

doi: 10.3978/j.issn.2095-6959.2020.09.021

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2020.09.021>

脓毒症患者行 CRRT 时合并严重血小板减少不同治疗的疗效比较

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[摘要] 目的: 目前脓毒症患者行连续性肾脏替代治疗(continuous renal replacement therapy, CRRT)治疗过程中合并严重血小板减少症者的发病率高。一般认为血小板数低于 $50 \times 10^9/L$ 者继续给予有创诊疗如CRRT者需给予相应治疗。本文通过回顾研究小样本的这类患者, 比较输新鲜血小板、输冰冻血小板、使用重组人血小板生成素、使用重组人血小板生成素联合输新鲜血小板的治疗效果, 以期脓毒症需持续给予CRRT合并血小板减少时的治疗提供一定的帮助。方法: 以2011年1月至2016年11月镇江市第一人民医院重症医学科118例行CRRT后外周血小板计数下降至 $\leq 50 \times 10^9/L$ 的118例脓毒症患者为研究对象, 依据治疗方法不同分为未治疗组(23例)、新鲜血小板组(29例)、冰冻血小板组(25例)、重组人血小板生成素组(20例)、重组人血小板生成素及新鲜血小板组(21例)。观察比较各组治疗后24 h与72 h时的治疗反应。结果: 当治疗前血小板处于不同水平对各种治疗疗效反应不同。当血小板数 $< 30 \times 10^9/L$ 时, 所有治疗方法疗效在24 h及72 h评估均不理想; 单用重组人血小板生成素疗效最差与未治疗组无统计学差异, 其余3组治疗疗效差异无统计学意义($P > 0.05$)。此时治疗上应以输血小板治疗为主, 输新鲜血小板与冰冻血小板疗效差异无统计学意义($P > 0.05$)。当血小板数 $(30 \sim 50) \times 10^9/L$ 时, 输冰冻血小板较新鲜血小板及新鲜血小板联合药物组治疗24 h疗效相近, 但治疗72 h后疗效差, 且联合治疗组在72 h时疗效略优于输新鲜血小板, 但无差异统计学意义($P > 0.05$); 单用重组人血小板生成素可在一定程度上减缓血小板的下降幅度; 最佳治疗为输新鲜血小板, 也可选用重组人血小板生成素联合输血小板共同治疗, 无血源时, 重组人血小板生成素亦可考虑使用。结论: 脓毒症患者行持续CRRT合并血小板减少时, 应根据患者外周血小板计数, 给予不同的治疗方案。

[关键词] 脓毒症; 连续性肾脏替代治疗; 血小板减少; 重组人血小板生成素

Comparing the efficacy of different treatments in sepsis patients using CRRT with serious thrombocytopenia

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Abstract **Objective:** Currently the prevalence rate of sepsis patient with serious thrombocytopenia during the treatment of continuous renal replacement therapy (CRRT) is still high, usually considered that platelet count less than $50 \times 10^9/L$ to continue to give invasive diagnosis and treatment, such as CRRT who need to give the corresponding

收稿日期 (Date of reception): 2020-03-26

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treatment. This article use a retrospective study of a small samples of these patients comparing the treatments response of transfusion of fresh platelets, frozen platelet transfusion, recombinant human thrombopoietin, recombinant human thrombopoietin combined with infusion of fresh platelets, it is desirable for provided some help to clinical treatment for sepsis patients with thrombocytopenia who need uninterrupted CRRT. **Methods:** All 118 patients with sepsis whose peripheral platelet count decreased to $\leq 50 \times 10^9/L$ after CRRT treatment in our department from January 2011 to November 2016 were selected as the research objects. According to the different treatment methods, they were divided into three groups: untreated group (23 cases), fresh platelet group (29 cases), frozen blood platelet group (25 cases), recombinant human thrombopoietin group (20 cases), and fresh platelet group (21 cases). The treatment reactions of 24 h and 72 h after treatment were compared and observed. **Results:** The platelet count before treatment was in different levels on the rest of the various treatment response is different. when the platelet count $< 30 \times 10^9/L$, all treatment methods were ineffective evaluated after 24 h and 72 h; the efficacy of recombinant human thrombopoietin alone and untreated group were the worst, and there were no significant differences in the other three groups curative effect; mainly therapy is platelet transfusion, lose fresh platelets and frozen apheresis platelets had no significant difference, when platelet count $(30-50) \times 10^9/L$, frozen platelet compared with fresh platelets and fresh platelets in the combination group treated curative efficiency was weaker after 24 h, but weaker after 72 h, and the combination group treatment was a little better than giving fresh platelets but no significant difference between the two group; using recombinant human thrombopoietin alone can slow down the platelet in a certain extent of the decline in margins; optimal treatment is transfusion of fresh platelets with or without recombinant human thrombopoietin, recombinant human thrombopoietin can also be considered with no blood products. **Conclusion:** Sepsis patient continued CRRT treatment with thrombocytopenia, should be based on the number of peripheral blood platelet count, to choose the different treatment option.

Keywords sepsis; continuous renal replacement therapy; thrombocytopenia; recombinant human thrombopoietin

既往对于治疗脓毒症行连续性肾脏替代治疗(continuous renal replacement therapy, CRRT)期间合并血小板减少至 $50 \times 10^9/L$ 以下者主要以输新鲜血小板为主^[1]。但鉴于现国内血源紧张,近年来冰冻血小板临床输注亦占很大比例,目前国内关于输注冰冻血小板与新鲜血小板治疗的研究仍较少,比如国内尚无关于血小板不同水平时输注冰冻血小板与新鲜血小板的疗效比较,期望本文研究结果可为临床治疗及后续研究提供一定的帮助及参考。近年来,对于重组人血小板生成素在脓症患者合并血小板减少症中的治疗国内亦开始了一些研究,且结果提示重组人血小板生成素对治疗有益^[2]。本研究以不同血小板水平的脓毒症行CRRT的患者为研究对象评估对其输注重组人血小板生成素、血小板的疗效,以期血小板来源紧张的临床治疗提供一定的参考。

1 对象与方法

1.1 对象

回顾性收集了2011年1月至2016年11月镇

江市第一人民医院重症医学科118例脓毒症行CRRT出现外周血血小板计数下降至 $\leq 50 \times 10^9/L$ 的患者的临床资料。这些患者均处在脓毒症发病急性期、血小板减少后未停用CRRT。患者年龄18~82(61.2 ± 12.7)岁。男66例,女52例。排除了合并血液病、严重肝病、脾功能亢进、自身免疫性疾病等合并慢性的血小板减少症的患者。本次研究获得镇江市第一人民医院医学伦理委员会批准。

1.2 方法

将上述对象根据治疗方法不同分为:未治疗组、输注新鲜血小板组、输注冰冻血小板组、皮下注射重组人血小板生成素组、输新鲜血小板联合皮下注射重组人促血小板生成素组。比较患者在治疗前外周血常规血小板计数处于不同水平 $[(30-50) \times 10^9/L, < 30 \times 10^9/L]$ 时各种方案治疗后24 h, 72 h血小板计数较治疗前的变化情况,并进一步评估治疗效果。每例患者给予上述治疗次数为每日1次,未治疗组未予任何治疗(表1)。新

鲜血血小板及冰冻血小板来源为镇江市血液中心, 使用方法为静脉输注, 每次用1个治疗量。重组人血小板生成素为沈阳三生制药有限公司生产, 规格为12 000 U/支, 用法为皮下注射12 000 U/d。

表1 各治疗应用前血小板不同水平相应的病例数

Table 1 Number of cases with different levels of platelets before each treatment

组别	治疗前血小板计数/($\times 10^9 \cdot L^{-1}$)	
	30~50	<30
未治疗组/例	13	10
新鲜血小板组/例	14	15
冰冻血小板组/例	12	13
重组人血小板生成素组/例	10	10
重组人血小板生成素及新鲜血小板组/例	10	11

未治疗组为每一例病例每24 h算1次, 其余治疗组每一例患者相应给予治疗为每日1次。

In the untreated group, each case was counted once every 24 hours, while in the other treatment groups, each patient was given treatment once a day.

1.3 统计学处理

采用SPSS 18.00软件进行统计处理, 计量资料以均数 \pm 标准差($\bar{x} \pm s$)表示, 采用 t 检验; 计数资料以例(%)表示, 采用方差分析。 $P < 0.05$ 表示差异有统计学意义。

2 结果

在治疗前外周血血小板计数在 $(30 \sim 50) \times 10^9/L$ 时, 输注新鲜血小板组和输注重组人血小板生成素联合新鲜血小板组治疗24 h及72 h, 差异无统计学意义($P > 0.05$), 当血小板数 $< 30 \times 10^9/L$ 时, 所有治疗方法疗效在24 h及72 h评估均不理想; 单用重组人血小板生成素疗效最差与未治疗组无统计学差异, 其余3组治疗疗效差异无统计学意义($P > 0.05$)。此时治疗上应以输血小板治疗为主, 输新鲜血小板与冰冻血小板疗效差异无统计学意义($P > 0.05$)。当血小板数 $(30 \sim 50) \times 10^9/L$ 时, 输冰冻血小板较新鲜血小板及新鲜血小板联合药物组治

疗24 h疗效相近, 但治疗72 h后疗效差, 且联合治疗组在72 h时疗效略优于输新鲜血小板, 但无差异统计学意义($P > 0.05$)。单用重组人血小板生成素可在一定程度上减缓血小板的下降幅度(表2~3)。

表2 不同血小板水平下给予不同治疗后24小时的治疗反应

Table 2 Treatment response 24 hours after different treatments given at different platelet levels

组别	治疗24 h血小板变化及均值/ 治疗前血小板水平/($\times 10^9 \cdot L^{-1}$)	
	30~50	<30
未治疗组	-14.0 ± 3.5	-9.2 ± 1.7
新鲜血小板组	6.7 ± 0.6	-4.3 ± 1.3
冰冻血小板组	7.0 ± 0.4	-4.6 ± 0.8
重组人血小板生成素组	-10.5 ± 2.3	-8.1 ± 1.0
重组人血小板生成素及新鲜血小板组	$+6.5 \pm 1.6$	-4.9 ± 1.1

数值为正示其较治疗前血小板增加值, 数值为负示其较治疗前较少值。

The positive value indicates that the platelet increase value is higher than that before treatment, and the negative value indicates that it is less than that before treatment.

表3 不同血小板水平下给予不同治疗后的72小时的治疗反应

Table 3 72-hour treatment response after different treatments at different platelet levels

组别	治疗72 h血小板变化 / 治疗前血小板水平 ($\times 10^9 \cdot L^{-1}$)	
	30~50	<30
未治疗组	-16.7 ± 2.4	-15.3 ± 3.1
新鲜血小板组	8.3 ± 0.5	-5.8 ± 0.9
冰冻血小板组	-5.1 ± 0.7	-7.0 ± 1.4
重组人血小板生成素组	-12.0 ± 1.9	-15.2 ± 2.7
重组人血小板生成素及新鲜血小板组	$+10.9 \pm 1.7$	-6.5 ± 0.6

数值为正示其较治疗前血小板增加值, 数值为负示其较治疗前较少值。

The positive value indicates that the platelet increase value is higher than that before treatment, and the negative value indicates that it is less than that before treatment.

3 讨论

脓毒症的定义为感染导致全身炎症反应综合征, 是机体对感染的反应失控引起的致命性器官功能障碍, 病情危重^[3]。脓毒症的发病率及病死率仍极高^[4]。而CRRT对于病情不稳定的及进展中的脓毒症患者的血液、体液平衡管理是一个极有效的疗法^[5]。脓症患者本身可因细菌、毒素、病毒、抗生素使用等引起骨髓移植抑制、血小板破坏、弥散性血管内凝血等因素导致血小板下降^[6]。而对脓症患者行CRRT会在一定程度上进一步加重血小板减少, 危重症行肝素化CRRT的患者有70%会出现血小板减少症^[7], 行无肝素化的CRRT导致患者血小板减少者亦占25%^[8]。国内有研究^[9]显示, 行CRRT期间新发的血小板减少主要与骨髓抑制有关, 并提示接受CRRT的患者出现血小板的严重下降预示着预后更差, 需要临床医师寻求可能的病因。目前临床已广泛并常规将重组人血小板生成素用于化疗后骨髓抑制及特发性血小板减少性紫癜等骨髓血小板生成障碍性血液系统疾病引起的血小板减少症。而近年来亦有国内研究开始着眼于脓毒症引起血小板减少症中重组人血小板生成素的疗效研究。

血小板减少症的定义为外周血血小板计数小于 $100 \times 10^9/L$, 严重血小板减少症为血小板小于 $50 \times 10^9/L$ 。血小板减少见于8.3%~67.6%的危重症患者中。研究^[10]提示: 血小板减少可增加脓症患者病死率, 且提示血小板减少与骨髓抑制程度呈正相关。Ronco等^[11]的研究中指出: 血小板减少症是危重症的常见并发症, 是重症监护病房(intensive care unit, ICU)出血和死亡的独立危险因素, 并指出在轻度血小板减少的患者中给予血小板治疗后存在较大的个体差异(单次输注血小板治疗后约6.7 h后血小板多数患者可提升约21%, 而少数患者升高幅度小于5%, 甚至可有下降), 多次输注可导致无效输注, 病死率升高。可见合理提升血小板水平在脓毒症行CRRT出现血小板减少时是非常必要的。

对该类患者提升血小板数的治疗国内外仍主要以输注血小板为主, 近年来国内亦开始着眼于重组人血小板生成素的治疗评价。有研究^[12]提示: 重组人血小板生成素对脓毒症相关血小板减少症中的应用可有助于血小板计数的恢复。而另一项国内关于重组人血小板生成素应用于脓毒症血小板减少患者的作用的小样本试验研究^[13]初步证实了重组人血小板生成素可以改善脓毒症血小

板减少患者的血小板计数, 在应用24 h有初步疗效, 在应用72 h即可有明显疗效。通过本文的回顾性研究可见, 对行CRRT的脓症患者, 在外周血血小板计数 $(30 \sim 50) \times 10^9/L$ 时输新鲜血小板、输新鲜血小板联合重组人血小板生成素疗效最佳, 单用重组人血小板生成素可减少血小板的下降幅度, 考虑可能与此时骨髓抑制尚不严重可能有关, 亦有可能与重组人血小板生成素可对脓毒症血小板有一定保护作用, 从而减少了血小板破坏有关; 而输冰冻血小板72 h疗效较输注新鲜血小板差, 考虑可能与CRRT管路及脓毒症对更易破坏的冰冻血小板有关, 亦不排除冰冻血小板多次输注更容易破坏所致; 无血源时可考虑使用重组人血小板生成素。在血小板数 $<30 \times 10^9/L$ 时, 输注冰冻血小板与新鲜血小板治疗的短期疗效相近、疗效有限, 对重组人血小板生成素治疗无反应, 考虑可能与此时脓毒症导致血小板破坏合并骨髓严重抑制有关, 以致对重组人血小板生成素治疗无反应, 亦不排除重组人血小板生成素可能此时对外周血小板已无保护作用; 此时最合理的治疗应在输血小板同时积极治疗原发病, 同时评估是否需继续进行CRRT。

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本文引用: 任艳艳, 金兆辰, 杨宏峰, 蔡燕, 赵东亚. 脓毒症患者行 CRRT 时合并严重血小板减少不同治疗的疗效比较[J]. 临床与病理杂志, 2020, 40(9): 2345-2349. doi: 10.3978/j.issn.2095-6959.2020.09.021

Cite this article as: REN Yanyan, JIN Zhaochen, YANG Hongfeng, CAI Yan, ZHAO Dongya. Comparing the efficacy of different treatments in sepsis patients using CRRT with serious thrombocytopenia[J]. Journal of Clinical and Pathological Research, 2020, 40(9): 2345-2349. doi: 10.3978/j.issn.2095-6959.2020.09.021