咽障碍以及意识障碍,需要进行有创机械通气治疗,并发 SAP 的危险更高^[14-16]。研究显示 SAP 的发生率能高达 7%~22%^[17-19]。采取积极的预防和治疗措施能有效降低卒中后肺炎的发生率,且显著降低病死率,从而有助于患者的进一步康复^[20-22]。引发 SAP 的危险因素主要包括卒中后的肢体运动功能障碍、免疫抑制综合征、吞咽障碍以及气管内插管等各种有创性的诊疗手段^[23-25]。近年来,卒中诱导免疫抑制被认为是 SAP 的重要因素,以全身炎症反应为主导,免疫抑制为辅助^[26,27]。脑组织损伤后,小胶质细胞激活,引起 T 淋巴细胞释放炎症因子,炎症因子刺激交感神经,诱导抗炎因子增加,引发卒中后免疫抑制,加重炎症反应,免疫抑制随之加剧。因此,无论实施抗炎或免疫刺激的单一治疗均不足以有效逆转免疫炎症反应紊乱,抗炎与免疫刺激治疗并举的免疫调理治疗策略为有效治疗方案^[28,29]。

乌司他丁是广谱蛋白酶抑制剂,可以抑制弹性蛋白酶、胰蛋白酶、纤溶酶、脂肪酶以及淀粉酶等多种酶的活性可以增强溶酶体膜的稳定性;改善由于外界因素导致的免疫功能降低,促进蛋白质代谢,从而恢复患者的肾功能;抑制溶酶体膜的释放,减少炎症介质释放以及清除氧自由基的功能,保护机体的重要脏器^[28-30]。乌司他丁的上述特性使其广泛应用于临床急危重症患者的救治。本研究结果显示不同剂量乌司他丁治疗的 SAP 患者临床总有效率明显高于常规治疗的患者,提示乌司他丁治疗重症卒中相关性肺炎的临床效果较为显著,其原因可能与乌司他丁能有效抑制多靶点炎症反应相关。此外,不同剂量乌司他丁治疗的 SAP 患者的住院时间、咳嗽减轻时间、体温复常时间、啰音消失时间均明显短于常规治疗的患者,且高剂量乌司他丁治疗的 SAP 患者以上指标明显短于低剂量乌司他丁治疗的 SAP 患者,提示乌司他丁治疗可明显缩短 SAP 患者的病程。

研究表明乌司他丁可以有效清除氧自由基,降低血液粘稠度,减少缺血再灌注损伤,保护肾脏、肝脏以及肺等重要脏器的功能^[31];并通过快速缓解重症卒中相关性肺炎患者炎症反应,有利于加速患者恢复。本研究中,所有患者治疗后的血清白介素-6、肿瘤坏死因子- α 以及 HMGB1 水平均较治疗前明显降

低,且不同剂量乌司他丁治疗的SAP患者以上指标明显低于常规治疗的患者,同时高剂量乌司他丁治疗的SAP患者以上指标明显低于低剂量乌司他丁治疗的SAP患者,提示乌司他丁可以明显改善重症卒中相关性肺炎患者的炎症反应,并且存在剂量依赖。分析其原因为乌司他丁发挥治疗重症卒中相关性肺炎的作用机制与显著减少白介素-6以及肿瘤坏死因子- α 的释放^[32],从而阻止白细胞与炎症因子间的相互作用有关,降低对肺功能的损害^[33]。

综上所述,乌司他丁可加快改善卒中相关性肺炎患者的临床症状,可能与降低患者血清炎症因子IL-6、TNF- α 和HMGB-1水平有关。

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