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Case Series on Use of Cytokine Adsorption System in Critically Ill Patients Presenting with Septic Shock and Needing Renal Replacement Thearpy

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Abstract

Background: In sepsis, severe coronavirus disease 19 (COVID-19) uncontrolled systemic inflammation leads to Multiple organ failure including acute kidney injury, respiratory failure and septic shock. As an adjuvant therapy, extracorporeal blood purification (EBP) is proposed and aims at controlling the dysregulated autoimmune system. **Material and Methods:** In COVID-19, sepsis some authors have proposed Renal Replacement Therapy in combination with sequential EBP as a means to support renal function and attenuate the systemic inflammation. Extracorporeal blood purification is being explored as an adjuvant therapy for sepsis, aiming at controlling the dysregulated auto-immune system. **Results:** Critically ill ICU patient with COVID-19,patients with sepsis,in this case series, underwent EBP with highly biocompatible membranes (oXiris) /cytosorbcharacterized by enhanced adsorptive properties for the cytokine. Levels of IL-6 markedly decreased in the first 24 h of treatment. **Conclusion:** In this case series the use of oXiris, cytosorb Filter decreased the levels of inflammatory markers like CRP (C- reactive protein), interleukin 6 and improved the clinical outcomes.

Keywords: COVID 19, Continuous Renal Replacement Therapy, oXiris, endotoxin adsorption, sepsis, shock.

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Introduction

In ICU, around 20 to 30 percent of patients present in sepsis with or without shock, and multiorgan dysfunction syndrome due to dysregulated immune regulation. SARS CoV2 Infection leads to the rapid activation of innate and adaptive immune systems which results in cytokine storm and multiple organ dysfunction. Severe COVID-19 infection shares common features with sepsis syndrome and with bacterial co-infection which may result in bacterial toxins which contributes to the disease severity. Covid 19 affected patients develop hypoxic respiratory failure and septic shock. The therapies for critical patients with COVID-19 include supportive care and low dose corticosteroids. Remdesivir helps to shorten the disease course and viral shedding duration but does not improve the patients survival chances. Acute kidney injury is one of the common findings in severely ill patients infected with COVID-19. In China up to 40% of all the patients hospitalized presented with abnormal proteinuria on admission and around 20 to 40% of those admitted to the intensive care unit had acute kidney injury. Another study done in New York showed that around 30% of the patients developed acute kidney injury. In critically ill patients with COVID-19 acute kidney injury appears to be a marker of disease severity and a negative predictor of survival and disposing additional challenge to the patient management. Early reports on COVID-19 have documented the need for renal replacement therapy in approximately 23 to 36% of the patients [versus 10% in the

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ICU general population], ensuring after a median of 15 days after the illness onset. And 67% of these additional multiple organ failures suggest a relevant role for organ support and cytokine blockade or removal. In COVID-19 some authors have proposed RRT in combination with sequential EBP as a means to support renal function and attenuate the systemic inflammation. Extracorporeal blood purification is being explored as an adjuvant therapy for sepsis, aiming at controlling the dysregulated auto-immune system.
In this case series, we describe the use of a highly adsorptive membrane oXiris, cyto sorb which is different from the traditional filters due to its unique four-in-one properties which include cytokine and endotoxin removal, renal replacement therapy, and anti-thrombogenic feature. Here we present our experience at a tertiary care medical college hospital.

Case 1

A 74-year-old male, known case of Type 2 Diabetes Mellitus and Hypertension since 20 years, Chronic Kidney Disease on maintenance hemodialysis presented to the hospital with complaints of fatigue and bilateral lower limb swelling and blebs on and off for 2 weeks. He tested COVID INAAT positive. At admission his pulse rate was 96 bpm, BP-60/40mmhg, Spo2 - 89% on room air with respiratory rate of 20 -26 cpm. He was started on oxygen and inotropic support and shifted to ICU. He was hypoglycemic with GRBS of 33, started on 50% dextrose. On examination, bilateral pitting pedal edema with dark discoloration of the legs was present (chronic venous ulcer/cellulitis). His IL6 was more than 5000, serum Procalcitonin 48, CRP- 10 with derranged coagulation profile and LFT and was started on severe COVID protocol treatment. CXR showed bilateral basal opacities. ECG was suggestive of atrial fibrillation with controlled rate. A diagnosis of severe COVID illness with septic shock (? Superimposed cytokine storm) was made. He underwent SLED with inotropic support. Antibiotics were escalated to Meropenem and Teicoplanin. He was planned for CRRT with oXiris cytokine adsorption system. After family's consent, patient underwent CRRT with oXiris for 16 hours (heparin free, through left femoral HD catheter). His inotropic requirement gradually reduced and was weaned off inotropes. His oxygen requirement reduced from intermittent NIV to 6 liters O2/min, his IL 6 reduced from 5000 to 180. 2D ECHO showed dilated RA, RV, LA, mild LV systolic dysfunction, global LV hypokinesia with LVEF 45%, PASP 65mm hg. Cardiology opinion was sought and followed in view of the same. Surgery opinion taken for chronic venous ulcer and was advised lower limb elevation with alternate day dressing. Blood culture grew pseudomonas (pan sensitive). Patient improved gradually, haemodynamically stable, weaned off inotropes maintaining saturation spo2 of 95% with 5l O2 Non rebreathing mask and shifted out to ward and was discharged.

Case 2

70-year-old female, known case of type 2 diabetes mellitus, hypertension, chronic kidney disease on conservative management (baseline creatinine of 2mg/dl) presented to the ICU in shock with 3days history of fever and chills. She was managed with fluid resuscitation, urine and blood cultures were sent .She was started on broad spectrum empiric antibiotics, insulin for glycaemic control, low dose ionotropes and other supportive measures. CT KUB was suggestive of perinephric fat stranding in left kidney with upper ureteric calculus measuring 3 cm. She underwent Retrograde Intra Renal surgery. Post operatively, she developed severe hypotension and metabolic acidosis,needing elective intubation and mechanical ventilation. .2D echo was normal. CRRT was intiated with cytosorb filter. However her condition did not improve and she succumbed

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Case 3

56 year old woman,was admitted to ICU with shortness of breath.She was in refractory septic shock and in multi organ dysfunction .She was intubated in view of respiratory distress,resuscitated with fluid and started on ionotropic support.2d echo was normal .Started on empiric broad spectrum antibiotics .Routine investigations revealed creatinine of 5 with potassium more than 7 meq/l. Urine routine showed plenty of pus cells ,blood and urine cultures were sent. She was intiated on SLEDD, She persisted to have refractory hypotension, CT KUB did not show evidence of pyelonephritis. CXR was suggestive of Acute Lung Injury. Her Serum procalcitonin was >100, with raised total counts and c reactive protein. CT abdomen and pelvis did not show evidence of infection. We intiated on cytosorb in the next dialysis session and was able to wean her off ionotropes after 2 sessions on cytosorb .Her condition improved and she was extubated and shifted to wards

Case 4

30-year-old male, chronic alcoholic, presented with severe pain abdomen and tachypnoea to the ICU. Clinical examination revealed tense abdomen. He was referred from outside hospital with a diagnosis of severe necrotizing pancreatitis with a CT score of 10/10.Investigations revealed acute kidney injury with a creatinine of 3. He was intiated on dialysis in view of oliguria probably due to abdominal hypertension. He was kept NPO and surgical gastro opinion taken, and was advised conservative management. He was started on ulinostatin, empiric antibiotics (in view of fever spikes), anticoagulation. Cultures were sent. He persisted to be tachypnoeic and tachycardic. In view of respiratory distress, he was intubated and put on mechanical ventilation. 2d echo was normal A trial of dialysis with cytosorb for 18 hrs reduced his work of breathing and tachyacardia. He was gradually weaned off ventilator, started on NJ feeds and was shifted to step down ICU.

Discussion

Baxter International designed the oXiris® filter and it was approved by the US Food and Drug Administration (FDA) in April 2020 under emergency use authorization to treat COVID-19 patients. Patients with COVID-19 were found to have high level of pro - inflammatory cytokines. Thus emphasizes the existence and impact of so-called “cytokine storm” in viral respiratory infection that deteriorates the clinical course. Extracorporeal therapy has been proposed to mitigate cytokine burden by cutting the peak of a specific

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foreign target (endotoxin), resulting in the restoration of immune homeostasis without a prolonged state of immunosuppression. Other potential therapy for cytokine storm, like IL-6 receptor inhibitor, may cause serious secondary infection from prolonged immunosuppressive effect. oXiris/cytosorb could provide cytokine and endotoxin adsorption with continuous dialysis therapy. Thus, oXiris is preferable in patient requiring CRRT in order to correct metabolic derangement and control fluid balance. The oXiris membrane is a hemodiafilterpregrafted with an average of 4.500 UI/m2 heparin during manufacturing, with a surface polyethyleneimine (PEI) treatment providing a high amount of free positively charged amino groups that allows to adsorb large weight molecules such as endotoxin. Studies have addressed the use of this membrane in critically ill patients with AKI, with a few specifically assessing its safety and feasibility in septic patients.[1,2] IL-6 is a leading mediator influencing systemic inflammation and has shown increased concentrations among COVID-19 patients with ARDS. Higher concentrations of cytokines in COVID-19 patients are associated with organ dysfunction and worse outcome, and generally, the higher IL-6 in the blood, the higher level of SOFA score. Critically ill ICU patient with COVID-19,sepsis in this case report, underwent EBP with highly biocompatible membranes (oXiris)/cytosorb characterized by enhanced adsorptive properties for the cytokine. Levels of IL-6 markedly decreased in the first 24 h of treatment. The improvement in multiorgan dysfunction during EBP was related to the restoring of hemodynamic stability - patient was weaned off inotropic support and NIV gradually. This case suggests a potential role of this treatment in reducing inflammatory mediators and improving multiorganfunction.[3-5]

Conclusion

The first patient showed significant IL-6 reduction, improvement in multiorgan dysfunction, hemodynamic stability and oxygenation index. EBP with the oXiris, cytosorb membrane is technically feasible in patients needing renal replacement therapy and is not associated with major adverse events. EBP with oXiris resulted in decreased inflammatory markers, ICU mortality rate; prevents multiorgan dysfunction from cytokine storm, attenuates systemic inflammation in COVID19 patients. Cost is a concern, and might not be feasible in patients not needing renal replacement. Large scale randomized controlled trials are needed specially in covid 19 patients regarding its usefulness.

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