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乌司他丁联合连续性肾脏替代疗法对急性重症胰腺炎患者炎症因子及免疫球蛋白的影响

木塔里甫·买合木提[1] 美克拉依·阿不都克里木[1]
买买提艾力·买托合提[2] 麦克热阿依·依米提[3] 肖 东[1△]
（1 新疆维吾尔自治区人民医院重症医学二科 新疆 乌鲁木齐 830001；
2 新疆维吾尔自治区和田地区人民医院急救中心 新疆 和田 848000；
3 新疆维吾尔自治区人民医院中心手术室 新疆 乌鲁木齐 830001）

摘要 目的：探讨乌司他丁联合连续性肾脏替代疗法（CRRT）对急性重症胰腺炎（SAP）患者炎症因子及免疫球蛋白的影响。**方法：**选取 2013 年 2 月至 2017 年 8 月期间我院收治的 SAP 患者 148 例为研究对象，根据随机数字表法分为对照组（n=74）与观察组（n=74），两组均给予常规治疗以及乌司他丁药物治疗，观察组则在此基础上联合 CRRT 治疗，两组均治疗 28d 后，观察并比较两组患者的临床疗效，治疗前后白细胞介素 -6（IL-6）、C- 反应蛋白（CRP）、降钙素原（PCT）及 IgA、IgG 、IgM 水平的变化。**结果：**观察组的总有效率为 90.54%（67/74），显著高于对照组的 67.57%（50/74）（*P<0.05*）。两组患者治疗 28d 后血清 IL-6、CRP、PCT 水平较治疗前均显著降低，且观察组低于对照组（*P<0.05*）。两组患者治疗 28d 后 IgA、IgG、IgM 较治疗前均显著升高，且观察组 IgG、IgM 显著高于对照组（*P<0.05*）。治疗后观察组 ICU 住院时间短于对照组（*P<0.05*），两组患者病死率比较差异无统计学意义（*P>0.05*）。**结论：**乌司他丁联合 CRRT 治疗 SAP 效果显著，可有效降低患者炎症因子水平，调节免疫系统，改善患者预后，值得临床推广应用。

关键词：乌司他丁；连续性肾脏替代疗法；急性重症胰腺炎；炎症因子；免疫球蛋白
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Effects of Ulinastatin Combine with Continuous Renal Replacement Therapy on Inflammatory Factors and Immunoglobulins in Patients with Severe Acute Pancreatitis

Mutalifu·Maihemuti[1], Meikelayi·Abudukelimu[1], Maimaitiaili·Maituoheti[2], Maikereayi·Yimiti[3], XIAO Dong[1△]
(1 Second Department of ICU,The People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, 830001, China;
2 Emergency Center, Hotan Prefecture People's Hospital of Xinjiang Uygur Autonomous Region, Hotan, Xinjiang, 848000, China;
3 Operation Room, The People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, 830001, China)

ABSTRACT Objective: To investigate the effect of ulinastatin combine with continuous renal replacement therapy (CRRT) on inflammatory factors and immunoglobulin in patients with severe acute pancreatitis (SAP). **Methods:** 148 SAP patients who were treated in our hospital from February 2013 to August 2017 were selected as the research object. They were divided into control group (n=74) and observation group (n=74) according to randomly number table, the two groups were given routine treatment and ulinastatin treatment, the observation group based on the combination of CRRT treatment, after treatment of 28d, the clinical efficacy of two groups, the levels of interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT) and IgA, IgG, IgM levels before and after treatment were compared. **Results:** The total effective rate of the observation group was 90.54% (67/74), which was significantly higher than 67.57% (50/74) of the control group (*P<0.05*). The levels of serum IL-6, CRP and PCT in the two groups after treatment were significantly lower than those before treatment, and the observation group was lower than that of the control group (*P<0.05*). The IgA, IgG and IgM of the two groups after treatment of 28d were significantly higher than those before treatment, the IgG and IgM in the observation group were significantly higher than those in the control group (*P<0.05*). The hospitalization time of ICU in observation group after treatment was shorter than that in control group (*P<0.05*), there was no significant difference in fatality rate between the two groups (*P>0.05*). **Conclusion:** Ulinastatin combine with CRRT is effective in the treatment of SAP, which can effectively reduce the level of inflammatory factors,regulate the immune system and improve the prognosis of patients, which is worthy of clinical application.

Key words: Ulinastatin; Continuous renal replacement therapy; Severe acute pancreatitis; Inflammatory factors; Immunoglobulin
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作者简介：木塔里甫·买合木提（1982-），男，硕士，主治医师，从事重症医学方面研究，E-mail: yubgtg@163.com
△ 通讯作者：肖东（1964-），女，硕士，主任医师，从事重症医学方面的研究，E-mail: outerg@163.com
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前言

急性胰腺炎(Acute pancreatitis,AP)是指由于胰腺内的胰酶被激活导致胰腺组织出现水肿、充血甚至坏死等一系列炎症反应的疾病[1,2]。其中急性重症胰腺炎(Severe acute pancreatitis,SAP)是 AP 的一种特殊类型,病理特征表现为胰腺弥漫性出血以及组织坏死[3,4]。该病发病迅速,病情凶险,且多伴有多种器官衰竭并发症,病死率极高,给患者的生命安全带来极大的危害[5,6]。目前 SAP 的主要治疗方式有药物治疗和手术治疗,手术治疗术后并发症较多,病死率极高,严重影响患者预后。相关研究表明[7,8],乌司他丁可抑制炎性介质的释放,避免细胞损伤,改善微循环,目前已成为治疗 SAP 的常用药物之一。连续性肾脏替代疗法(Continuous renal replacement therapy,CRRT)是一种血液净化治疗方式,可清除循环中存在的毒素和中分子物质[9,10]。目前临床关于乌司他丁联合 CRRT 治疗 SAP 的相关报道较多,但对患者炎症因子及免疫球蛋白的考察较少,因此,本研究通过研究采用乌司他丁联合 CRRT 治疗 SAP 的临床效果,以及上述治疗方式对患者炎症因子及免疫球蛋白的影响,现报道如下。

1 资料与方法

1.1 一般资料

选取 2013 年 2 月至 2017 年 8 月期间来我院诊治的 148 例 SAP 患者为研究对象。纳入标准:(1)均符合中华医学会制定的《中国急性胰腺炎诊治指南》[11]中有关 SAP 的诊断标准,经 CT 或彩超确诊,(2)具有以下并发症如胰腺脓肿、坏死,假性囊肿;(3)临床表现为血尿淀粉酶异常,伴有发热、恶心、上腹疼痛等;(4)患者发病后 3d 内入院;(5)急性生理学与慢性健康状况评分系统(APACHEⅡ)超过 8 分者[12];(6)符合 CRRT 手术指征;(7) 患者及其家属知情本研究并签署知情同意书。排除标准:(1)伴自身免疫性疾病者;(2)对本次研究药物过敏者;(3)入院前因其他疾病接受过 CRRT 治疗者;(4) 肝肾功能严重不全者;(5)伴有恶性肿瘤、精神疾病者。根据随机数字表法分为对照组(n=74)与观察组(n=74)。其中对照组男 41 例,女 33 例,年龄 33～65 岁,平均年龄(42.35± 3.23)岁;APACHEⅡ评分为 12~21 分,平均(15.31± 2.55)分;发病原因:胆石症 31 例,高脂血症 19 例,饮酒 14 例,其他 10 例。观察组男 39 例,女 35 例,年龄 32～66 岁,平均年龄(43.75± 4.12)岁;APACHEⅡ评分为 13~20 分,平均(16.02± 3.03)分;发病原因:胆石症 30 例,高脂血症 20 例,饮酒 15 例,其他 9 例。两组一般资料比较无差异(*P>0.05*)。我院伦理委员会已批准此次研究。

1.2 研究方法

两组患者入院行包括禁食水、营养支持、脏器功能检测、胃肠减压、抗菌抗感染、积极补液维持水电解质平衡等的常规治疗。同时两组均应用乌司他丁(广东天普生化医药股份有限公司;国药准字:H19990134;规格:10 万单位)治疗,20 万单位 / 次,加入 50 mL 0.9%的生理盐水中持续静脉滴注,3 次 /d,每次持续 1h 以上。两组均连续治疗 28d。观察组则在治疗的 72h 内加入 CRRT 治疗,CRRT 血管通路选择股静脉或者颈内静脉,过滤机采用德国费森尤斯 4008B 血液滤过机,选择连续性静脉 - 静脉血液滤过 (continuousvenous venous hemofiltration,CVVH)模式,透析器为聚砜膜,膜面积 1.3 m^2。治疗一次置换液总量为 50~60 L,采取稀释方式输入,流速为 40~50 mL/(kg·h),血流量则保持在 150~200 mL/min,超滤率、超滤量由患者的实际情况决定,针对存在活动性出血的患者进行无肝素透析治疗,而针对有出血倾向患者,则以相同剂量的鱼精蛋白与肝素进行有肝素透析治疗,透析过程以生理盐水为冲洗液定期对管道进行冲洗,CRRT 治疗次数应视患者情况而定,一般不超过 2 次。

1.3 观察指标

1.3.1 观察并比较两组患者治疗 28d 后的临床疗效 疗效评价标准[13]:(1)痊愈:患者基本临床症状消失,经 CT 或彩超均提示正常,血和尿淀粉酶恢复正常;(2)显效:14d 内患者基本临床症状有所缓解,血和尿淀粉酶较治疗前显著降低;(3)有效:28d 内患者基本临床症状有所缓解,血和尿淀粉酶较治疗前显著降低;(4)无效:患者基本临床症状无变化甚至加重,血和尿淀粉酶较治疗前无明显变化或升高。总有效率计算方式为痊愈率、显效率以及有效率之和。

1.3.2 观察两组患者治疗前与治疗 28d 后炎症因子及免疫球蛋白的变化 分别于治疗前及治疗 28d 后采集患者清晨空腹静脉血 6 mL,3000 r/min 离心 8 min,离心半径 6cm,取上清液置于 -70℃温箱中待测。采用酶联免疫吸附试验检测血清白细胞介素 -6(Interleukin -6,IL-6)、C- 反应蛋白(C- reactive protein,CRP)水平,采用化学发光分析法检测降钙素原(Procalcitonin,PCT)水平,试剂盒均购自深圳晶美生物科技有限公司,采用免疫比浊法检测 IgA、IgG 、IgM, 试剂盒购自武汉博士德有限公司,均严格按照试剂盒说明书进行操作。其中检测 CRP 的全自动免疫化学分析仪来源于美国贝克曼公司, 检测 PCT 的化学发光分析仪来源于德国 BRAHMS 公司。

1.3.3 术后指标 观察并对比两组患者ICU 住院时间、病死率。

1.4 统计学方法

本研究数据均采用 SPSS20.0 软件进行检测分析, 临床总有效率、年龄构成、病死率等计数资料以率表示,采用 x^2 检验,IL-6、CRP、PCT 水平及免疫球蛋白水平、ICU 住院时间等计量资料用($\bar{x}\pm s$)表示,实施 t 检验,检验标准设置为 $\alpha=0.05$。。

2 结果

2.1 两组患者临床疗效比较

对照组的总有效率为 67.57%, 观察组的总有效率为 90.54%,观察组总有效率较对照组明显升高(*P<0.05*),详见表 1。

2.2 两组患者治疗前后 IL-6、CRP、PCT 水平比较

两组患者治疗前血清 IL-6、CRP、PCT 水平比较差异无差异(*P>0.05*),治疗 28d 后血清 IL-6、CRP、PCT 水平较治疗前均显著降低,且观察组低于对照组(*P<0.05*),详见表 2。

2.3 两组患者治疗前后 IgA、IgG、IgM 水平比较

两组患者治疗前 IgA、IgG、IgM 比较无差异(*P>0.05*),治疗 28d 后 IgA、IgG、IgM 较治疗前均显著升高,且观察组 IgG、IgM 显著高于对照组(*P<0.05*),观察组治疗 28d 后 IgA 与对照组比较无差异(*P>0.05*)。详见表 3。

表 1 两组患者临床疗效比较[n(%)]

Table 1 Comparison of clinical efficacy between the two groups [n(%)]

Groups	n	Recovery	Apparent effective	Effective	Invalid	Total effective rate
Control group	74	22(29.73)	19(25.68)	9(12.16)	24(32.43)	50(67.57)
Observation group	74	37(50.00)	19(25.98)	11(14.86)	7(9.46)	67(90.54)
x^2						11.793
P						0.001

表 2 两组患者治疗前后 IL-6、CRP、PCT 水平比较($\bar{x}\pm s$)

Table 2 Comparison of the levels of IL-6, CRP, PCT between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	IL-6(ng/mL)		CRP(ng/mL)		PCT(ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment of 28d	Before treatment	After treatment of 28d
Control group	74	90.18± 6.42	46.03± 4.76*	167.71± 60.63	141.80± 30.59*	5.57± 1.03	2.64± 1.22*
Observation group	74	91.34± 6.06	27.21± 5.13*	166.16± 61.53	119.64± 29.55*	5.42± 0.78	1.61± 0.82*
t		1.130	23.134	0.154	4.482	0.999	6.028
P		0.260	0.000	0.878	0.000	0.320	0.000

Note: compared with before treatment,*$P<0.05$.

表 3 两组患者治疗前后 IgA、IgG、IgM 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the levels of IgA, IgG, IgM between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n	IgA(g/mL)		IgG(g/mL)		IgM(g/mL)	
		Before treatment	After treatment of 28d	Before treatment	After treatment of 28d	Before treatment	After treatment of 28d
Control group	74	2.31± 0.13	3.11± 0.12*	9.13± 1.26	15.46± 4.92*	1.35± 0.62	1.87± 0.84*
Observation group	74	2.36± 0.73	3.20± 0.62*	9.11± 1.27	21.74± 5.86*	1.27± 0.48	2.98± 0.52*
x^2		0.580	1.226	0.096	7.060	0.878	9.662
P		0.563	0.222	0.924	0.000	0.372	0.000

Note: compared with before treatment, *$P<0.05$.

2.4 两组患者 ICU 住院时间、病死率比较

治疗后观察组 ICU 住院时间优于对照组($P<0.05$),两组患者病死率比较无差异($P>0.05$),详见表 4。

表 4 两组患者 ICU 住院时间、病死率比较

Table 4 Comparison of ICU hospitalization time and fatality rate between two groups of patients

Groups	n	ICUhospitalization time(d)	Fatality rate(%)
Control group	74	10.68± 2.67	5(6.76)
Observation group	74	7.26± 2.73	3(4.05)
t/x^2		7.704	0.529
P		0.000	0.467

3 讨论

SAP 发病机制较为复杂,有学者指出其主要发病机制为胰腺内胰酶被激活,从而产生的胰腺组织坏死、出血等一系列炎症反应,导致患者营养不良、代谢紊乱,促使机体免疫功能下降[14-16]。血清 IL-6、CRP、PCT 等炎症因子的过度释放,易使血管过度扩张,血管通透性加强,从而机体微循环产生障碍,损伤胰腺以及其他脏器[17-19]。相关研究表明[20,21],血清 IL-6、CRP、PCT 等炎症因子水平升高与 SAP 的严重程度及预后关系密切。因此,如何迅速降低炎症因子水平可成为 SAP 的治疗方向之一。免疫球蛋白是指有抗体活性的动物蛋白,由 B 淋巴细胞分泌,可分为 IgA、IgG、IgM、IgD、IgE 五类[22]。其中 IgA 可抑制病原体增殖,当机体发生感染时,IgA 大量消耗,导致免疫功能降低[23];IgG 具有中和内外毒素的作用[24];IgM 是最高效能的抗生物抗体,在机体早期防御中起重要作用[25]。在治疗过程中如何增强机体免疫功能,亦成为临床工作者们的研究热点之一。近年来,CRRT 已逐渐成为危重症患者的救治措施之一,有研究结果表明[26],CRRT 可有效清除炎症因子,减轻全身炎性反应,阻止炎

症介质对机体的再次损伤,有利于 SAP 临床治疗以及预后。而乌司他丁是一种高效、活性强的广谱酶抑制剂,有报道指出乌司他丁治疗 SAP 可缩短住院时间,减轻炎症反应,从而提高临床疗效[27-29]。

本次研究结果表明观察组的总有效率为 90.54%(67/74),显著高于对照组的 67.57%(50/74)(*P<0.05*),且治疗后观察组 ICU 住院时间短于对照组(*P<0.05*)。提示乌司他丁联合 CRRT 治疗较单纯乌司他丁治疗效果更佳,可有效改善患者预后并缩短住院时间,提高存活率。本次研究还显示两组患者治疗 28d 后血清 IL-6、CRP、PCT 水平均显著低于治疗前,且观察组低于对照组(*P<0.05*)。表明乌司他丁联合 CRRT 治疗可有效降低血清 IL-6、CRP、PCT 水平,抑制机体炎症反应,改善患者临床症状。赵珊珊等研究结果表明[30],乌司他丁联合 CRRT 治疗 SAP 可有效降低机体炎症因子水平,本研究与其结果基本一致。分析其原因主要是乌司他丁是一种提取自健康男性尿液中的蛋白抑制剂,安全性较高,其作用机制表现为抑制溶酶体膜、炎症因子的释放,减少组织损伤,改善微循环。另 CRRT 可滤过、吸附大中分子物质以及炎症介质,且 CRRT 渗透压较小,血流动力学稳定,透析时溶质清除量更大,同时创造了良好的营养支持条件,促进患者尽快恢复健康。本研究通过对两组患者免疫球蛋白比较发现,两组患者治疗 28d 后 IgA、IgG、IgM 较治疗前均显著升高,且观察组 IgG、IgM 显著高于对照组(*P<0.05*)。表明两组患者经治疗后,IgA、IgG、IgM 等免疫球蛋白均提高,提示两种治疗方式均可改善机体免疫功能,且乌司他丁联合 CRRT 治疗 SAP 改善程度更佳,通过有效改善机体、肠粘膜的免疫功能,使患者抵抗力增强。

综上所述,乌司他丁联合 CRRT 治疗 SAP 临床效果较好,可有效抑制炎症因子释放,并通过调节免疫系统维持体内微循环,具有较高的临床应用价值。

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