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CRRT 治疗剂量对脓毒症休克合并急性肾损伤患者免疫功能及预后的影响 *

张红伟¹ 胡金涛^{2△} 徐放¹ 于占彪¹ 韩丹丹¹

(1 河北大学附属医院重症医学科 河北 保定 071000; 2 保定大午医院内科 河北 保定 071000)

摘要 目的:探讨连续性肾脏替代治疗(Continuous renal replacement therapy, CRRT)治疗剂量对脓毒症休克合并急性肾损伤(acute kidney injury, AKI)患者免疫功能及预后的影响。**方法:**选择 2016 年 3 月到 2017 年 12 月我院 ICU 科收治的脓毒症休克合并急性肾损伤(AKI)患者 120 例,随机分为高剂量组、中剂量组、低剂量组和对照组四组,每组各 30 例。对照组采用常规治疗,低剂量组采用 20 mL/kg CRRT 治疗,中剂量组采用 35 mL/kg CRRT 治疗,高剂量组采用 60 mL/kg CRRT 治疗。比较 4 组治疗前后肾功能、免疫功能指标、APACHE II (Acute Physiology and Chronic Health Evaluation II, APACHE II)评分和 SOFA(sequential organ failure assessment)评分分数的变化。**结果:**治疗后,各组患者血尿素氮(blood urea nitrogen, BUN)和血肌酐(Serum creatinine, Scr)水平、APACHE II 评分和 SOFA 评分均较治疗前显著降低($P<0.05$),且高剂量组 BUN、Scr、APACHE II 评分和 SOFA 评分均显著低于其他 3 组($P<0.05$),中剂量组和低剂量组以上指标均显著低于对照组($P<0.05$),而低剂量组 BUN 和 Scr 明显低于对照组($P<0.05$)。治疗后,各组患者 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值均较治疗前显著升高 ($P<0.05$),且高剂量组 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值高于其他 3 组($P<0.05$),中剂量组以上指标显著高于低剂量组和对照组($P<0.05$),低剂量组以上指标明显高于对照组($P<0.05$)。**结论:**连续性肾脏替代治疗能显著改善脓毒症合并急性肾损伤患者肾功能和免疫功能,且效果呈一定的剂量依赖性。

关键词:CRRT;脓毒症休克合并急性肾损伤;免疫功能;肾功能;预后

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Effect of CRRT Treatment Dose on Immune Function and Prognosis in Patients with Septic Shock Complicated with Acute Kidney Injury*

ZHANG Hong-wei¹, HU Jin-tao^{2△}, XU Fang¹, YU Zhan-biao¹, HAN Dan-dan¹

(1 Intensive Care Unit, Affiliated Hospital of Hebei University, Baoding, Hebei, 071000, China;

2 Internal medicine department, Baoding Dawu Hospital, Baoding, Hebei, 071000, China)

ABSTRACT Objective: To investigate the effect of continuous renal replacement therapy (CRRT) treatment dose on immune function and prognosis in patients with septic shock and acute kidney injury (AKI). **Methods:** 120 patients with septic shock and acute kidney injury (AKI) admitted to our hospital from March 2016 to December 2017 were randomly divided into high-dose group, middle-dose group, low-dose group and control group, with 30 cases in each group. The control group received routine treatment, while the small dose group was treated with 20 mL/kg CRRT. The medium dose group was treated with 35 mL/kg CRRT, while the high-dose group was treated with 60 mL/kg CRRT. The renal function, immune function index, acute Physiology and Chronic Health Evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) score were compared between the 4 groups before and after treatment. **Results:** After treatment, the renal function indexes blood urea nitrogen (BUN) and Serum creatinine (Scr), APACHE II score and SOFA score were significantly lower in each group ($P<0.05$). After treatment, BUN and Scr, APACHE II score and SOFA score of the high dose group were lower than the other three groups. BUN and Scr, APACHE II score and SOFA score in the middle dose group and the low dose group were lower than in the control group, and BUN and Scr in the low dose group were lower than those in the control group ($P<0.05$). After treatment, the immune function indexes CD3⁺, CD4⁺ percentage and CD4⁺/CD8⁺ ratio were significantly increased in each group ($P<0.05$). The ratio of CD3⁺, CD4⁺ percentage and CD4⁺/CD8⁺ ratio in the high-dose group were higher than that in the other three groups. The middle-dose group were higher than the low-dose group and the control group, and the low-dose group were higher than the control group. The difference was statistically significant ($P<0.05$). **Conclusion:** CRRT can significantly improve the renal function and immune function of patients with sepsis and acute kidney injury, which can contribute to the recovery of patients' condition, and the high-dose group is better than the middle-dose and the low-dose.

Key words: CRRT; Septic shock combined with acute kidney injury; Immune function; Renal function; Prognosis

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作者简介:张红伟(1975-),硕士,主治医师,主要从事危重病方面的研究,电话:13932233518, E-mail:zhw3212@163.com

△ 通讯作者:胡金涛(1977-),本科,副主任医师,主要从事心脑血管病方面的研究

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前言

脓毒症是感染和重症医学的常见的疾病,发病原因是细菌侵入血液,并在血液中大量繁殖扩散,进而导致多器官功能衰竭,其中肾脏是最易损伤的脏器之一^[1,2]。早期目标导向治疗(Early goal directed therapy, EGDT)对脓毒症患者的治疗效果欠佳,其中脓毒症及脓毒症休克致急性肾损伤(acute kidney injury, AKI)的发病率和致死率较高^[3,4]。临床研究显示免疫功能紊乱在 AKI 的进展中发挥关键作用,调节免疫功能是该疾病的治疗目标之一^[5,6]。

连续肾脏替代治疗(Continuous renal replacement therapy, CRRT)具有清除溶质和炎症介质、调节免疫功能的作用^[7]。但近些年来,CRRT 治疗该疾病的剂量尚未统一,存在一些分歧。因此,本研究通过采用不同剂量 CRRT 治疗脓毒症休克合并急性肾损伤(AKI),探讨其对患者免疫功能、肾功能及预后的影响,旨在为临床治疗提供参考依据。

1 资料与方法

1.1 临床资料

选择 2016 年 3 月到 2017 年 12 月我院 ICU 科收治的脓毒症休克合并急性肾损伤(AKI)患者 120 例,纳入标准:符合《2012 国际严重脓毒症及脓毒性休克诊疗指南》中脓毒症诊断标准和《2012 年改善全球肾脏病预后组织(KDIGO)指南对急性肾损伤》的诊断标准^[8,9]。依据随机数字表将所有患者随机分为高剂量组、中剂量组、低剂量组和对照组,高剂量组 30 例,男 17 例,女 13 例,年龄 34-70 岁,平均年龄为(52.65±5.63)岁;中剂量组 30 例,男 16 例,女 14 例,年龄 35-70 岁,平均年龄为(53.12±5.31)岁;低剂量组 30 例,男 15 例,女 15 例,年龄 35-71 岁,平均年龄(53.24±5.33)岁;对照组 30 例,男 16 例,女 14 例,年龄 35-72 岁,平均年龄(53.11±5.32)岁,四组患者性别、平均年龄比较差异无统计学意义($P>0.05$),具有可比性。排除标准:1)肾损伤病史;2)已接受过 CRRT 治疗;3)凝血功能严重障碍者。本研究纳入病例均自愿参与且签订知情同意书。本研究经医院伦理委员会批准。

1.2 治疗方法

1)对照组患者接受抗感染、脏器功能支持、控制血糖、营养

支持和生命体征监护等治疗;2)其他 3 组患者均在对照组基础上连用 CRRT 治疗,选用连续性静-静脉血液滤过(CVVH),治疗时间为 10 h/d,连续治疗 7 d,所有患者均行右颈内或右股静脉置管,Fresenius 4008S 血滤机和 FreseniusAV600S 血滤机均购自北京费森尤斯卡比医药有限公司,置换液使用 batter 置换液,以稀释方式输入,使用普通肝素(购自天津药业焦作有限公司)抗凝;3)高剂量组置换量为 60 mL/k·h,中剂量组置换量为 35 mL/k·h,低剂量组置换量为 20 mL/k·h。对于有出血倾向者,可在血液回路加入鱼精蛋白。对于有活动性出血者则采用无肝素法透析,透析过程中需定期使用生理盐水冲洗管道。

1.3 观察指标

1) 采用 ELASA 法检测患者治疗前 1 d 和治疗后 7 d 后空腹静脉外周血尿素氮(blood urea nitrogen, BUN)和血肌酐(Serum creatinine, SCr)等肾功能指标水平,上述试剂盒均购自上海酶联生物有限公司。2)采用 Coulter Epics XL 流式细胞仪(购自上海寰熙医疗器械有限公司)检测患者治疗前 1 d 和治疗后 7 d 后空腹静脉外周血中 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值;3)对患者治疗前后进行急性生理与慢性健康评分(Acute Physiology and Chronic Health Evaluation II, APACHE II)、序贯器官衰竭估计评分(sequential organ failure assessment, SOFA)评分。APACHE II 评分包括 34 项参数,总分为 71 分,分数越高表示疾病程度越严重;SOFA 评分包含呼吸、凝血、循环、神经等项目,分数越高,病情越严重。

1.4 统计学处理

采用 SPSS17.0 统计学软件对数据进行分析,计量资料采用($\bar{x} \pm s$)表示,多组间比较采用方差分析,两组间比较采用 t 检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 各组治疗前后肾功能的比较

治疗前,各组间血肌酐和尿素氮比较差异均无统计学意义($P>0.05$)。治疗后,各组患者血肌酐和尿素氮水平均较治疗前显著降低($P<0.05$),高剂量组血肌酐和尿素氮水平显著低于其他 3 组,中剂量组血肌酐和尿素氮水平低于低剂量组和对照组,低剂量组血肌酐和尿素氮水平低于对照组($P<0.05$),结果见表 1。

表 1 各组治疗前后肾功能指标的比较($\bar{x} \pm s$)

Table 1 Comparison of the renal function among different groups before and after treatment ($\bar{x} \pm s$)

Groups	Time	BUN(mmol/L)	Scr(μ mol/L)
High dose group	Before treatment	28.29±2.83	311.26±31.26
	After treatment	14.06±1.41* ^{###}	172.66±17.29* ^{###}
Medium dose group	Before treatment	28.31±2.83	308.69±30.87
	After treatment	15.17±1.52* ^{##}	190.88±19.12* ^{##}
Low dose group	Before treatment	28.44±2.85	312.55±31.26
	After treatment	16.29±1.57* [#]	211.39±21.16* [#]
Control group	Before treatment	28.43±2.84	310.59±31.06
	After treatment	18.32±1.83*	251.64±25.23*

Note: Compared with before treatment, * $P<0.05$; compared with the control group, [#] $P<0.05$; compared with the low dose group, [△] $P<0.05$; compared with the middle dose group, [△] $P<0.05$

2.2 各组治疗前后免疫功能指标的比较

治疗前, 各组间 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值比较差异均无统计学意义($P>0.05$)。治疗后, 各组患者 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值均较治疗前显著升高($P<0.05$), 且高

剂量组 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值高于其他 3 组, 中剂量组 CD3⁺、CD4⁺ 百分比及 CD4⁺/CD8⁺ 比值高于低剂量组 and 对照组, 差异均具有统计学意义($P<0.05$), 结果见表 2。

表 2 各组治疗前后免疫功能指标的比较($\bar{x} \pm s, \%$)

Table 2 Comparison of immunological function indicators among different groups before and after treatment ($\bar{x} \pm s, \%$)

Groups	Time	CD3 ⁺	CD4 ⁺	CD4 ⁺ /CD8 ⁺
High dose group	Before treatment	42.36 $\pm$ 4.23	22.25 $\pm$ 2.23	0.91 $\pm$ 0.10
	After treatment	50.52 $\pm$ 4.95 ^{*#}	34.03 $\pm$ 3.41 ^{*#}	1.67 $\pm$ 0.16 ^{*#}
Medium dose group	Before treatment	42.58 $\pm$ 4.26	23.01 $\pm$ 2.31	0.94 $\pm$ 0.09
	After treatment	46.99 $\pm$ 4.74 ^{*#}	32.15 $\pm$ 3.22 ^{*#}	1.48 $\pm$ 0.15 ^{*#}
Low dose group	Before treatment	42.61 $\pm$ 4.26	23.17 $\pm$ 2.31	0.97 $\pm$ 0.10
	After treatment	45.28 $\pm$ 4.49 ^{*#}	29.14 $\pm$ 3.02 ^{*#}	1.32 $\pm$ 0.13 ^{*#}
Control group	Before treatment	42.36 $\pm$ 4.23	22.99 $\pm$ 2.29	0.95 $\pm$ 0.09
	After treatment	44.19 $\pm$ 4.52 [*]	25.63 $\pm$ 2.66 [*]	1.17 $\pm$ 0.10 [*]

Note: Compared with before treatment, ^{*} $P<0.05$; compared with the control group, [#] $P<0.05$; compared with the low dose group, [△] $P<0.05$; compared with the middle dose group, [△] $P<0.05$

2.3 各组治疗前后 APACHE II 评分和 SOFA 评分的比较

治疗前, 各组 APACHE II 评分和 SOFA 评分比较差异无统计学意义 ($P>0.05$)。治疗后, 各组患者 APACHE II 评分和 SOFA 评分分数均较治疗前显著降低($P<0.05$), 且高剂量组 A-

PACHE II 评分和 SOFA 评分分数低于其他 3 组, 中剂量组和低剂量组 APACHE II 评分和 SOFA 评分分数显著低于对照组 ($P<0.05$), 中剂量组和低剂量组 APACHE II 评分和 SOFA 评分分数比较差异不显著($P>0.05$), 结果见表 3。

表 3 各组治疗前后 APACHE II 评分和 SOFA 评分的比较($\bar{x} \pm s$, 分)

Table 3 Comparison of the APACHEII score and SOFA score among different groups before and after treatment ($\bar{x} \pm s$, points)

Groups	Time	APACHEII score	SOFA score
High dose group	Before treatment	22.47 $\pm$ 2.25	9.25 $\pm$ 0.95
	After treatment	11.55 $\pm$ 1.16 ^{*#}	4.32 $\pm$ 0.43 ^{*#}
Medium dose group	Before treatment	21.59 $\pm$ 2.20	9.30 $\pm$ 0.96
	After treatment	13.26 $\pm$ 4.74 ^{*#}	5.59 $\pm$ 0.56 ^{*#}
Low dose group	Before treatment	21.87 $\pm$ 2.17	9.19 $\pm$ 0.92
	After treatment	14.42 $\pm$ 1.35 ^{*#}	6.71 $\pm$ 0.71 [#]
Control group	Before treatment	22.08 $\pm$ 2.21	9.26 $\pm$ 0.94
	After treatment	15.84 $\pm$ 1.52 [*]	8.13 $\pm$ 0.82 [*]

Note: Compared with before treatment, ^{*} $P<0.05$; compared with the control group, [#] $P<0.05$; compared with the low dose group, [△] $P<0.05$; compared with the middle dose group, [△] $P<0.05$.

3 讨论

临床研究报道脓毒症休克合并 AKI 发生率逐年上升^[10,11], 急性肾损伤是脓毒症患者进入 ICU 的重要原因, 且脓毒症休克并急性肾损伤的病死率较高, 显著高于不伴急性肾损伤的患者^[12,13]。脓毒症可导致血流动力学改变、肾缺血、炎性细胞浸润及血管内皮功能失调, 机体在内毒素的作用下, 炎性细胞通过级联反应释放出大量炎性介质, 表现为淋巴细胞增殖能力降低, 免疫功能抑制状态, 增加了机体对病原体的易感性。脓毒症发病后期会损伤多种器官导致多器官功能障碍, 肾脏为主要损伤脏器之一^[14]。

脓毒性休克致急性肾损伤的治疗方式主要有对症治疗和对因治疗。对因治疗选用最佳的抗生素进行抗感染治疗, 同时清除感染灶。对症治疗给予血管活性药保持血压的稳定, 乌司他丁抑制炎症因子释放, 还原性谷胱甘肽减轻肾脏细胞损伤, 提高细胞膜对自由基的耐受性^[16]。血液净化疗法是脓毒症休克致急性肾损伤的常用方法, 主要包括间歇性肾脏替代治疗和 CRRT 疗法^[17,18]。CRRT 疗法又称为连续性血液净化, 可替代受损的肾脏清除血液中的炎性物质, 维持血液动力学和内环境的稳定, 改善免疫功能和抑制炎症级联反应, 并同时补充大量液体为营养支持提供保障^[19]。因此, 本研究在常规治疗上联用不同剂量的 CRRT 治疗, 旨在探讨其最佳治疗剂量^[15]。

BUN 和 SCr 均为反映肾代谢功能的常用指标^[20,21]。本研究结果显示 CRRT 可显著改善脓毒症合并 AKI 患者血清肾功能并呈现剂量依赖性,高剂量组患者的 BUN、SCr 水平明显低于其余 3 组,可见高剂量 CRRT 可有效阻止患者肾功能的持续恶化。推测其原因是 CRRT 治疗可通过过滤作用大分子的炎性介质,降低炎性介质对肾脏的损伤,并且可显著改善肾缺血 - 再灌注损伤,维持血流动力学的稳定,改善肾脏微循环,有助于肾功能的恢复。研究表明 CRRT 治疗脓毒症合并急性肾损伤的机制主要是通过对流和吸附可溶性炎症介质和毒素,减轻免疫抑制,抑制体内的淋巴细胞的凋亡,增强免疫功能,抑制炎症级联反应,发挥改善肾功能的作用^[22]。脓毒症患者体内细胞免疫功能紊乱,淋巴细胞是细胞免疫应答的重要成分,主要由 CD4⁺T 细胞和 CD8⁺T 细胞组成。CD4⁺T 细胞主要发挥协助细胞免疫的功能,CD8⁺T 细胞主要起到杀死靶细胞的功能,CD4⁺与 CD8⁺的变化是不同步的,而 CD3⁺与 CD4⁺变化是同步法,因此可通过 CD4⁺与 CD8⁺细胞百分比及比值评价患者的免疫功能。刘金涛等发现 CRRT 治疗能显著提高外周血淋巴细胞计数、CD4⁺T 细胞百分比及 CD14⁺细胞 HLA-DR 的表达^[23]。吴晓弟等也发现不同剂量 CRRT 治疗能提高脓毒症患者免疫功能指标免疫球蛋白及 CD4⁺与 CD8⁺细胞比值的水平,改善预后,并认为与清除炎症因子有关^[24]。本研究结果显示 CRRT 可显著改善脓毒症合并 AKI 患者免疫并呈现剂量依赖性,高剂量组患者的 CD3⁺、CD4⁺百分比及 CD4⁺/CD8⁺比值高于其他 3 组,可见高剂量 CRRT 可有效改善患者免疫功能紊乱,与以往研究一致^[25]。

APACHE- II 评分可用于评价危重症患者病情严重程度及预后,对脓毒症休克合并急性肾损伤患者病情和预后的评估可靠性较高,APACHE- II 总分越高,表明患者病情越严重,死亡的可能性也越高^[26]。临床研究表明 APACHE- II 评分、PCT 均是脓毒性休克患者预后的独立危险因素^[27]。罗运山等报道脓毒症患者的血清乳酸水平、APACHE II 评分均是重症患者预后评估的可靠指标^[28]。SOFA 评分是目前临床上常用的对脓毒症患者预后评估的评价体系,具有内容简洁、数据易得的优点,较适合于急诊科医师应用。有研究报道 APACHE- II 评分、SOFA 评分及血清 D 一二聚体水平等因素与脓毒症患者的预后有关^[29]。刘欧亚等发现抗凝血酶 III 与 SOFA 评分具有相关性,可有效评价脓毒症患者的病情严重程度^[30]。本研究结果显示各组患者治疗后 APACHE II 评分和 SOFA 评分分数均显著降低,且随着 CRRT 治疗剂量增加而逐渐降低。可见,CRRT 能改善脓毒症合并 AKI 患者的预后,可能与 CRRT 能够改善免疫功能和肾功能有关。

综上所述,连续性肾脏替代治疗能显著改善脓毒症休克合并急性肾损伤患者肾功能和免疫功能,有助于患者病情恢复,且效果呈一定的剂量依赖性。但本研究尚存在一定局限性。如入选患者来自本医院,且样本例数偏少,未深入研究 CRRT 治疗如何影响肾功能和免疫功能的具体机制,今后仍需扩大样本例数并进行机制的深入研究。

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