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Original Article

The application value of oXiris-endotoxin adsorption in sepsis

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Abstract: Objectives: This study explored and analyzed the application value of oXiris- endotoxin adsorption technology in patients with sepsis. Methods: 23 sepsis patients hospitalized from January 2018 to September 2019 in our ICU center and received oxiris-endotoxin adsorption were enrolled as the observation group, and another 30 sepsis patients hospitalized during the same period were selected as the control group who treated with routine continuous renal replacement therapy (CRRT). The heart rate, respiratory rate, norepinephrine (NE) dosage, lactic acid, procalcitonin (PCT), urine volume, and sofa scores that evaluate organ failure after systemic infection, as well as ICU stay, organ support duration, and incidence of cardiovascular events were compared between the two groups before and after treatment. Results: The heart rate, respiratory rate and NE dosage of the two groups post-treatment were dramatically lower than those pre-treatment *(P<0.05*), and these indexes in observation group after treatment were critically lower than those in control group (*P<0.05*). The lactic acid, PCT, urine volume and sofa scores of the two groups were dramatically lower than those before treatment (*P<0.05*), and the indexes in observation group after treatment were notably lower than those in control group (*P<0.05*). The degree of serum IL-6, IL-10 and endotoxin in two groups after operation decreased remarkably than that before treatment (*P<0.05*), and the observation group had obviously lower indicator degree than the control group (*P<0.05*). The ICU stay, organ support duration, and incidence of cardiovascular events in the observation group were notably lower than those in the control group (*P<0.05*). Conclusion: compared with the traditional CRRT technology, the oXiris membrane based CRRT technology can effectively improve the hemodynamic indicators of patients with sepsis, reduce the level of inflammation, and improve the metabolic function of body, thereby improving the patients' organ function. It has good clinical application value in patients with sepsis.

Keywords: oXiris, endotoxin adsorption technology, sepsis, application value

Introduction

Sepsis, in the latest definition, is a life-threatening organ dysfunction caused by a host response to infection disorders [1]. In sepsis and septic shock, bacterial toxins and other pathogen-related molecules can directly damage cells and/or trigger an immune response in the host, resulting in excessive production of cytokines and damage of tissues. While the damaged tissue releases damage-related molecules (such as activated complement, high mobility group protein B1, etc.) into the bloodstream, causing more organ damage [2, 3]. The various in vitro blood purification techniques can be used as adjuvant measures for sepsis by removing bacterial toxins and/or cytokines, inhibiting the excessive inflammatory response and restoring the immune homeostasis [4]. At present, technologies of high-volume hemofiltration and high-cut-off hemodialysis have been rejected by large number of clinical studies, and no longer recommended by the guidelines. Other therapies such as coupled plasma filtration adsorption (CPFA), cascade hemofiltration, etc. are limited in application due to the difficulty of operation and lack of clinical research evidence [5, 6]. Researchers in recent years have primarily focused on the improvement of membrane materials, expecting that the endotoxin and inflammatory mediators can be removed through the melioration of membrane materials, and thereby the prognosis of sepsis patients can be improved [7]. Currently, endo-

toxin elimination products are limited to polymyxin B blood adsorption column (Toraymyxin, PMX) and Primaflex supporting oXiris membrane. oXiris membrane material has been marketed in Europe and China with some small clinical studies and animal randomized control experiments have confirmed its good clinical efficacy [8, 9]. In this study, the application value of oxiris-endotoxin adsorption technology in patients with sepsis was discussed and analyzed.

Materials and methods

Clinical material

23 sepsis patients hospitalized from January 2018 to September 2019 in our ICU center and received oXiris-endotoxin adsorption were enrolled as the observation group, and another 30 sepsis patients hospitalized during the same period were selected as the control group treated with routine continuous renal replacement therapy (CRRT). The study acquired the approval by hospital ethics committee.

Inclusive criteria and exclusive criteria

Inclusive criteria: (1) Patients met the diagnostic criteria for sepsis; (2) All patients were treated with oXiris-endotoxin adsorption; (3) Patients aged between 18-65 years old; (4) The patients' families voluntarily signed the informed consent forms.

Exclusive criteria: (1) Patients aged <18 or >65 years old; (2) Patients also suffered from other serious life-threatening diseases, such as malignant tumors, severe hemorrhagic diseases or immunosuppression-related diseases; (3) Patients who could not complete the treatment or abandoned the treatment during the course; and (4) Female patients during pregnancy or lactation.

Methods

Both groups of patients received standard treatment for sepsis after admission to ICU, including fluid resuscitation, antibiotics and vasoactive agents based on drug sensitivity results, cardiopulmonary and nutritional supports, and vital signs monitoring. On the basis of the above treatment, the control group was given conventional CRRT treatment by Gambro Prismaflex-113080, while the observation group received oXiris membrane for CRRT. Each treatment lasted for 8-10 h, with blood flow of 150-200 ml/min and water dewatering of 200-300 ml/h. The rate and volume of ultrafiltration were determined after measuring the patient's central venous pressure (CVP). Heparin was used as anticoagulant with the first dose of 2000-3000 U and the additional dose of 500-1000 U/h. For patients with bleeding tendency, protamine with a ratio of 1:1 to heparin in the blood circuit was infused; as for patients with active bleeding, heparin-free dialysis was performed and saline pipeline flushing was used regularly during dialysis.

Observation of indexes

(1) The baseline data of two groups were recorded, including gender, age, APACHE II score, mean arterial pressure (MAP), and urine volume.

(2) The heart rate, respiratory rate and dosage of norepinephrine (NE) were kept before and 3 days after treatment.

(3) The lactic acid, procalcitonin (PCT), urine volume and systemic infection related organ failure assessment (sofa) scores were recorded before and 3 days after treatment. Lactate was detected by automatic blood gas analyzer; PCT was detected by immunoluminescence method.

(4) The changes of serum inflammatory factors interleukin-6 (IL-6), interleukin-10 (IL-10) and endotoxin degree prior-treatment and 3 d after treatment were compared between the two groups of patients. The peripheral venous blood of the two groups of patients was drawn and the serum was separated after centrifugation. The serum was analyzed by enzyme-linked immunosorbent assay (ELISA), and the operation was carried out in strict accordance with the kit instructions.

(5) The ICU stay, organ support duration, and incidence of cardiovascular events were compared between the two groups. Organ support includes CVVH, CVVHD, CVVHDF, molecular adsorbent recirculating system MARS and extracorporeal membrane oxygenation ECMO, etc. Adverse cardiovascular events included acute coronary syndrome, acute heart failure, serious arrhythmia and cardiac death, etc.

Table 1. Comparison of clinical data between two groups of patients

Group	Number of Cases	Gender		Age (years old, $\bar{x}$±sd)	APACHE II score (points, $\bar{x}$±sd)	MAP (mmHg, $\bar{x}$±sd)	Urine volume (ml, $\bar{x}$±s)
		Male	Female				
Observation group	23	13	10	59.73±13.02	21.46±2.55	74.81±13.40	416.92±78.69
Control group	30	18	12	58.97±12.51	21.58±3.10	71.02±9.85	438.39±85.62
t/X^2	-	0.065		0.215	0.151	1.187	0.937
P	-	0.799		0.830	0.881	0.241	0.353

Table 2. Comparison of heart rate, respiratory rate and dosage of NE between the two groups before and after treatment ($\bar{x}$±sd)

Group	Phase	Heart rate (Times/min)	Respiratory rate (Times/min)	Dosage of NE (μg·kg·min)
Observation group (n=23)	Before treatment	113.62±18.95	25.84±3.94	1.09±0.57
	After treatment	76.48±10.13*	16.58±2.79*	0.38±0.23*
	t	9.177	10.018	6.209
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	115.02±19.27	25.18±3.75	1.17±0.42
	After treatment	85.62±10.85	19.27±2.66	0.61±0.32
	t	7.282	7.041	5.809
	P	0.000	0.000	0.000

Note: **P<0.05* compared with before treatment.

Statistical analysis

The data processing and analysis were conducted by the researcher via statistical software SPSS 25.0. The measurement data were expressed by mean ± standard deviation ($\bar{x}$ ±sd), and compared by *t*-test; the numeration data were expressed by percentage and compared by X^2. The difference with statistical significance was accepted with *P<0.05*.

Results

Clinical data

There was no significant difference in gender, age, APACHE II score, MAP, and urine volume between the two groups (P>0.05), see **Table 1**.

Comparison of heart rate, respiratory rate and dosage of NE between the two groups

The heart rate, respiratory rate and NE dosage of the two groups post-treatment were dramatically lower than those pre-treatment *(P<0.05*), and these indexes in observation group after treatment were critically lower than those in control group (*P<0.05*), as listed in **Table 2**.

Lactate, PCT, urine volume and SOFA score were compared between the two groups

After treatment, the scores of lactate, PCT, breast and sofa in the two groups were significantly lower than those before treatment (P<0.05), and the scores of lactate, PCT, breast and sofa in the observation group were significantly lower than those in the control group (P<0.05), as shown in **Table 3**.

Comparison of serum inflammatory factors and endotoxin degree between the two groups

The serum IL-6, IL-10 and endotoxin degree of the two sets of patients post-treatment decreased obviously than those prior-treatment (*P<0.05*), and the observation group had obviously lower indicator degree than the control group (*P<0.05*), as shown in **Table 4**.

Comparison of ICU stay, organ support duration, and incidence of cardiovascular events between the two groups

The ICU stay, organ support duration, and incidence of cardiovascular events in observation group were notably lower than those in control group (*P<0.05*), as shown in **Table 5**.

Table 3. Comparison of lactate, PCT, urine volume and SOFA score between the two groups before and after treatment ($\bar{x}$±sd)

Group	Phase	Lactate (mmol/L)	PCT (ng/ml)	Urine output (ml)	Sofa score (score)
Observation group (n=23)	Before treatment	4.83±1.25	41.62±13.98	416.92±78.69	12.64±2.85
	After treatment	1.79±0.63*	9.87±2.15*	1093.84±120.37*	8.93±1.52*
	t	10.415	10.765	22.574	5.509
	P	0.000	0.000	0.000	0.000
Control group (n=30)	Before treatment	5.02±1.52	40.27±15.20	438.39±85.62	12.97±3.01
	After treatment	2.54±0.71	15.64±4.29	891.25±117.58	10.22±1.20
	t	8.097	8.542	17.053	4.648
	P	0.000	0.000	0.000	0.000

Note: **P<0.05* compared with before treatment.

Table 4. Comparison of serum inflammatory factors and endotoxin degree between the two groups ($\bar{x}$ ±sd)

Group	Time-point	IL-6 (pg/ml)	IL-10 (pg/ml)	Endotoxin (EU/ml)
Observation group (n=23)	Before treatment	2187.47±528.37	674.82±125.46	64.72±12.10
	After treatment	128.30±40.22*	50.37±21.23*	16.47±3.26*
	t	18.637	23.536	18.465
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	2006±476.27	693.27±131.65	65.08±15.28
	After treatment	227.28±108.29	130.85±40.38	25.09±6.39
	t	17.465	19.589	11.580
	P	0.000	0.000	0.000

Note: **P<0.05* compared with before treatment.

Table 5. Comparison of ICU stay, organ support duration, and incidence of cardiovascular events between the two groups

Group	Number of Cases	ICU stay (d, $\bar{x}$±sd)	Organ support duration (d, $\bar{x}$±sd)	Incidence of cardiovascular events [n (%)]
Observation Group	23	8.17±1.75	3.16±1.20	1 (4.35)
Control Group	30	10.21±2.18	4.85±1.39	9 (30.00)
t/X^2	-	3.667	4.650	4.046
P	-	0.001	0.000	0.044

Discussion

Sepsis and its induced multi-organ dysfunction are currently one of the dominating causes of death in ICU patients [10]. Endotoxin is crucial factor in human body that leads to cascade reaction of sepsis, and widely exists in the outermost layer of the cell wall of Gram-negative bacteria. Endotoxin is composed of lipids, polysaccharides and proteins, which can be released after bacterial death, dissolution or artificial destruction of bacterial cell wall structure [11]. When large amount of endotoxin enters the blood, and the concentration exceeds 40 μg/L, the endotoxemia occurred and the clinical manifestations of patients are chills, fever, hypotension, etc. High levels of endotoxin in the body can stimulate the activation of a variety of cells, such as monocytes, macrophages, granulocytes and endothelial cells, and produce a large number of inflammatory mediators, such as TNF-α, IL-1β, IL-6 and IL-8. In addition, endotoxin can activate the coagulation system and the complement system, leading to systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syn-

drome (MODS), and even multi-organ failure [12-14]. Studies have confirmed that the increase of endotoxin levels in the body can dramatically increase patient mortality [15]. Therefore, prompt and effective removal of endotoxins and inflammatory mediators in patients and the regulation of sepsis cascade have become the research hotspots in the treatment of sepsis at present.

At present, the most promising treatment method of sepsis is blood purification, which removes the multiple mediators and circulates toxins in blood non-selectively. The method is beneficial to the regulation of human inflammatory response, thereby improving the treatment outcome of patients with sepsis [16, 17]. In recent years, with the continuous development and progress of blood purification technologies, various blood purification technologies have been widely used in clinical practice, such as high-volume hemofiltration, cascade hemofiltration, blood adsorption, plasma exchange, paired plasma filtration and adsorption, high-volume hemodialysis technology and high-adsorption hemofiltration, etc. [18, 19]. However, an increasing number of scholars are focusing on the improvement of membrane materials to remove endotoxin and inflammatory mediators, thereby improving the prognosis of patients with sepsis. oXiris membrane material is a new iterative product based on the hydrogel structure of AN69. The basic membrane material AN69 (polymer of propylene and sodium methanesulfonate) can absorb a variety of pro-inflammatory and anti-inflammatory factors, with the surface modified by polyethyleneimine cationic polymer with multilayer linear structure to make the surface positively charged. While filtering and removing blood, endotoxin with negative surface charge can be absorbed through ionic bond, and it thus has the most comprehensive function among the existing blood purification products [20, 21].

This study explored and analyzed the application value of OXiris-endotoxin adsorption technology in patients with sepsis. The results showed that compared with the traditional CRRT, the heart rate, respiratory rate, NE dosage, lactic acid, PCT, urine volume and sofa score in both groups with OXiris membrane were critically lower 3 d after treatment than before treatment, and the above indicators in observation group were notably lower than those in control group. The results are similar to those of other studies [22, 23]. Compared with the traditional CRRT, the CRRT technology with OXiris membrane can effectively improve patients' hemodynamic indicators, reduce their heart rate, and reduce the usage of hypertensive. Meanwhile, it can also improve patients' organ function, reduce sofa score, and promote the body metabolism, thus effectively reducing lactic acid level in body. Moreover, the ICU stay, organ support duration, and incidence of cardiovascular events in observation group were critically lower than those in control group. It is considered that oXiris membrane can effectively adsorb endotoxin and cytokines, thus improving the inflammation of the body, rapidly relieving the cascade reaction caused by inflammatory factors, so that the patients' treatment outcome can be improved [24, 25]. Patients with high risk of bleeding were treated with non-anticoagulant CRRT, and no bleeding events occurred during the treatment.

However, due to the limited sample size included in this study, it is necessary to expand the sample quantity in order to obtain more reliable clinical research data and better guide the clinical work.

In summary, compared with the traditional CRRT technology, the oXiris membrane based CRRT technology can effectively improve the hemodynamic indicators of patients with sepsis, reduce the level of inflammation, and improve the metabolic function of body, thereby improving the patients' organ function. It has good clinical application value in patients with sepsis.

Disclosure of conflict of interest

None.

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References

[1] Lameire N and Vanmassenhove J. Timing of dialysis in sepsis and acute respiratory distress syndrome. Am J Respir Crit Care Med 2018; 198: 4-5.

[2] Sakhuja A, Nanchal RS, Gupta S, Amer H, Kumar G, Albright RC and Kashani KB. Trends and outcomes of severe sepsis in patients on maintenance dialysis. Am J Nephrol 2016; 43: 97-103.
[3] Premuzic V, Basic-Jukic N, Jelakovic B and Kes P. Differences in CVVH vs. CVVHDF in the management of sepsis-induced acute kidney injury in critically ill patients. J Artif Organs 2017; 20: 326-334.
[4] Miyamoto Y, Iwagami M, Aso S, Yasunaga H, Matsui H, Fushimi K, Hamasaki Y, Nangaku M and Doi K. Association between intravenous contrast media exposure and non-recovery from dialysis-requiring septic acute kidney injury: a nationwide observational study. Intensive Care Med 2019; 45: 1570-1579.
[5] Honoré PM, Jacobs R, De Waele E, Van Gorp V and Spapen HD. Evaluating sepsis during continuous dialysis: are biomarkers still valid? Blood Purif 2014; 38: 104-105.
[6] Shum HP, Chan KC, Kwan MC and Yan WW. Application of endotoxin and cytokine adsorption haemofilter in septic acute kidney injury due to Gram-negative bacterial infection. Hong Kong Med J 2013; 19: 491-497.
[7] Malard B, Lambert C and Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp 2018; 6: 12.
[8] Nelveg-Kristensen KE, Laier GH and Heaf JG. Risk of death after first-time blood stream infection in incident dialysis patients with specific consideration on vascular access and comorbidity. BMC Infect Dis 2018; 18: 688.
[9] Mitaka C and Tomita M. Polymyxin B-immobilized fiber column hemoperfusion therapy for septic shock. Shock 2011; 36: 332-338.
[10] Shimohata T, Mawatari K, Uebanso T, Honjo A, Tsunedomi A, Hatayama S, Sato Y, Kido J, Nishisaka R, Yoshimoto A, Yamashita T, Amano S, Maetani-Yasui M, Iba H, Harada Y, Nakahashi M, Yasui-Yamada S, Hamada Y, Nakagawa T, Sogabe M, Emoto T, Akutagawa M, Okahisa T, Kinouchi Y and Takahashi A. Bacterial contamination of hemodialysis devices in hospital dialysis wards. J Med Invest 2019; 66: 148-152.
[11] Marshall JC. Endotoxin in the pathogenesis of sepsis. Contrib Nephrol 2010; 167: 1-13.
[12] yen DM and Guilhot J. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 2015; 41: 975-84.
[13] Putzu A, Schorer R, Lopez-Delgado JC, Cassina T and Landoni G. Blood purification and mortality in sepsis and septic shock: a systematic review and meta-analysis of randomized trials. Anesthesiology 2019; 131: 580-593.
[14] Schiffl H, Fischer R and Lang SM. Assessment of dialysis dose in critically ill maintenance dialysis patients. Ther Apher Dial 2014; 18: 468-472.
[15] Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S and Walker PM; EUPHRATES Trial Investigators. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level. JAMA 2018; 320: 1455-1463.
[16] Hattori N and Oda S. Cytokine-adsorbing hemofilter: old but new modality for septic acute kidney injury. Ren Replace Ther 2016; 2: 41.
[17] Turani F, Barchetta R, Falco M, Busatti S and Weltert L. Continuous renal replacement therapy with the adsorbing filter oxiris in septic patients: a case series. Blood Purif 2019; 47: 1-5.
[18] Schwindenhammer V, Girardot T, Chaulier K, Grégoire A, Monard C, Huriaux L, Illinger J, Leray V, Uberti T, Crozon-Clauzel J and Rimmelé T. oXiris® use in septic shock: experience of two French centres. Blood Purif 2019; 47: 1-7.
[19] Broman ME, Hansson F, Vincent JL and Bodelsson M. Endotoxin and cytokine reducing properties of the oXiris membrane in patients with septic shock: a randomized crossover double-blind study. PLoS One 2019; 14: e0220444.
[20] Angus DC and Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369: 840-851.
[21] Jaer U, Wade RG and Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. HSR Proc Intensive Care Cardiovasc Anesth 2010; 2: 161-175.
[22] Kellum JA, Pike F, Yealy DM, Huang DT, Shapiro NI and Angus DC. Relationship between alternative resuscitation strategies, host response and injury biomarkers, and outcome in septic shock: analysis of the protocol-based care for early septic shock study. Crit Care Med 2017; 45: 438-445.
[23] Ward PA. The dark side of C5a in sepsis. Nat Rev Immunol 2004; 4: 133-142.
[24] Esteban E, Ferrer R, Alsina L and Artigas A. Immunomodulation in sepsis: the role of endotoxin removal by polymyxin B-immobilized cartridge. Mediat Inflamm 2013; 2013: 507539.
[25] Vincent JL, Mendonça A and Cantraine F. Working Group on “Sepsis-Related Problems” of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998; 26: 1793-1800.