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Effects of different therapeutic doses of CRRT on serum PGE2 and I-FABP levels and prognosis in patients with severe sepsis

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Abstract: Objective To analyze the effects of continuous renal replacement therapy (CRRT) dose on serum prostaglandin-2 (PGE2) and intestinal fatty acid-binding protein (I-FABP) levels and prognosis in patients with severe sepsis, and to reveal the dynamic pattern of change. **Methods** A total of 115 patients with severe sepsis treated in Qianjiang Central Hospital of Chongqing from May 2021 to May 2024 were selected as the study subjects. They were divided into Group A (38 cases), Group B (37 cases) and Group C (40 cases). Group A, Group B, and Group C were given CRRT treatment doses of 20 mL/ (kg·h), 25 mL/ (kg·h), and 30 mL/ (kg·h), respectively. After 7 days of treatment, enzyme-linked immunosorbent assay (ELISA) was used to detect intestinal mucosal barrier function indicators [endotoxin, diamine oxidase (DAO), D-lactic acid]as well as the levels of PGE2 and I-FABP. Flow cytometry was employed to measure immune function indicators ($CD4^+$, $CD8^+$, and $CD4^+/CD8^+$). The Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score and Sequential Organ Failure Assessment (SOFA) score were used to evaluate prognosis. **Results** After treatment, the levels of endotoxin, DAO, D-lactic acid, $CD8^+$, PGE2 and I-FABP in all groups were decreased, and which in Group C were lower than those in Group A and Group B (P<0.05). After treatment, the levels of $CD4^+$ and $CD4^+/CD8^+$ in all groups were increased, and the levels in Group C were higher than those in Group A and Group B (P<0.05). After treatment, APACHE Ⅱ and SOFA scores were decreased in all groups, and which in Group C were lower than those in Group A and Group B (P<0.05). **Conclusion** Patients with severe sepsis who receive different doses of CRRT treatment can improve their intestinal mucosal barrier function and immune function, inhibit serum PGE2 and I-FABP levels, and high-dose patients have better treatment effects, which can promote patient prognosis.

Keywords: Severe sepsis; Continuous renal replacement therapy; Dose of treatment; Prostaglandin-2; Intestinal fatty acid binding protein; Intestinal mucosal barrier function; Immune function; Prognosis

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Sepsis is a systemic inflammatory disease caused by infection. After clinical onset, symptoms such as chills and shortness of breath may appear, which might affect the prognosis of patients. When organ failure occurs in septic patients, it can lead to severe sepsis [1-2]. Severe sepsis primarily manifests as gastrointestinal dysfunction, immune system disorders, exacerbated inflammatory response, accompanied by impaired consciousness and hypotension. This can further damage the patient's intestinal mucosal barrier, lead to multiple organ failure, and result in a high mortality rate [3]. Continuous renal replacement therapy (CRRT) is an effective treatment for severe sepsis, capable of removing inflammatory factors and toxic substances from the patient's body, with relatively good clinical efficacy [4]. The effectiveness of CRRT with different doses for treating severe sepsis varies clinically. Based on this, this study analyzes the impact of different doses of CRRT on the prognosis and outcomes of patients with severe sepsis.

1 Data and Methods

1.1 General Data

The sample size for this study was determined based on $N=Z^2\times[P\times(1-P)]/E^2$. N referred to the sample size; Z refereed to the statistic (Z=1.96 for 95% confidence level); E referred to the margin of error (0.05); P referred to the probability value (0.08). The calculated sample size was $N=1.96^2\times[0.08\times(1-0.08)]/0.05^2 \approx 114$. Considered there might be a 2% dropout rate, a total of 120 patients with severe sepsis treated at Qianjiang Hospital Affiliated to Chongqing University from May 2021 to May 2024 were selected as study subjects. The patients were divided into three groups according to the clinical treatment dose, with 40 cases in each group. During the study, 2 cases from Group A and 3 cases from Group B withdrew. The general data of each group were balanced and comparable (P>0.05). See **Table 1**. This study was approved by the Ethics Committee of Qianjiang Hospital Affiliated to Chongqing University [Approval No.: (2021) Ethics Review (17)].

Inclusion criteria: Meeting the diagnostic criteria in the *Expert Consensus on Diagnosis and Treatment of Sepsis-Induced Immunosuppression* [5]; Patients able to communicate normally; Presence of water-electrolyte and acid-base imbalance; Patients and their families provided informed consent.

Exclusion criteria: Recent use of antibiotics or immunosuppressants; Complicated with gastro-intestinal tumors; Suffering from severe organ dysfunction; Previous gastrointestinal surgery; End-stage chronic disease; Coagulation dysfunction.

Tab.1 Comparison of general data among 3 groups

Indicator	Group A (n=38)	Group B (n=37)	Group C (n=40)	F/χ^2 value	P value
Age(years, $\bar{x}\pm s$)	65.22±2.14	65.19±2.12	65.27±2.16	0.014	0.986
Gender [case(%)]					
Male	20(52.63)	18(48.65)	22(55.00)	0.316	0.854
Female	18(47.37)	19(51.35)	18(45.00)		

1.2 Treatment Methods

After admission, patients received anti-infective treatment, blood glucose control, and correction of the internal environment. Vital signs were monitored, and health education and dietary guidance were provided. Subsequently, patients underwent CRRT treatment. Anticoagulation was performed using low molecular weight heparin calcium. A double-lumen catheter was placed in the internal jugular vein to establish vascular access, with a blood flow rate set at 160-250 mL/min for continuous treatment over 24 hours. Group A (38 patients) received a treatment dose of 20 mL/(kg·h); Group B (37 patients) received 25 mL/(kg·h); Group C (40 patients) received 30 mL/(kg·h). All patients were treated for 7 days.

1.3 Indicator Detection

1.3.1 Intestinal Mucosal Barrier Function, Prostaglandin-2 (PGE2), and Intestinal Fatty Acid Binding Protein (I-FABP) Levels

Four mL of venous blood was collected from patients under fasting conditions, left to stand for 30 minutes, and centrifuged (15 min, 3,500 r/min, radius 5 cm) to separate serum. The serum was stored in a -80 °C freezer for later use. Levels of endotoxin, diamine oxidase (DAO), *D*-lactic acid (*D*-Lac), PGE2, and I-FABP were detected by ELISA. Sample wells, standard wells, and blank wells were designed in the microplate. 50 μL of the test sample was added to the sample wells. Then, 50 μL of standard solutions for endotoxin, DAO, *D*-Lac, PGE2, and I-FABP from patients receiving different doses were added to the standard wells. Fifty μL of horseradish peroxidase was added to each well, followed by incubation at room temperature for 60 minutes. The wells were washed with wash buffer. Then, 50 μL of Substrate A and Substrate B were added to each well, followed by incubation at 37 °C for 15 minutes. After that, stop solution was added. The OD value of each well at 450 nm wavelength was measured using a microplate reader, and the levels of endotoxin, DAO, *D*-Lac, PGE2, and I-FABP were calculated.

1.3.2 Immune Function Detection

Four mL of venous blood was collected from patients under fasting conditions for later use. Flow cytometry was used to detect $CD4^+$ and $CD8^+$ levels, and the $CD4^+/CD8^+$ ratio was calculated.

1.3.3 Prognosis Observation

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score were used to assess prognosis. The maximum APACHE II score is 71 points, and the maximum SOFA score is 24 points. Higher scores indicate a worse prognosis.

1.4 Statistical Methods

SPSS 19.0 software was used to analyze the data. Measurement data conforming to a normal distribution were described by $\bar{x}\pm s$. Paired *t*-test was used to analyze differences before and after treatment within each group. One-way analysis of variance (ANOVA) was used for comparisons among multiple groups, and further pairwise comparisons were performed using the LSD-*t* test. Count data were expressed as case (%), and comparisons between groups were made using the chi-square test. $P<0.05$ was considered statistically significant.

2 Results

2.1 Comparison of Intestinal Mucosal Barrier Function Indicators

Before treatment, there was no significant difference in the levels of intestinal mucosal barrier function indicators among the groups ($P>0.05$). After treatment, the levels of endotoxin, DAO, and *D*-Lac in each group were significantly lower than those before treatment ($P<0.05$). Furthermore, the levels of endotoxin, DAO, and *D*-Lac in Group C were lower than those in Group A and Group B ($P<0.05$). See **Table 2**.

2.2 Comparison of Immune Function Indicators

Before treatment, there was no significant difference in the levels of immune function indicators among the groups ($P>0.05$). After treatment, the levels of $CD4^+$ and $CD4^+/CD8^+$ increased in each group, while the $CD8^+$ level decreased. The levels of $CD4^+$ and $CD4^+/CD8^+$ in Group C were higher than those in Group A and Group B, and the $CD8^+$ level in Group C was lower than that in Group A and Group B ($P<0.05$). See **Table 3**.

2.3 Comparison of Serum PGE2 and I-FABP

Before treatment, there was no significant difference in serum PGE2 and I-FABP levels among the groups ($P>0.05$). After treatment, the levels of PGE2 and I-FABP in Group C were lower than those in Group A and Group B ($P<0.05$). See **Table 4**.

2.4 Comparison of Prognostic Indicators

Before treatment, there were no statistically significant differences in APACHE II and SOFA scores among the groups ($P>0.05$). After treatment, the APACHE II and SOFA scores decreased in all groups, and the APACHE II and SOFA scores in Group C were significantly lower than those in Group A and Group B ($P<0.05$). See **Table 5**.

Tab.2 Comparison of the indicators of intestinal mucosal barrier function among 3 groups ($\bar{x}$ ±*s*)

Group	Endotoxin(u/L)		DAO(u/L)		*D*-Lac(mmol/L)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Group A (*n*=38)	10.23±2.14	8.02±0.93a	14.25±2.33	8.23±0.95a	35.21±4.36	21.52±3.69a
Group B (*n*=37)	10.26±2.16	7.32±0.85ab	14.31±2.36	6.59±0.73ab	35.18±4.33	18.25±2.74ab
Group C (*n*=40)	10.21±2.12	3.25±0.43abc	14.22±2.30	4.11±0.56abc	35.25±4.39	12.15±2.15abc
***F* value**	0.005	446.393	0.015	290.678	0.003	103.865
***P* value**	0.995	<0.001	0.985	<0.001	0.998	<0.001

Note: Compared with before treatment, $^{a}P<0.05$; compared with Group A, $^{b}P<0.05$; compared with Group B, $^{c}P<0.05$.

Tab.3 Comparison of the indicators of immune function among 3 groups ($\bar{x}$ ±*s*)

Group	$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Group A (*n*=38)	22.25±3.12	27.21±3.48a	23.56±3.45	20.14±3.04a	0.94±0.09	1.35±0.23a
Group B (*n*=37)	22.28±3.14	30.45±4.11ab	23.52±3.41	17.25±2.85ab	0.95±0.07	1.77±0.26ab
Group C (*n*=40)	22.23±3.10	35.96±4.77abc	23.54±3.46	13.22±2.16abc	0.94±0.08	2.72±0.31abc
***F* value**	0.003	44.113	0.001	64.764	0.194	265.449
***P* value**	0.998	<0.001	0.998	<0.001	0.824	<0.001

Note: Compared with before treatment, $^{a}P<0.05$; Compared with Group A, $^{b}P<0.05$; Compared with Group B, $^{c}P<0.05$.

Tab.4 Comparison of the levels of serum PGE2, I-FABP among 3 groups (μg/L, $\bar{x}$ ±*s*)

Group	PGE2		I-FABP	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Group A (*n*=38)	756.36±88.47	632.25±75.14^{a}	38.82±4.33	29.54±3.96^{a}
Group B (*n*=37)	758.41±89.23	601.33±71.36^{ab}	39.01±4.39	26.11±3.75^{ab}
Group C (*n*=40)	755.23±87.58	564.12±64.25^{abc}	38.95±4.36	21.02±3.11^{abc}
***F* value**	0.013	9.197	0.019	64.969
***P* value**	0.987	<0.001	0.982	<0.001

Note: Compared with before treatment, $^{a}P<0.05$; Compared with Group A, $^{b}P<0.05$; Compared with Group B, $^{c}P<0.05$.

Tab.5 Comparison of the prognosis indicators among 3 groups (point, $\bar{x}$ ±*s*)

Group	APACHE II		SOFA	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Group A (*n*=38)	26.11±3.42	17.25±2.36^{a}	14.65±2.75	8.79±0.95^{a}
Group B (*n*=37)	26.08±3.40	14.55±2.12^{ab}	14.53±2.73	5.36±0.66^{ab}
Group C (*n*=40)	26.14±3.44	11.02±2.03^{abc}	14.68±2.77	3.11±0.42^{abc}
***F* value**	0.003	80.781	0.032	635.941
***P* value**	0.997	<0.001	0.969	<0.001

Note: Compared with before treatment, $^{a}P<0.05$; Compared with Group A, $^{b}P<0.05$; Compared with Group B, $^{c}P<0.05$.

3 Conclusion

Sepsis is mostly caused by infection. Deterioration of the patient's condition can progress to severe sepsis, leading to an increased clinical mortality rate [6-7]. CRRT is a common method for treating critical illnesses. It removes harmful factors and excess fluid from the patient's body through extracorporeal circulation, thereby restoring the stability of the internal environment [8-9]. This study showed that treatment with different doses of CRRT resulted in varying degrees of improvement in patients' APACHE Ⅱ and SOFA scores. High-dose CRRT was more effective than low-dose CRRT, as it reduced APACHE Ⅱ and SOFA scores and $CD8^+$ levels, increased $CD4^+$ and $CD4^+/CD8^+$ levels, and improved immune function and patient prognosis. The reason for this may be that high-dose CRRT treatment can restore the function of immune cells, correct the internal environment, and thereby improve patient prognosis.

After the development of severe sepsis, damage exists in multiple organs within the body. Damage to the gastrointestinal tract can manifest as decreased intestinal mucosal barrier function and disruption of the balance between beneficial and harmful bacteria [10]. The occurrence of sepsis damages the body's immune function, affecting the patient's clinical recovery. Impaired intestinal mucosal barrier function can promote the release of inflammatory mediators and endotoxins, worsening the patient's condition [11-12]. Endotoxin is an important product produced by Gram-negative bacilli, primarily derived from intestinal bacteria. When intestinal barrier function is impaired, endotoxin translocate through the intestinal mucosal epithelium into the circulation, forming endotoxemia, which can assess the status of bacterial translocation. DAO is a marker enzyme of intestinal mucosal cells, located in the upper layer of small intestinal villi. When the intestinal mucosa is damaged, DAO is released in large quantities into the blood, reflecting the structural integrity of the intestinal mucosa. *D*-Lac is a metabolic end product of indigenous intestinal bacteria. *D*-Lac in the blood basically originates from the intestine and is an indicator for assessing intestinal wall permeability [13-15]. This study showed that as the CRRT treatment dose increased, the serum levels of endotoxin, DAO, and *D*-Lac in patients with severe sepsis gradually decreased, with the lowest levels found in patients receiving the highest treatment dose. This indicates that high-dose CRRT can promote the recovery of intestinal mucosal barrier function in patients. The reason may be that high-dose CRRT treatment has a better clearance effect on endotoxins and inflammatory factors in the body, which can reduce intestinal mucosal barrier damage, decrease cell apoptosis, and restore intestinal mucosal barrier function.

The core of sepsis lies in the overactivation of the immune system after pathogen invasion, releasing a large number of inflammatory factors and leading to a "cytokine storm", which damages the body's own tissues [16-18]. PGE2 is an important mediator of inflammatory responses. It can inhibit the activity of T lymphocytes, macrophages, and neutrophils, reduce the release of leukocyte factors. Furthermore, PGE2 can inhibit the expression of inflammatory factors and has anti-inflammatory effects [19]. After the onset of sepsis, it stimulates macrophages, promoting downstream cells to secrete PGE2 and

increasing the level of PGE2 in the body [20]. I-FABP is a specific small molecular cytoplasmic protein secreted by mature intestinal epithelial cells. Under physiological conditions, its level in the peripheral circulation is very low. It is rapidly released into the bloodstream after intestinal mucosal injury. Studies have confirmed that serum I-FABP levels can reflect early (⩽ 24 h) intestinal epithelial cell damage in septic patients; evidence suggests that I-FABP is very sensitive, and its elevated levels can be detected in the blood even when histological damage is only mild during the early stages of intestinal ischemia [21-22]. This study showed that after CRRT treatment, the levels of PGE2 and I-FABP in Group C were lower than those in Groups A and B, and the levels in Group B were lower than those in Group A. This indicates that increasing the CRRT treatment dose can enhance the inhibitory effect on the expression of PGE2 and I-FABP, reduce the patient's inflammatory response, and promote the recovery of intestinal function. The reason may be that high-dose CRRT has a higher clearance effect on inflammatory mediators, which can reduce intestinal mucosal barrier damage, restore the patient's immune function, and improve patient prognosis.

In summary, different doses of CRRT result in different clinical treatment effects. High-dose CRRT treatment has a more significant effect on reducing serum PGE2 and I-FABP levels in patients with severe sepsis, can protect intestinal mucosal barrier function, restore the body's immune function, and enable patients to achieve a better prognosis.

Conflict of Interest None

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·论 著·

不同CRRT治疗剂量对严重脓毒症患者血清PGE2和I-FABP水平及预后的影响

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摘要：目的 分析连续性肾脏替代疗法（CRRT）治疗剂量对严重脓毒症患者血清前列腺素-2（PGE2）、肠型脂肪酸结合蛋白（I-FABP）表达水平及预后的影响，揭示其动态变化规律。**方法** 选取2021年5月至2024年5月在重庆大学附属黔江医院治疗的115例严重脓毒症患者进行研究，按照CRRT临床治疗剂量分为3组，A组38例，B组37例，C组40例，A组给予治疗剂量25 mL/（kg·h），B组给予治疗剂量30 mL/（kg·h），C组给予治疗剂量35 mL/（kg·h）。治疗7 d后，采用酶联免疫吸附法（ELISA）检测肠黏膜屏障功能[内毒素、二胺氧化酶（DAO）、*D*-乳酸]和PGE2、I-FABP水平，采用流式细胞仪检测免疫功能（$CD4^+$、$CD8^+$及$CD4^+/CD8^+$），采用急性生理学及慢性健康状况（APACHE Ⅱ）评分、序贯器官衰竭评估（SOFA）评分评估预后。**结果** 治疗后，各组患者内毒素、DAO、*D*-乳酸、$CD8^+$、PGE2、I-FABP水平显著降低，且C组低于A组、B组（$P<0.05$）。治疗后，各组患者$CD4^+$、$CD4^+/CD8^+$水平显著升高，且C组高于A组、B组（$P<0.05$）。治疗后，各组患者APACHE Ⅱ、SOFA评分显著降低，且C组低于A组、B组（$P<0.05$）。**结论** 严重脓毒症患者采用CRRT治疗，可改善患者肠黏膜屏障功能，降低血清PGE2、I-FABP水平，且大剂量患者治疗效果较好，可改善患者预后。

关键词： 严重脓毒症；连续性肾脏替代疗法；治疗剂量；前列腺素-2；肠型脂肪酸结合蛋白；肠黏膜屏障功能；免疫功能；预后
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Effects of different therapeutic doses of CRRT on serum PGE2 and I-FABP levels and prognosis in patients with severe sepsis

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Abstract: Objective To analyze the effects of continuous renal replacement therapy (CRRT) dose on serum prostaglandin-2 (PGE2) and intestinal fatty acid-binding protein (I-FABP) levels and prognosis in patients with severe sepsis, and to reveal the dynamic pattern of change. **Methods** A total of 115 patients with severe sepsis treated in Qianjiang Central Hospital of Chongqing from May 2021 to May 2024 were selected as the study subjects. They were divided into group A (38 cases), group B (37 cases) and group C (40 cases). Group A, group B, and group C were given CRRT treatment doses of 25 mL/(kg·h), 30 mL/(kg·h), and 35 mL/(kg·h), respectively. After 7 days of treatment, enzyme-linked immunosorbent assay (ELISA) was used to detect intestinal mucosal barrier function indicators [endotoxin, diamine oxidase (DAO), *D*-lactic acid] as well as the levels of PGE2 and I-FABP. Flow cytometry was employed to measure immune function indicators ($CD4^+$, $CD8^+$, and $CD4^+/CD8^+$). The Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score and Sequential Organ Failure Assessment (SOFA) score were used to evaluate prognosis. **Results** After treatment, the levels of endotoxin, DAO, *D*-lactic acid, $CD8^+$, PGE2 and I-FABP in all

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groups were decreased, and which in group C were lower than those in group A and group B (P<0.05). After treatment, the levels of $CD4^+$ and $CD4^+/CD8^+$ in all groups were increased, and the levels in group C were higher than those in group A and group B (P<0.05). After treatment, APACHE Ⅱ and SOFA scores were decreased in all groups, and which in group C were lower than those in group A and group B (P<0.05). **Conclusion** CRRT treatment with different doses can improve intestinal mucosal barrier function and immune function in patients with severe sepsis, reduce serum PGE2 and I-FABP levels, and the high-dose group achieves better therapeutic effects, which can improve patient prognosis.

Keywords: Severe sepsis; Continuous renal replacement therapy; Therapeutic dose; Prostaglandin-2; Intestinal fatty acid binding protein; Intestinal mucosal barrier function; Immune function; Prognosis

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脓毒症是由感染引起的全身炎症性疾病，发病后可出现寒战、气促等症状，影响患者的预后，当脓毒症患者发生器官功能衰竭时，即为严重脓毒症[1-2]。严重脓毒症主要表现为胃肠道功能障碍、免疫系统紊乱、炎症反应加重，且伴有意识障碍、低血压，可进一步损伤患者肠道黏膜屏障，使患者多器官功能衰竭，导致较高的病死率[3]。连续性肾脏替代治疗(continuous renal replacement therapy，CRRT)为严重脓毒症的有效治疗方式，可清除患者体内的炎症因子、有毒物质，其临床治疗效果较好[4]。临床对于不同剂量CRRT治疗严重脓毒症的效果不同。基于此，本研究分析不同剂量CRRT治疗对严重脓毒症患者预后转归的影响。

1 资料与方法

1.1 一般资料 本次研究样本量选取依据$N=Z^2\times[P\times(1-P)]/E^2$。其中$N$为样本量；$Z$为统计量，置信度为95%时，$Z$=1.96，置信度为90%时，$Z$=1.64；$E$为误差值0.05；$P$为概率值0.08，经计算样本量$N=1.96^2\times[0.08\times(1-0.08)]/0.05^2\approx114$例，考虑到2%的脱落率，本研究共选取120例于2021年5月至2024年5月在重庆大学附属黔江医院接受治疗的严重脓毒症患者为研究对象。按照临床治疗剂量分为3组，各40例。研究过程中A组2例退出研究，B组3例退出研究。各组一般资料均衡可比(P>0.05)。见表1。本研究经重庆大学附属黔江医院伦理委员会批准[批件编号：(2021)伦审第(17)号]。纳入标准：符合《脓毒症免疫抑制诊治专家共识》[5]中的诊断标准；患者均可正常交流；水电解质、酸碱失衡；患者及家属均知情同意。排除标准：近期服用抗生素、免疫抑制剂治疗；合并胃肠道肿瘤；患有严重脏器功能不全；进行过胃肠道手术；患有终末期慢性疾病；合并凝血功能障碍。

1.2 治疗方法 患者入院后，给予抗感染、控制血糖、纠正内环境治疗，并监测患者生命体征，对患者进行健康教育、饮食指导。随后，对患者采用CRRT治疗，使用低分子肝素钙进行抗凝处理，并于颈内静脉处留置双腔导管，建立血管通道，设置血流量160~250 mL/min，连续治疗24 h。A组患者给予治疗剂量25 mL/(kg·h)；B组患者给予治疗剂量30 mL/(kg·h)；C组患者给予治疗剂量35 mL/(kg·h)，所有患者均治疗7 d。

表1 3组一般资料比较

Tab.1 Comparison of general data among 3 groups

指标		A组(n=38)	B组(n=37)	C组(n=40)	F/χ^2值	P值
年龄(岁)[a]		65.22±2.14	65.19±2.12	65.27±2.16	0.014	0.986
性别[b]	男	20(52.63)	18(48.65)	22(55.00)	0.316	0.854
	女	18(47.37)	19(51.35)	18(45.00)		

注：[a]以$\bar{x}\pm s$表示；[b]以例(%)表示。

1.3 指标检测

1.3.1 肠黏膜屏障功能、前列腺素-2(prostaglandin-2，PGE2)、肠型脂肪酸结合蛋白(intestinal fatty acid binding protein，I-FABP)水平检测 空腹下采集患者4 mL静脉血，静置30 min，用离心机(15 min，3 500 r/min，半径5 cm)进行操作，分离血清，于-80 ℃冰箱内存储，待用。采用酶联免疫吸附法(ELISA)检测内毒素、二胺氧化酶(diamine oxidase，DAO)、*D*-乳酸(*D*-lactic acid，*D*-Lac)、PGE2、I-FABP水平，在微孔酶标板中设置样品孔、标准品孔、空白孔，将50 μL待测样品加入样品孔，后在标准品孔中加入不同浓度的内毒素、DAO、*D*-Lac、PGE2、I-FABP标准品各50 μL，并在各个孔中加入50 μL辣根过氧化物酶，室温下孵育60 min，加入洗涤缓冲液进行清洗，后在各个孔中加入50 μL底物A与底物B，37 ℃下，孵育15 min，加入终止液，采用酶标仪测定450 nm波长下各孔的OD值，计算内毒素、DAO、*D*-Lac、PGE2、I-FABP水平。

1.3.2 免疫功能检测 空腹采集患者4 mL静脉血待用，采用流式细胞仪检测$CD4^+$、$CD8^+$水平，并计算

$CD4^+/CD8^+$比值。

1.3.3 预后观察 采用急性生理学及慢性健康状况（APACHE Ⅱ）评分、序贯器官衰竭评估（SOFA）评分评估预后，APACHE Ⅱ总分71分，SOFA总分24分，分数越高，预后越差。

1.4 统计学方法 采用SPSS 19.0软件分析数据。符合正态分布的计量资料采用$\bar{x}\pm s$描述，行配对t检验分析各组治疗前后差异，多组间比较采用单因素方差分析，进一步两两比较采用LSD-t检验；计数资料采用例（%）表示，组间比较采用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 各组患者肠黏膜屏障功能指标水平对比 治疗前，各组肠黏膜屏障功能指标水平比较，差异无统计学意义（$P>0.05$）；治疗后各组内毒素、DAO、*D*-Lac均显著低于治疗前（$P<0.05$）；且C组内毒素、DAO、*D*-Lac均低于A组、B组（$P<0.05$）。见表2。

2.2 各组患者免疫功能指标水平对比 治疗前，各组免疫功能指标水平比较，差异无统计学意义（$P>0.05$）；治疗后，各组$CD4^+$、$CD4^+/CD8^+$水平升高，$CD8^+$水平降低，且C组$CD4^+$、$CD4^+/CD8^+$水平高于A组、B组，$CD8^+$低于A组、B组（$P<0.05$）。见表3。

2.3 各组患者血清PGE2、I-FABP水平对比 治疗前，各组血清PGE2、I-FABP水平对比，差异无统计学意义（$P>0.05$）；治疗后，C组PGE2、I-FABP水平均低于A组、B组（$P<0.05$）。见表4。

2.4 各组患者预后指标水平对比 治疗前，各组APACHE Ⅱ、SOFA评分对比，差异无统计学意义（$P>0.05$）；治疗后，各组APACHE Ⅱ、SOFA评分均降低，且C组APACHE Ⅱ、SOFA评分显著低于A组、B组（$P<0.05$）。见表5。

表2 3组患者肠黏膜屏障功能指标对比 （$\bar{x}\pm s$）

Tab.2 Comparison of the indicators of intestinal mucosal barrier function among 3 groups （$\bar{x}\pm s$）

组别	例数	内毒素（u/L）		DAO（u/L）		*D*-Lac（mmol/L）	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
A组	38	10.23±2.14	8.02±0.93[a]	14.25±2.33	8.23±0.95[a]	35.21±4.36	21.52±3.69[a]
B组	37	10.26±2.16	7.32±0.85[ab]	14.31±2.36	6.59±0.73[ab]	35.18±4.33	18.25±2.74[ab]
C组	40	10.21±2.12	3.25±0.43[abc]	14.22±2.30	4.11±0.56[abc]	35.25±4.39	12.15±2.15[abc]
F 值		0.005	446.393	0.015	290.678	0.003	103.865
P 值		0.995	<0.001	0.985	<0.001	0.998	<0.001

注：与治疗前相比，[a]$P<0.05$；与A组相比，[b]$P<0.05$；与B组相比，[c]$P<0.05$。

表3 3组患者免疫功能指标水平对比 （$\bar{x}\pm s$）

Tab.3 Comparison of the indicators of immune function among 3 groups （$\bar{x}\pm s$）

组别	例数	$CD4^+$（%）		$CD8^+$（%）		$CD4^+/CD8^+$	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
A组	38	22.25±3.12	27.21±3.48[a]	23.56±3.45	20.14±3.04[a]	0.94±0.09	1.35±0.23[a]
B组	37	22.28±3.14	30.45±4.11[ab]	23.52±3.41	17.25±2.85[ab]	0.95±0.07	1.77±0.26[ab]
C组	40	22.23±3.10	35.96±4.77[abc]	23.54±3.46	13.22±2.16[abc]	0.94±0.08	2.72±0.31[abc]
F 值		0.003	44.113	0.001	64.764	0.194	265.449
P 值		0.998	<0.001	0.998	<0.001	0.824	<0.001

注：与治疗前相比，[a]$P<0.05$；与A组相比，[b]$P<0.05$；与B组相比，[c]$P<0.05$。

表4 3组患者血清PGE2、I-FABP水平对比 （μg/L，$\bar{x}\pm s$）

Tab.4 Comparison of the levels of serum PGE2, I-FABP among 3 groups （μg/L，$\bar{x}\pm s$）

组别	例数	PGE2		I-FABP	
		治疗前	治疗后	治疗前	治疗后
A组	38	756.36±88.47	632.25±75.14[a]	38.82±4.33	29.54±3.96[a]
B组	37	758.41±89.23	601.33±71.36[ab]	39.01±4.39	26.11±3.75[ab]
C组	40	755.23±87.58	564.12±64.25[abc]	38.95±4.36	21.02±3.11[abc]
F 值		0.013	9.197	0.019	64.969
P 值		0.987	<0.001	0.982	<0.001

注：与治疗前相比，[a]$P<0.05$；与A组相比，[b]$P<0.05$；与B组相比，[c]$P<0.05$。

表5 3组患者预后指标对比 （分，$\bar{x}\pm s$）

Tab.5 Comparison of the prognosis indicators among 3 groups （point，$\bar{x}\pm s$）

组别	例数	APACHE Ⅱ		SOFA	
		治疗前	治疗后	治疗前	治疗后
A组	38	26.11±3.42	17.25±2.36[a]	14.65±2.75	8.79±0.95[a]
B组	37	26.08±3.40	14.55±2.12[ab]	14.53±2.73	5.36±0.66[ab]
C组	40	26.14±3.44	11.02±2.03[abc]	14.68±2.77	3.11±0.42[abc]
F 值		0.003	80.781	0.032	635.941
P 值		0.997	<0.001	0.969	<0.001

注：与治疗前相比，[a]$P<0.05$；与A组相比，[b]$P<0.05$；与B组相比，[c]$P<0.05$。

3 讨　论

脓毒症多为感染导致，患者病情恶化，可发展为严重脓毒症，导致患者临床病死率升高[6-7]。CRRT为治疗危重症的常用方式，通过体外循环清除患者体内有害因子、多余液体，从而恢复内环境的稳定[8-9]。本研究显示，采用不同剂量CRRT治疗，对患者APACHE Ⅱ、SOFA评分改善程度不同，大剂量CRRT的治疗效果优于小剂量CRRT，可降低APACHE Ⅱ、SOFA评分与$CD8^+$水平，升高$CD4^+$、$CD4^+/CD8^+$水平，改善免疫功能和患者预后。分析其原因可能为，采用大剂量CRRT治疗，可促进免疫细胞功能恢复，纠正内环境，进而改善患者的预后。

严重脓毒症发生后，机体内多个器官均存在损伤，胃肠道的损伤可表现为肠黏膜屏障功能下降，有益菌、有害菌的平衡状态被打破[10]。脓毒症发生后，机体的免疫功能受损，患者的临床恢复受到影响，且肠黏膜屏障功能受损可促使炎症介质、内毒素释放，使患者病情加重[11-12]。内毒素是革兰阴性杆菌的一种重要产物，其主要来自肠道细菌，当肠屏障功能发生障碍时，内毒素通过肠黏膜上皮易位进入循环形成内毒素血症，可用于评价细菌易位情况。DAO是肠黏膜细胞的标志酶，存在于小肠绒毛上层，肠黏膜受损时，DAO大量释放入血，其能反映肠黏膜结构的完整性。*D*-Lac是肠道固有细菌的代谢终产物，血液中的*D*-Lac基本上来源于肠道，是评估肠壁通透性的指标[13-15]。本研究显示，随着CRRT的治疗剂量增加，严重脓毒症患者血清中内毒素、DAO、*D*-Lac水平逐渐降低，且最大治疗剂量患者水平最低，表明大剂量CRRT可促使患者的肠黏膜屏障功能恢复。分析原因可能为，采用大剂量CRRT治疗对机体内毒素、炎症因子的清除效果较好，可使肠黏膜屏障损伤减轻，细胞凋亡量减少，恢复肠黏膜屏障功能[16-17]。

脓毒症的核心在于病原体侵入后，免疫系统过度激活，释放大量炎症因子，导致“细胞因子风暴”，损伤自身组织[18-20]。PGE2为炎症反应发生的重要介质，可抑制T淋巴细胞、巨噬细胞、中性粒细胞的活性，减少细胞因子的释放，且PGE2可抑制炎症因子的表达，具有抗炎作用[21]。脓毒症对巨噬细胞产生刺激作用，促进下游细胞分泌PGE2，体内PGE2水平增加[22]。I-FABP是成熟肠上皮细胞特有的小分子胞质蛋白，生理条件下在外周循环中水平很低，在肠黏膜损伤后迅速释放到血液循环中，研究证实血清I-FABP水平可反映脓毒症患者早期(≤24 h)肠上皮细胞损伤情况。有证据表明I-FABP非常敏感，在小肠缺血的早期阶段即使组织学损伤仅为轻度时，也可在血液中检测到其水平升高[23-24]。本研究显示，采用CRRT治疗后，C组PGE2、I-FABP水平低于A组、B组，且B组低于A组，表明随着CRRT的治疗剂量增加，对PGE2、I-FABP表达的抑制作用增强，使患者炎症反应减轻，促使肠道功能的恢复。分析原因可能为，大剂量CRRT对炎性介质的清除效果较高，可减少肠黏膜屏障损伤，恢复患者免疫功能，改善患者的预后[25]。

综上所述，采用不同剂量CRRT治疗，临床治疗效果不同，大剂量CRRT治疗对严重脓毒症患者血清PGE2、I-FABP水平的降低效果更为明显，可保护肠黏膜屏障功能，使机体免疫功能得到恢复，促使患者获得较好的预后。

利益冲突　无

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