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ORIGINAL RESEARCH **CORONA EXPERIENCE**

Effectiveness of HA330 hemoperfusion as an adjunctive therapy for severe COVID-19 patients: a single center experience

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ABSTRACT

Background & objective: Cytokine storms play a significant role in conditions leading to multi-organ failure in patients with severe corona virus disease-2019 (COVID-19). The eradication of pro-inflammatory cytokines through hemoperfusion has been suggested to be a possible strategy to improve outcomes in these patients. We evaluated the impact of adjunctive HA330 hemoperfusion on outcomes in severe COVID-19 patients.

Methodology: A single-center retrospective cohort study was conducted from December 2021 to December 2022. We included severe COVID-19 patients with elevated pro-inflammatory markers, who received three consecutive sessions of HA330 hemoperfusion in addition to the standard treatment protocol. Clinical data, including demographic information, baseline characteristics, and treatment outcomes, were analyzed.

Results: We evaluated 24 severe COVID-19 patients. We observed a significant reduction in levels of CRP ($P < 0.001$) and IL-6 ($P = 0.042$), as well as a significant increase in arterial partial pressure of oxygen ($P = 0.041$). Importantly, no patient experienced cytotoxicity after the HA330 hemoperfusion sessions, confirming the biocompatibility of the treatment.

Conclusion: Three consecutive sessions of HA330 hemoperfusion, used as an adjunctive therapy to standard care in severe COVID-19 patients, effectively reduced pro-inflammatory cytokine levels and improved oxygenation. However, large multicenter trials are required to validate these clinical outcomes.

Abbreviations: APACHE-II - Acute Physiology and Chronic Health Evaluation**;** ARDS - acute respiratory distress syndrome; COPD - chronic obstructive pulmonary disease; ECMO - extracorporeal membrane oxygenation; IL-6 - interleukin 6; MCP-1 - monocyte chemoattractant protein-1; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; SOFA - Sequential Organ Failure Assessment; TNFα - tumor necrosis factor-α

Keywords: Hemoperfusion; Coronavirus Disease-2019; Cytokine; Extracorporeal Membrane Oxygenation

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1. INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contributes to a respiratory infection known as coronavirus disease 2019 (COVID-19), that emerged in early 2019. Shortly thereafter, COVID-19 became a significant global pandemic with broad ranging public health impact.[1] According to epidemiologic data from World Healthcare Organization (WHO) reports, as of August 27, 2023, there have been over 770 million cases worldwide and over 6.9 million attributable deaths.[2] This emphasizes the importance of understanding COVID-19 pathophysiology for precision medical management.

Cytokines are polypeptides that play a vital role in ensuring the proper functioning of the immune system in terms of anti-inflammatory reactions in the body.[3] An excess of these pro-inflammatory cytokines results in immune system dysfunction, and this state of systemic hyperinflammation is known as a cytokine storm.[4,5] Studies have found the relationship between high-severity COVID-19 disease and increased levels of various types of pro-inflammatory cytokines, such as interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor α (TNFα).[6–8] This phenomenon has a strong linear correlation with acute respiratory distress syndrome (ARDS) and subsequent death. Moreover, the uncontrolled release of pro-inflammatory cytokines may cause multi-organ failure in the effected patients. Thus, controlling the cytokine storm may ultimately result in improved clinical outcomes.[7]

Hemoperfusion, a form of blood purification therapy, is considered an adjunctive treatment option for mitigating the deleterious effects of a cytokine storm, along with the use of corticosteroid drugs or other immunomodulators. In blood purification therapies, the adsorbent-containing cartridge adsorbs cytokines through the blood circulation system.[9] HA330 is an adsorption cartridge that can remove cytokine molecular sizes of 10–60 kilodalton (kDa), with good biocompatibility.[10] The HA330 cartridge has been widely used in a range of different clinical settings. However, the efficacy of adjunctive hemoperfusion to lessen the cytokine storm and impact on patient-centered outcomes in COVID-19 patients has not been established with strong evidence.[11] Thus, we sought to determine the effectiveness of adjunctive HA330 hemoperfusion in the treatment of patients with severe COVID-19 infections.

2. METHODOLOGY

2.1. Study design

This retrospective cohort study was conducted in Songklanagarind Hospital, Thailand, between December 2021 to December 2022. All severe COVID-19 patients that were confirmed by testing oropharyngeal specimen using polymerase chain reaction, were included in the study. The diagnosis of severe COVID-19 was made by one of the following conditions: patients who had oxygen saturation (SpO_2) < 94% on room air, a respiratory rate > 30 breaths/min, or lung infiltrates > 50% on chest x-ray. The patient also had to have at least one of the elevated pro-inflammatory markers, defined as a CRP ≥ 20 mg/L, IL-6 ≥ 20 pg/ml, or ferritin ≥ 300 ng/mL. We excluded patients with severe thrombocytopenia (< 20,000/μL) or history of heparin-induced thrombocytopenia.

2.2. Treatment protocol

The treatment of severe COVID-19 consisted of standard of care in ICU settings, including volume management and ventilation support, overseen by the intensive care team. All patients received corticosteroids based on individualized dosages of dexamethasone (6-10 mg per day). Antiviral remdesivir was prescribed 200 mg as the first dose and then 100 mg daily for 5 days to all patients. Tocilizumab was used in patients who presented initially with severe pneumonia then developed ARDS. Hemoperfusion as an adjunctive treatment was administered during the 3-day admission period, following the recommendation of the attending intensivist and the nephrologist. Hemoperfusion was conducted using the Jafron model JF-800 machine with the HA330 hemoperfusion adsorbent cartridge. The procedure began with priming and involved the use of 5,000 IU of unfractionated heparin. Temporary double lumen catheter was inserted by the treating physician to facilitate hemoperfusion. The blood flow rate through the hemoperfusion circuit was 200 ml/min with three 3-hourly sessions performed on 3 consecutive days. No anticoagulation was used on the hemoperfusion circuit. Monitoring of the circuit was undertaken by the hemodialysis nurses under supervision of the nephrologist.

2.3. Data collection

Information regarding baseline demographics, medical history, clinical data, biochemical indices, management, therapeutic effect, and the clinical outcomes were retrieved from the electronic medical records. Baseline data collection included age, gender, height, weight, comorbidities, history of COVID-19 vaccination, other agents and interventions regarding COVID-19 and its complications, treatment such as extracorporeal membrane oxygenation (ECMO) and hemodialysis. The data at hemoperfusion started included hemodynamics profile (blood pressure), oxygenation profile (oxygen

saturation and arterial partial pressure of oxygen), severity score (Acute Physiology and Chronic Health Evaluation (APACHE-II), Sequential Organ Failure Assessment (SOFA) score), laboratory tests (complete blood count, liver, and kidney function tests, and arterial pH); inflammatory markers (CRP, IL-6, ferritin, and LDH). Based upon the in-hospital mortality, patients were categorized into survivors and non-survivors. We compared the oxygenation profile, laboratories and inflammatory marker between the pre- and post-treatment sessions, with values collected at the end of the third session.

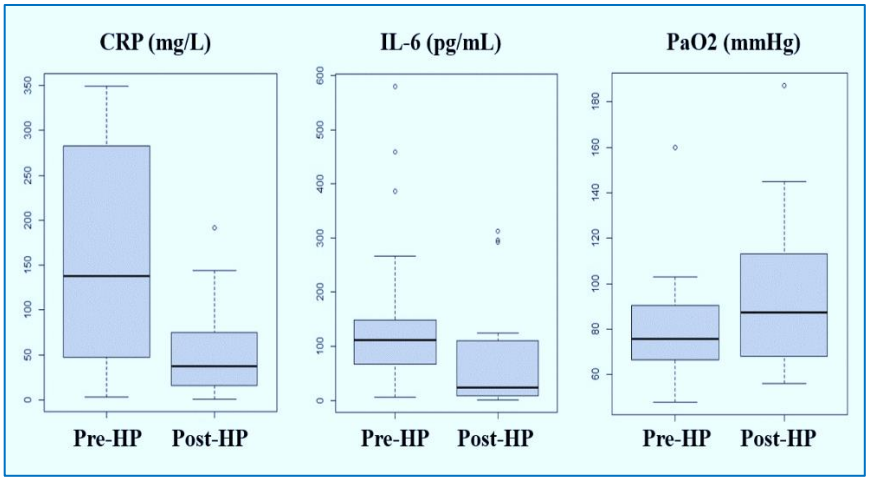

Figure 1: Box plots (median with interquartile) for significantly parameters change during pre and post hemoperfusion.

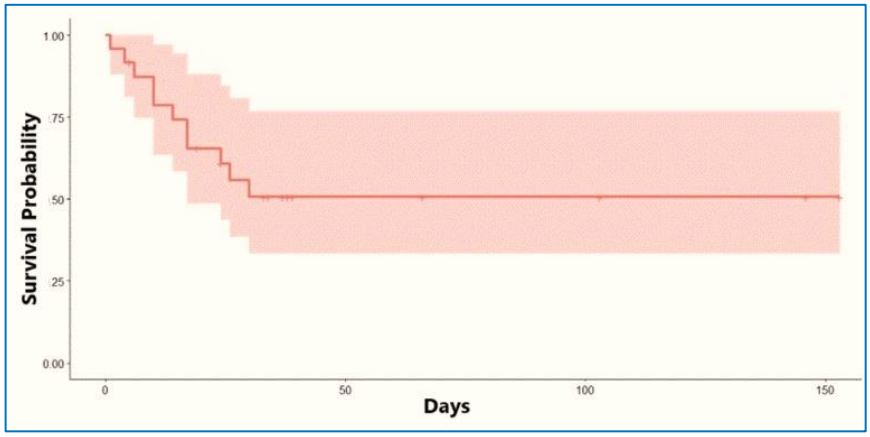

Figure 2: Survival from hemoperfusion initiation (in days)

2.4. Statistical analysis

Continuous data are expressed as the means and standard deviations (SD) or median and interquartile range. Categorical data are presented as numbers and percentages. Comparison between two groups is done using Fisher's exact test for categorical data and Mann-Whitney test for continuous data. The overall survival probability curve was analyzed using the Kaplan-Meier method. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R software version 3.4.3.

3. RESULTS

3.1. Baseline characteristics and parameters

We included 24 severe COVID-19 patients who received hemoperfusion between December 2021 to December 2022. Baseline characteristics are shown in Table 1. The mean age was 63.9 ± 16.4 y and there were 8 (33.3%) female and 18 (66.7%) male patients. The median weight was 70 kg (IQR 65.8-80.0 kg). The most common comorbidities among evaluated patients were hypertension (62.5%) followed by diabetes mellitus (37.5%). Only 1 patient had had chronic obstructive pulmonary disease (COPD) or asthma. Less than half of population received COVID-19 vaccination (37.5%); 12.5% of all patients received tocilizumab as anti-IL-6 during the admission. The ECMO and hemodialysis were implied in 4 (16.7%) and 3 (12.5%) patients, respectively.

3.2. Efficacy of hemoperfusion

The mean PaO_2 increased after treatment sessions from 77.85 mmHg to 97.01 mmHg ($P = 0.041$). The mean serum bicarbonate levels increased after treatment (20.15 vs. 24.33, $P = 0.002$). The mean hemoglobin slightly decreased after treatments (12.82 vs. 10.67, $P = 0.004$). Regarding the inflammatory markers, we found a statistically significant reduction in mean CRP (158.73 vs. 50.24, $P < 0.001$) and mean IL-6 (585.64 vs. 101.60, $P < 0.042$) as shown in Figure 1. There was no statistically significant decrease in serum ferritin level after the end of sessions ($P = 0.091$). Figure 2 shows the survival probability from the time of starting hemoperfusion. Of the 24 adult patients who received

Table 1: Baseline characteristics of the population

Variables	Total (n = 24)
Age (y)	63.9 ± 16.4
Female, n (%)	8 (33.3)
Height (cm)	162 ± 8.6
Weight (kg)	70 (65.0-80.0)
Comorbidities	17 (75)
▪ Hypertension	15 (62.5)
▪ Diabetes mellitus	9 (37.5)
▪ CKD	5 (20.8)
▪ Morbid obesity	2 (8.3)
▪ IHD	2 (8.3)
▪ COPD	1 (4.2)
▪ Asthma	1 (4.2)
COVID-19 vaccination	9 (37.5)
Mechanical ventilation	23 (95.8)
Vasopressors usage	20 (88.3)
Tocilizumab	3 (12.5)
ECMO	4 (16.7)
Hemodialysis	3 (12.5)

Data expressed as number (%), mean ± SD, or median (IQR)
Abbreviations: CKD - chronic kidney disease; IHD - ischemic heart disease; ECMO - extracorporeal membrane oxygenation

HA330 hemoperfusion therapy, 11 died in the hospital, which account to 45.83% of in-hospital mortality rate.

3.3. Comparative parameters prior to hemoperfusion between survivors and non-survivors

The oxygen saturation trend was lower in non-survivors (P = 0.063). The survivors had a significantly lower APACHE II score (P = 0.002) and SOFA score (P = 0.02). Potassium was significantly higher in non-survivors (P = 0.045). No significant difference in inflammatory markers was identified. There were no statistically significant baseline characteristics between survivors and non-survivors. During the period prior to the time of hemoperfusion, the hemodynamic parameters and oxygenation indices were comparable between the groups (Table 2).

4. DISCUSSION

In our retrospective cohort study, we evaluated the effectiveness of adjunctive HA330 hemoperfusion in the treatment of severe COVID-19 patients who received standard treatment concomitantly and demonstrated a high mortality rate among this population. However, a significant decrease in concentration of pro-inflammatory cytokines including CRP and IL-6, and improvement in oxygenation after hemoperfusion therapy was also found. While the absence of a control group prevents us from establishing causality, it is reasonable to conclude that the combination of HA330 hemoperfusion therapy was safe and practical. This approach holds promise as a potentially novel strategy in to lessen the potential deleterious effects of cytokine storms in cases of severe COVID-19 infection.

Growing evidence revealed a crucial role of higher concentration of CRP as an important marker that changes significantly in severe COVID-19 infection.[12] Moreover, it was shown that CRP levels were significantly greater in COVID-19 patients with lower oxygen saturation (SpO2 ≤90%) than in those with higher oxygen saturation (SpO2 > 90%).[13] Additionally, the elevated of IL-6 linked to the overproduction of pro-inflammatory cytokines predicting the possibility of multi-organ failure progression in patients with severe COVID-19.[14] Based on this evidence, considerable focus has been directed towards removing pro-inflammatory cytokines via hemoperfusion with the objective of diminishing pro-inflammatory reactions and lowering mortality rates in COVID-19 patients. Our study demonstrated the benefit of using HA 330 hemoperfusion in terms of ability to remove cytokine via cartridge containing neutron-macroporous resin adsorbing beads as we found that the average CRP and IL-6 significantly decreased around 68% and 83%, respectively after completing hemoperfusion therapies. This was similar to a study from Iran that reported the significant reduction in CRP in severe COVID-19 patients underwent 3 times of HA330 and HA280 filters hemoperfusion.[15] Another research found that the level of IL-6 in critically ill COVID-19 patients significantly decreased after hemoperfusion[16]. Although the filters in the mentioned studies are of different types than ours, they share similar characteristics as numerous pores and can bind various substances, including cytokines with a size of 55-60 kD.[9]

The reduction in cytokine levels was paralleled with the improvement of oxygenation, as evidenced by an increased partial pressure of oxygen. Similarly, in a prospective cohort study reported a significant improvement of hypoxemia in 15 severe COVID-19 patients receiving complete 3 sessions of HA330 hemoperfusion.[17] While we observed improvements in oxygenation, the mortality rate in our patient population remains high, consistent with findings in previous studies.[15,17] However, most of the studies had limited number of patients that may not have a significant impact on determining overall mortality rates. Therefore, further

Table 2: Comparing parameters prior to hemoperfusion between in-hospital survivors and non-survivors.

Variables	Survivors (n= 13)	Non-survivors (n= 11)	Total (24)	P-value
Vital signs				
RR (/min)	28.7 ± 5	31.5 ± 9	30.0 ± 7.1	0.354
SBP (mmHg)	129.2 ± 21.8	137.8 ± 31	133.2 ± 26.2	0.435
DBP (mmHg)	75.8 ± 9.9	76.4 ± 17.6	76.0 ± 13.6	0.918
MAP (mmHg)	92.8 ± 11.5	97.1 ± 20	94.8 ± 15.7	0.523
Oxygen saturation (%)	93.2 ± 5	87.0 ± 10.1	90.4 ± 8.2	0.063
PaO_2 (mmHg)	78.2 (72-87.5)	69 (55.5-85.7)	73 (64.8-88.2)	0.234
24-hr urine output (mL)	1101.7 ± 757.6	960 ± 546.1	1036.8 ± 659	0.611
APACHE II score	16 ± 6.2	23.8 ± 3.9	19.4 ± 6.5	0.002
SOFA score	6.8 ± 3.1	9.9 ± 2.6	8.2 ± 3.2	0.020
Laboratories				
WBC ($x10^3/\mu L$)	11 ± 5.3	16.6 ± 8.6	13.4 ± 7.3	0.065
PMN (%)	84.2 ± 12.3	87.9 ± 8.1	85.8 ± 10.6	0.424
Lymphocyte (%)	4 (2-6.3)	3.5 (1.9-7.8)	4 (2-7.6)	0.926
Hb (g/dL)	12.6 ± 2.1	13.1 ± 3.3	12.8 ± 2.7	0.678
Platelet ($x10^3/\mu L$)	211 (199-256)	197.5 (170.5-321)	211 (175.5-257)	0.733
ALT (U/L)	54 (42-58)	46 (30-63.2)	49 (31-62)	0.877
Albumin (mg/dL)	3.3 ± 0.4	3 ± 0.7	3.2 ± 0.5	0.210
Creatinine (mg/dL)	1 (0.6-1.3)	1.4 (0.8-2.1)	1.1 (0.7-1.9)	0.417
Sodium (mEq/L)	136.7 ± 5	137 ± 4.8	136.8 ± 4.8	0.874
Potassium (mEq/L)	3.9 ± 0.5	4.4 ± 0.8	4.1 ± 0.7	0.045
Chloride (mEq/L)	100.9 ± 7.4	101.3 ± 6	101.1 ± 6.7	0.876
Bicarbonate (mEq/L)	20.2 ± 3.3	20 ± 3.6	20.1 ± 3.4	0.888
Arterial pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	0.693
Inflammatory marker				
CRP (mg/L)	191.6 ± 121.1	119.8 ± 103.2	158.7 ± 116.7	0.136
IL-6 (pg/mL)	126 (81-459)	125 (74.6-326.5	126 (76.4-422.5)	0.877
Ferritin (ng/mL)	1074.5 (824.2-1423)	1485.5 (832.8-72000)	1074.5 (824.2-1745.8)	0.504
LDH (U/L)	589.2 ± 281.6	679.3 ± 378.2	626.3 ± 316.8	0.581

Data expressed as number (%), mean ± SD, or median (IQR)
***Abbreviations**: CKD, chronic kidney disease; IHD, ischemic heart disease; ECMO, extracorporeal membrane oxygenation*

investigation should be conducted in the future to explore the potential benefits of removing pro-inflammatory cytokines in COVID-19 patients, aiming to enhance patient survival outcomes.

The biocompatibility reaction has been raised as one of the potentially life-threatening complications associated with the use of cartridges and may impact the decision to initiate hemoperfusion. This reaction occurs when blood comes into direct contact with the sorbent material, leading to subsequent activation of the complement system and presenting symptoms such as fever, chills, thrombocytopenia, and leukopenia. However, these concerns were mitigated by in vitro studies that reported no cytotoxic effects when using the HA cartridge.[18] Furthermore, our findings emphasize that the addition of

HA330 hemoperfusion does not result in significant thrombocytopenia or leukopenia. This can be attributed to the positive safety outcomes resulting from advancements in sorbent material coatings when applied in clinical applications.

5. LIMITATIONS

Our study also has limitations. Firstly, it was a single-center study. As a result, the clinical severity of our patient population may not be representative of other settings. Furthermore, the criteria for initiating hemoperfusion may differ at other medical centers. Secondly, our study employed a retrospective design, which introduces the potential for a positive publication bias. However, in real-life clinical practice, we must prioritize the prompt management of severe COVID-19 patients to prevent multi-organ failure and progression to a fatal outcome. Thirdly, due to the small sample size, the study was not adequately powered to examine clinical outcomes. Nevertheless, the primary focus of this study was to assess the effectiveness and safety of cytokine reduction. Fourthly, we were unable to conduct a long-term follow-up due to the constraints of our data collection timeframe. Lastly, the absence of a control group posed challenges in conclusively determining the isolated impact of HA330 on patient outcomes. Future large-scale randomized controlled trials are necessary to address these limitations.

6. CONCLUSION

Adjunctive therapy involving three consecutive sessions of HA330 hemoperfusion in addition to standard care for severe COVID-19 patients with high pro-inflammatory cytokine levels led to a reduction in CRP and IL-6 levels and an improvement in oxygenation. Importantly, it also proved to be safe, with no incident of bioincompatibility issues following the sessions. This approach demonstrated effectiveness and feasibility in real clinical practice. Nevertheless, it is imperative to conduct large multicenter trials to further assess the clinical outcomes.

7. Data availability

The numerical data generated during this research is available with the corresponding author.

8. Acknowledgement

We gratefully thank all nephrology and ICU staffs at Songklanagarind Hospital for their invaluable assistance in caring for COVID cases

9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Author's contribution

AP, PS, SW and UB were included in conceptualization. AP, SW and UB collected data. PS analyzed data. AP and UB interpreted the results and worked on original manuscript. All authors have read the manuscript and endorse for publishing.

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