Combined Use of CytoSorb and ECMO in Patients with Severe Pneumogenic Sepsis

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Abstract

Background High morbidity and mortality are frequently reported in intensive care patients suffering from severe sepsis with systemic inflammation. With the development of severe respiratory failure, extracorporeal membrane oxygenation (ECMO) is often required. In this study, cytokine adsorption therapy in combination with ECMO is applied in patients with acute respiratory distress syndrome (ARDS) due to severe pneumogenic sepsis. The efficacy of this therapy is evaluated compared with a historical cohort without hemoadsorption therapy.

Methods Between January and May 2018, combined high-flow venovenous ECMO and CytoSorb therapy (CytoSorb filter connected to ECMO circuit) was applied in patients (*n* 13) with pneumogenic sepsis and ARDS. These patients were prospectively included (CytoSorb group). Data from patients (*n* 7) with pneumogenic sepsis and ECMO therapy were retrospectively analyzed (control group).

Results All patients survived in the CytoSorb group, where the 30-day mortality rate reached 57% in the control group. After CytoSorb therapy, we instantly observed a significant reduction in procalcitonin (PCT) and C-reactive protein (CRP) levels compared with the control group. Within 48 hours, the initial high doses of catecholamine could be weaned off only in the CytoSorb group.

Conclusions Our results indicate that CytoSorb in combination with ECMO is an effective therapy to prevent escalation of sepsis with rapid weaning off high-dose catecholamine infusions and quick reduction in PCT and CRP levels. Optimal timing of immunomodulatory therapy and impact on ECMO-related inflammation still need to be furtherly investigated.

Keywords
- extracorporeal membrane oxygenation
- ECMO
- inflammation
- systemic; including cells
- mediators
- shock; systemic
- cardiac
- or circulatory

Introduction

Sepsis due to severe infection represents a critical clinical condition associated with high morbidity and mortality in intensive care patients.[1,2] If sepsis escalates, or recurs, mortality rates reach up to 90 to 100%. Especially, patients with pneumogenic sepsis often develop a severe systemic inflammatory response syndrome (SIRS) resulting in hemodynamic instability and multiple organ dysfunction. This is frequently associated with severe respiratory failure requiring the application of extracorporeal membrane oxygenation (ECMO).[3] However, it is reported that ECMO induces SIRS leading to

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pulmonary and cardiocirculatory disturbance. In addition, ECMO therapy may even pronounce inflammatory overstimulation.[4,5] Therefore, a broadly optimized therapeutic approach is necessary to reduce inflammation and prevent sepsis escalation.

The dysregulation of circulating pro-inflammatory and anti-inflammatory cytokines plays a central role during sepsis.[2] For this purpose, adjuvant cytokine-adsorbing systems have been developed to improve the outcome in patients with severe sepsis with the goal to prevent progression. Different clinical and experimental studies have demonstrated the efficacy of extracorporeal hemofiltration for cytokine removal in these patients with beneficial effects on survival rate.[6–9]

The beneficial effect of the extracorporeal cytokine hemoadsorption device CytoSorb (CytoSorbents Europe GmbH, Berlin, Germany) in controlling severe sepsis has been reported in intensive care patients and cardiac surgery patients.[7,8] A recently established international registry on the use of CytoSorb in different clinical settings involving 20 study centers suggested that CytoSorb should be considered as an ultimate treatment option for sepsis therapy.[9]

The aim of the study was to investigate the effect of cytokine adsorption on inflammatory response in patients with severe pneumogenic sepsis and respiratory failure requiring ECMO compared with patients with severe pneumogenic sepsis requiring ECMO, but with no additional cytokine adsorption therapy. We already presented our initial experience with CytoSorb therapy in intensive care patients at the 27th European Conference on General Thoracic Surgery in Dublin.[10]

Methods

The study was performed between January and May 2018. All patients with septic shock and SIRS were evaluated for eligibility for the study. Combined ECMO and CytoSorb therapy was applied in patients with acute respiratory failure due to pneumonia with severe pneumogenic sepsis. These patients were included prospectively in this study (CytoSorb group). In addition, we collected clinical parameters and outcome data from a historical cohort at our institution with acute respiratory failure due to pneumogenic sepsis, which were treated with ECMO and standard of care therapy at the period before January 2018, when the CytoSorb system was not available at our institution.

Patients' demographic data are summarized in ►**Table 1**. Inclusion and exclusion criteria were as following.

Inclusion Criteria

Patients with pneumogenic septic shock accompanying acute respiratory failure, invasive hemodynamic monitoring, and demand for norepinephrine 0.3 µg/kg per minute; elevated lactate concentrations 2.0 mmol/L; and procalcitonin (PCT) serum level 1 ng/mL were eligible for this study. Patients were considered for eligibility within 6 hours after admission to our intensive care unit (ICU), when no improvement was noticed, as indicated by increased norepinephrine requirement in the last 24 hours after the onset of septic shock.

Table 1 Baseline characteristics

	CytoSorb group (*n* 13)	Control group (*n* 7)
Mean age (y)	61 3 (32–76)	61 2 (39–71)
Gender (female/male)	8/5	5/2
BMI (kg/m^2)	27.7 3.3	26.4 4.3
Diabetes mellitus (no.)	4	2
Arterial hypertension (no.)	5	3
Heart failure (LVEF 50%, no.)	0	0
Positive blood cultures[a]	4	1
Positive BAL[b]	10	5
Acute renal failure	5	4
ICU stay (d)	26 6 (7–63)	26 5 (8–43)
SAPS II score	58.3 2.13 (49–66)	49.5 2.2 (42–55)

Abbreviations: BMI, body mass index; ICU, intensive care unit; LVEF, left ventricular ejection fraction; SAPS, The Simplified Acute Physiology Score.
[a]Blood culture findings were *Staphylococcus aureus* (*n* 1), *Enterococcus faecium* (*n* 1), *Streptococcus pyogenes* (*n* 1), *Candida albicans* (*n* 1) in the CytoSorb group, and *Enterococcus faecalis* (*n* 1) in the control group.
[b]Bronchoalveolar lavage (BAL) findings were *Staphylococcus aureus* (*n* 1), *Enterococcus faecium* (*n* 2), *Streptococcus pneumoniae* (*n* 3), influenza A (*n* 3), *Aspergillus fumigatus* (*n* 1) in the CytoSorb group. BAL findings in the control group were influenza A (*n* 2), *Candida albicans* (*n* 1), *Pseudomonas aeruginosa* (*n* 1), and *Serratia marcescens* (*n* 1).

Exclusion Criteria

Patients under 18 years of age, pregnancy, cardiogenic shock, and contraindications for extracorporeal therapy (coagulopathy, thrombocytopenia) were excluded from the study.

All patients developed severe acute respiratory distress syndrome (ARDS) and were treated following the sepsis' treatment guidelines. Standard therapy included fluid resuscitation, differentiated catecholamine therapy including administration of norepinephrine to achieve mean arterial pressure 60 mm Hg, antibiotic treatment according to resistogram, and lung-protective ventilation.

The primary end point of the study was the 30-day mortality rate. Duration of ICU stay, changes of infection parameters (C-reactive protein [CRP], leucocytes, and PCT serum levels), as well as lactate levels and vasopressor therapy pre-ECMO/CytoSorb application, post-ECMO/CytoSorb application, after 12, 24, 48, and 72 hours represented the secondary endpoints of the study. Additionally, The Simplified Acute Physiology Score (SAPS) II was recorded directly on admission to the ICU, on day 1, day 2, and day 3 after admission, to estimate the probability of mortality for patients in both groups.

Indication for ECMO therapy was the clinical deterioration due to acute respiratory failure. In all patients, a peripheral high-flow venovenous ECMO system (high-flow VV ECMO) was implemented in combination with a CytoSorb

immunomodulation filter after admission to the ICU and within 12 hours of sepsis diagnosis. Pre-ECMO cardiac assessment was achieved by transthoracic echocardiography. For systemic anticoagulation, direct thrombin inhibition with Argatroban was continuously administered intravenously with a target-activated partial thromboplastin time of 50 to 60 seconds after initiation of treatment.

Indication for CytoSorb was sepsis-related hemodynamic instability with high-dose infusions of catecholamine (0.3 µg/kg per minute). The CytoSorb system was connected to the ECMO circuit. All patients received a minimum of two CytoSorb treatments. Adsorbers were changed every 24 hours without interruption between the treatment sessions. The CytoSorb treatment was continued until no further catecholamine infusions were required or until shock reversal.

Statistical Analysis

Data were analyzed using the statistical program GraphPad Prism 7 (GraphPad Software, United States). *p*-Values 0.05 were considered statistically significant.

Results

Thirteen patients presented with pneumogenic sepsis and ARDS (CytoSorb group) fulfilled the inclusion criteria and were enrolled in this study. From the historical cohort, seven patients with pneumogenic sepsis and ARDS supported with high-flow VV ECMO were identified and retrospectively analyzed (control group). The mean age was 61 3 years (range: 32–76) in the CytoSorb group and 61 2 years (range: 39–71) in the control group.

Five patients in the CytoSorb group and four patients in the control group developed anuric renal failure requiring continuous VV hemodialysis.

Subsequent analysis of bronchial secretion from direct bronchoscopy revealed the presence of influenza pneumonia in three patients, fungal pneumonia in one patient, and bacterial pneumonia in nine patients (►**Table 1**).

Thirty-Day Mortality

The 30-day mortality rate was 0% in the CytoSorb group, compared with 57% (4 out of 7 patients) in the control group. The cause of death in the control group was sepsis with multiorgan failure. Noteworthy, at further follow-up (6 2.5 months; range: 3–10 months), survival remained 100% in the CytoSorb group.

SAPS II Score

On admission to the ICU, the median SAPS II score was 58 2 (range: 49–66) in the CytoSorb group compared with 50 2 (42–55) in the control group (95% confidence interval [CI]: 15.75 to 1.85, p 0.02). SAPS II score decreased significantly on day 1 (43 4, p 0.004), day 2 (41 4, p 0.0006), and day 3 (30 4, p 0.0001) after initiation of CytoSorb, indicating a reduction in the risk for mortality in the CytoSorb group. In contrast, we did not observe any remarkable changes in the SAPS II score for the control group at day 1, 2, and 3 after admission to ICU.

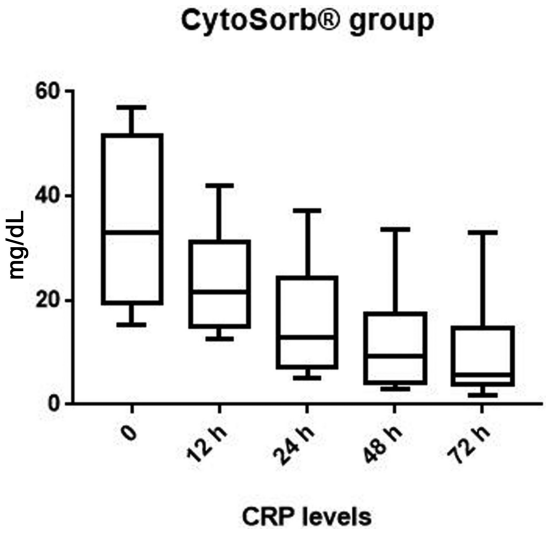

Fig. 1 CRP levels (CytoSorb group). CRP values were assessed prior to treatment, after 12 hours, 24 hours, 48 hours, and 72 hours. Difference versus "hour 0" (CytoSorb and ECMO start): 12 hours: p 0.1, 24 hours: p 0.008, 48 hours: p 0.002 and 72 hours: p 0.0009. CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation.

CRP Levels

The initially high CRP levels (CRP_0 35 5, range: 15–57) were reduced during ECMO/CytoSorb therapy after 12 hours (CRP_{12} 24 3, p 0.1), 24 hours (CRP_{24} 16 3, p 0.008), 48 hours (CRP_{48} 12 3, p 0.002), and 72 hours (CRP_{72} 10 3, p 0.0009), respectively (►**Fig. 1**). In contrast, we did not observe any significant reduction in CRP levels (CRP_0 27.2 2.9; CRP_{12} 29 3.3, p 0.69; CRP_{24} 25.01 2.8, p 0.58; CRP_{48} 22.6 3.1, p 0.31; CRP_{72} 20.02 2.4, p 0.09) in the control group (►**Fig. 2**).

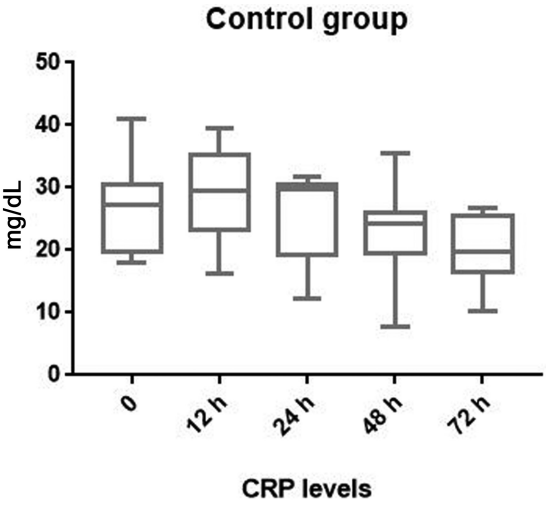

Fig. 2 CRP levels (control group). CRP values were analyzed prior to ECMO support, 12 hours, 24 hours, 48 hours, and 72 hours after ECMO implementation. Difference versus "hour 0" (ECMO start): 12 hours: p 0.69, 24 hours: p 0.58, 48 hours: p 0.31 and 72 hours: p 0.09. CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation.

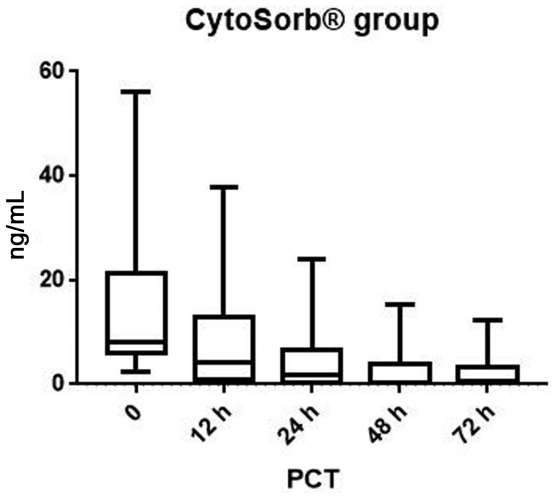

Fig. 3 PCT levels (CytoSorb group). PCT values were assessed prior to treatment, after 12 hours, 24 hours, 48 hours, and 72 hours. Difference versus "hour 0" (CytoSorb and ECMO start): 12 hours: *p* 0.34, 24 hours: *p* 0.08, 48 hours: *p* 0.03 and 72 hours: *p* 0.02. ECMO, extracorporeal membrane oxygenation; PCT, procalcitonin.

PCT Levels

A reduction in PCT levels was noticed with ECMO/CytoSorb therapy after 12 hours (PCT_{12} 9.05 3.9 ng/mL, *p* 0.34), 24 hours (PCT_{24} 4.71 2.3 ng/mL, *p* 0.08), 48 hours (PCT_{48} 2.71 1.5 ng/mL, *p* 0.03), and 72 hours (PCT_{72} 2.3 1.2 ng/mL, *p* 0.02), respectively, compared with the initially high levels prior to treatment (PCT_0 15.6 5.4 ng/mL, range: 2.5–56.04 ng/mL) (►**Fig. 3**). In the control group, no significant differences in PCT levels were noted (PCT_0 13.14 9.7 ng/mL, range: 1.18–70.81 ng/mL; PCT_{12} 18.95 16.32 ng/mL, *p* 0.75; PCT_{24} 12.5 10.5 ng/mL, *p* 0.96; PCT_{48} 8.14 5.9, *p* 0.68; PCT_{72} 4.1 2.4, *p* 0.4) (►**Fig. 4**.).

Leucocyte Levels

Both groups did not show any significant reduction in leucocyte levels at 12, 24, 48, and 72 hours of ECMO therapy.

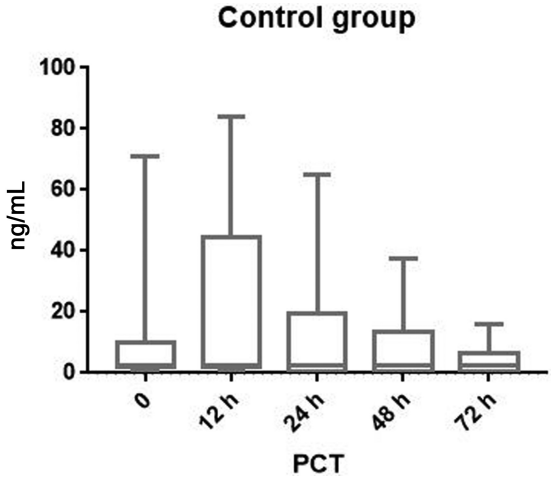

Fig. 4 PCT levels (control group). PCT values were analyzed prior to ECMO support, 12 hours, 24 hours, 48 hours, and 72 hours after ECMO implementation. Difference versus "hour 0" (ECMO start): 12 hours: *p* 0.75, 24 hours: *p* 0.96, 48 hours: *p* 0.68 and 72 hours: *p* 0.4. ECMO, extracorporeal membrane oxygenation; PCT, procalcitonin.

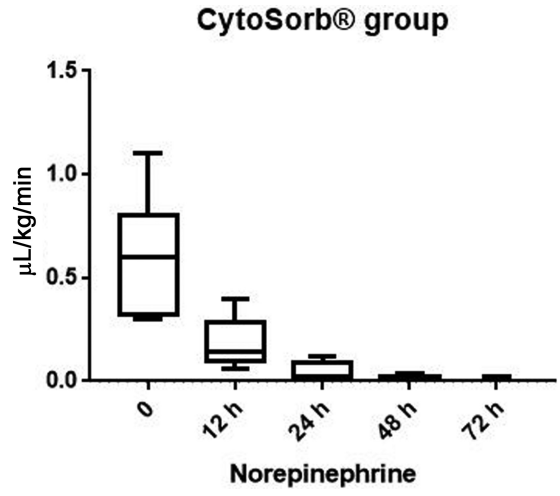

Fig. 5 Changes in norepinephrine administration (CytoSorb group). Norepinephrine dose before and during treatment with CytoSorb. The initial very high doses of catecholamine could be weaned off within 48 hours.

Changes in Norepinephrine Administration over Time of Therapy

The mean initial norepinephrine dose was 0.603 0.08 µg/kg/min (range: 0.3–1.1 µg/kg/min) in the CytoSorb group and 0.83 0.16 µg/kg/min (range: 0.3–1.2 µg/kg/min) in the control group (95% CI: 0.2016–0.5556, *p* 0.3309). Noteworthy, in the CytoSorb group norepinephrine requirements were significantly reduced after 12, 24, and 48 hours of treatment compared with the initial dose (12 hours: 0.19 0.04 µg/kg/min, *p* 0.0002; 24 hours: 0.045 0.01 µg/kg/min, *p* 0.0001; 48 hours: 0.009 0.005 µg/kg/min, *p* 0.0001). After 72 hours, noradrenaline support was not required in all patients (►**Fig. 5**). In the control group, however, high noradrenalin doses were still required after 12 hours (0.6 0.13 µg/kg/min, *p* 0.28), 24 hours (0.47 0.14 µg/kg/min, *p* 0.12), 48 hours (0.38 0.11 µg/kg/min, *p* 0.05), and 72 hours (0.37 0.13, µg/kg/min, *p* 0.05), respectively, after admission to the ICU (►**Fig. 6**).

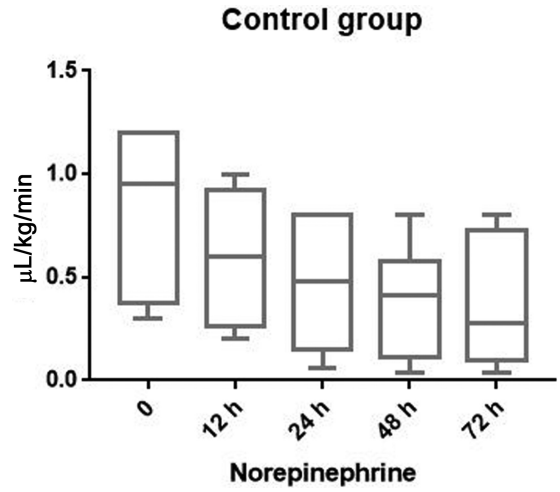

Fig. 6 Changes in norepinephrine administration (control group). Patients in the control group still require high norepinephrine dose also after 72 hours after admission to intensive care unit.

Lactate Levels

In the CytoSorb group, we observed a remarkable decrease in lactate levels after 12 hours (2.1 0.57 mmol/L, *p* 0.09), 24 hours (1.6 0.48 mmol/L, *p* 0.03), 48 hours (1.3 0.37 mmol/L, *p* 0.02), and 72 hours (1.1 0.3 mmol/L, *p* 0.009), respectively, compared with the initial high levels (4.1 0.97 mmol/L, range: 2.1–12.4 mmol/L). On the other side, no significant reduction in lactate levels was noted in the control group (initial lactate 2.7 0.34 mmol/L, range: 2–4.4 mmol/L; lactate 12 hours: 1.7 0.55 mmol/L, *p* 0.16; lactate 24 hours: 1.57 0.5 mmol/L, *p* 0.08; lactate 48 hours: 1.7 0.29 mmol/L, *p* 0.05; lactate 72 hours: 2 0.37 mmol/L, *p* 0.18).

Duration of Extracorporeal Support with and without CytoSorb

The mean duration of ECMO support was 8 2 days (range: 2–23 days) in the CytoSorb group and 19 3 (range: 13–30 days) in the control group. The immunomodulatory therapy was consistently applied for three treatment sessions in seven patients and terminated after 3 days. Three patients consistently received two CytoSorb treatments for 2 days. Blood flow rates through the adsorber membrane were kept between 200 and 400 mL/min and monitored by a flow probe. We did not observe any adverse events related to the treatment and the adsorber.

The mean ICU stay was 26 6 days (range: 7–63 days) in the CytoSorb group and 26 5 days (range: 8–43 days) in the control group. All patients were discharged for further rehabilitation.

Discussion

Rapid treatment of sepsis is important for the prevention of escalation of sepsis escalation and consequently impacts on survival. Among others, cytokines, PCT, and CRP are inflammatory biomarkers with important diagnostic value and correlation with mortality risk.[11] CRP is a well-defined marker for the detection and monitoring of acute sepsis.[12] Recently, PCT has gained favorability over CRP in improving the diagnosis, monitoring, and prediction of outcome in both sepsis and septic shock.[11,13] In addition, during the acute phase response, levels of a pro-inflammatory cytokine interleukin-6 (IL-6) has been reported to correlate with sepsis severity and play a role in the prediction of septic complications.[11,14] Moreover, levels of serum lactate serve as indicators for occult shock and help in monitoring the response to therapy.[15]

Here, patients with acute respiratory failure due to severe pneumonia with pneumogenic sepsis received high-flow VV ECMO support in combination with immunomodulatory therapy. Data from a historical control group who received high-flow VV ECMO without CytoSorb therapy were retrospectively analyzed. Notably, an early significant reduction in CRP and PCT levels was observed in the CytoSorb cohort. The mortality risk in the CytoSorb group after hemoadsorption treatment was lower than the mortality risk in the control group predicted by SASP II score. CytoSorb treatment resulted in rapid hemodynamic stabilization and a reduction in blood lactate levels. All patients had a remarkable significant decrease in catecholamine requirement during CytoSorb treatment and all survived, compared with four death out of seven patients in the control group.

Septic shock with severe sepsis with increased levels of cytokines is one of the major indications for the implementation of the CytoSorb system that is now available for clinical use and considered so far safe and well-tolerated. CytoSorb application is also reported in severe SIRS in cardiac surgery patients.[9,16] Pro-inflammatory cytokines including tumor necrosis factor-α and IL-6 are efficiently removed from the blood with the application of CytoSorb. This cytokine adsorption therapy improves hemodynamic stability by reducing vasopressor requirement and lowering serum inflammatory markers in septic patients.[6,17] Although we did not measure cytokine levels during CytoSorb therapy, we could demonstrate a reduction in CRP, PCT, and lactate levels as well as a rapid decrease in noradrenalin requirements within 12 hours, compared with the control group. Our findings, therefore, echo different studies that have reported that CytoSorb is considered as an effective therapy, thereby stabilizing hemodynamics, decreasing vasopressor requirements, and improving lactate clearance in context of sepsis and septic shock, and consequently, leading to a favorable outcome.

Several clinical trials reported the beneficial effect of CytoSorb in reducing inflammatory response. In a recent study by Friesecke et al, the treatment of patients with refractory septic shock with CytoSorb resulted in reduction in norepinephrine requirement after 6 hours and 12 hours as well as improvement in lactate clearance leading to septic shock reversal in 65% of the patients.[18] In this study, CytoSorb was connected to a renal replacement therapy circuit.

In a case series reported by Kogelmann et al, the actual mortality was lower than that predicted by the APACHE II (Acute Physiology And Chronic Health Evaluation II) score.[19] Notably, the efficacy of the treatment was better in patients who received CytoSorb within 24 hours of sepsis diagnosis compared with patients with a delayed therapy onset beyond 24 hours of diagnosis. In our study, we assumed to initiate combined ECMO and CytoSorb therapy within 6 hours after admission to our ICU and within 12 hours of sepsis diagnosis, to achieve the best possible effect according to the limited data available.

So far, the application of CytoSorb hemoadsorption is mainly reported in patients with cardiogenic sepsis. In a retrospective case series, Träger et al reported the application of CytoSorb connected to continuous renal replacement therapy in 16 patients who underwent cardiac surgery following prolonged cardiopulmonary bypass (CPB) with post-SIRS and subsequent acute kidney failure. CytoSorb therapy in these patients, by reducing elevated cytokine levels, enabled a stabilization of hemodynamic, metabolic, and organ function parameters.[5]

Bruenger et al reported the successful application of CytoSorb in combination with left ventricular assist device and a right ventricular extra corporeal life support system for a patient with ARDS and septic cardiogenic failure, thereby showing a reduction in plasma IL-6 and PCT levels as well as vasopressor requirement. In this singular case, CytoSorb was

connected to the continuous venovenous hemofiltration circuit.[8]

One of the largest retrospective clinical trials involved 39 cardiac surgery patients with confirmed acute infectious endocarditis who obtained valve replacement during CPB surgery in combination with intraoperative CytoSorb hemoadsorption. This study reflects the benefits of such combined therapy especially for cytokine reduction (IL-6 and IL-8) and hemodynamic stability in comparison to a historical group of 28 patients without intraoperative hemoadsorption.[20]

As known, ECMO leads to an inflammatory response itself, thereby activating the complement system and consequently increasing the levels of pro-inflammatory cytokines.[4] Furthermore, due to later activation of endothelium, artificial surfaces in ECMO circuits and membranes may contribute to inflammation and consequent end-organ damage. Additionally, the constellation of sepsis and artificial ECMO surfaces may lead to an overrunning systemic hyperinflammatory state, often resulting in hemodynamic instability.[21] In our study, stabilization of hemodynamic conditions reflected by continuous reduction in noradrenalin administration within 48 hours was observed during combined ECMO and CytoSorb treatment. This was not the case in the control group and indicates the indirect effect of cytokine adsorption in achieving hemodynamic stability already during the early sepsis state.

Limitations of this study include the small number of patients in both groups and the absence of prospective randomization of patients in the control group. Here, we reported our initial experience using this novel cytokine adsorber technique. The main aim of this study was to address the role of this novel technique in the treatment of pneumogenic sepsis and reducing sepsis related mortality. Although the beneficial effect of the combined ECMO and CytoSorb treatment was reflected by the fact that the mortality rate was higher in the control group, the small number of patients restricts the comparability between both groups. Furthermore, we also did not perform cytokine measurements, which is the main molecular target of the hemoadsorption therapy.

To our knowledge this is the first study on patients with severe pneumogenic sepsis and ARDS treated successfully with combined high-flow VV ECMO and cytokine adsorption therapy. The intriguing finding in this study needs to be further investigated in multi-institutional prospective trials on patients with ARDS and pneumogenic sepsis.

Conflict of Interest

None.

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