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乌司他丁联合生长抑素辅助连续血液净化对重症胰腺炎患者血清HSP70、IL-15、HMGB1水平的影响*

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摘要 目的：研究乌司他丁联合生长抑素辅助连续血液净化对重症胰腺炎患者血清热休克蛋白70(Heat shock protein 70，HSP70)、白介素-15(Interleukin-15，IL-15)、高迁移率族蛋白B1(high mobility group protein1，HMGB1)水平的影响。**方法：**选择2018年5月~2019年10月在我院就诊的82例重症胰腺炎患者，依据入院先后顺序分为对照组(40例)和研究组(42例)。对照组采用生长抑素辅助连续血液净化治疗，研究组采用乌司他丁联合生长抑素辅助连续血液净化治疗。观察和比较两组临床疗效，症状改善时间，治疗前后血清白蛋白(albumin，Alb)、尿素氮(Urea nitrogen，BUN)、血肌酐(Serum creatinine，Scr)、血淀粉酶(amylase，AMY)、HSP70、IL-15、HMGB1水平及急性生理学及慢性健康状况(APACHEⅡ)评分的变化情况和不良反应的发生情况。**结果：**治疗后，研究组总有效率显著高于对照组(P<0.05)，症状改善时间及住院时间均少于对照组(P<0.05)。治疗后，两组Alb均较治疗前显著上升，BUN、Scr、AMY、APACHEⅡ评分、血清HSP70、IL-15、HMGB1水平均较治疗前明显下降，研究组以上指标的变化较对照组更明显(P<0.05)。两组不良反应总发生率比较无统计学差异(P>0.05)。**结论：**乌司他丁联合生长抑素辅助血液净化有利于重症胰腺炎患者病情恢复，减轻临床症状，降低HSP70、IL-15和HMGB1水平。

关键词：重症胰腺炎；连续血液净化；乌司他丁；生长抑素；热休克蛋白70；白介素-15；高迁移率族蛋白B1

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Effects of Ulinastatin Combined with Somatostatin Assisted Continuous Blood Purification on the Serum HSP70, IL-15, HMGB1 Levels in Patients with Severe Pancreatitis*

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ABSTRACT Objective: To study the effect of ulinastatin combined with somatostatin on serum 70 (Heat shock protein 70 (HSP70), interleukin-15 (IL-15) and B1(high mobility group protein1 B1 (HMGB1) levels in patients with severe pancreatitis. **Methods:** 82 patients with severe pancreatitis admitted to our hospital from may 2018 to October 2019 were selected and divided into control group (40 cases) and research group (42 cases) according to the admission order. The control group was treated with somatostatin assisted continuous blood purification, while the research group was treated with ulinastatin combined with somatostatin assisted continuous blood purification. The clinical efficacy, improvement time of symptoms, changes of serum albumin (ALB), Urea nitrogen (BUN), Serum creatinine (Scr), serum amylase (AMY), HSP70, IL-15, HMGB1, acute physiology and chronic health status (APACHEⅡ II) scores and occurrence of adverse reactions were observed and compared between the two groups before and after treatment. **Results:** After treatment, the total effective rate of the research group was significantly higher than that of the control group (P<0.05), and the time of symptom improvement and hospitalization were lesser than that of the control group (P<0.05). After treatment, Alb in both groups increased significantly compared with that before treatment. BUN, Scr, AMY, APACHEⅡ scores, serum HSP70, IL-15, HMGB1 levels were significantly decreased compared with that before treatment. the changes of above indexes in the research group were more obvious than those in the control group (P<0.05). There was no significant difference in the total incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Ulinastatin combined with somatostatin assisted blood purification is beneficial to the recovery of patients with severe pancreatitis, alleviating clinical symptoms and reducing the levels of HSP70, IL-15 and HMGB1.

Key words: Severe Pancreatitis; Continuous blood purification; Ulinastatin; Somatostatin; Heat shock protein 70; Interleukin-15; high mobility group protein

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前言

重症胰腺炎为急性胰腺炎的危重类型，病情险恶、并发症多，且病死率高[1,2]。持续血液净化为重症胰腺炎的主要治疗手段，其可连续性清除溶质，在肺气体交换、血流动力学稳定及减轻液体超负荷等方面有较好的疗效，能够起到脏器功能支持作用[3]。目前，药物支持治疗在重症胰腺炎治疗中也有重要作用，生长抑素作为肽激素，主要分布在垂体后叶、胃肠道神经、胃黏膜等系统，其可减轻患者临床症状，减少并发症，降低病死率[4]。

乌司他丁为蛋白酶抑制剂，可抑制多种糖、蛋白及脂类水解酶活性，减轻胰酶对胰腺组织的溶解及破坏，延缓病情进展[5]。Han A H 等[6]研究表明乌司他丁对阻断急性胰腺炎休克的发生及进展有重要作用，能够减少局部及远处脏器损伤。研究显示[7]急性胰腺炎的发生和大量细胞因子所致的级联反应有直接关联。热休克蛋白 70(HSP70)为机体主要应激蛋白之一，机体发生生理及病理应激时其水平能够快速增加，Arriaga-Pizano L 等[8]研究显示 HSP70 可能是早期参与胰腺和胰外请组织细胞抗损伤的重要因子。国外研究报道[9]白细胞过度激活是导致胰腺病情加重、多器官功能衰竭和死亡的重要因素，白介素 -15(IL-15)能够导致血管内皮损伤，增加通透性，产生血容量不足、微循环障碍等表现。高迁移率族蛋白 B1(HMGB1)为新型晚期的促炎性因子，和胰腺炎的发生发展有关[10]。因此，本研究主要探讨了乌司他丁联合生长抑素辅助连续血液净化对重症胰腺炎患者血清 HSP70、IL-15、HMGB1 水平的影响。

1 资料与方法

1.1 一般资料

选择 82 例重症胰腺炎患者，纳入标准：符合重症急性胰腺炎诊断标准[11]：具备急性胰腺炎的生化改变及临床表现，并满足以下任一项：① CT 分级为 D、E 级；② 急性生理学及慢性健康状况 (acute physiology and chronic health evaluation scoring system，APACHEⅡ)评分在 8 分以上；③ 器官衰竭，胰腺囊肿、假性囊肿、胰腺坏死等并发症；无手术指征；年龄 22~66 岁。排除标准：急性肠炎、肠梗阻；严重心肝肾基础疾病；恶性肿瘤；妊娠、哺乳期妇女；凝血功能异常；血液净化禁忌证。

82 例患者依据入院先后顺序分为对照组(40 例)和研究组(42 例)。对照组男 22 例，女 18 例；年龄(46.19± 6.71)岁；病因：胆源性 15 例，高脂血症 8 例，酗酒 6 例，其他 11 例。研究组男 17 例，女 25 例；年龄(45.61± 6.98)岁；病因：胆源性 18 例，高脂血症 9 例，酗酒 7 例，其他 8 例。两组一般资料比较无统计学差异(P>0.05)，具有可比性。

1.2 治疗方法

所有患者均参照重症急性胰腺炎诊治指南进行治疗，包含禁饮食、镇静、止痛、预防感染、营养支持、液体复苏、胃肠减压、维持水电介质平衡等治疗。并给予连续血液净化治疗：通过深静脉置管创建血管通路，选择血液净化系统、聚砜膜血滤器进行，选择碳酸氢盐配方作置换液，前稀释方式输入，置换液量为 50~100 mL/kg·h^{-1}，血流量为 200~300 mL/min，治疗时间为 12~24 h/ 次，并以低分子肝素抗凝。

对照组在此基础上给予生长抑素治疗，持续泵入 3 mg 生长抑素 +250 mL 生理盐水，每天 2 次，持续 14 天；研究组基于对照组联合乌司他丁治疗，持续泵入 10 万单位乌司他丁联合 5%葡萄糖 500 mL，每天 2 次，持续 7 天，再依据患者体征、症状改变调整乌司他丁用量，持续治疗 14 天。

1.3 观察指标

(1)临床疗效：治疗 5 天内临床症状、体征明显改善，血淀粉酶浓度恢复正常为显效；临床症状、体征有所改善，血淀粉酶浓度较治疗前下降，但未恢复正常为有效；未达到以上标准或死亡为无效，显效率、有效率为总有效率。(2)治疗前及治疗 7 天时生命体征，用全自动生化分析仪测定治疗前、治疗 7 天时白蛋白(Alb)、尿素氮(BUN)及血肌酐(Scr)水平，用速率法测定血淀粉酶 (AMY) 水平，用酶联免疫吸附法测定 HSP70、IL-15、HMGB1 水平。(3)APACHEⅡ评分[12]：包含慢性健康状况、年龄、急性生理评分，总分为 0~71 分，病情程度与分数呈正比。(4)观察两组治疗期间的不良反应。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料用($\bar{x}$± s)表示，组间比较选用 t 检验，计数资料用[例(%)]表示，组间比较用 x^2 检验比较，以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床疗效的分析

治疗后，研究组总有效率高于对照组 (90.48% vs. 70%，P<0.05)，见表 1。

表 1 两组临床疗效分析[例(%)]

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

Groups	n	Take effect	Effective	Invalid	Total Effective Rate
Control group	40	20(50.00)	8(20.00)	12(30.00)	28(70.00)
Research group	42	30(71.43)	8(19.05)	4(9.52)	38(90.48)a

Note: vs the control group, [a]P<0.05.

2.2 两组症状改善时间分析

研究组症状改善时间及住院时间均少于对照组(P<0.05)，见表 2。

2.3 两组治疗前后生命体征分析

治疗前，两组生命体征指标比较无统计学差异(P>0.05)；治疗后，两组稳定、呼吸频率、心率、平均动脉压均下降，且研究组低于对照组(P<0.05)，见表 3。

2.4 两组治疗前后 Alb、BUN 和 Scr 分析

治疗前，两组 Alb、BUN 和 Scr 比较无统计学差异(P>0.05)；治疗后，两组 Alb 均上升，BUN 及 Scr 均下降，研究组以上指标的变化更明显(P<0.05)，见表 4。

表 2 两组症状改善时间分析($\bar{x}\pm s$)

Table 2 Analysis of the symptom improvement time of the two groups($\bar{x}\pm s$)

Groups	n	Intestinal function recovery time(d)	Fever disappearance time(d)	Urine amylase recovery time(d)	Blood amylase recovery time(d)	Hospitalization time(d)
Control group	40	7.14± 0.92	6.11± 0.81	7.03± 0.83	6.05± 0.76	21.05± 3.41
Research group	42	5.98± 0.64[a]	4.19± 0.52[a]	5.41± 0.67[a]	4.29± 0.51[a]	16.27± 2.44[a]

vs the control group, [a]P<0.05.

表 3 两组治疗前后生命体征分析($\bar{x}\pm s$)

Table 3 Analysis of vital signs before and after treatment in the two groups($\bar{x}\pm s$)

Groups	n	Time	Body temperature (℃)	Respiratory frequency (times/minute)	Heart rate (times/minute)	Mean arterial pressure(mmHg)
Control group	40	Before treatment	39.75± 1.34	34.19± 4.02	132.16± 16.02	94.29± 14.05
		After treatment	37.81± 1.33	28.41± 3.75	118.43± 15.95	88.12± 13.29
Research group	42	Before treatment	39.91± 1.42	33.58± 4.96	130.91± 16.24	93.48± 15.02
		After treatment	36.25± 1.04	25.27± 3.22	105.77± 13.22	84.26± 11.09

vs the control group, [a]P<0.05; vs the same group before treatment, [b]P<0.05.

表 4 两组治疗前后 Alb、BUN 和 Scr 分析($\bar{x}\pm s$)

Table 4 Analysis of Alb, BUN and Scr before and after treatment in the two groups($\bar{x}\pm s$)

Groups	n	Time	Alb(g/L)	BUN(mmol/L)	Scr(μmol/L)
Control group	40	Before treatment	28.44± 3.21	20.17± 2.61	397.55± 45.29
		After treatment	35.03± 4.03[b]	9.53± 1.52[b]	99.63± 15.08[b]
Research group	42	Before treatment	27.85± 3.67	19.54± 2.84	402.04± 42.16
		After treatment	39.71± 4.81[ab]	7.95± 1.03[ab]	81.65± 11.24[ab]

vs the control group, [a]P<0.05;vs the same group before treatment, [b]P<0.05.

2.5 两组治疗前后 AMY 和 APACHEⅡ评分分析

治疗前,两组 AMY 和 APACHEⅡ评分比较无统计学差异(P>0.05);治疗后,两组 AMY、APACHEⅡ评分下降,研究组低于对照组(P<0.05),见表 5。

表 5 两组治疗前后 AMY 和 APACHEⅡ评分分析($\bar{x}\pm s$)

Table 5 Analysis of AMY and APACHEⅡ score before and after treatment in the two groups($\bar{x}\pm s$)

Groups	n	Time	AMY(U/L)	APACHEⅡ score(points)
Control group	40	Before treatment	3419.86± 396.51	21.03± 3.42
		After treatment	250.82± 30.09[b]	12.03± 1.75[b]
Research group	42	Before treatment	3406.15± 405.81	20.63± 3.71
		After treatment	139.71± 15.29[ab]	9.11± 1.42[ab]

vs the control group, [a]P<0.05; vs the same group before treatment, [b]P<0.05.

3 讨论

重症胰腺炎为危重急腹症，近年来其发生率呈上升趋势，已成为危及机体生命安全的主要疾病之一[13,14]。尽管近年来重症胰腺炎的综合治疗已取得较大进展，但其病死率仍较高[15]。连续性血液净化通过模仿机体肾小球滤过原理,以对流、吸附等方式清除血液中的代谢产物及炎症介质，终止瀑布反应,阻断病情进展[16];通过模拟肾小管重吸收,补充置换液回体内,纠正酸碱、水、电解质失衡,保持内环境稳定,且可改善脏器功能及组织氧代谢[17];明显改善单核细胞分泌功能,纠正其过度抑制或过度活跃状态,重建机体免疫系统内环境平稳;减轻组织间质水肿,减小呼吸膜厚度,加强气体弥散,改善组织氧利用,为重症患者的治疗创造良好条件[18]。尽管如此,但单一的连续性血液净化治疗模式对部分患者的治疗效果仍不理想,因此临床存在一定局限性。

生长抑素是重症胰腺炎的常用治疗药物，能够抑制胰岛素、生长激素和胰高血糖素的分泌,且可抑制胃泌素和胃蛋白酶释放[19,20]。但有研究报道[21,22]单用生长抑素治疗的重症胰腺炎

患者死亡率较高,预后不甚理想。乌司他丁可稳定机体内细胞膜中酶生物活性,调节细胞内、外离子稳定,预防细胞内钙离子超负荷,改善局部血液灌注,促进受损组织器官功能及形态的恢复[23]。乌司他丁还可降低肠源性内毒素吸收,抑制机体炎症反应,纠正负氮平衡,改善机体循环,降低胰腺组织和周围器官损伤[24]。Wang Y 等[25]研究发现乌司他丁能够减少心肌抑制因子合成,从而减轻胰腺炎病理损伤,尽可能的降低全身多器官功能损伤风险。本研究数据显示联合乌司他丁治疗组总有效率相对较高,且此组肠功能恢复时间、发热消失时间、尿淀粉酶恢复时间、血淀粉酶恢复时间和住院时间相对较少,生命体征恢复指标相对较优,提示在连续血液净化基础上联合乌司他丁及生长抑素能够缩短症状改善时间,促进机体恢复,提高临床疗效,可能原因为联合用药能够抑制胰酶激活和释放,阻断胰腺内消化过程。

Alb 是由肝脏产生的负向急性时相蛋白,重症胰腺炎时机体消化增加,胶体液大量渗出,导致 Alb 下降。Alb 降低能够直接影响组织器官代谢及功能,引起组织器官水肿及缺氧,进一步加重机体病情[26]。BUN 为机体蛋白质分解代谢的最终产物,机体发生应激反应时能够增加 BUN 合成, 另外重症胰腺炎发生后能够增加抗利尿激素的分泌,增强肾素血管紧张素系统活性,减少肾血流量,降低肾小球滤过率,增加 BUN 浓度[27]。Scr 为肌肉代谢产物,正常状态下其浓度较平稳,肾小球滤过率降低时 BUN 及 Scr 浓度明显增加。本研究结果显示,乌司他丁治疗后 Alb 增加更明显,BUN 及 Scr 水平则明显下降, 进一步证实其可有效缓解病情,改善机体状态。血淀粉酶为急性胰腺炎最常用的实验室指标,可辅助判断病情改变。APACHEⅡ评分是目前 ICU 中最常用且权威性的危急重症严重程度的评分方法,具有准确性高、简便等特点,其有效性已得到多个研究证实。本研究中,两组治疗后血淀粉酶及 APACHEⅡ评分均较治疗前下降,但乌司他丁组降低更明显,提示加用乌司他丁治疗更能有效降低疾病危重程度。

目前临床研究认为炎症细胞因子在重症胰腺炎发生、发展中有重要作用。HSP70 为细胞内含量丰富的热休克因子,具有参与新生蛋白质折叠、解聚和移位等作用,HSP70 多在细胞内发挥作用,但血液中 HPS70 高表达能够抑制内毒素、高热或缺血再灌注等所致的肾脏、心脏等细胞凋亡。另外 HSP70 作为炎症因子的负性调节因子,可抑制单核巨噬细胞中多种炎症因子的生成及释放。IL-15 为新型细胞因子,为免疫调节剂,可促进细胞因子产生,在调节机体免疫力中有重要作用。IL-15 主要来自于单核巨噬细胞,高水平的 IL-15 可刺激干扰素及肿瘤坏死因子的生成,参与局部炎症反应。HMGB1 为新型促炎介质,在机体广泛分布,可由炎症细胞主动分泌,机体正常状态下其浓度较低。研究报道重症胰腺炎患者 HMGB1 水平较急性胰腺炎患者高, 并发现 HMGB1 水平和 APACHEⅡ评分有良好相关性, 可作为机体病情程度的评价指标。目前重症胰腺炎患者 HSP70、IL-15 和 HMGB1 水平呈上升趋势。本研究结果发现,治疗后两组患者 HSP70、IL-15 和 HMGB1 水平均下降,但乌司他丁联合生长抑素组变化更明显,提示在连续血液净化基础上联合用药更能有效减轻机体炎症反应,延缓病情进展。另外两组仅有少数患者发生不良反应,且不良反应发生率相似,说明乌司他丁、生长抑素的安全性高。

综上所述,乌司他丁联合生长抑素辅助血液净化有利于重症胰腺炎患者病情恢复,减轻临床症状,降低 HSP70、IL-15 和 HMGB1 水平。

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