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不同 CRRT 治疗时机对脓毒症合并急性肾功能不全患者疗效及预后的影响

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摘要 目的:探讨不同持续性肾脏替代治疗(CRRT)治疗时机对脓毒症合并急性肾功能不全患者的临床疗效及预后的影响。**方法**:将我院 ICU 收治的 60 例脓毒症合并急性肾功能不全患者,按照 CRRT 治疗时机分为早期组(1-2 期,n=30)和晚期组(3 期,n=30)。比较两组患者治疗前后不同时点平均动脉压(MAP)、白细胞(WBC)计数、血红蛋白(HB)、血小板(PLT)计数、急性生理学与慢性健康状况(APACHE)II 评分等临床资料的变化,机械通气时间,肾功能恢复率及 28 d 病死率等。**结果**:与早期组比较,晚期组治疗后 WBC 计数明显升高(P<0.05)。治疗后 12 h、24 h、72 h,早期组 ACHEII 评分较晚期组显著降低(P<0.05)。与晚期组比较,早期组机械通气时间显著缩短,肾功能恢复明显升高,28d 内病死率也明显降低(P<0.05)。**结论**:脓毒症合并急性肾功能不全患者应早期启动 CRRT 治疗,最佳介入时间是 KDIGO-AKI 3 期之前,有助于改善患者预后。

关键词:持续性肾脏替代治疗;治疗时机;脓毒症;急性肾功能不全;预后

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Effect of Continuous Renal Replacement Therapy Started at Different Time on the Sepsis Patients with Acute Renal Insufficiency

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ABSTRACT Objective: To explore the effect of continuous renal replacement therapy (CRRT) started at different time in sepsis patients with acute renal insufficiency. **Methods:** 60 critical patients who were admitted in the ICU of our hospital were divided into two groups including early group (stage 1-2, n=30) and late group (stage 3, n=30). The clinical data such as mean arterial pressure (MAP), white blood cells (WBC) count, hemoglobin (HB), platelet (PLT) count were compared before treatment, and change of APACHE II scores at different time, the duration of mechanical ventilation, and the mortality within 28days were analyzed. **Results:** Before treatment, there was no significant difference in the levels of MAP, HB, PLT count and lactic acid between two groups (P>0.05). Compared with early group, the WBC count in late group was obviously increased (P<0.05). The APACHE II score in early group were significantly lower than those in late group at 12 h, 24 h and 72h after treatment(P<0.05). Compared with early group, the duration of mechanical ventilation in late group were shortened, renal function recovery rate were increased, and the mortality within 28 days were reduced (P<0.05). **Conclusions:** The CRRT for sepsis patients with acute renal insufficiency should be started early, the optimal timing of initiating CRRT may predate to KDIGO-AKI 3 phase, which can contribute to improve the prognosis.

Key words: Continuous renal replacement therapy; Treatment timing; Sepsis; Acute renal insufficiency; Prognosis

Chinese Library Classification(CLC): R631.2; R459.5; R692 Document code: A

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前言

脓毒症是 ICU 常见的临床危重疾病，其中超过 50%的患者可能并发急性肾功能不全[1-3]。研究显示脓毒症合并急性肾功能不全患者的病死率高达 60%-75%，明显高于无脏器损伤的脓毒症患者[4,5]。连续性肾脏替代治疗(CRRT)作为一种体外循环血液净化治疗方式,在清除有毒物质时不仅具有良好的血流动力学稳定性,对脏器功能还能发挥一定支持作用,近年来已广泛应用于治疗脓毒症[6-8]。2012 年,《国际严重脓毒症和脓毒性休克诊疗指南》推荐对严重脓毒症合并急性肾功能不全的患者采取 CRRT[9],但如何优化选择 CRRT 介入时机仍然是目前的争议焦点。本研究通过比较 CRRT 不同介入治疗时机对脓毒症合并急性肾功能不全患者的临床疗效及预后影响,探讨 CRRT 最佳治疗时机,以期为脓毒症的救治提供参考经验。

1 资料与方法

1.1 一般资料

选择 2015 年 1 月 ~2017 年 1 月同济大学附属杨浦医院 EICU 收治的 60 例脓毒症患者。入选标准:① 符合急性肾功能不全的临床诊断[10],即:48 h 内血肌酐(Scr)水平增加超过 26.5 μmol/L;过去 1 周内 Scr 增加至基础值的 1.5 倍以上;尿量少于

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0.5 mL·kg^{-1}·h^{-1}，且至少持续 6 h。⓪ 年龄≥ 18 岁，ICU 住院时间≥ 48 h；⓪ 排除慢性肾功能衰竭病史、规律透析者，或转院、放弃治疗等原因导致治疗中断者。其中，男 37 例，女 23 例；年龄 31~76 岁，平均(58.4± 6.7)岁；感染部位：肺部感染 41 例，泌尿系统感染 5 例，腹腔感染 10 例，血流感染 4 例。将所有患者根据行 CRRT 治疗时的急性肾功能不全分期 [10]，分为早期组(1-2 期，n=30)和晚期组(3 期，n=30)。两组患者在性别构成比、年龄、感染部位等方面差异均无统计学意义(P>0.05)，具有可比性。

1.2 治疗方法

所有患者均给予常规对症治疗，包括抗感染、清除感染灶、营养支持、脏器功能支持等，必要时行机械通气。所有患者均采用 Seidinger 技术行深静脉(颈内静脉或股静脉)穿刺置入双腔导管建立血管通路，采用采用 Edwards 血液净化器，Baxter 血液滤过器 HF1200 及其配套管路，选择聚砜膜(AV600S)，治疗模式为连续静脉 - 静脉血液滤过(CVVH)，每次 12 h，血流量为 100~180 mL/min，透析液流量 4 L/h，12 h 更换一次透析器，连续治疗 5 d 以上。治疗过程中密切监测患者的血气、肾功能及电解质，并据此调整置换液成分。

1.3 观察指标

收集患者治疗前的相关临床实验室指标，包括平均动脉压(MAP)、血红蛋白(HB)、白细胞(WBC)计数、血小板(PLT)计数、乳酸水平，分别于治疗前(0 h)、治疗后 12 h、24 h、72 h 评估两组患者的患者急性生理学与慢性健康状况(APACHE)II 评分的变化，并记录机械通气时间、肾功能恢复率及 28d 病死率等。

1.4 统计学方法

采用 SPSS18.0 版软件进行统计分析。计数资料以率表示，组间比较采用 χ^2 检验，计量资料采用均数± 标准差 ($\bar{x}\pm s$)表示，组间比较采用独立样本 t 检验，以 P<0.05 视为差异有统计学意义。

2 结果

2.1 两组治疗前基本临床资料比较

治疗前，两组 MAP、HB、PLT 计数、乳酸水平比较差异无统计学意义(P>0.05)；与早期组比较，晚期组 WBC 计数明显升高，差异有统计学意义(P<0.05)，见表 1。

表 1 两组基本临床资料比较($\bar{x}\pm s$)

Table 1 Comparison of the baseline clinical data between two group($\bar{x}\pm s$)

Group	N	MAP(mmHg)	HB(g/L)	WBC count (× 10^9/L)	PLT count (× 10^9/L)	Lactic acid (mmol/L)
Early group	30	87.4± 6.4	102.4± 13.4	12.2± 8.5	144.6± 29.6	3.2± 0.7
Late group	30	90.7± 7.3	96.7± 11.4	16.8± 8.1	153.4± 34.2	3.4± 0.9
P		>0.05	>0.05	<0.05	>0.05	>0.05

2.2 两组不同时刻 APACHE II 评分的变化比较

治疗前(0 h)，两组 APACHEII 评分比较差异无统计学意义(P>0.05)；治疗后 12、24、72 h，早期组 ACHEII 评分较晚期组显著降低，差异有统计学意义(P<0.05)。见表 2。

表 2 两组治疗前后不同时刻 APACHE II 评分变化的比较($\bar{x}\pm s$，分)

Table 2 Comparison of the changes of APACHE II score between two group before and after treatment($\bar{x}\pm s$, scores)

Group	N	0 h	12 h	24 h	72 h
Early group	30	19.4± 5.5	17.4± 3.6	13.7± 0.5	12.85± 1.1
Late group	30	21.0± 4.0	20.2± 4.3	16.2± 0.6	15.53± 0.9
P		>0.05	<0.05	<0.05	<0.05

2.3 两组患者的预后比较

与晚期组比较，早期组机械通气时间显著缩短，肾功能恢复明显升高，28 d 内病死率也明显降低，差异均有统计学意义(P<0.05)，见表 3。

表 3 两组患者的预后比较

Table 3 Comparison of the prognosis between two group

Group	N	Duration of mechanical ventilation (h)	Renal function recovery rate (%)	Mortality within 28 days (%)
Early group	30	27.2± 7.5	28(93.3)	9(30.0)
Late group	30	33.2± 10.1	22(73.3)	17(56.7)
P		<0.05	<0.05	<0.05

3 讨论

近年来，脓毒症并发急性肾功能不全的发生率以每年 0.3%的速度呈不断上升，且病死率一直居高不下，其发病机制较为复杂，与血流动力学与应激激素的剧烈变化、内毒素与炎症介质的影响、细胞凋亡及弥漫性血管内凝血均有关，其中炎症是疾病发生的关键环节[11-13]。目前，尚无证据证实对无肾功能障碍的脓毒症患者预防性使用连续性血液净化治疗，但多项研

究表明在脓毒症合并急性肾功能不全患者应早期应启动血液净化治疗[14-16]。脓毒症患者治疗的治疗核心原则除控制感染源外，还应加强对器官功能支持和免疫调理，同时此类患者肾功能不全多为可逆性，及时发现并介入干预对于防止其进一步发展为实质性肾功能衰竭，改善预后具有重要意义[17-19]。

CRRT 作为器官支持技术之一，在脓毒症合并急性肾功能不全患者的救治中具有独特的优势，但对于治疗时机的选择尚未达成一致，且不同时机的介入对治疗效果及预后是否存在明显影响尚需确认[20-22]。脓毒症合并急性肾功能不全的患者与单纯肾功能不全患者不同，炎症介质在脓毒症的发生、发展中发挥着十分重要的作用，炎症介质水平越高，患者的预后越差。CRRT 治疗脓毒症合并急性肾功能不全主要通过以下两个方面：一是针对急性肾功能不全的直接肾脏支持治疗，二是对脓毒症失控的炎性反应进行免疫调理。基于上述两个方面的治疗目的，脓毒症合并急性肾功能不全患者行 CRRT 治疗的最佳启动时机选择变得更为困难。近年来，随着对国内外对急性肾功能不全或急性肾功能损伤(AKI)诊断及危险分级的不断细化，越来越多的研究以 KDIGO-AKI 分期作为肾功能不全、AKI 患者行 CRRT 的参考指标，结果提示在 KDIGO-AKI 分期早期行 CRRT 能明显改善患者的预后[23,24]。KDIGO 标准是在 RIFLE 标准、AKIN 标准的基础上进行完善与更新，对 AKI、急性肾功能不全诊断的灵敏度和预后的评估预测上明显改善。故本研究将脓毒症患者按照 KDIGO-AKI 分期进行 CRRT 治疗，AKI 1-2 期归为早期组，3 期归为晚期组，结果显示晚期组患者 WBC 计数较早期组明显升高，说明晚期组的病情更重更复杂，与相关研究结果[25,26]一致。陈敏华等[27]采用 Kaplan-Meier 生存分析法绘制生存曲线，结果显示，AKI 1-2 期行 CRRT 的患者生存率明显高于 AKI 3 期行 CRRT 的患者。

研究显示经过 CRRT 治疗后 12、24、72 h，早期组 ACHEII 评分较晚期组显著降低，提示对脓毒症伴急性肾功能不全患者而言，CRRT 治疗的最佳介入时机应早于患者 KDIGO-AKI 3 期，同时也说明 KDIGO-AKI 分期作为 CRRT 治疗介入时机标准具有较好的可靠性[28-30]。另外，研究结果显示两组的病死率仍较高，但早期组在机械通气时间、肾功能恢复率甚至是 28d 病死率方面仍具有优势，预后改善明显。Chou 等 [31] 也以 KDIGO-AKI 标准为行 CRRT 治疗的依据，发现对脓毒症患者而言，在出现明显的肾脏并发症之前，以在 2 期时启动 CRRT 治疗效果最佳，能明显减少 ICU 住院时间及机械通气时间，降低 28 d 病死率。

综上所述，脓毒症合并急性肾功能不全患者病死率高，应早期启动 CRRT 治疗，最佳介入时间是 KDIGO-AKI 3 期之前，有助于提供临床疗效，改善患者预后。但由于本研究样本量较少，所得结论需下一步积累更大样本、多中心的随机对照研究予以证实。

参 考 文 献(References)

[1] Suh SH, Kim CS, Choi JS, et al. Acute kidney injury in patients with sepsis and septic shock: risk factors and clinical outcomes [J]. Yonsei Med J, 2013, 54(4): 965-972

[2] Zahar JR, Timsit JF, Garrouste-Orgeas M, et al. Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality [J]. Crit Care Med, 2011, 39 (19): 1886-1895

[3] Allegretti AS, Steele DJ, David-Kasdan JA, et al. Continuous renal replacement therapy outcomes in acute kidney injury and end-stage renal disease: a cohort study[J]. Crit Care, 2013, 17(20): R109

[4] Zarbock A, Gomez H, Kellum JA, et al. Sepsis-induced acute kidney injury revisited: pathophysiology, prevention and future therapies[J]. Curr Opin Crit Care, 2014, 20(6): 588-595

[5] Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit[J]. N Engl J Med, 2016, 375(2): 122-133

[6] Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level [J]. J Am Soc Nephrol, 2015, 26 (7): 2231-2238

[7] Legrand M, Payen D. Understanding urine output in critically ill patients[J]. Ann Intensive Care, 2011, 1(12): 13-18

[8] Allegretti AS, Steele DJ, David-Kasdan JA, et al. Continuous renal replacement therapy outcomes in acute kidney injury and end-stage renal disease: a cohort study[J]. Crit Care, 2013, 17(12): 109-115

[9] 高戈,冯喆,常志刚,等 2012 国际严重脓毒症及脓毒性休克诊疗指南[J].中华危重病急救医学, 2013, 25(8): 501-505
Gao Ge, Fen Zhe, Chang Zhi-gang, et al. International guidelines for severe sepsis and septic shock 2012 [J]. Chinese Critical Care Medicine, 2013, 25(8): 501-505

[10] Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1)[J]. Crit Care, 2013, 17(1): 204

[11] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis 3)[J]. JAMA, 2016, 315(8): 801-810

[12] Poukkanen M, Wilkman E, Vaara S T, et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study [J]. Crit Carem, 2013, 17(6): 295

[13] Baek S D, Yu H, Shin S, et al. Early continuous renal replacement therapy in septic acute kidney injury could be defined by its initiation within 24 hours of vasopressor infusion [J]. J Crit Care, 2016, 39(12): 108-114

[14] Lee J, Cho JH, Chung BH, et al. Classical indications are useful for initiating continuous renal replacement therapy in critically ill patients[J]. Tohoku J Exp Med, 2014, 233(18): 233-241

[15] Jae JP, Jung NA, Jong HJ, et al. Early initiation of continuous renal replacement therapy improves survival of elderly patients with acute kidney injury: a multicenter prospective cohort study [J]. Crit Care, 2016, 20(12): 260-271

[16] Zahar JR, Timsit JF, Garrouste-Orgeas M, et al. Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality [J]. Crit Care Med, 2011, 39 (18): 1886-1895

[17] 许涛,盛晓华,崔勇平,等.CRRT 在脓毒血症急性肾损伤患者救治中的临床研究[J].中国血液净化, 2013, 12(12): 646-650
Xu Tao, Sheng Xiao-hua, Cui Yong-ping, et al. The clinical study of continuous renal replacement therapy in the treatment of severe sepsis

complicated with acute kidney injury [J]. Chinese Journal of Blood Purification, 2013, 12(12): 646-650

[18] Lee J, Cho JH, Chung BH, et al. Classical indications are useful for initiating continuous renal replacement therapy in critically ill patients[J]. Tohoku J Exp Med, 2014, 233(10): 233-241

[19] Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit[J]. N Engl J Med, 2016, 375(2): 122-133

[20] Oh HJ, Min HK, Jin YA, et al. Can early initiation of continuous renal replacement therapy improve patient survival with septic acute kidney injury when enrolled in early goal-directed therapy[J]. Journal of Critical Care, 2016, 35(13): 51-56

[21] Pannu N, James M, Hemmelgarn B, et al. Kidney Disease Network Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge[J]. Clin J Am Soc Nephrol, 2013, 8 (12): 194-201

[22] Silversides JA, Pinto R, Kuint R, et al. Fluid balance, intradialytic hypotension, and outcomes in critically ill patients undergoing renal replacement therapy: a cohort study[J]. Crit Care, 2014, 18(17):624-629

[23] 陈思睿,赵双平,蔡茜.以 KDIGO-AKI 分期作为脓毒症患者血液净化治疗时机的研究[J].中国医师杂志, 2016, 18(1): 66-69, 73
Chen Si-rui, Zhao Shuang-ping, Cai Qian. Research of timing of hemopurification therapy for sepsis patients according to KDIGO AKI classification[J]. Journal of Chinese Physician, 2106, 18(1): 66-69, 73

[24] Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by Urine Output versus Serum Creatinine Level[J]. Am Soc Nephrol, 2015, 26 (9): 2231-2238

[25] Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial [J]. JAMA, 2016, 315(18): 2190-2199

[26] Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial [J]. JAMA, 2016, 315(5): 2190-2199

[27] 陈敏华,孙仁华,李茜,等.脓毒症伴急性肾损伤患者连续性肾脏替代治疗时机的探讨[J].中华危重症医学杂志(电子版), 2016, 9(3): 149-153
Chen Min-hua, Sun Ren-hua, Li Qian, et al. Timing of continuous renal replacement therapy in sepsis patients with acute kidney injury [J]. Chin J Crit Care Med(Electronic Edition), 2016, 9(3): 149-153

[28] Zhang Z, Xu X, Ni H, et al. Urine output on ICU entry is associated with hospital mortality in unselected critically ill patients [J]. J Nephrol, 2014, 27(19): 65-71

[29] 王黎明, 柴艳芬, 董佳月, 等. 连续性血液净化治疗脓毒症临床疗效的 Meta 分析 [J]. 中华危重症医学杂志：电子版, 2014, 7 (5): 302-307
Wang Li-ming, Chai Yan-fang, Dong Jia-yue, et al. Clinical effect of continuous blood purification in patients with sepsis: a meta-analysis [J]. Chinese Journal of Critical Care Medicine (Electronic Edition), 2014, 7(5): 302-307

[30] Park JY, An JN, Jhee JH, et al. Early initiation of continuous renal replacement therapy improves survival of elderly patients with acute kidney injury: a multicenter prospective cohort study[J]. Critical Care, 2016, 20(1): 260

[31] Chou YH, Huang TM, Wu VC, et al. Impact of timing of renal replacement therapy initiation on outcome of septic acute kidney injury [J]. Crit Care, 2011, 15(3): R134

(上接第 2929 页)

[18] Zhou L, Zhang LZ, Wang JY, et al. Perioperative safety analysis of transcatheter arterial chemoembolization for hepatocellular carcinoma patients with preprocedural leukopenia or thrombocytopenia [J]. Mol Clin Oncol, 2017, 7(3): 435-442

[19] Chang G, Xie LL, Li WY, et al. Application of oxaliplatin in combination with epirubicin in transcatheter arterial chemoembolization in the treatment of primary liver carcinoma [J]. J Biol Regul Homeost Agents, 2017, 31(2): 459-464

[20] Hong CX, Lv LW, Hua LZ, et al. Epidemiology and Management of Acute Kidney Injury in Hepatocellular Carcinoma Patients Undergoing Transcatheter Arterial Chemoembolization [J]. Curr Protein Pept Sci, 2017, 18(12): 1218-1223

[21] Drennan MB, Govindarajan S, De Wilde K, et al. The thymic microenvironment differentially regulates development and trafficking of invariant NKT cell sublineages [J]. J Immunol, 2014, 193 (12): 5960-5972

[22] Xu Q, Wang J, Chen F, et al. Protective role of magnesium isoglycyrrhizinate in non-alcoholic fatty liver disease and the associated molecular mechanisms[J]. Int J Mol Med, 2016, 38(1): 275-282

[23] 宋裕萍,赵擎宇,李松,等.非侵入性肝纤维化诊断模型对肝癌介入治疗后急性肝功能恶化的预测作用[J].中华医学杂志, 2016, 96(9): 716-719
Song Yu-ping, Zhao Qing-yu, Li Song, et al. Non-invasive fibrosis indexes in predicting acute liver function deterioration after transcatheter arterial chemoembolization [J]. National Medical Journal of China, 2016, 96(9): 716-719

[24] Nhu QM, Knowles H, Pockros PJ, et al. Pulmonary complications of transcatheter arterial chemoembolization for hepatocellular carcinoma [J]. World J Respirol, 2016, 6(3): 69-75

[25] Zhu C, Qi X, Li H, et al. Correlation of serum liver fibrosis markers with severity of liver dysfunction in liver cirrhosis: a retrospective cross-sectional study[J]. Int J Clin Exp Med, 2015, 8(4): 5989-5998

[26] Xie S, Li Q, Cheng Y, et al. Impact of Liver Fibrosis and Fatty Liver on T1rho Measurements: A Prospective Study [J]. Korean J Radiol, 2017, 18(6): 898-905

[27] Ramadass M, Ghebrehiwet B, Kew RR. Enhanced recognition of plasma proteins in a non-native state by complement C3b. A possible clearance mechanism for damaged proteins in blood[J]. Mol Immunol, 2015, 64(1): 55-62