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The absorbing filter Oxiris in severe coronavirus disease 2019 patients: A case series

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Abstract

Hypercytokines cause acute respiratory distress syndrome (ARDS) in coronavirus disease 2019 (COVID-19) patients, which is the main reason for intensive care unit treatment and the leading cause of death in COVID-19 patients. Cytokine storm is a critical factor in the development of ARDS. This study evaluated the efficacy and safety of Oxiris filter in the treatment of COVID-19 patients. Five patients with COVID-19 who received continuous renal replacement therapy (CRRT) in Henan provincial people's hospital between January 23, 2019 and March 28, 2020, were enrolled in this study. Heart rate (HR), mean arterial pressure (MAP), oxygenation index (PaO_2/FiO_2), renal function, C-reactive protein (CRP), cytokines, procalcitonin (PCT), acute physiology and chronic health evaluation II (APACHE II), sequential organ failure score (SOFA), and prognosis were compared after CRRT. Five COVID-19 patients, three males and two females, aged 70.2 ± 19.6 years, were enrolled. After treatment, HR (101.4 ± 14.08 vs. 83.8 ± 6.22 bpm/min), CRP (183 ± 25.21 vs. 93.78 ± 70.81 mg/L), IL-6 (3234.49 (713.51, 16038.36) vs. 181.29 (82.24, 521.39) pg/mL), IL-8 (154.86 (63.97, 1476.1) vs. 67.19 (27.84, 85.57) pg/mL), and IL-10 (17.43 (9.14, 41.22) vs. 4.97 (2.39, 8.70) pg/mL), APACHE II (29 ± 4.92 vs. 18.4 ± 2.07), and SOFA (17.2 ± 1.92 vs. 11.2 ± 3.4) significantly decreased ($P < .05$), while MAP (75.8 ± 4.92 vs. 85.8 ± 6.18 mm Hg), and PaO_2/FiO_2 (101.2 ± 7.49 vs. 132.6 ± 26.15 mm Hg) significantly increased ($P < .05$). Among the five patients, negative conversion of nucleic acid test was found in three cases, while two cases died. No adverse events occurred during the treatment. Our study observed a reduced level of overexpressed cytokines, stabilization of hemodynamic status, and staged improvement of organ function during the treatment with Oxiris filter.

KEYWORDS
coronavirus disease 2019, cytokine storm, hemodynamics, Oxiris

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, in December 2019 and rapidly spread to more than 185 countries worldwide. By May 26, 2020, about 5.5 million confirmed cases with COVID-19 were reported in the world, resulting in a public health emergency of international concern and posing a serious threat to global public health security.[1,2] The overall population is generally susceptible, and COVID-19 patients with chronic underlying diseases tend to quickly develop severe and critical forms of the disease, presenting with acute respiratory distress syndrome, septic shock, intractable metabolic acidosis, coagulation dysfunction, and multiple organ failure.[3] The mortality in severe patients is as high as 49%.

The rapid deterioration of conditions in severe patients is closely associated with cytokine storm-induced sepsis/septic shock, which are the leading causes of death in critical patients.[4] At present, organ support therapy is the main treatment for severe COVID-19 patients. Accordingly, continuous renal replacement therapy (CRRT), which is a widely used organ support therapy technology, has been widely used in acute respiratory distress syndrome coronavirus, middle east respiratory distress syndrome coronavirus and other coronavirus associated pneumonias.[5,6] The expert consensus on diagnosis and treatment of patients with severe and critical COVID-19 suggests that CRRT treatment, which can regulate the unbalanced inflammatory response, correct the immune disorder, and improve the clinical symptoms of severe patients, should be given when necessary.

Oxiris is a new generation of extracorporeal blood purification filters, which has good adsorption function of cytokines and endotoxins, as well as a routine renal support function of the CRRT filter and has an improvement effect on hemodynamics, metabolism, and respiratory response.[7] At present, there have been no reports of Oxiris in the treatment of severe COVID-19 patients. The purpose of this study was to provide new ideas and inspirations for the treatment of severe COVID-19 patients. The clinical characteristics and outcomes of five severe COVID-19 patients who received CRRT with Oxiris filter were retrospectively analyzed.

2 | PATIENTS AND METHODS

2.1 | Research design and patients

This retrospective study included five patients (43-89 years old) with COVID-19 who were admitted to Henan provincial people's hospital between January 23, 2020 and March 28, 2020, and met the diagnostic criteria of critical COVID-19.[3] Patients who discontinued or abandoned treatment, patients with chronic organ failure (including hemodialysis for chronic renal dysfunction), intracranial hemorrhage or other uncontrollable hemorrhagic diseases, organ transplantation or hematological malignancy, pregnant or lactating women, patients with positive human immunodeficiency virus, and patients with suspected active tuberculosis were excluded. In line with the medical ethics standards, with the approval of the ethics committee of Henan Provincial People's hospital, signed informed consent was obtained from patients' families for all treatments.

2.2 | General therapies

Blood and secretion cultures were obtained from all patients, who were given antiviral, antibacterial, traditional Chinese medicine and other drug treatments, hemodynamic monitoring and treatment (capacity reactivity assessment, use of vasoactive drugs, severe ultrasound examination), ventilator-assisted ventilation, etc.

2.3 | CRRT with Oxiris filter

CRRT was operated in continuous venovenous hemodialysis (CVVHDF) using Oxiris (Baxter, Deerfield, IL, USA) through Prismaflex CRRT system (Baxter). Due to the clinical condition, blood flow rates were kept in the range of 180-200 mL/min. Meanwhile, the dialysis doses were 25 and 30 mL/kg/h. A venous double lumen catheter (12Fr, Gambro, Sweden) was inserted in the femoral venous under ultrasound guidance. The Oxiris filter was changed every 24 hours.

2.4 | Anticoagulation

Citrate regional anticoagulation or heparin anticoagulant regimens were adopted, and the anticoagulant doses were individually adjusted according to the patients' coagulation state. Anticoagulation of unfractionated heparin: the initial dose was 20-30 mg, the additional dose was 8-15 mg/h, which decreased with the extension of treatment time, and the extra dose was stopped 30-60 minutes before the end of the treatment. In patients with regional citrate anticoagulation, a sterile citrate-containing solution without calcium was infused in predilution mode. In postdilution, a sterile saline solution containing calcium chloride was infused to maintain postfilter Ca^{++} 0.25-0.35 mmol/L, arterial line Ca^{++} 1-1.5 meq/L.

2.5 | Clinical data collection

The clinical and biochemical indexes, acute physiology and chronic health evaluation II (APACHE II), sequential organ failure score (SOFA), continuous monitoring of the mean arterial pressure (MAP), heart rate (HR), blood gas analysis, oxygenation index (PaO_2/FiO_2), C-reactive protein (CRP), calcitonin (PCT) and anteroposterior chest radiograph of all patients before and after Oxiris treatment were recorded, and enzyme-linked immunosorbent assay

(ELISA) kit (eBioscience, San Diego, CA, USA) was used to measure plasma levels of IL-1 β, IL-4, IL-6, IL-8, IL-10, and TNF-α.

2.6 | Statistical analysis

SPSS 19.0 software was used for statistical analysis. The measurement data conforming to normal distribution were expressed by mean ± standard deviation, while those not conforming to normal distribution were expressed by the median + interquartile range. The comparison of data before and after treatment was performed by paired *t* test or nonparametric test. $P < .05$ was considered statistically significant.

3 | RESULTS

A total of five patients (including three males and two females) with severe COVID-19 combined with septic shock, with an average age of 70.2 ± 19.6 years old, were treated with CRRT by Oxiris filter between January 23, 2020 and March 8, 2020. The average time of Oxiris initiation was 21.6 ± 19.2 hours, the average treatment time was 172.8 ± 82.1 hours, and the average use of filters was 7.2 ± 3.4 sets. All patients were treated with auxiliary ventilation, where two patients with extracorporeal membrane oxygenation (ECMO) survived. Regional citrate was used for anticoagulation in two cases, and heparin was used for anticoagulation in three cases. During this period, the transmembrane pressure (TMP) and filter pressure were stable with no obvious fluctuation (Table 1)

After Oxiris treatment, the level of IL-1 β, IL-6, IL-10, and CRP significantly decreased ($P < .05$), while the level of IL-4, IL-8, and PCT decreased after treatment, but there was no significant difference (Table 2).

After Oxiris treatment, HR significantly decreased while PaO_2/FiO_2 significantly increased ($P < .05$). During the treatment, the improvement of MAP and lactate was consistent with the improvement of PaO_2/FiO_2 (Table 3).

After Oxiris treatment, APACHE II and SOFA scores significantly decreased ($P < .05$). At the same time, serum creatinine (Scr) and D-Dimer also showed a downward trend, although without significant difference after treatment compared with that before (Table 4).

4 | DISCUSSION

COVID-19 is an epidemic of global concern. Although the fatality rate of infection caused by coronavirus is lower than that caused by other coronaviruses, and most patients only show mild flu symptoms or no symptoms, it has strong

TABLE 1 Main clinical characteristics of the study population treated with Oxiris filter

Case	Sex	Age (y)	Mode	Connected with ECMO	Anticoagulation	AKI stage	Time from ICU admission (h)	Dosage (mL/Kg/h)	Treatment times	Filter changing time (h)	Outcomes
1	M	58	CVVHDF	Yes	Heparin	Stage 3	36	30	12	24	Survived
2	F	87	CVVHDF	No	RCA	Stage 3	6	28	6	24	Death
3	M	43	CVVHDF	Yes	RCA	Stage 3	12	30	9	24	Survived
4	M	89	CVVHDF	No	RCA	Stage 3	48	25	6	24	Survived
5	F	74	CVVHDF	No	Heparin	Stage 3	6	28	3	24	Death

TABLE 2 Inflammatory biomarkers changes during CRRT with the Oxiris filter

	Pretreatment (n = 5)						Posttreatment (n = 5)						
	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	*P* value
CRP (mg/L)	143.4	172.6	200	200	200	183 ± 25.21	34.1	43.7	55.8	196.2	139.1	93.78 ± 70.81	.025
PCT (ng/mL)	9.8	0.77	3.13	0.46	5.01	0.77 (0.29, 4.07)	0.11	5.91	1.31	0.2	1.32	1.32 (0.76, 3.76)	.893
IL-1β (pg/mL)	34.07	15.85	5.99	21.04	0.08	15.85 (3.04, 27.55)	0.13	0.13	0	3.64	0	0.13 (0.00, 1.89)	.043
IL-4 (pg/mL)	0.75	1.38	0.94	0.93	0.93	0.93 (0.84, 1.16)	0.41	0.52	0.61	1.43	0.74	0.61 (0.47, 1.09)	.345
IL-6 (pg/mL)	26042.09	6034.64	717.77	3234.49	709.25	3234.49 (713.51, 16038.36)	110.42	683.17	54.05	181.29	359.6	181.29 (82.24, 521.39)	.043
IL-8 (pg/mL)	2783.73	58.37	69.56	154.86	168.47	154.86 (63.97, 1476.1)	78.32	67.19	20.85	34.84	92.81	67.19 (27.84, 85.57)	.08
IL-10 (pg/mL)	11.13	19.41	63.04	17.43	7.16	17.43 (9.14, 41.22)	1.33	11.17	3.45	4.97	6.22	4.97 (2.39, 8.70)	.043
TNF-α (pg/mL)	80.66	0.1	1.05	0.25	0.68	0.68 (0.18, 40.85)	0	1.34	0.9	1.34	0	0.9 (0, 1.34)	.893

TABLE 3 Hemodynamic and respiratory changes during CRRT with the Oxiris filter

	Pretreatment (n = 5)						Posttreatment (n = 5)						
	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	*P* value
HR (bpm/min)	125	89	98	102	93	101.4 ± 14.1	87	79	78	93	82	83.8 ± 6.2	0.032
MAP (mm Hg)	74	82	80	72	71	75.8 ± 4.9	90	88	92	77	82	85.8 ± 6.2	0.008
PaO_2/FiO_2 (mm Hg)	97	102	113	93	101	101.2 ± 7.5	142	98	168	119	136	132.6 ± 26.2	0.036
NE ($\mu g \cdot Kg^{-1} \cdot min^{-1}$)	1	2	2	1	2	1.6 ± 0.5	0.5	1	1.5	0.5	1.5	1.3 ± 0.7	0.004
Lac (mmol/L)	2.23	2.04	0.86	5.14	0.85	2.24 ± 1.75	0.76	1.45	0.79	1.05	1.55	1.12 ± 0.37	0.175

TABLE 4 Organ function changes during CRRT with the Oxiris filter

	Pretreatment (n = 5)						Posttreatment (n = 5)						
	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD medium (quartile)	*P* value
Scr (μmol/L)	63	84	36	79	138	80.0 ± 37.4	52	46	38	43	117	59.2 ± 32.7	0.051
D-Dimer (mg/L)	17.78	6.83	14.84	1.1	1.92	8.50 ± 7.54	4.39	7.66	6.04	1.83	1.06	4.20 ± 2.78	0.210
APACHE II	24	26	29	34	32	29 ± 4.92	16	20	17	18	21	18.4 ± 2.07	0.004
SOFA	16	20	15	18	17	17.2 ± 1.92	10	15	6	13	12	11.2 ± 3.4	0.001

infectivity.[8] The significant difference between COVID-19 and previous viral pneumonia and SARS is that some patients have mild early symptoms and the condition suddenly aggravates and rapidly deteriorates in the 2nd to 3rd week of the course of the disease, with 13.8% of patients developing the severe type of the disease and 4.7% of patients developing the critical type.[9] Previous studies have pointed out cytokine storms as a possible cause of aggravation.[8] Cytokine storm is a systemic inflammatory reaction that releases a series of cytokines, including TNF-α, IL-1 β, IL-2, IL-6, IFN - α, and MCP-1. These cytokines induce immune cells to release large amounts of free radicals, which are the leading cause of ARDS and multiple organ failure.[10] Approximately 67% of critical COVID-19 patients experienced multiple organ failures, which were, to some extent, cytokine storm-induced.[11] The indexes of inflammatory factors (IL-1 β, IL-4, IL-6, IL-8, IL-10, and TNF-α) in the five enrolled patients in this study were consistent with previous reports, which were significantly higher than normal, suggesting the occurrence of cytokine storm and the critical condition of patients. Blood purification therapy is considered as an important means for removing cytokines from patients with sepsis and also the main advocated technology of organ support therapy for patients with severe COVID-19.

Oxiris is a new generation of CRRT filter of blood purification membrane material, which is modified on the surface of AN69 (polyacrylonitrile) basement membrane and has the functions of supporting renal function, adsorbing endotoxin and removing inflammatory mediators.[12] We observe a sharp decrease of most inflammatory factors (IL-6, IL-1β, IL-8, and IL-10) which extraordinary increased before CRRT, and is in accordance with previous studies.[13] The overall value of PCT and TNF-α showed an upward trend, which is inconsistent with existing studies.[13,14] However, we found that there was only one case whose value of PCT substantially increased after CRRT, which may be associated with uncontrolled exacerbation of secondary infection; therefore, we assume that the upward trend of PCT was a deviation due to small sample size. TNF-α is excreted by leukocytes and macrophages following recognition of an antigen. Its main function is to recruit additional leukocytes and monocytes in the blood and to increase the inflammatory process by increasing adhesion to the endothelium and secretion of molecules belonging to the complement system by the liver.[14] CRRT is considered as an adjunctive therapy in hypercytokinemia to remove excess cytokines due to the peak concentration hypothesis raised by Prof. Ronco, rather than removing normal levels of cytokines which may be beneficial to patients.[15] Since there was only one case with elevated initial concentration of TNF-α, and it was sharply decreased after CRRT while others' were normal initially, the overall upward trend of TNF-α may also result from the small sample size and the low initial concentration.

In this study, we observed a significant improvement of hemodynamics among hemodynamically instable patients after Oxiris-CRRT, which has already been widely confirmed by domestic and foreign researchers.[13,14,16-18] However, the mechanism remains unclear. Researchers have found that the main manifestations of microcirculation disorder were leukocyte adhesion and plasma extravasation, which may explain the possible mechanism of shock in sepsis patients; namely, plasma extravasation caused a decrease in the effective circulation capacity.[19] It was shown in a study that reducing the level of overexpressed cytokines—such as IL-1β—through cytokine scavenging therapy, could induce a significant decrease in leukocyte adhesion and plasma extravasation, which lead to the improvement of microcirculation disorder,[19] indicating that overexpressed cytokine removal may contribute to improve hemodynamic status. However, this hypothesis needs to be explored further in larger studies. In addition, it should be noted that blood lactate concentrations did not decrease along with the improvement of hemodynamics, which indicated an oxygen utilization disorder of tissues and organs among critically ill COVID-19 patients.

Organ function, represented by SOFA score and APACHE II score, was improved significantly after treatment with the Oxiris filter in our study, which was also shown in other studies among patients with hypercytokinemia such as sepsis.[13,18] This shows that CRRT has become a multi-organ support rather than pure renal replacement among these patients with the development of medical and membrane technology, and provides opportunity and conditions for further treatment, which may improve patients' outcome. We found that even in conditions of aggravated secondary infection or coagulation and fibrinolysin disorder, organ function could be staged improved with Oxiris-CRRT, which shows a potential benefit for critically ill COVID-19 patients.

There were several limitations to this study. First, it was just a descriptive research study without a control group due to the specificity of the disease. Second, it was a small sample size study which may lead to a deviation of the results.

5 | CONCLUSION

Our study observed a reduced level of overexpressed cytokines, stabilization of hemodynamic status, and staged improvement of organ function during the treatment with Oxiris filter.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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