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CytoSorb® Therapy in the Treatment of a Patient with Chronic Kidney Disease (CKD) Associated with Symptoms of Sepsis: A Case Report

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Abstract

Sepsis and multiple organ dysfunctions due to cytokine storm are the leading cause of chronic kidney disease (CKD) worsened due to acute kidney injury (AKI). CytoSorb® therapy, a new hemoadsorption technology could be an alternative therapy to be used as an adjuvant in the hyper-cytokinemic state in patients with CKD. This is a case report of a 37-year-old male patient with CKD secondary to biopsy-proven chronic tubulointerstitial nephritis (CTIN) on conservative treatment. He was admitted to the emergency care department with complaints of dyspnea for the last 20 days and decreased urine output and constipation for the last 3 days. His dysregulated kidney and respiratory functions, deranged acid-base balance, and presence of elevated inflammatory markers were indicative of sepsis and cytokine storm. CytoSorb® therapy improved the outcomes remarkably for the patient. By the end of the treatment, serum lactate improved by 75.5% and urine output was improved by 167%. Mechanical ventilation was continued for six days, and regular dialysis was performed throughout the treatment. On Day 10, the patient's condition had considerably stabilized. On Day 13, the patient was discharged in a hemodynamically stable condition. CytoSorb® device is a safe and effective treatment and can be used as an adjuvant therapy to stabilize critically ill CKD patients.

Keywords: ***Cytokine storm; Sepsis; Chronic kidney disease; Renal replacement therapy; CytoSorb® therapy***

1. Introduction

The global prevalence of chronic kidney disease (CKD) has increased by about 29% since 1990 and is associated with significant mortality and morbidity. Not with standing, the rising treatment costs for renal replacement therapy (RRT), and the

long-term use of dialysis for patients with end-stage renal disease (ESRD) also affect the patient adversely [1]. Patients with CKD often have anemia that worsens with the severity of CKD. Therefore, blood transfusion and RRT are common practices in patients with CKD [2]. It is estimated that the number of people receiving RRT exceeds 2.5 million and is projected to double to 5.4 million by 2030 [3]. Patients with other associated comorbidities; diabetes mellitus, arterial hypertension, dyslipidaemia, with glomerular or congenital diseases, are at high risk. These risk factors further aggravate the clinical condition and lead to ESRD. Acute kidney injury (AKI) is recently identified as an additional risk factor for the worsening of CKD or the development of CKD de novo [4]. Sepsis, burns, and organ transplantation are the leading factors that contribute to AKI and result in the dysregulation of the immune system to cause an inflammatory response triggered via an uncontrolled cytokine storm [5].

CytoSorb® (CytoSorbents, Corporation, New Jersey, USA), therapy is an extracorporeal hemadsorption technology and a well-established treatment for overcoming cytokine storms in critically ill patients with septic shock [6,7].

Since CKD is associated with electrolyte imbalance, acid-base disturbances, hemodynamic instability, and other secondary complications [8], CytoSorb® therapy could be an alternative therapy to be used as an adjuvant in the hyper-cytokinemic state in patients with CKD caused due to septic shock and other secondary causes. The therapy purifies the circulatory system by removing inflammatory mediators in blood including both pro and anti-inflammatory cytokines, chemokines, and bacterial exotoxins, and provides hemodynamic stability [9]. In this case report, we used this therapy as an adjuvant therapy for our patient with CKD and sepsis-induced AKI due to varied causes. The patient showed a speedy recovery and was discharged from the hospital in a stable condition.

2. Case Presentation

A 37-year- old Asian man with complaints of shortness of breath (SOB) for the last 20 days, dry cough which was progressive at the time of admission even at rest and decreased urine output for the last 3 days, was admitted to the hospital. The patient also had difficulty in passing stools for the last 3 days. He was a known case of hypertension, anemia of CKD that worsened due to acute kidney injury (AKI), chronic tubulointerstitial nephritis (CTIN) and had pedal edema. He was also diagnosed with lower respiratory tract infection (LRTI) due to severe community acquired pneumonia with recovered septic shock and pulmonary edema. His complete blood count (CBC) report showed a low hemoconcentration (Hb: 6.4 g/dL, hematocrit: 23%), platelet count ($1.4 \times 10^3/mm^3$) and leukocytosis ($15.87 \times 10^3/mm^3$). At the time of admission, he was also diagnosed with uremic encephalopathy. Renal impairment was also evident with high serum creatinine level (19.17µmol/L). Acid-base balance was deranged, revealing metabolic acidosis. Considering the criticality of the condition, an immediate dialysis was performed. However, the patient's condition kept worsening and he was supported with mechanical ventilation to overcome the respiratory distress. He was started with antibiotic and antifungal therapies; Meropenem 1 gm BD, Colistin BD, and Clexane 60 mg. Post one day of dialysis and intubation, his blood sample reports showed high level of inflammatory markers and indicated sepsis with septic shock. CytoSorb® therapy was started within 48 hours of admission to ICU by incorporating the CytoSorb® device in the hemodialysis (HD) circuit and maintained at a flow rate at 140 ml/min. Two CytoSorb® devices were used; each device ran for 16 hours in pre-dialyzer position in a Fresinius 4008s Machine. During treatment, regular sessions of dialysis were continued.

Post CytoSorb® therapy, there was a remarkable reduction in PCT values; 27% and 98% after the use of first and second device respectively. Similarly, serum creatinine reduced by 35% and 68.4% from baseline after use of first and second device, respectively. The total bilirubin value decreased from 0.7 to 0.5 µmol/L after the use of the first device and the patient's general status improved considerably.

By the end of the treatment, serum lactate improved by 75.5% and urine output was improved by 167%. Improvement was also observed in other parameters as shown in (FIG. 1 and 2 and TABLE 1). The patient was intubated for six days. His FiO_2 increased by 60%. During this time, he also developed sepsis induced bicytopenia (low Hb and low platelet count). Therefore, choice of drugs was optimized, and doses were readjusted as per the creatinine clearance level checks (CrCl). By the end of therapy, his condition was stable, and he was shifted to the general ward from ICU on Day 10. He was kept under observation for three more days and then discharged from hospital. At discharge, the patient's condition was hemodynamically stable. He was fully conscious and oriented. Due to deranged renal function tests (RFT), he was recommended hemodialysis thrice a week along with routine blood and urine investigations to regulate kidney functions. He was recommended a follow up treatment for one week.

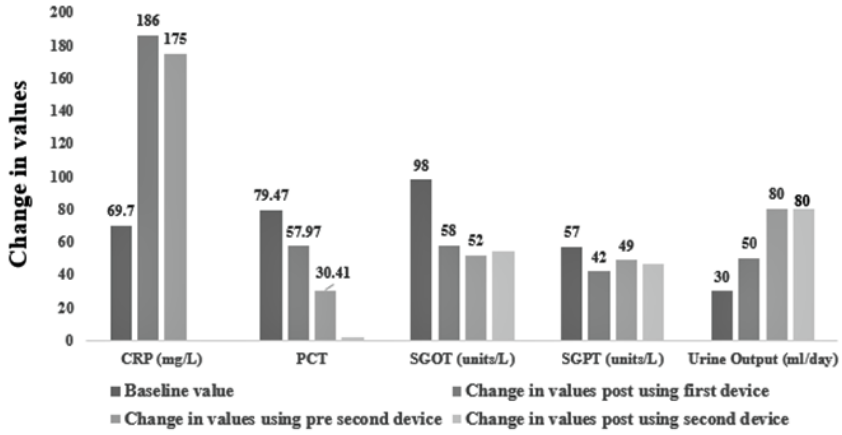

FIG. 1. **Change in Values of Biomarkers of Sepsis (From Baseline to Pre and Post Use of First and Second CytoSorb® Device).**

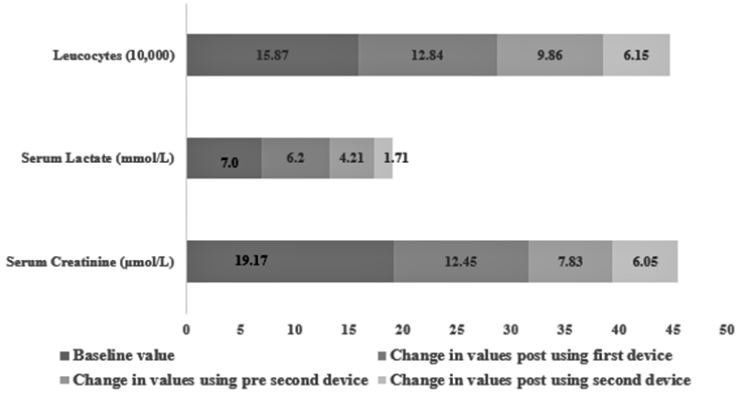

FIG. 2. **Change in Values of Biomarkers of Sepsis (From Baseline to Pre and Post Use of First and Second CytoSorb® Device).**

TABLE 1. **Change in Clinical Parameters from Baseline (Day of Hospital Admission) Pre and Post Use of First and Second CytoSorb® Device).**

Laboratory Findings	**Pre CytoSorb® (Baseline)**	**Post first CytoSorb® device**	**Post second CytoSorb® device**	**Percentage change post use of first device**	**Percentage change post use of second device**
Hemoglobin (g/dL)	6.4	7.7	6.1	20.31%	-4.69%
Hematocrit (%)	23.3	22.4	18.6	-3.86%	-20.17%
Leucocytes (10^3)	15.87	12.84	6.15	-19.09%	-61.25%
Platelet Count ($10^3/mm^3$)	1.4	0.71	0.72	-49.29%	-48.57%
Serum Creatinine (µmol/L)	19.17	12.45	6.05	-35.05%	-68.44%
BUN (mmol/L)	281	182	53	-35.23%	-81.14%
Serum Lactate (mmol/L)	7	6.2	1.71	-11.43%	-75.57%
Bilirubin (µmol/L)	0.7	0.5	0.7	-28.57%	0.00%
SGOT (units per litre)	98	58	54	-40.82%	-44.90%
SGPT (units per litre)	57	42	47	-26.32%	-17.54%
CRP (mg/L)	69.7	186		166.86%	-100.00%
Ferritin (ng/mL)	1124	924	624	-17.79%	-44.48%
Sodium (mEq/L)	128	137	144	7.03%	12.50%
Potassium (mEq/L)	4.2	2.9	4	-30.95%	-4.76%
Albumin (g/dL)	2.9	2.1	2.4	-27.59%	-17.24%
Arterial Ph	7.313	7.374	7.421	0.83%	1.48%
Bicarbonates (mEq/L)	18	21	28	16.67%	55.56%
PaO2 (kPa)	93.6	92.4	93.6	-1.28%	0.00%
PaCO2 (kPa)	39.2	41.6	44.1	6.12%	12.50%
FiO2	50	70	80	40.00%	60.00%
Interleukin 6	1271	716.33	291.8	-43.64%	-77.04%
PCT	79.47	57.97	1.72	-27.05%	-97.84%
Body Temperature (^oF)	100.55	99	98.8	-1.54%	-1.74%
Heart Rate (beats/min)	140	115	110	-17.86%	-21.43%

Respiratory Rate (breaths/min)	28	24	22	-14.29%	-21.43%
Urine Output (ml/day)	30	50	80	66.67%	166.67%
Systolic Blood Pressure (mm Hg)	190/80	180/80	140/80	-5.26%	-26.32%
MAP (mm Hg)	80	82	84	2.50%	5.00%
PEEP	8	6	6	-25.00%	-25.00%

Hb: Hemoglobin, BUN: Blood urea nitrogen, MAP: Mean arterial pressure, PaO2: Partial pressure of oxygen, PaCO2: partial pressure of carbon dioxide, FiO2: Fraction of inspired oxygen, IL: Interleukin, PEEP: Positive end-expiratory pressure,

3. Discussion

Despite progress in critical care and highly specialized ICUs, the use of RRT and repeated blood transfusions to support critically ill patients with AKI and CKD has become a routine. Though hemadsorption and dialysis are proven to be a safe and efficacious modality of bridging therapy in patients with CKD for treating complications of kidney failure such as uremic encephalopathy, hemodynamic instability, and progressive anemia; repeated blood transfusions are known to cause iron overload and other associated risks such as transfusion reactions and allo-sensitization, which limit potential kidney transplantation [2]. RRT and haemodialysis (HD) are the most commonly adopted options by nephrologists to support the critically ill patients. However, both treatment options have their own complications and risks. Repeated dialysis and blood transfusions results in chronic inflammatory dialysis syndrome including uremic syndrome, heart failure, vascular access infections, bioincompatible dialysis solutions, progressive decrease of glomerular filtration rate, and blood-membrane interaction [10]. RRT remains associated with multiple risks – including catheter-related complications from insertion and infection; mechanical complications associated with the extracorporeal circuit, including the risk of severe blood loss; electrolyte imbalance and hemodynamic compromise associated with fluid and electrolyte shifts during treatment; and activation of humoral and cellular mediators [8].

CytoSorb® has a large surface area that gives greater capacity for clearance than available dialyzers. It is a bead based, biocompatible adsorptive technology which is proven to remove size selective molecules (approx. 10 kDa - 50 kDa) in a concentration dependent manner. The beads are made up of polystyrene-divinylbenzene porous particles (450 µm average particle diameter, 0.8 nm - 5 nm pore diameter, 850 m^2/g surface area) with a biocompatible polyvinyl-pyrrolidone coating. Further, the CytoSorb® therapy is easy to setup with HD, SLED, CRRT, ECMO and HLM. Its use is compatible with both systemic heparin and regional citrate anti-coagulation [11,12].

Considering the septic condition of the patient along with numerous co-existing ailments, we utilized the CytoSorb® therapy with a rationale to restore a balanced proinflammatory and anti-inflammatory mediators' response with minimal blood loss. The therapy was given in two sessions of 16 hrs each for two consecutive days with a gap of 6 hrs. Within this duration, the outcomes were improved remarkably. However, mechanical ventilation continued for six days as the patient had complications of LRTI and SOB. Though intubation was weaned off before shifting to general ward from ICU indicating the improvement in respiratory rate (RR) from 28 to 22 breath/min. With the use of the first device, we found significant reduction in key biomarkers

of sepsis; IL-6 (44%), CRP (167%) and PCT (27%). Hb and bilirubin level was also rapidly improved (20.3%) and (28.5%) respectively with the use of first device (TABLE 1). At the time of discharge from hospital, Hb and bilirubin were restored to normal level.

Our results are consistent with various studies; Griger et al in their retrospective study of 16 patients with severe post-cardiopulmonary bypass severe systemic inflammatory response syndrome (CPB SIRS), and AKI showed the use of CytoSorb® device in combination with CRRT. The study results showed reduction in IL-6 and IL-8 compared to baseline and improvement in hemodynamics [13]. Mitzner and coworkers' study reported that the use of CytoSorb® in a patient with septic shock and acute kidney failure decreased the levels of IL-6, CRP, serum creatinine, PCT, and leucocytes during the treatment and in the following days. CytoSorb® hemoadsorber treatment appeared to be safe and was well tolerated by the patient [14]. Another study showed the use of CytoSorb® therapy in combination with standard RRT in 55 critically ill septic patients. The study results showed an overall improvement in significant increase in the urine output and a significant decrease in white blood cell count, CRP, PCT and platelet count. Overall, the use of hemoadsorption was associated with an improvement in neurological and renal function and a decrease in inflammatory markers [15]. However, the use of CytoSorb is accepted by clinicians and researchers to remove various hydrophobic substances of size <55kDa viz, cytokines, PAMPs, DAMPs, Bilirubin, Myoglobin etc whereas, RRTs are recommended to remove hydrophilic substances of lower molecular size. It is important to note that CytoSorb follows the standard of care and should be deployed on a case-case basis. The above case report is being evaluated retrospectively, and the improvement of the patient is due to multiple interventions and cannot be solely attributed to CytoSorb treatment. Nevertheless, we have observed multiple cases at our hospital benefiting directly because of the CytoSorb application. Therefore, prospective comparative (case-control) studies in different populations/ healthcare settings are needed to demonstrate and ascertain the success of CytoSorb® therapy in CKD patients.

4. Conclusion

CytoSorb® therapy can be considered as a bridge to stabilize critically ill CKD patients, until more definitive therapies take place. The therapy provides hemodynamic stability and improves organ dysfunction and with no significant adverse events.

5. Acknowledgement

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6. Conflict of Interest

The authors have no conflicts of interest to declare.

7. Author Contributions

The above authors have equally contributed towards ideation, data analysis and manuscript review.

8. Data Availability Statement

All data generated or analysed during this study are included in this published article. However, any further details can be made available from the corresponding author on reasonable request.

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