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Hemoperfusion with CytoSorb® in Critically Ill COVID-19 Patients

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Coronavirus disease 2019 · Hemoperfusion · Cytokines · IL-6

Abstract
Introduction: Systematic inflammatory response occurred in some critically ill patients with COVID-19. Cytokine reduction by hemadsorption is a mechanism of treatment. However, whether CytoSorb hemoperfusion works for critically ill COVID-19 patients remains unknown. ***Materials and Methods:*** We observed case series of critically ill COVID-19 patients receiving CytoSorb hemoperfusion as rescue therapy from 3 hospitals in Hubei, China from February 28, 2020, to April 7, 2020. Their demographic, laboratory, and clinical data were collected. The parameters for organ function and IL-6 levels were compared before and after treatments. ***Results:*** A total of 10 cases were included. The median age of the patients was 67.7 years (range = 50–85) with APACHE II (23.5) and SOFA (11.4). Patients received a median of 3 attempts of hemoperfusion (range = 1–6). The median CytoSorb perfusion time was 47 h (12–92 h). The level of IL-6 significantly decreased after treatments (712.6 [145–5,000] vs. 136.7 [46.3–1,054] pg/mL, $p = 0.005$). Significant improvement was found in PaO_2/FiO_2 (118 [81–220] vs. 163 [41–340] mm Hg, $p = 0.04$) and lactate levels (2.5 [1–18] vs. 1.7 [1.1–10] mmol/L, $p = 0.009$). The hemodynamics measured by norepinephrine/MAP slightly improved after treatment (17 [0–68] vs. 8 [0–39], $p = 0.09$). Albumin mildly decreased after CytoSorb. No significant changes were found in red blood cell counts, white cell counts, and platelets. ***Conclusion:*** Treatment with CytoSorb in critically ill COVID-19 patients was associated with decreased IL-6 improvement in oxygenation. However, these effects cannot be confirmed as the direct effects of CytoSorb owing to lack of controls. Establishing causality requires large-scale randomized clinical trials.

Introduction

The COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a worldwide pandemic. As of May 8, 2020, the World Health Organization reported >3,845,607 cases and >269,564 deaths globally [1]. Epidemiological studies in China have shown that the overall mortality rate of COVID-19 patients is 2.3%, and the mortality rate of critically ill patients is 49% [2]. Unfortunately, no specific antiviral treatment is recommended for COVID-19, and no vaccine is currently available.

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The pathogenesis of the highly pathogenic human coronavirus is still not completely understood. Systematic inflammatory response is believed to play an important role in disease severity [3]. Accumulating evidence has revealed that some patients with severe COVID-19 have an elevated cytokine profile resembling systematic inflammatory response in SARS and MERS. Huang et al. [4] reported elevated levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα in severe COVID-19 patients. Another retrospective, multicenter cohort study reported significant elevation of IL-6 in nonsurvivors of COVID-19 compared with that of the survivor [5]. Several other reports have also revealed elevated IL-6 in critically ill COVID-19 patients [6, 7]. The immune response may be exaggerated and may challenge tissue integrity, in some cases leading to multiple organ failure, ARDS, and death [3].

Therefore, cytokine reduction and reprogrammed immune status by hemadsorption is an alternative treatment option. Several clinical and in vitro data have demonstrated that additional treatment with an extracorporeal cytokine absorber results in effective removal of toxic cytokine levels and may help patients with septic multi-organ failure [8–11].

The CytoSorb whole-blood absorber is an EU-approved medical device and used in clinical situations in which cytokines are elevated. CytoSorb therapy has been safely used in >80,000 treatments worldwide. The highly porous, biocompatible polymer with its specific properties can bind a broad spectrum of hydrophobic compounds with molecular weights of up to 55 kDa, a range where most cytokines reside. The removal of substances is concentration dependent. Low plasma-cytokine concentrations are unaffected, but high plasma-cytokine levels are effectively reduced [12].

A case series of 16 patients undergoing cardiopulmonary bypass with CytoSorb therapy and CRRT has demonstrated decreased serum levels of circulating cytokines, improved organ function, and enhanced hemodynamic stability [13]. Kogelmann et al. [12] also reported a retrospective case series of 26 septic patients with 2-system organ failure who were exposed to CytoSorb therapy. These patients had increased hemodynamic stability, decreased serum lactic acid levels, and decreased vasopressor demands with this therapy. The authors posited that the use of this therapy within 24 h of diagnosis could lead to decreased mortality in medical and postsurgical patients [12]. The findings of improved serum lactate levels and decreased vasopressor requirements were replicated in a single-center prospective cohort of 20 patients with refractory septic shock, although this study's conclusions were limited by the lack of a control group with which to compare clinical outcomes [14]. However, whether CytoSorb hemoperfusion works for critically ill COVID-19 patients remains unknown. Thus, in the present case series, we evaluated the impact of CytoSorb used as an adjunctive therapy on clinically relevant outcome parameters in 10 critically ill COVID-19 patients.

Methods

Patients

This case series was performed from February 28, 2020, to April 7, 2020, in the Department of Critical Care Medicine of 3 COVID-19 designated hospitals, including Zhongnan Hospital of Wuhan University, the Central Hospital of Wuhan, and Shiyan Renmin Hospital. This study was approved by the Zhongnan Hospital of Wuhan University Ethics Committee (#2020088K), and informed oral consents were obtained from the patients' families owing to the specific circumstances of the SARS-CoV-2 pandemic. All included patients were critically ill with COVID-19 and had elevated levels of inflammatory mediators. Patients with severe COVID-19 met the diagnostic criteria for the Handbook of COVID-19 Prevention and Treatment (7th Trial Version, Revised) promulgated by the National Health Commission of the People's Republic of China. The diagnostic criteria for critically ill COVID-19 patients were as follows. Patients with pneumonia tested positive for SARS-CoV-2 and had respiratory failure and required mechanical ventilation; or developed shock or other organ failure; and required ICU care. Exclusion criteria included maternal, lactating women, <18 years old, normal or low IL-6 levels (<7 pg/mL), end-of-disease status, and survival time of patients treated with CytoSorb devices for <24 h.

Treatment Protocols

The treatment of critically ill COVID-19 patients was conducted in accordance with the Handbook of COVID-19 Prevention and Treatment (7th Trial Version, Revised) issued by the National Health Commission of the People's Republic of China. All patients received at least 1 session of CytoSorb hemoperfusion (donated by CytoSorbents Europe, Berlin, Germany). The timing of initiation of CytoSorb therapy and the number of CytoSorb treatment sessions depended on the clinical judgment of the treating physicians based on clinical abnormalities (abruptly worsening oxygenation and hemodynamics) and elevated inflammatory markers (IL-6 >500 pg/mL). This threshold level of IL-6 >500 pg/mL was from our previous observational studies [15, 16] and other reports from Wuhan [5–7]. We found that it indicated cytokine storm and worse outcome when IL-6 >500 pg/mL. The flow rate through the CytoSorb device was set at 150 mL/min. Anticoagulation with CytoSorb perfusion was unfractionated heparin, and the CytoSorb columns were replaced every 12–24 h. When patients required renal replacement therapy, the CytoSorb device was connected in series with CRRT and placed prior to the filter for CRRT (Fresenius CRRT machine). The CRRT mode was CVVHD with a dialysate dose of 35 mL/kg/h. CytoSorb irrigation devices were used in tandem with Extracorporeal Membrane Oxygenator (ECMO) via CRRT machines when patients were treated with ECMO.

Table 1. Demographic data of the patients receiving hemoperfusion

	Patient									
	1	2	3	4	5	6	7	8	9	10
Sex	Male	Male	Male	Female	Female	Male	Male	Male	Male	Male
Age, years	59	77	50	58	85	76	68	73	66	65
Height, cm	154	170	170	158	155	170	170	172	175	172
Weight, kg	48	60	85	50	50	70	70	70	72	72
APACHE II pre-cytosorb, D0	21	22	14	24	23	17	28	27	35	24
SOFA pre-cytosorb, D0	11	11	3	12	6	15	14	15	16	11
CytoSorb columns, *n*	4	3	4	3	3	6	3	1	1	2
Treatment duration, h	78.5	42.5	75	44.5	53.5	92	36	12	12	24
Hours on ECMO	0	0	0	0	0	0	624	696	0	0
Days on IMV	23	15	0	6	0	25	27	31	8	7
Days on CRRT	2	1	4	1	0	6	27	31	8	6
ICU stay, days	30	33	5	6	15	15	35	32	5	16
Hospital stay, days	56	49	21	8	15	25	46	36	5	39
Coexisting chronic diseases										
Hypertension	N	N	N	N	Y	N	Y	Y	Y	Y
COPD	N	N	N	N	N	N	N	N	N	N
Diabetes	Y	N	N	N	N	N	N	Y	N	N
Myocardial infarction	N	N	N	Y	Y	Y	N	N	N	N
Cerebral infarction	Y	Y	Y	N	Y	N	N	Y	Y	N
Chronic renal dysfunction	N	N	Y	N	Y	N	N	N	N	Y
Steroid use	N	Y	N	Y	Y	N	N	N	N	Y
Outcome (ICU survival)	N	N	Y	Y	N	Y	Y	N	N	Y

ECMO, extracorporeal membrane oxygenator; IMV, invasive mechanic ventilation; N, no; Y, yes.

Data Collection and Statistics

Therapeutic effect was evaluated by collecting and analyzing APACHE II score, SOFA score, metabolic indices (lactic acid and BE), hemodynamic indices (blood pressure and vasoactive drug dose), oxygenation indices (arterial blood oxygen pressure and oxygenation index), organ function indices (blood routine, coagulation function, liver and kidney function, and myocardial enzyme), and inflammatory reaction indices (IL-6, procalcitonin, erythrocyte sedimentation rate, and CRP). All these data were compared between pre- and post-treatment (collected at the end of treatments). Continuous variables were described using mean with standard deviations or median with range values. Means for continuous variables were compared using paired *t* tests when the data were normally distributed; otherwise, the Wilcoxon test was used. All data charts were prepared with GraphPad Prism 5.01 software. *p* values <0.05 represented statistical significance, and all reported *p* values were 2 sided. All statistical analyses were performed using SPSS version 13.0 software (SPSS Inc.).

Results

A total of 10 patients were included. Table 1 provides an overview of patient vital signs, diagnosis, treatment method, and outcome. The median age was 67.7 years (range = 50–85), and the majority were males (8 vs. 2). No one received IVIG, antiviral drugs, or convalescent plasma. Four of the 10 patients received steroids prior to hemoperfusion but without any effects. Two patients used only CytoSorb. Six patients used CRRT and CytoSorb. The 2 other patients used ECMO, CRRT, and CytoSorb. The APACHE II and SOFA scores, which reflect disease severity, were 23.5 and 11.4 (mean values), respectively, before CytoSorb hemoperfusion. All patients received at least 1 session of perfusion of CytoSorb up to 6 sessions, averaging 3 sessions per patient. The median CytoSorb perfusion time was 47 h (12–92 h). For inflammatory parameters, the level of IL-6 significantly decreased after treatment (712.6 [145–5,000] vs. 136.7 [46.3–1,054] pg/mL, $p = 0.005$) (Fig. 1). The average IL-6 from 2 patients receiving ECMO at initiating treatments was 3,854.6 pg/mL, and it decreased around 80% after the treatments. The levels of CRP and PCT did not change significantly after treatment ($p = 0.34$ and $p = 0.37$, respectively, CRP with missing data and imputed with the data of the nearest time points or with mean/average values). The hemodynamics measured by norepinephrine/MAP slightly decreased after treatments (17 [0–68] vs. 8 [0–39] μg/h/mm

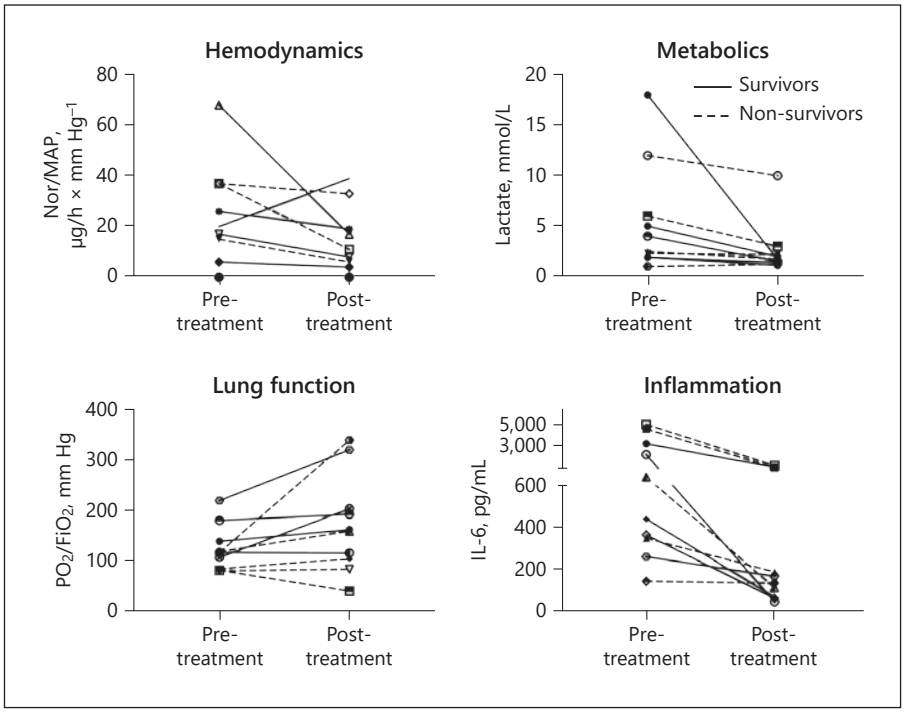

Fig. 1. The comparison of IL-6 and organ functions between pre- and post-treatments by CytoSorb. Nor, norepinephrine, Nor/MAP reflecting the hemodynamics; P/F, PaO_2/FiO_2, reflecting the severity of ARDS. $p = 0.09$ for Nor/MAP; $p = 0.005$ for IL-6; $p = 0.04$ for P/F, $p = 0.009$ for lactate.

Hg, $p = 0.09$). Blood lactate levels also decreased after treatment (2.5 [1–18] vs. 1.7 [1.1–10] mmol/L, $p = 0.009$), especially in surviving patients. With respect to the effects of respiratory function, we found statistically significant improvements in PaO_2/FiO_2 (118 [81–220] vs. 163 [41–340] mm Hg, $p = 0.04$). Although all patients used unfractionated heparin as anticoagulant, levels of D-dimer were generally elevated. We found no significant reduction in SOFA score after treatment ($p = 0.75$).

All patients were hospitalized in the ICU from 5 to 35 days (median 19.2 days). Five out of 10 patients survived in the ICU. Five ICU survivors had an average hospitalization of 25.8 days, and 5 ICU nonsurvivors had an average hospitalization of 12.6 days. The overall hospital survival rate of 10 patients was 40%; 1 patient died of sudden cerebral hemorrhage on the floor; 1 patient died of sudden refractory hypoxemia and shock, likely owing to acute massive pulmonary embolism; 1 patient consented for DNR owing to old age; and 3 patients died of refractory multi-organ failure. Eight of 10 patients received invasive mechanical ventilation for 17.8 days (median value, range = 6–31 days) during hospitalization. Five ICU survivors had longer mechanical ventilation (19.4 days) than 3 ICU nonsurvivors (15 days). Nine of the 10 patients received CRRT during hospitalization with a median of 9.6 days (range = 1–31 days), 5 ICU survivors had shorter CRRT time (8.4 days) than 4 ICU nonsurvivors (11 days). No significant complications such as gastrointestinal bleeding, cerebrovascular accidents, and thromboembolic events were observed during CytoSorb hemadsorption therapy. However, we found that some patients had mild decreased albumins ($p = 0.06$) and platelets ($p = 0.07$) after CytoSorb perfusion (Fig. 2) but did not require additional infusions. No significant bleeding events were observed, and no technical difficulties were identified with CytoSorb therapy.

Discussion

In this case series, we reported a total of 10 critically ill COVID-19 patients who were treated with CytoSorb perfusion as adjunctive therapy owing to their critical conditions. We found that these patients' overall conditions were improved by reducing vasoactive drug use, improving oxygenation index, and decreasing IL-6 levels. Although we cannot establish causality owing to the lack of a control group, we could conclude that CytoSorb perfusion combination was safe, feasible, and simple. To our knowledge, this case series is the first one reporting on the use of CytoSorb therapy specifically for critically ill COVID-19 patients.

Although COVID-19 pathogenesis is not fully understood, recent studies have shown that inflammatory fac-

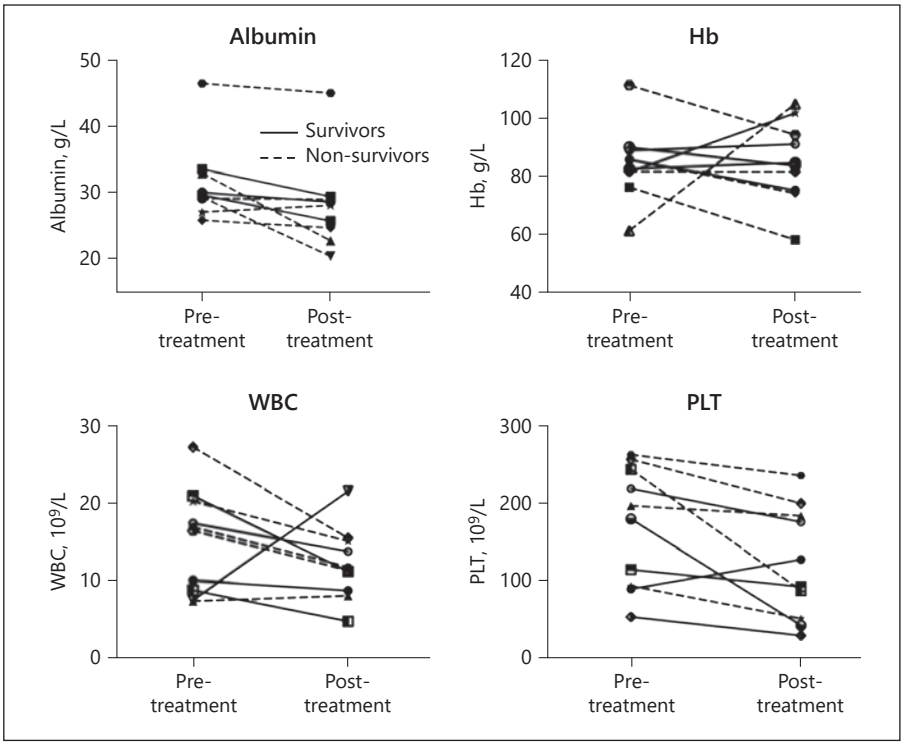

Fig. 2. The changes of albumin, Hb, white cells, and PLT pre- and post-treatments with CytoSorb. Hb, hemoglobin; WBC, white blood cells; PLT, platelets. $p = 0.06$ for albumin; $p = 0.07$ for PLT; $p = 0.09$ for WBC; $p = 0.77$ for Hb.

tors are generally elevated in patients with COVID-19, especially in severe cases. These factors induce immune cells to release a vast number of free radicals, which are the major causes of ARDS and multi-organ failure [17]. Therefore, inflammatory storm may be an important cause of deterioration and disease aggravation in patients with COVID-19. Effectively controlling inflammatory storms in patients with COVID-19 may be an important target for the treatment of critically ill ones.

A growing body of evidence provides reasonable proof that cytokine adsorption by using the CytoSorb hemoadsorber results in effective cytokine removal in vitro [18, 19] and in vivo [20, 21]. Additionally, the removal spectrum of CytoSorb seems to encompass other inflammation-related trigger substances such as pathogen-associated molecular patterns or damage-associated molecular patterns, substances that can provoke and maintain a generalized inflammatory host response [17, 22].

IL-6 can block CD8+ cytotoxic T-cell by inhibiting the secretion of gamma-interferon. Moreover, IL-6 can paralyze the cell-mediated antiviral response during a systematic inflammatory response by inducing the suppression of cytokine signaling and increasing PD-1 expression [23]. Several reports have also confirmed the elevation of IL-6 in critically ill COVID-19 patients [6, 7]. In our set of patients, plasma IL-6 concentrations significantly decreased post-CytoSorb in the first attempt, independent of eventual outcome. Additional treatments of CytoSorb did not result in further decreases in those with already low levels of cytokines. The average IL-6 from 2 patients receiving ECMO at initiating was 3,854.6 pg/mL, and it decreased around 80% after the treatments. It could be a kind of "role of engagement" for its use in the patients. This finding was consistent with the known concentration-dependent nature of CytoSorb sorbent, which rendered it very effective at high concentrations but not at low ones. Actually, the eliminative effects were minimal in 1 case whose IL-6 level was <200 ng/mL. This safety aspect is important as the immune system needs low to moderate concentrations of cytokines to maintain a normal physiologic response.

The decrease in cytokine levels was paralleled by a stabilization of hemodynamic parameters, as demonstrated by a reduction of catecholamine support. Many publications on CytoSorb to date have demonstrated the immediate effects of improved hemodynamics [12–14, 21]. Prolonged catecholamine administration has been shown to reduce peripheral (extremities and phalanges), renal, and hepato-splanchnic blood flow, contribute to late-phase immunosuppression, increase apoptotic and anti-inflammatory responses, and stimulate bacterial growth, leading to poor clinical outcomes [24–26]. Any therapeu-

tic option enabling faster weaning from vasopressors may result in better recovery and outcome.

In our case series, treatment combined with CytoSorb hemoperfusion also improved the oxygenation index. ARDS is the leading cause of death in patients with COVID-19. Yang et al. [27] reported a 28-day mortality rate of 62% in patients who required ICU care; among patients who required intubation, 28-day mortality rate was >80%. The ICU mortality in our series was 50% despite patients in our study being sicker than those in Yang's study (APACHE II; 23.5 vs. 16). This finding indicated that the combination of CytoSorb hemoperfusion may further improve the outcome in critically ill COVID-19 patients in addition to conventional therapy.

This study has several limitations. First, this study is an observational one with limited sample size, leading to missing data at some time points. The missing data (CRP) were imputed with the data of the nearest time points or with mean/average values. Second, initiating hemoperfusion in all cases was too late, affecting the overall outcome of CytoSorb therapy. Further studies should focus on early treatment with CytoSorb in COVID-19. Indications for treatment based on the initial cytokines in critically ill COVID-19 also need to be discussed. Third, the lack of a control group and the complexity of the patients' treatment regimens conferred difficulty in determining the effect of CytoSorb hemoperfusion alone on patient outcomes. Lastly, we could not exclude concomitant bacterial infections that could account for the increase of inflammatory markers. Therefore, more rigorous clinical studies in the future are needed to further define the role of CytoSorb hemoperfusion in patients with COVID-19.

Conclusion

Treatment with the CytoSorb device was safe and well tolerated, with no device-related adverse events during or after treatment sessions. It was also easy to implement only in hemoperfusion mode or as part of the CRRT and ECMO circuits. Therefore, randomized controlled trials are warranted to further delineate the potential benefits of this new treatment option.

Acknowledgment

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Statement of Ethics

The study protocol was approved by the Zhongnan Hospital of Wuhan University Ethics Committee (#2020088K). Informed consents were obtained from patients' family members. Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Drs. Lu Li and Xu Zhao collected the patients' data. Drs. Jin-Yu Peng and Lu Li analyzed the data and wrote the manuscript. Drs. Feng Ding and Dr. Xiaotong Hou provided consultations for the extracorporeal life supports. Dr. Zhiyong Peng designed the study and finalized the manuscript.

Availability of Data and Material

The datasets during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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