Cytokine Hemoadsorption As Rescue Therapy for Critically Ill Patients with SARS-CoV-2 Pneumonia with Severe Respiratory Failure and Hypercytokinemia

Juan Carlos Ruiz-Rodríguez

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Luis Chiscano-Camón (✉ lchiscano@vhebron.net)

Hospital Vall d'Hebron   https://orcid.org/0000-0003-0037-0610

Adolf Ruiz-Sanmartin

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Clara Palmada

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Erika Paola Plata-Menchaca

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Clara Franco-Jarava

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Marcos Pérez-Carrasco

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Manuel Hernandez-Gonzalez

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Ricard Ferrer

Vall d'Hebron Hospital: Vall d'Hebron Hospital Universitari

Research

Cytokine hemoadsorption as rescue therapy for critically ill patients with SARS-CoV-2 pneumonia with severe respiratory failure and hypercytokinemia

Juan Carlos Ruiz-Rodríguez [1-2], Luis Chiscano-Camón [1-2], Adolf Ruiz-Sanmartin [1-2], Clara Palmada[1-2], Erika Paola Plata-Menchaca [1-2], Clara Franco-Jarava [3], Marcos Pérez-Carrasco[1-2], Manuel Hernández-González [3], Ricard Ferrer [1-2].

[1] Intensive Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Barcelona Hospital Campus, Barcelona. Spain.

[2] Shock, Organ Dysfunction and Resuscitation Research Group. Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital, Vall d'Hebron Barcelona Hospital Campus, Barcelona. Spain.

[3] Immunology Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain.

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*Corresponding Author:

Full name: Luis Silvestre Chiscano Camón

Department: Intensive Care Department

Institute/University/Hospital: Vall d'Hebron University Hospital

Street Name & Number: Passeig de la Vall d'Hebron, 119-129

City, State, Postal code, Country: 08023 Barcelona, Spain

Tel: 34932746000(4735)

E-mail: lchiscano@vhebron.net

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Abstract

Background: A dysregulated inflammatory response, known as "cytokine storm", plays an important role in the pathophysiology of coronavirus 2019 disease (COVID-19). There is a subgroup of patients who develop a hyperinflammatory response with severe respiratory failure and organ dysfunction with high mortality. Identifying these patients is outstanding as they could benefit from specific therapies, such as cytokine removal by hemoadsorption.

Methods: Single-center, observational and prospective study of critically ill patients with SARS-CoV-2 pneumonia, severe acute respiratory failure and hypercytokinemia. All patients received cytokine hemoadsorption using Cytosorb® (Cytosorbents Europe, Berlin, Germany). The indication for treatment was acute respiratory failure, inadequate prone response, and hypercytokinemia.

Results: A total of 343 patients were admitted to the ICU due to SARS-Cov-2 infection between March 3, 2020, to June 22, 2020. Of these, six patients [5 (83.3%) men; mean age 57 (10.5) years; SOFA 5 (1.4); mean Acute Physiology And Chronic Health Evaluation (APACHE) II score 19.5 (6)] underwent hemoadsorption with Cytosorb ®. All patients fulfilled the Berlin criteria for severe acute respiratory distress syndrome (ARDS), underwent prone positioning, and were on mechanical ventilation for 15.2 (7.2) days. One session of 16 (9.0) hours duration was performed. IL-6 levels were significantly reduced [(pre-hemoadsorption levels 17.367 (4.539– 22.532) pg/ml; post-hemoadsorption levels 2.403 (917 – 3.724) pg/ml, $p = 0.043$], and improvements in oxygenation were observed [pre-hemoadsorption PaO_2/FiO_2 ratio was 103 (18.4), post-hemoadsorption $PaO2/FiO2$ ratio was 222 (20.9), $p = 0.029$]. We documented the clinical improvement and rapid reversal of organ dysfunction [pre-hemoadsorption Sequential Organ Failure Assessment (SOFA) score 9 (4.7); post- hemoadsorption SOFA score 7.7 (5.4), $p = 0.046$]. Inflammatory markers (C-reactive protein, D-dimer, and ferritin) also improved significantly. Mean ICU stay was 17.2 (8.0) days. ICU and in-hospital mortality was 33.7%.

Conclusions: In our cohort, patients with SARS-CoV-2 pneumonia and severe acute respiratory failure and hypercytokinemia who received cytokine hemoadsorption, an important reduction in IL-6 levels and improvements in oxygenation and SOFA score were observed.

Background

There are several challenges when taking care of COVID-19 patients[1]. An abnormal proinflammatory response, known as "cytokine storm", plays an important role in the pathophysiology of the disease[2]. In the first reports from China, the cytokine storm was recognized as an important clinical feature associated with the severity of the clinical picture[3]. In the lung, hypercytokinemia leads to diffuse alveolar damage, hyaline membrane formation, thrombus formation, fibrin exudates, and fibrotic healing[4]. These pathologic changes result in acute respiratory distress syndrome (ARDS)[5], whose frequency is up to 26% in SARS-CoV-2[6 7]. Indeed, identifying the subgroup of patients who develop a hyperinflammatory response is outstanding[8], as they can benefit from specific therapies. Thus, blood purification with cytokine removal could be a promising therapeutic intervention[9 10].

Three phases characterize the progression of the severity of SARS-CoV-2 pneumonia: early, pulmonary and hyperinflammatory. These evolutive stages correspond to the different clinical profiles showing individual clinical responses to therapy and prognoses [11]. During the initial or early infection stage, both the viral inoculation and the onset of the clinical disease occur. The early clinical disease is asymptomatic or mildly symptomatic. In the second stage, the pulmonary phase, the virus replication and progressive lung inflammation occur. From a clinical point of view, it corresponds to viral pneumonia (atypical pneumonia of viral origin). Inflammatory markers may be moderately elevated. The treatment consists mainly of supportive measures and antiviral treatment. The third stage, the hyperinflammatory phase, is characterized by a multisystemic inflammatory syndrome. Serum levels of inflammatory biomarkers are considerably high, and mortality is significant. Thus, immunomodulation may be attempted in this phase.

Similarly, the inflammatory response is different depending on the severity of the disease, and it is not homogeneous throughout the course of the disease[12]. There is no hypercytokinemia during the asymptomatic phase. In the subsequent stages, massive cytokine release increases the clinical severity[13]. Although an important cytokine elevation begins in the first 24 or 48 hours of presentation, the hyperinflammatory state appears later, on day 7. This pathophysiological sequence correlates with the natural history of the disease. After 7-10 days of clinical presentation, clinical deterioration is ubiquitous, and acute respiratory failure appears progressively. Therefore, potentially useful treatments do not fit all patients.

In the early stages of COVID-19, avoiding immunosuppression is recommended. Conversely, in advanced stages, immunomodulating interventions are a cornerstone. In patients with severe acute respiratory failure due to COVID-19, cytokine hemoadsorption could provide clinical benefits.

We hypothesized that cytokine hemoadsorption may improve hyperinflammatory state and organ dysfunction in critically ill patients with COVID-19. We aimed to evaluate cytokine hemoadsorption as rescue therapy in critically ill patients with SARS-CoV-2 pneumonia, severe respiratory failure and hypercytokinemia.

Methods

We performed a single-center, observational and retrospective study of critically ill COVID-19 patients treated with cytokine hemoadsorption using Cytosorb® (Cytosorbents Europe, Berlin, Germany) adsorbent, between March 3, 2020, to June 22, 2020. The inclusion criteria were the presence of refractory acute respiratory failure (PaO_2/FiO_2 ratio < 100) with inadequate response to prone positioning,

hyperinflammatory state manifested as IL-6 hypercytokinemia (interleukin 6 (IL-6) greater than 1000 pg / mL), and increased levels of ferritin and D-dimers.

All patients were admitted to the Intensive Care Unit (ICU) of Vall d'Hebron University Hospital, Barcelona, Spain. The CytoSorb® filter was connected post-hemofilter via a close loop circuit to the CRRT pump (Prismaflex, Gambro Lundia AB, Lund, Sweden). CRRT was performed in continuous hemodiafiltration mode (CVVHDF) using a MA 150® hemofilter (Baxter, Illinois, US) at a blood flow rate of 200 ml/min. Anticoagulation was performed with citrate or heparin.

We analyzed the plasma concentrations of inflammatory biomarkers, including IL-6, interleukin 10 (IL-10), D-dimer, and C-reactive protein. upon ICU admission, immediately before hemoadsorption initiation (pre-hemoadsorption), and after the procedure (post-hemoadsorption). Other laboratory parameters were measured to evaluate organ function .

The severity of the disease was evaluated with the Acute Physiology and Chronic Health disease Classification System II (APACHE II)[14] and sequential organ failure assessment (SOFA) scores[15]. Both scores were calculated during the first 24 hours of admission. Organ dysfunction was assessed using the SOFA score before and after the hemoadsorption session. We defined sepsis and septic shock according to the Sepsis 3 criteria[16]and acute respiratory distress syndrome (ARDS) according to the Berlin criteria[17]. We collected data on the incidence of acute kidney injury or failure, and the need for continuous renal replacement therapy, according to the Improving Global Outcomes (KDIGO) Clinical Practice Guideline criteria[18]. We collected clinical data on oxygenation before and after the hemoadsorption session. We defined a poor response to the prone position when the PaO2/FiO2 ratio remained below 150 with the prone position. The use of methylprednisolone at a dose of 2mg/kg, and systemic anticoagulation, was also registered[19]. We also recorded the number of days on mechanical ventilation, the time of ICU admission, ICU and in-hospital outcomes.

Plasmatic levels of IL-6 were measured using the automated quantitative immunoassay Cobas® (Roche diagnostics International Ltd, Switzerland), following the manufacturer´s instructions. Circulating levels of IL-10 and soluble CD25 (IL-2Ra) were determined using the microfluidics-based quantitative immunoassay, ELLA® (ProteinSimple, USA), following the manufacturer's instructions.

Descriptive data were expressed as mean (standard deviation) or as median (interquartile range 25-75%, IQR) according to variable distribution. Mann-Whitney U test was used to compare continuous variables and Fisher's test for categorical variables. All statistical tests were 2-sided, and a p-value <0.05 was considered statistically significant. Data analysis was conducted using the statistical software package PASW Statistics for Windows, Version 18.0 (SPSS Inc, Chicago, IL, USA).

The study was approved by the local Clinical Research Ethics Committee (PR (AG) 270/2020), and the need for informed consent was waived.

Results

A total of 343 patients were admitted to the ICU due to SARS-Cov-2 infection. Of these, 6 patients received treatment with Cytosorb ® (table 1). Hemoadsorption was performed in another patient whose indication was refractory septic shock secondary to intestinal perforation. This patient was excluded from this study.

All patients fulfilled the Berlin criteria for severe ARDS and required prone positioning. The mean duration of mechanical ventilation was 15.2 (7.2) days. All patients received cytokine hemoadsorption between day 3 and day 4 of ICU admission, after confirmation of hypercytokinemia and inadequate response to prone positioning. There were no patients with sepsis, and one patient had noninfectious distributive shock. One session of 16 (9) hours of duration was performed, which significantly reduced IL-6 plasma levels and was associated with improvements in oxygenation and the SOFA score. Five patients received one session of Cytosorb ® hemoadsorption, and one received two 24-hour sessions. The circuit patency determined the duration of hemoadsorption sessions in 3 patients (circuit clotting occurred at 3, 8, and 16 hours). Inflammatory biomarkers (C-reactive protein, D-dimer, and ferritin) also improved significantly after treatment (Table 2). Three (50%) patients developed COVID-19-associated acute kidney injury with continuous renal replacement therapy requirements. Mean ICU stay was 17.2 (8.0) days. ICU and in-hospital mortality was 33.7%.

Discussion

This retrospective study describes the potential benefits of CytoSorb ® hemoadsorption in critically ill patients with refractory acute respiratory failure due to COVID-19 pneumonia and hypercytokinemia. Hemoadsorption was associated with a reduction in inflammatory biomarkers, improved oxygenation, and multiorgan dysfunction.

Cytosorb® is a highly bio- and hemocompatible cytokine adsorber approved for use in conditions with elevated cytokines. The device is composed of porous polymer beads within an enormous and efficient surface area. It allows for adsorption and permanent binding of molecules in the 5-60 kDa range. This range includes the vast majority of cytokines and other inflammatory molecules. The rate of removal is dependent on the presence of high concentration levels of cytokines in plasma[20].

Several recommendations regarding the use of cytokine HA in SARS-CoV-2 pneumonia have recently been published. The National Health Commission & National Administration of Traditional Chinese Medicine recommends Cytosorb ®

hemoadsorption to treat severe and critical COVID-19 cases in the early and middle stages of the cytokine storm[21]. The Brescia Renal Covid Task Force recommends Cytosorb ® hemoadsorption in COVID-19 patients admitted to ICU who have ARDS or Acute Kidney Injury requiring continuous extrarenal replacement therapy[22]. The Panamanian Association of Critical Medicine and Intensive Therapy recommends Cytosorb ® therapy in patients with deep vasoplegia, with high levels of lactate and high-dose vasopressors that do not respond to standard therapy, severe ARDS with high ventilatory support requirements, and who are candidates for the use of extracorporeal membrane oxygenation (ECMO) therapy[23]. The Colombian consensus suggests using Cytosorb ® therapy in patients with cytokine storm syndrome when there is a lack of treatment response and while evaluating the individual prognosis of the patient[24]. On April 10, 2020, the United States of America Food and Drug Administration (FDA) issued an Emergency Use Authorization for Cytosorb ® to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure and specifically early acute lung injury or early acute respiratory distress syndrome, severe disease or life-threatening disease defined as respiratory failure, septic shock or multiorgan dysfunction[25].

Despite these recommendations, clinical experience is scarce and comes mainly from case reports[26] [27] [28]and some case series. Rampino et al[29].reported a case series of 9 consecutive critically ill patients with SARS-CoV-2 and respiratory failure requiring continuous positive airway pressure. There were no patients meeting the clinical criteria for invasive mechanical ventilation at the hemoadsorption initiation. Five patients received Cytosorb ® hemoadsorption. Eligibility criteria besides a confirmed SARS-CoV-2 pneumonia were PaO2/FiO2 ratio < 200 mm Hg, C-reactive protein levels >10 mg/dL, and a lymphocyte count < 1,500/mm^3. Hemoadsorption was started 6 - 7 days after hospital admission and was delivered to each patient for 4 h sessions on 2 consecutive days. Hemoadsorption reduced pro-inflammatory cytokines, like IL-6, TNF-α, and interleukin 8 but not interleukin 2, interleukin 1, and IL-10 in treated patients compared to not treated patients. All treated patients except 1 survived, and only 2 of them needed endotracheal intubation. Damiani et al.[30] delivered hemoadsorption with Cytosorb ® for 24 to 48 hour-sessions to 11 COVID-19 patients requiring mechanical ventilation due to rapidly progressive ARDS after a median of 3 days (range 0-4 days) from hospital admission. Two patients were treated only with one 24-hour session, and 9 patients were treated for 48 hours. The median values of IL-6 prior to hemoadsorption were 355 pg/mL (IQR 263-466) and 118 pg/mL (IQR 19-221, p = 0.003) at treatment end and 169 pg/mL (IQR 61-253, p = 0.03) 24 hours after therapy. A significant decrease in C-reactive protein and an increase in PaO2/FiO2 ratio were observed. The improvement in the inflammatory profile was associated with progressive improvement in respiratory function. In a multicenter study, Vila et al[31]. evaluated 37 patients who had received cytokine hemoadsorption using the oXiris ® membrane. The indication for oXiris ® was biochemical and clinical evidence of systemic inflammation associated with acute kidney injury or hemodynamic instability, or multiorgan dysfunction. All patients received mechanical ventilation. The extracorporeal treatment was delivered after a median of 3.6 days (IQR 3.7) from ICU admission and 14 days (IQR 10.0) from the symptom onset. The median treatment time was 37 h (IQR 56). The median baseline IL-6 was 1230 pg/ml (IQR 895). The decrease of IL-6 concentration was very significant, especially during the first 24 of treatment [479 pg/ml (IQR 531) at 24 h, 320 pg/ml (IQR 259) at 48 h, and 160 pg/ml (IQR 141) at

72 h (p = 0.001 for each time point)]. The reduction in serum IL-6 concentration levels correlated with improved organ function, particularly the hemodynamic and pulmonary function. A slight decrease in observed mortality rate compared with predicted mortality rate, calculated by APACHE IV score, was also observed.

The selection of COVID-19 patients for receiving hemoadsorption is critical. There are two clinical phenotypes of COVID-19 patients[11]. One phenotype is characterized by a mild or moderate disease and reduced viral loads. These patients have a competent interferon response with low cytokine generation and show a rapid recovery from initial lymphopenia. These patients are unlikely to benefit from cytokine hemoadsorption. However, the second phenotype, which is characterized by a severe disease with a high risk of death, higher viral loads, insufficient interferon response, sustained lymphopenia, and a very significant elevation of cytokines, could benefit from cytokine hemoadsorption. Thus, we consider that patients more likely to benefit from cytokine hemoadsorption are more severely ill and develop a prominent hyperinflammatory state. The selection of these patients should probably be based on their clinical characteristics, such as the presence of severe acute respiratory failure, in conjunction with increased inflammatory biomarkers such as cytokines, ferritin, and D-dimers, among others. Consequently, we established that the indication criteria for hemoadsorption should be the presence of severe acute respiratory failure refractory or poorly responsive to prone positioning, associated with hyperinflammatory state as reflected by very high levels of IL-6, ferritin, and D-dimers.

Unlike the previous study by Rampino *et al*. [29], in which the mean PaO2/FiO2 ratio was higher and patients did not require invasive mechanical ventilation, all our patients presented a considerable deleterious clinical situation, with a mean PaO_2/F_IO_2 ratio of 103 (18.4), and 2 of them needed ECMO support. The hemoadsorption delivering strategy in our study was different from Rampino´s study. In their study, hemoadsorption was delivered in the form of fixed-duration 4-hour sessions on 2 consecutive days. We sought to provide a single 24-hour session of hemoadsorption (only one patient required 2 sessions of 24 hours). However, the median duration of hemoadsorption was shorter than 24 hours (16 h; IQR 9h), as the duration of treatment was dependent on the circuit patency. We monitored IL-6 levels in real-time during hemoadsorption sessions, which allowed us to withhold the treatments at 24 hours if IL-6 levels had been significantly reduced, and the patient had improved clinically.

Our case series report similar findings to the previous studies performed by Damiani *et al* [30]. and Vila *et al* [31]. However, our patients had evidence of a significant cytokine storm as manifested by a severe hyperinflammatory state. The median IL-6 levels of our patients were higher than theirs [17367 (4539-22532) pg/mL], and the reduction in IL-6 levels and inflammatory biomarkers was substantial. Similar to Damiani *et al.*[30], we did not observe significant differences in the decrease of IL-10. However, this lack of effect over IL-10 levels was probably secondary to the initial slightly high levels and small sample size.

Our results are engaging and coincide with previously published studies discussed above. The significant recovery of the patient's inflammatory status was associated with improvements in organ dysfunction scores, particularly respiratory function. Thus, we

consider cytokine hemoadsorption an effective and safe rescue therapy for highly selected critically ill COVID-19 patients. Further observational and larger studies on the benefits of cytokine hemoadsorption should be performed to validate our findings. Well-designed randomized controlled trials of critically ill COVID-19 patients with refractory acute respiratory failure and hypercytokinemia should be carried out to evaluate the clinical effects of cytokine hemoadsorption.

This study has significant limitations that should be noted. First, this is a single-center study including a very small number of patients, thus our results cannot be extrapolated to other ICU settings. Second, the patient inclusion process was not consecutive. Given the unprecedented pandemic situation, it was impossible to ensure that all patients meeting the inclusion criteria for receiving cytokine hemoadsorption were evaluated for eligibility..

Conclusions

In our case series of critically ill patients with SARS-CoV-2 pneumonia, severe acute respiratory failure and hypercytokinemia who were poorly responsive to prone positioning, cytokine hemoadsorption was associated with an improvement in the hyperinflammatory profile and organ dysfunction. The cytokine hemoadsorption is a safe and probably effective rescue therapy for patients with severe and refractory COVID-19 acute respiratory failure.

List of abbreviations

AKI: Acute Kidney Injury

COVID-19. Coronavirus infectious disease 2019

CRP: C-Reactive Protein

CRRT: Continuous renal replacement therapy

DD: D Dimers

ICU: Intensive Care Unity

IL-6: Interleukin 6

IL-10: Interleukin 10

SARS-CoV-2: Severe Acute Respiratory Syndrome due to Coronavirus type 2

VAP: Ventilator associated pneumonia

Declarations

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- Table1.jpg