Hemoperfusion that was popular during the COVID-19 pandemic: A case series

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Abstract

The medical world has been seeking solutions in solving the Coronavirus disease 2019 (COVID-19) outbreak since 2019. Amongst several alternatives, hemoperfusion therapy has been reported to be beneficial for alleviating symptoms and reducing mortality in severely ill COVID-19 patients. Hemoperfusion is a process of filtering blood to eliminate toxins and inflammatory factors from the body. This case series aims to highlight the unexpected adverse clinical and laboratory outcomes in the majority of COVID-19 patients treated with hemoperfusion in our hospital. We included fifteen patients admitted to the Intensive Care Unit (ICU) with moderate-to-severe COVID-19 between August and December 2020 and were all given two to four sessions of hemoperfusion using the MG150® cartridge. All ten men and five women showed no improvement in their neutrophil-lymphocyte ratio (NLR), ferritin, D-dimer, and C-reactive protein (CRP) values after the hemoperfusion regiments, both survivors and non-survivors. In addition, eleven out of twelve patients with respiratory failure who were then intubated resulted in death. Based on our findings and previous evidence, we recommended only performing hemoperfusion for investigational instead of therapeutic purposes due to its poorly understood pathophysiology in COVID-19. We also recommended further research regarding the usage of hemoperfusion in COVID-19 patients, especially in the matter of determining the best time to start the therapy.

Key words: Hemoperfusion, COVID-19, outcome.

Introduction

The ongoing Coronavirus disease 2019 (COVID-19) pandemic has been causing a worldwide health crisis. Its patients show a wide variety of symptoms, with fever and cough being the most common clinical manifestations. (1) The most recent statistics recorded up to 158,000 deaths in Indonesia caused by this virus, reflecting how deadly this disease can get. This case series included confirmed COVID-19 patients who, during their hospitalization period, developed critical complications such as sepsis, acute kidney injury (AKI), and acute respiratory distress syndrome (ARDS) that did not resolve with standard medications - indicating the need for invasive interventions such as hemoperfusion, hemodialysis, and mechanical ventilation.

Hemoperfusion is a process of filtering blood to eliminate toxins and inflammatory factors from the body. Several studies have reported this extracorporeal procedure beneficial in alleviating severe and critical COVID-19 symptoms, (2-9), which was hypothesized to be owing to its downregulating effect towards the "cytokine storm" triggered by the viral infection. The cytokine storm refers to a condition where inflammatory mediators, particularly cytokines, are overproduced due to a dysregulated pro/anti-inflammatory response balance during severe infections. This condition usually leads to fatal

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clinical sequels such as ARDS and multiple organ dysfunction syndrome (MODS). (10)

However, despite its favorable reputation, hemoperfusion did not improve our patients' conditions, as shown by their worsened clinical state, high mortality outcome, and increased inflammatory markers. There was a significant possibility that this unfavorable result might be influenced by the patient's multiple comorbidities, lack of vaccine-induced immunity, wrong timing in initiating hemoperfusion, or the ineffectiveness of the treatment itself.

In this case series, we report our findings in fifteen confirmed COVID-19 patients who underwent multiple cycles of hemoperfusion using the MG150® cartridge and discuss the possible causes behind the adverse outcomes of this adjunctive therapy.

Case series

Patients

This single-center case series reported adult COVID-19 patients confirmed by a positive reverse transcriptase polymerase chain reaction (RT-PCR) test result treated in the Intensive Care Unit (ICU) of Pelni Hospital, Indonesia, between August 17 and December 15, 2020. The data included in this study were retrieved from the hospital's electronic medical records. All patients enrolled in this research have fulfilled the diagnostic criteria for moderate and severe COVID-19 upon admission according to the Indonesian COVID-19 Treatment Guideline (4th edition). (11) Patients with moderate COVID-19 severity presented with clinical pneumonia symptoms (fever, cough, breathlessness, and/or tachypnea) only, while those with severe COVID-19 showed signs of severe pneumonia such as respiratory rate (RR) of >30/minute, severe respiratory distress, or oxygen saturation (SpO2) of <93% on room air. The patients' profiles and initial vital signs were obtained upon admission to the Emergency Room (ER).

Treatments

All patients in this report were planned for four sessions of a 2-hour hemoperfusion cycle using the MG150® cartridge (manufactured by Biosun Medical Technology Co., Ltd., China) for two days in a row, with an interval of 12 hours after each session. The blood flow (Qb) rate through the device was set at 200 ml/minute, with a regular heparin of 500 IU/hour. Patients complicated with kidney failure underwent both hemoperfusion and hemodialysis.

The treating physicians relied purely on their clinical judgment toward the patients' condition when deciding to initiate or discontinue the hemoperfusion procedure. All patients were also administered COVID-19 standard pharmacological treatment while receiving extracorporeal blood purification therapies. These encompass a combination of antivirus (favipiravir, remdesivir, or oseltamivir), antibiotics (levofloxacin, meropenem, imipenem, ceftriaxone, or azithromycin), corticosteroids (methylprednisolone or dexamethasone), immunomodulator (tocilizumab), and mucolytic agent (acetylcysteine). Patients with respiratory failure were also given oxygenation support using mechanical ventilators. The patients' laboratory markers (NLR, ferritin, D-dimer, and CRP) were serially measured before and after hemoperfusion.

Results

A total of 15 confirmed moderate-to-severe COVID-19 patients were included in this report. The summarized patients' baseline characteristics, treatments received, and outcomes are presented in **Table 1**. The mean age was 53, with a standard deviation of ±16 years. The number of male patients was twice the number of female ones (10 male vs. five female patients). The majority of patients (66.7%) presented with or developed diabetes mellitus (DM) type II as a complication, while eight of them had hypertension (53.3%). The initial vital signs measurements upon admission in the ER showed relatively normal values - although the median values of heart rate (HR) and RR, respectively, 107 (90-115) per minute and 20 (20-25) per minute, were borderline above normal suggesting tachycardia and tachypnea. Ten patients (66.7%) completed four sessions of hemoperfusion, while the remaining five failed to complete the regimen due to clinical deterioration and only received 2-3 sessions as a consequence. Hemoperfusion was initiated on day 5 (4-8) of hospitalization, and the patients were hospitalized for 7 to 24 days (median of 12 days). Twelve patients (80%) were intubated for a median of 3 (3-8) days. By the end of the treatment, there was an 80% mortality rate, with only three patients (20%) being discharged from the hospital. The laboratory measurement comparison of NLR, ferritin, D-dimer, and CRP before and after hemoperfusion can be seen in **Table 2** and **Figure 1**. The laboratory results pre- and post-hemoperfusion of each patient were averaged, and the cumulative values of all patients were then presented as the median and interquartile range (IQR). The general trend of NLR, D-dimer, and CRP showed a notable increase after treatment. In contrast, ferritin values after hemoperfusion relatively decreased, albeit its 1st quartile (1515.36 ng/ml) still were higher than the value (766.63 ng/ml) before treatment. The maxi-

mum measurable value of ferritin in our laboratory is 2000 ng/ml, posing the possibility of the circulating amount being more than 2000 ng/ml.

Discussion

Our results showed that only 3 out of 15 patients with severe COVID-19 underwent hemoperfusion therapy and were discharged from the hospital, yielding an 80% mortality rate in our case series. This led us to question whether or not hemoperfusion is a beneficial adjuvant therapy for COVID-19. A randomized controlled trial that investigated cytokine adsorption in COVID-19 patients on extracorporeal membrane oxygenation (ECMO) reported that the treatment cohort did not experience any decrease in their interleukin (IL) 6 concentrations and had a lower survival rate. (12) It was hypothesized that the adsorption device (CytoSorb®) was not selective enough, causing protective factors to be unintentionally eliminated along with the cytokines. The MG150® cartridge used in our research was made of porous adsorptive resin that was claimed to be capable of adsorbing toxins: IL-1, IL-6, homocysteine, and oxidative products. The product was fabricated to perform hemoperfusion and hemodialysis simultaneously due to its ability to bind middle to large molecular and protein-bound uremic toxins by Van der Waals force and hydrogen bonds. However, this process of eliminating both pro- and anti-inflammatory cytokines might not be selective enough - unintendedly and ironically causing further mitochondrial dysfunction and immoderate immunosuppression, heightening the chance of complications such as MODS, hypotension, arrhythmias, and death. (13-15) Furthermore, there is a potential to eliminate concomitant COVID-19 medications via hemoperfusion, which is uniquely determined by each drug's pharmacokinetic profile, encouraging the need to administer additional doses before performing hemoperfusion to maintain their bioavailability. (13,16) Unfortunately, the pathophysiology of hemoperfusion is a matter yet to be explored adequately, especially in severe COVID-19 infection and its hypercoagulability. Therefore, experts have re-stated that hemoperfusion should strictly be performed only in the context of well-designed controlled experiments. (14,15)

Ugurov P. et al., in their case series (9) of COVID-19 patients with pneumonia that were given an early-initiated (within 4-12 hours after admission) extracorporeal blood purification using the oXiris® hemofilter presented favorable results as shown by reduced cytokine levels, inflammatory markers (CRP, NLR, etc.), coagulation markers (D-dimer, etc.), and duration of ICU stay. This emphasizes the need to formulate the right time to initiate and terminate hemoperfusion therapy, which up till now remains unanswered and purely relies on physicians' judgments, (13) although several previous reports unanimously suggested: "the earlier, the better." (2,9,17-19) We initiated hemoperfusion on day 5 (4-8) of hospitalization, with 80% of our patients being intubated, suggesting that we might have viewed hemoperfusion as more of a curative treatment towards critical conditions when it should have been performed as a preventive strategy.

Strengths and limitations

Our case series contributed novel insights as it was the first report regarding hemoperfusion as an additional treatment for COVID-19 in a secondary hospital in Indonesia. On top of that, the device we used (Biosun MG150®) has not been previously reported in any scientific literature. However, the lack of a control cohort and the limited number of subjects weakened our findings, making it impossible for us to conclude the effectiveness of hemoperfusion for COVID-19. Another important limitation was the unavailability of IL-6 serial measurement data due to the hospital's budget constraint. Nevertheless, this lack of resources was compensated by substituting IL-6 and IL-18 with CRP and ferritin, respectively, as they have a reasonable correlation with infection-induced systemic inflammation. (2)

Conclusion

Our results suggested that hemoperfusion did not improve most of our patients' conditions, as shown by the high mortality rate and worsened laboratory indicators (NLR, D-dimer, and CRP). We underlined the need to carefully consider performing hemoperfusion as a curative measure for COVID-19, as there are still many grey areas regarding its safety and effectiveness. However, it is worth remembering that this report cannot conclude the efficacy of hemoperfusion. Further randomized controlled trials, particularly regarding the factors needed to be considered when deciding to initiate/terminate hemoperfusion, are essential to determine whether or not hemoperfusion should even be considered as a potential adjuvant therapy in severe COVID-19 and other infectious diseases.

Conflict of interest

None to declare.

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Table 1. Patients' baseline characteristics, treatments, and outcomes

	n=15
Age (years), mean (±SD)	53 (±16)
Sex, n (%)	
- Male	10 (66.7)
- Female	5 (33.3)
Comorbidities and complications, n (%)	
- Hypertension	8 (53.3)
- Diabetes mellitus type II	10 (66.7)
- Hypertensive heart disease	4 (26.7)
- Acute kidney injury	5 (33.3)
- Lung tuberculosis	1 (6.7)
Initial vital signs, median (Q1-Q3)	
- Consciousness level (Glasgow coma scale)	15 (15-15)
- Systolic blood pressure (mmHg)	131 (114-161)
- Diastolic blood pressure (mmHg)	76 (67-88)
- Heart rate (beats/minute)	107 (90-115)
- Respiratory rate (breaths/minute)	20 (20-25)
- Temperature (°C)	37 (36-37)
- Oxygen saturation (%)	99 (85-100)
Treatments, n (%)	
- Hemoperfusion	10 (66.7)
- Hemoperfusion + hemodialysis	5 (33.3)
- Mechanical ventilation	12 (80)
Frequency of hemoperfusion	
- Two times	1 (6.7)
- Three times	4 (26.7)
- Four times	10 (66.7)
Standard treatment before hemoperfusion (days), median (Q1-Q3)	5 (4-8)
Hospital length of stay (days), median (Q1-Q3)	12 (7-24)
Duration of intubation (days), median (Q1-Q3)	3 (3-8)
Final outcome, n (%)	
- Discharged	3 (20)
- Death	12 (80)

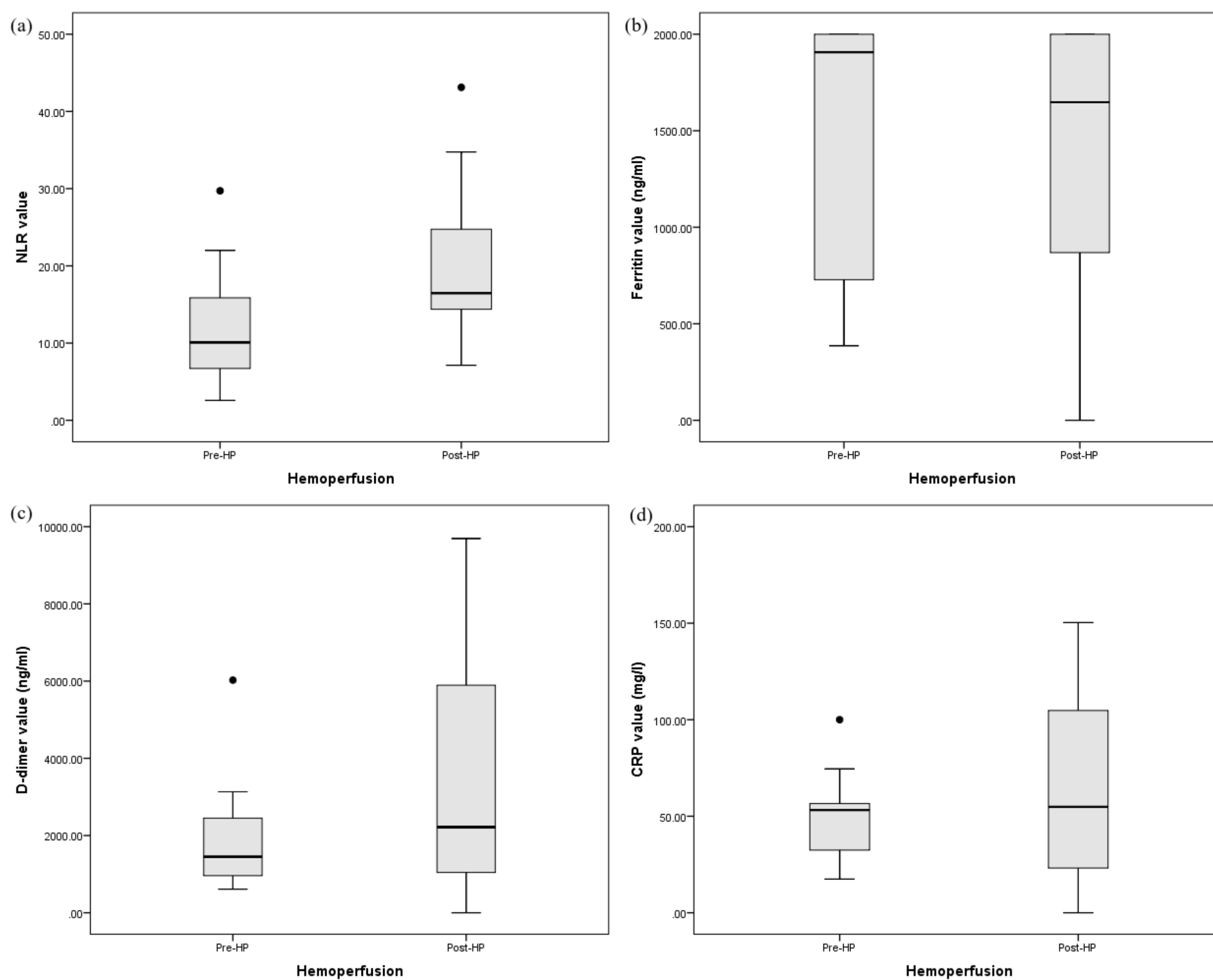
Legend: SD=standard deviation.

Table 2. Laboratory marker values comparison before and after hemoperfusion

Test	Ref value	Pre-HP, median (Q1-Q3)	Post-HP, median (Q1-Q3)	Trend
NLR	<3.13	10.09 (6.72-15.86)	16.47 (14.39-24.74)	Increased
Ferritin (ng/ml)	22-275	1907 (766.63-2000)	1713.02 (1515.36-2000)	Decreased
D-dimer (ng/ml)	0-500	1450 (960-2450)	3142 (1234.17-5939.58)	Increased
CRP (mg/l)	0-5	53.23 (32.45-56.59)	55.83 (44.82-104.75)	Increased

Legend: NLR=neutrophil-lymphocyte ratio; CRP=C-reactive protein; Ref=reference; HP=hemoperfusion.

Figure 1. Graphic visualization of laboratory marker values comparison



Legend: NLR=neutrophil-lymphocyte ratio; CRP=C-reactive protein; HP=hemoperfusion.
Data are presented as box and whisker plots representing the median, IQR, minimum, maximum, and outliers.
(a) NLR value of patients pre-HP and post-HP, with two outliers.
(b) Ferritin serum level of patients pre-HP and post-HP.
(c) D-dimer serum level of patients pre-HP and post-HP, with one outlier.
(d) CRP serum level of patients pre-HP and post-HP, with one outlier.

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