乌司他丁在急性呼吸窘迫综合征的临床应用研究

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摘要 目的:观察乌司他丁(UTI)对急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)的临床应用。方法:选择我院ICU自2008年1月至2011年1月收治的160例ARDS患者作为研究对象,采用随机对照的方法,并且经患者或患者家属知情并签字同意分组。分为UTI组(A组)和对照组(B组)。两组均给予相同综合治疗措施,A组除综合治疗外还给予注射用乌司他丁,每次30万U,每日2次。分别记录两组患者开始治疗、治疗后第3天、治疗第7天的生命体征,动脉血气分析、血生化检查结果、并且记录患者在ICU治疗的转归,应用SPSS13.0软件对结果进行统计学分析。结果:经治疗3天A组呼吸频率低于B组,动脉血气分析提示两组PO_2、PO_2/FiO_2、SaO_2均有上升。比较后发现A组PO_2、PO_2/FiO_2、SaO_2高于B组($P<0.05$),两组PO_2、SaO_2比较有统计学差异。经治疗3天A组与B组生化指标比较、白细胞计数、肾功及血乳酸均有下降,有统计学差异,$P<0.05$。全部治疗结束后A组与B组死亡率比较(UTI组34.29%,对照组38.26%,$P=0.0097$)及机械通气时间比较(UTI组7.54± 3.27天,对照组11.78± 2.69天,$P=0.0086$),均有统计学差异。结论:大剂量UTI用于ARDS的临床治疗可有效改善患者氧合指数,减少机械通气时间,降低患者的病死率。

关键词:乌司他丁;急性呼吸窘迫综合征
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Clinical Study of Ulinastatin on the Patients with Acute Respiratory Distress Syndrome

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ABSTRACT Objective: To evaluate the clinical efficacy of ulinastatin (UTI) in the patients with acute respiratory distress syndrome (ARDS). Methods: 160 patients suffered from ARDS in our department from January 2008 to January 2011 were selected and divided into UTI group (group A) and control group (group B). Two groups of patients are given the same synthetical treatment. The patients from group A were received UTI 60 units intravenous in addition to the synthetical treatment. We recorded the patients' vital signs, arterial blood gas analysis, blood biochemistry test results and outcomes respectively on starting treatment, treatment for 3 days and 7 days. SPSS 13.0 software was applied for statistical analysis of the results. Results: In group A the respiratory rate was less than the control group after treatment for 3 days; arterial blood gas analysis showed that all the patients' PO_2, PO_2/FiO_2, SaO_2 were increased, PO_2, PO_2/FiO_2, SaO_2 of group A was higher than that of group B . PO2/FiO_2, SaO_2 had significant difference between the two groups after three days of treatment ($P<0.01$). The blood biochemistry test results had significant statistical difference between the two groups after three days of treatment, ($P<0.05$). The mortality rate had significant statistical difference between the two groups (group A 34.29%, group B 38.26 %, $P=0.0097$) after three days of treatment. The duration of mechanical ventilation had significant statistical difference between the two groups [group A 7.54± 3.27 day, group B 11.78 ± 2.69 day, $P=0.0086$] after three days of treatment. Conclusions: High-dose UTI for ARDS may improve the clinical treatment effect of oxygenation index and reduce the duration of mechanical ventilation.

Key words: Ulinastatin; Acute respiratory distress syndrome
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前言

急性呼吸窘迫综合征(ARDS)是在多种原发病的诱因作用下发生的严重急性呼吸衰竭。发病率及病死率非常高,虽然随着中国危重病医学专业的进展,近年来临床诊断越来越准确及时,而且治疗也越来越规范,但是其病死率仍然很高,据报道上海重症加强治疗病房收治的ARDS患者病死率竟然高达70%[1]。虽然经过大量的基础和临床研究,但是ARDS发生机制仍未明确,对于其具体发生机制目前大部分研究表明炎症反应是引起肺泡上皮和毛细血管屏障损伤的重要机制[2],研究认为炎症反应可能会造成肺血管内皮和肺泡上皮细胞通透性明显增强,使大量液体聚积在肺泡腔及肺间质,导致肺水肿及透明膜形成,阻碍了肺泡与血液间气体交换,使血液氧合不足,进而引起呼吸困难,甚至呼吸衰竭。而乌司他丁(UTI)是一种高效广谱的水解酶抑制剂,有许多文献报道其能抑制炎症介质及氧自由基的释放[3],从而改善ARDS患者的氧合情况,改善呼吸衰竭,改善肺功能,提高患者生存率。本实验在观察ARDS患者接受ICU

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综合治疗的基础上加用 UTI 治疗带来的益处，评价本药对这类患者肺组织的保护作用并探讨其可能的作用机制。

1 资料与方法

1.1 一般资料

研究对象为我院重症医学科自 2008 年 1 月至 2011 年 1 月收治的 160 例 ARDS 患者。本试验全部 ARDS 患者均符合中华医学会呼吸病学分会 2000 年制定的诊断标准[4]：①有 ARDS 的高危因素。②急性起病、呼吸频数和（或）呼吸窘迫。③低氧血症，动脉血氧分压（PO）/ 吸氧浓度（FiO_2）≤200。④胸部 X 线检查显示两肺浸润阴影。⑤肺毛细血管楔压（PAWP）≤ 18mmHg 或临床上能除外心源性肺水肿。入住 ICU 的 ARDS 患者根据随机对照原则分成两组，分别为 UTI 组（A 组）和对照组（B 组）。归纳后发现在 160 例患者中，A 组共 76 例，年龄 59± 34 岁；其中男 54 例，女 22 例。病因分类如下：重症肺炎 42 例，脓毒症 14 例，创伤 11 例，胸腹部术后 6 例，中毒 3 例，大量输血 1 例，肝移植术后 1 例。B 组共 84 例，患者年龄 64± 29 岁；其中男 46 例，女 38 例。病因分类如下：重症肺炎 48 例，脓毒症 20 例，创伤 9 例，胸腹部术后 4 例，中毒 2 例，肝移植术后 1 例。两组患者在年龄、性别及病因分类间比较无统计学差异。其中有些患者本来应该随机被分为 B 组，但是因为患者或其家属不同意应用乌司他丁而归为 B 组，所以两组例数有所差别。

1.2 方法

两组治疗措施除 UTI 外基本相同：包括积极治疗基础疾病、极纠正各种类型的休克、给予有效的抗感染治疗、局部病变行外科处理、维持水电解质及酸碱平衡、加强营养支持及对症治疗。另外一项针对呼吸衰竭的治疗就是机械通气。根据患者全身状况及呼吸衰竭程度给予有创或无创机械通气，其中有创机械通气共 140 例，包括经口气管插管 102 例，气管切开 38 例，均为气管插管一段时间后评估短期无法撤离呼吸机而改为气管切开。无创机械通气 20 例。有创机械通气时呼吸机辅助通气治疗模式，A/C 或 SIMV+PSV，其中 VT 6~8ml/kg，气道平台压不超过 30~35cmH_2O，呼吸末正压（PEEP）由 3cmH_2O 开始逐步增加，FiO_2 尽量维持在 60%以下，并使动脉血氧饱和度维持在 90%以上，动脉血气分压（PO）维持在 60mmHg 以上。两组患者的机械通气模式及参数设定无统计学差异。A 组除上述治疗外，使用注射用 UTI（广东天普生化医药股份有限公司，10 万 U/ 瓶，国药准字：H19990134）30 万 U 加入 0.9%氯化钠注射液静脉泵注 1h（患者或其家属已知情并签字同意），每日 2 次，连续应用 5~21 天。

1.3 监测项目

记录两组患者开始治疗、治疗后第 3 天、治疗第 7 天的生命体征、动脉血气分析，计算氧合指数，每 3 天复查胸片，记录每日液体出入量，血生化检查结果；记录患者在 ICU 治疗的转归，包括病死率、住 ICU 时间、住院时间、机械通气时间。

1.4 统计学分析

SPSS13.0 软件对结果进行统计学分析。数据采用 $\bar{x}\pm s$ 表示，计量资料均数之间的比较，采用 t 检验；两样本率之间的比较，采用 X^2 检验，率以百分数（%）表示。

2 结果

经治疗 3 天 A 组呼吸频率低于 B 组，动脉血气分析提示两组 PO_2、PO_2/FiO_2、SaO_2 均有上升。A 组 PO_2/FiO_2 高于 B 组（$P<0.05$），两组 PO_2、SaO_2 比较有统计学差异（表 1）。

经治疗 3 天 A 组与 B 组生化指标、白细胞计数、肾功及血乳酸均有下降，且两组间比较差异有统计学意义（表 2）。

全部治疗结束后 A 组与 B 组病死率（A 组 34.29%，B 组 38.26%，P=0.0097）及机械通气时间（A 组 7.54± 3.27 天，B 组 11.78± 2.69 天，P=0.0086）比较，均有统计学差异（表 3）。

表 1 两组患者治疗前后呼吸频率及血气分析比较（$\bar{x}\pm s$）

Table 1 Comparison of respiratory frequency and arterial blood gas analysis before and after treatment for three days in two groups

项目 (Item)	A 组 (Group A)			B 组 (Group B)		
	治疗前 (Before treatment)	治疗 3 天 (Treatment for 3 days)	治疗 7 天 (Treatment for 7 days)	治疗前 (Before treatment)	治疗 3 天 (Treatment for 3 days)	治疗 7 天 (Treatment for 7days)
Respiratory frequency (Beats/min)	31.8± 3.6	22.3± 2.9*△△	17.3± 2.7*	32.7± 3.1	29.6± 2.4	18.3± 2.8
PO_2 (mmHg)	55.4± 7.6	79.4± 9.1**△	87.6± 8.7 **△	58.6± 8.2	71.3± 6.4	84.5± 8.9
SO_2(%)	79.7± 5.9	92.4± 4.5**△	94.9± 1.6**△	78.6± 6.7	83.2± 3.7	90.8± 3.9
PO_2/FiO_2	135.4± 35.9	196.6± 30.1**△	224.5± 34.4**△	145.5± 39.6	179.5± 27.4	189.9± 29.5

注：与 B 组比较△P<0.05，△△P<0.01；与治疗前比较 *P<0.05，**P<0.01；

Note: compared with group B △P<0.05，△△P<0.01; compared with before treatment *P<0.05，**P<0.01.

3 讨论

ARDS 是由心源性以外的各种肺内外因素导致的急性、进行性缺氧性呼吸衰竭。ARDS 的发病机制有以下几个方面：①炎症／抗炎症[5,6]和凝血／纤溶系统失衡。炎症、氧化反应和机体免疫调节的紊乱导致多形核细胞、肺泡巨噬细胞等炎症细胞的激活引起大量促炎因子的释放。②水通道蛋白和酸敏感离子通道参与：水通道蛋白参与了 ARDS 的液体的异常转运。③分子遗传学的参与：遗传因素在 ARDS 的发生和发展中过程中有重要作用[7]。

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表 2 两组患者治疗前后血液学指标的比较($\bar{x}\pm s$)

Table 2 Comparison of blood biochemistry test results before and after treatment for three days in two groups

项目 (Item)	A 组 (Group A)			B 组 (Group B)		
	治疗前 (Before treatment)	治疗 3 天 (Treatment for 3 days)	治疗 7 天 (Treatment for 7 days)	治疗前 (Before treatment)	治疗 3 天 (Treatment for 3 days)	治疗 7 天 (Treatment for 7 days)
WBC 计数 (WBC count) ($\times 10^9$/L)	15.6± 5.4	12.4± 4.9*	9.7± 2.9	15.9± 4.8	14.3± 5.5	9.5± 3.8
BUN(mmol/L)	11.3± 3.4	12.5± 3.6*△	12.4± 5.2	12.1± 4.2	18.6± 2.6	13.1± 3.5
Scr(μmol/L)	156.3± 123.4	127.4± 113.6*△	118.7± 112.8	150.2± 132.7	144.2± 111.51	121.5± 110.17
ALT(μ/L)	32.2± 23.3	30.4± 19.9	34.8± 19.3	40.1± 23.5	35.4± 15.4	38.3± 13.9
血乳酸 (Blood lacic acid)	2.1± 1.3	1.8± 1.5*△	1.5± 0.9	2.4± 1.8	2.2± 1.1	1.6± 1.3

注:与 B 组比较△P<0.05,与治疗前比较 *P<0.05;

Note: compared with group B △P<0.05; compared with before treatment *P<0.05.

表 3 两组患者在治疗及预后情况的比较

Table 3 Comparison of prognosis before and after treatment in two groups

组别(Group)	例数(Noun)	机械通气天数(Mechanical ventilation days)(d)	住 ICU 时间(Duration of ICU stay)(d)	ICU 病死率(Mortality of ICU)(%)
Group A	76	7.45± 3.27	8.34± 4.02△	34.29△
Group B	84	11.78± 2.69	12.89± 2.35	38.26

注:与 B 组比较△P<0.01;

Note: compared with group B △P<0.01.

为了解 ALI/ARDS 流行病学现状。2002 年白春学和孙波教授研究的 108 例 ALI/ARDS 患者,最常见原发病为肺炎和脓毒症,ALI/ARDS 的住院病死率及 90d 病死率分别为 68.5%和 70.4%[8]。2004 年张淑文课题组调查发现 383 例 ALIARDS 患者,其中脓毒症、肺炎、外科术后和重症胰腺炎是 ALI/ARDS 最常见的病因,ALI/ARDS 的总病死率为 52.0%[9]。

目前临床上针对 ARDS 的治疗主要有以下几个方面[10]:①积极诊断和治疗原发基础疾病。②氧疗及机械通气纠正缺氧:机械通气时适合使用 PEEP 和小潮气量。③液体管理:在血压稳定和保证组织器官灌注前提下,液体出入量宜轻度负平衡。④营养支持与监护。UTI 可以抑制多种水解酶的活性。UTI 分子中还具有与细胞膜受体识别和结合的位点,加上第 10 位丝氨酸带负电荷的硫酸软骨素糖链,使其表现出稳定细胞膜和溶酶体膜的生理功能[11]。UTI 通过抑制过度的炎症反应、改善循环器官灌注,而发挥保护组织器官的作用。UTI 的临床应用最早被用于重症急性胰腺炎的治疗。现在 UTI 还应用于治疗全身炎症反应综合征及多器官功能障碍综合征[12];休克及弥漫性血管内凝血[13,14]以及 ALIA/ARDS[15]。并且 UTI 还可以减轻肝移植围术期炎性反应和新肝缺血再灌注的损伤[16];减轻体外循环术后肺水肿,改善术后肺气体交换,防止肺功能恶化,并且减少肾小管的功能障碍发生,改善肾血流[17,18]。

本文主要研究 UTI 治疗 ARDS。既往研究证实,UTI 可以从多个方面减轻体外循环中各种因素对肺的损害,其中包括减少炎症细胞的迁移与聚集;抑制肿瘤坏死因子 -α 的合成以及抑制中性粒细胞趋化和血小板聚集以稳定溶酶体膜的作用,从而可以减轻体外循环中各种因素对肺的损害。本研究提示应用足量的 UTI 可明显改善血气指标,并且改善生化指标,减少机械通气及住 ICU 的时间,降低病死率。

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