Hemoperfusion as an Adjuvant Therapy in Maintenance Hemodialysis Patients with Severe COVID-19: A Single Centre Experience

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ABSTRACT

Mortality rate among maintenance hemodialysis (HD) patients with COVID-19 is alarmingly high. In Fatmawati Hospital, most of HD patients with COVID-19 presented with acute respiratory distress syndrome (ARDS). Hemoperfusion (HP) is a blood purification therapy used to remove cytokines and inflammatory mediators to prevent ARDS worsening and organ failure. We report 6 cases of COVID-19 in maintenance HD patients. HP and HD were performed in two consecutive days when patient developed early ARDS as indicated by inflammatory markers elevation. HP and HD were conducted by using resin-containing cartridge and high-flux dialyzer, respectively, for 4 hours. Improvements in CRP levels, PaO_2/FiO_2 ratios, and chest X-rays were observed after 2 sessions of HP in most of our patients. Based on our clinical experience, the timing of HP delivery is critical and should be undertaken in the early phase of ARDS, but larger studies are still needed.

Keywords: *hemoperfusion, hemodialysis, COVID-19, cytokines, resin.*

INTRODUCTION

COVID-19 mortality among hemodialysis (HD) patients in Fatmawati Hospital, Jakarta, Indonesia, has been found to be higher than among non-dialysis patients, and most of HD patients with COVID-19 have acute respiratory distress syndrome (ARDS). Hemoperfusion (HP) is a blood purification therapy that is used to remove cytokines and inflammatory mediators to prevent worsening of ARDS and organ failure.[1–3] In our hospital, HP is performed with resin-containing cartridges in HD patients with severe COVID-19 when their clinical condition and inflammatory markers are worsening. We assess room air oxygen saturation, PaO_2/FiO_2 ratios, and C-reactive protein (CRP) levels to determine the severity of the disease. We present a case study of 6 maintenance HD patients with ARDS who were admitted to our hospital and treated with hemoperfusion.

CASE ILLUSTRATION

Six maintenance HD patients with COVID-19 were admitted to our hospital and treated with hemoperfusion between September 2020 and January 2021.

Case 1

Female 42 years old came with shortness of breath, cough, and fever for 2 days. She had been on maintenance dialysis for 25 months due to diabetes. Blood glucose was controlled with oral hypoglycemic agent and during hospitalization insulin was initiated. She also had coronary artery disease with history of PCI. She came with pO2 124 with non rebreathing mask 10 L/min and high CRP 30.7 mg/dl. She underwent intermittent hemodialysis during hospitalization. On day 16, she was desaturated with PaO2/FiO2 114 and CRP 19.8 mg/dl. Hemoperfusion was initiated on day 17. After second hemoperfusion, PaO2/FiO2 was increased, and CRP decreased to 7 mg/dl. She was discharged from high care unit to ward on day 22.

Case 2

Female 44 years old came with shortness of breath and cough for 2 days. She had been on maintenance hemodialysis for 5 years due to staghorn kidney stones and residual kidney function of 50 ml. She was admitted with PaO2/FiO2 150 and received high flow nasal cannule 60LPM/FiO2 80%. She came with CRP 2.1 mg/dl. On day 5, she was desaturated with PaO2/FiO2 130 and elevated CRP 32 mg/dL. Hemoperfusion was initiated on day 5. After second hemoperfusion, PaO2/FiO2 was increased to 256 and CRP decreased to 1.1 mg/dl. She was discharged home on day 12.

Case 3

Male 67 years old, came with cough for 4 days. He had been on maintenance hemodialysis for 8 months due to type 2 diabetes. He had coronary artery disease with no history of PCI. He was somnolent with PaO2/FiO2 ratio 206 and being given NRM 10LPM. At admission, CRP was 3 mg/dl. On day 5, PaO2/FiO2 was decreased to 141 and CRP was elevated to 26.9 mg/dl. Hemoperfusion was initiated on day 5. After second hemoperfusion, PaO2/FiO2 ratio was elevated to 318 and CRP was decreased to 4.7 mg/dl. On day 12 he developed sepsis with fever, increased procalcitonin to >32 ng/ml, and blood culture showed *Klebisella pneumoniae*. Despite antibiotic escalation, on day 15, the patient's clinical condition worsened, and he was intubated. He went into septic shock, and his procalcitonin level remained high. He succumbed to the disease on day 17.

Case 4

Male 62 years old came with fever and cough for 2 days. He was on maintenance hemodialysis for 71 months due to type 2 DM. On admission, CRP was 19.9 mg/dl. On day 3, he was desaturated to 94% on NRM 15 LPM. Then he received HFNC FiO2 70% flow 50 LPM. CRP was elevated to 24 mg/dl and IL-6 was 32.8 pg/ml. Hemoperfusion was initiated on day 3. After second hemoperfusion, shortness of breath was reduced, PaO2/FiO2 ratio was increased to 240, CRP and IL-6 was decreased to 11.8 mg/dl and 17.6 pg/ml respectively. He was discharged on day 16.

Case 5

Female, 31 years old, came with shortness of breath, fever, and malaise for 10 days. She was on maintenance hemodialysis for 67 months due to chronic glomerulonephritis. On day 5, she was desaturated to 70% on HFNC FiO2 90% flow 60 LPM. CRP was elevated from 4.6 mg/dl to 7.1 mg/dl and IL-6 was 35.9 pg/ml. Hemoperfusion was initiated on day 5. After first hemoperfusion, PaO2/FiO2 ratio was slightly elevated to 101 but then after second hemoperfusion it was decreased to 66. Although CRP and IL-6 was decreased after second hemoperfusion, she succumbed to the disease on day 8 due to respiratory failure and disseminated intravascular coagulation.

Case 6

Male, 41 years old, came with shortness of breath and cough for 4 days. He was admitted right after finishing hemodialysis in other hospital. He came with PaO2/FiO2 90, CRP 11.8 mg/dl, IL-6 20.6 pg/ml. Hemoperfusion was initiated on day 1. After second hemoperfusion, PaO2/FiO2 was elevated to 192, CRP and IL-6 was decreased to 6 mg/dl and 5 pg/ml, respectively. He was discharged to ward on day 10.

All patients received standard of care i.e. oseltamivir 30 mg after every HD session, unfractionated heparin, empirical antibiotic, acetylcysteine, and intravenous dexamethasone 6 mg QD. Case 1-5 received intermittent hemodialysis during hospitalization to achieve euvolemia. Ultrafiltration was performed to

achieve their dry weight. Case 6 was admitted to our hospital after finishing hemodialysis session in other hospital. All patients had ARDS with euvolemic state when underwent HP. HP was performed using HA-330 resin-containing cartridges (Jafron Biomedical Company, China). To wash the extracorporeal circulation tubing and HP cartridges, 2000 ml of 0.9% NaCl and 12,500 units of heparin were used.

The patients underwent HP concomitantly with HD using a Surdial™ 55 Plus machine (Nipro, Japan) with the high-flux dialyzer Elisio™ 13H. Heparin was injected as an anticoagulant agent throughout HD via the arterial line at 10–20 IU/kg/h depending on the patient's coagulation status. The blood flow rate was 200–300 ml/minute and the dialysate flow rate 500 ml/minute. Each session was performed for 4 hours. A second course of HP was performed 24 hours after the first.

The PaO_2/FiO_2 ratio in all the patients improved after the first HP, but only 5 patients showed further improvement after the second HP. The PaO_2/FiO_2 ratio of case 5 deteriorated after the second HP (**Figure 1**). The CRP levels of 4 patients improved after the first HP, and 5 patients had improved CRP levels after the second HP. Case 5 developed increased CRP levels after the second HP (**Figure 2**). Serial chest X-ray after second HP showed improvement, except for case 5.

Facilities to determine interleukin-6 (IL-6) levels were not available in our hospital in the early phase of the COVID-19 pandemic. IL-6 tests were therefore only performed for the last 3 patients, all of whom showed lower levels after the first and second HPs (**Figure 3**).

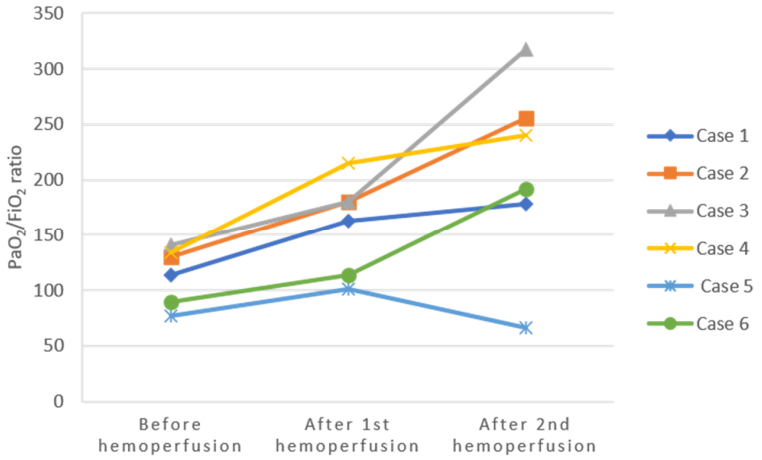

Figure 1. Serial PaO_2/FiO_2 ratio before and after hemoperfusion.

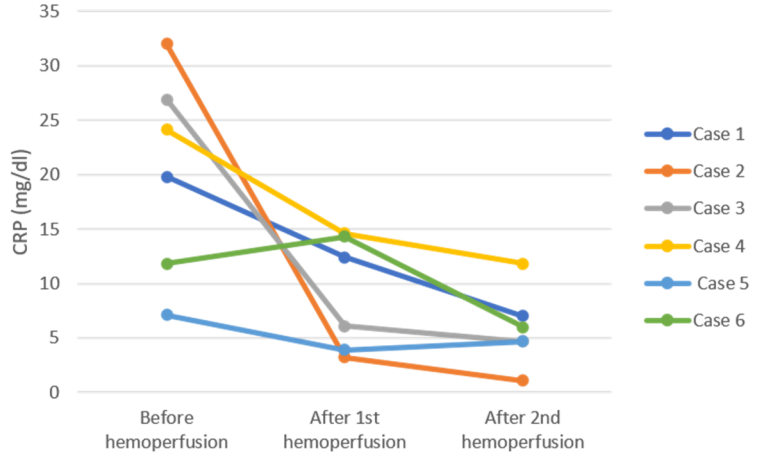

Figure 2. Serial CRP level before and after hemoperfusion.

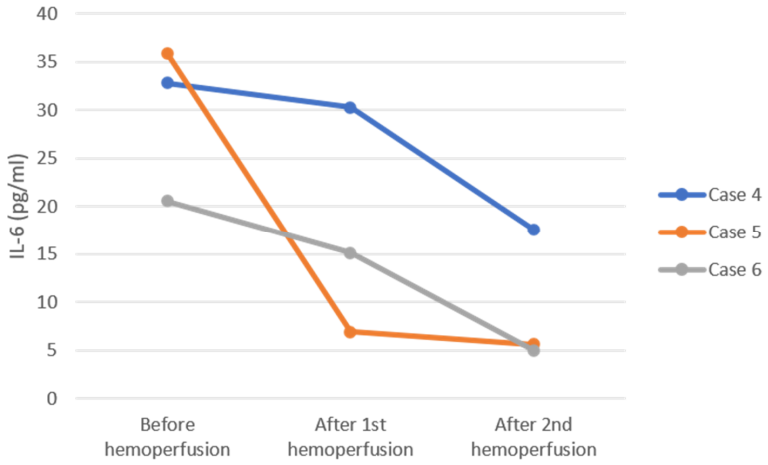

Figure 3. Serial IL-6 before and after hemoperfusion.

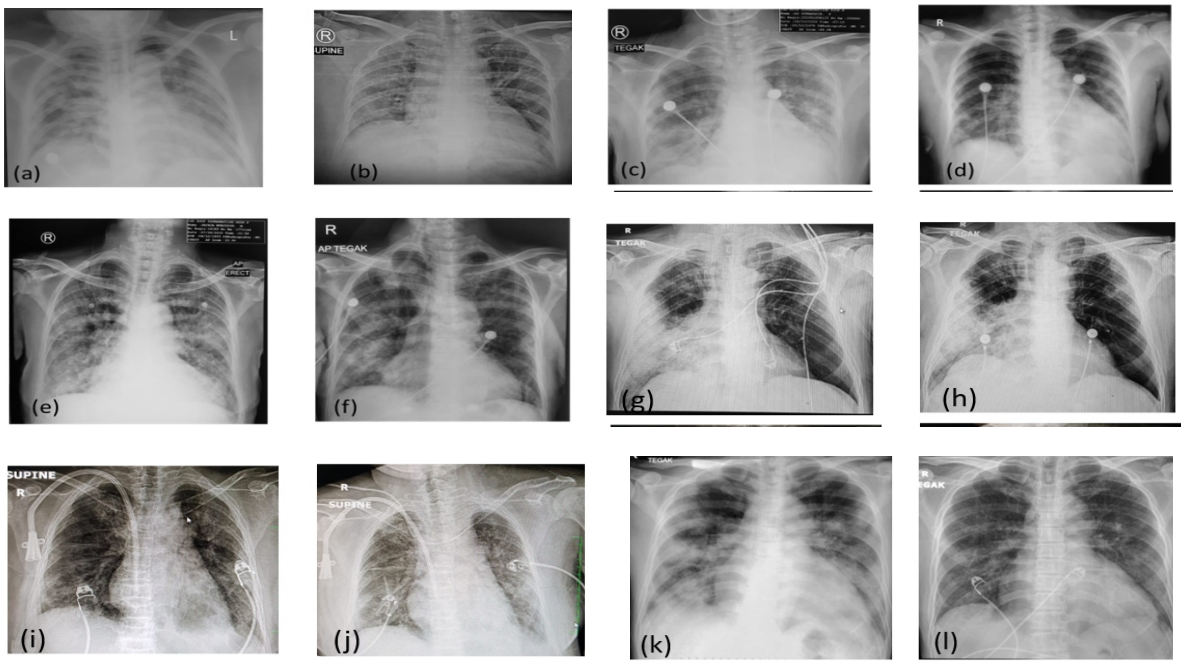

Figure 4. Serial chest X-ray before and after hemoperfusion.
Left: before HP, Right: after second HP
(a),(b) Case 1; (c),(d) Case 2; (e),(f) Case 3; (g),(h) Case 4; (i),(j) Case 5; (k),(l) Case 6

DISCUSSION

Cytokine storm is one of the contributing factors leading to ARDS. Three of the most important proinflammatory cytokines of the innate immune response are IL-1, TNF-α, and IL-6. In COVID-19, a cytokine storm results from a sudden acute increase in circulating levels of pro-inflammatory cytokines and leads to acute lung injury and a more severe form of ARDS, which is a major cause of mortality in this disease.[4] Emerging evidence has indicated the potential benefits of managing this cytokine storm to prevent severe ARDS and mechanical ventilation.

Extracorporeal blood purification has been proposed as one of the treatments to remove pro-inflammatory cytokines and could potentially be beneficial in severe COVID-19.[1–3,5] HP is a blood

Table 1. Baseline characteristics.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Female	Male	Male	Female	Male
Age (years)	42	44	67	62	31	41
Glasgow coma score	15	15	14	15	15	15
Hemoglobin (g/dl)	9.3	8.5	9	9	10.9	7
Leucocyte (/μl)	8100	1100	10300	5900	4200	3800
Thrombocyte (x10^3/μl)	343	340	160	191	123	210
ALC (/μl)	729	88	1030	413	588	760
NLR	9.3	10.5	8.7	12.1	5.7	3.5
CRP (mg/dl)	30.7	2.1	3.0	19.9	4.6	11.8
Procalcitonin (ng/ml)	5.4	>32	4.11	1.2	2.16	31.4
d-dimer (ng/ml)	3040	850	3814	2040	1520	4360
Lactate (mmol/l)	1.2	1	1.4	0.7	2.4	2.8
Glucose (mg/dl)	150	90	120	125	84	83
AST (U/l)	35	40	29	32	21	43
ALT (U/l)	33	32	23	35	10	25
Ureum (mg/dl)	190	120	150	157	124	218
Creatinine (mg/dl)	7.5	5.4	6.7	15.5	10.8	18.5
Oxygenation	NRM	HFNC	NRM	HFNC	HFNC	HFNC
PaO2/FiO2 ratio (mmHg)	155	150	206	134	77	90
Hemodialysis vintage (months)	25	60	8	. 71	67	36
Residual urine volume (ml)	600	50	800	50	50	500
mSOFA score	7	8	8	8	9	8
Dialysis access	AVF	AVF	AVF	AVF	CDL	AVF
Symptoms onset to admission (days)	2	2	4	2	10	4
Admission to hemoperfusion (days)	17	5	5	3	5	1
Diabetes mellitus	Yes	No	Yes	Yes	No	No
Hypertension	Yes	Yes	Yes	Yes	No	Yes
Coronary artery disease	Yes	No	Yes	Yes	No	Yes
Mortality	No	No	Yes	No	Yes	No

NRM: non-rebreathing mask; HFNC: high flow nasal cannule; AVF: arterio-venous fistula; CDL: double lumen catheter

purification therapy that was introduced in the early 1960s to increase HD efficiency in reducing uremia. During HP, blood passes through a cartridge containing a sorbent material, and a physicochemical process allows the material to retain specific molecules. HP has also been used to treat drug and chemical intoxication and fulminant hepatic encephalopathy.[6] Its indications have further expanded to include the treatment of acute inflammatory conditions such as sepsis, pancreatitis, and acute lung injury.[7–9]

In our experience, we used HP in patients with ARDS and elevated serial C-reactive protein (CRP) levels. ARDS is diagnosed when patients with confirmed diagnosis of COVID-19 meet the Berlin 2012 ARDS diagnostic criteria of (i) acute hypoxemic respiratory failure; (ii) presentation within 1 week of worsening respiratory symptoms; (iii) bilateral airspace disease on chest X-ray or computed tomography (CT); and (iv) acute hypoxemic respiratory failure without cardiac failure as the primary cause. The severity of ARDS is defined as mild (200 mmHg < PaO_2/FiO_2 ≤300 mmHg), moderate (100 mmHg < PaO_2/FiO_2 ≤200 mmHg), and severe (PaO_2/FiO_2 ≤100 mmHg).[10] Among the 6 patients in this report, 2 had severe ARDS, 3 had moderate ARDS, and 1 had mild ARDS.

HP is a blood purification modality that can be performed alone or in conjunction with other modalities such as HD, continuous renal replacement therapy (CRRT), and extracorporeal membrane of oxygenation (ECMO). HP with resin-containing cartridges in combination with CRRT and ECMO has been reported to be beneficial in increasing SpO_2, decreasing IL-6 and CRP, and preventing intubation.[11–14] HP alone has also been shown to provide good results in a few case reports.[15,16]

The sorbent material in the HP cartridge

comprises activated carbons (charcoal), ion-exchange resins and/or non-ionic resins. HA-330 cartridges contain neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymers with loading capacity of 330 ml. The average diameter of the resin beads is 0.8 mm, and the pore size distribution is 500 Da–60 kDa. The resin beads can remove medium-sized molecules such as cytokines and complements with a molecular weight ranging from 10–60 kDa.[17]

In this study, the timing of HP played a critical role in providing an optimal outcome. The HP timing for case 1 was quite different from that of the other cases. Case 1 initially had a high CRP level. During close daily observation, her clinical and CRP levels improved with standard of care. However, we found elevated CRP levels and a worsening condition on day 17. This suggested systemic cytokine release and provided perfect timing for cytokine and inflammatory mediator removal. In cases 2, 3, and 5, increased CRP levels and worsening clinical conditions were observed on day 5, so HP was performed earlier than case 1. This finding suggests that it is crucial to observe inflammatory markers in COVID-19 patients together with their clinical condition to detect early increases in the markers and early worsening of their condition.

Among cytokines, IL-6 is a biomarker for disease severity and mortality. As we did not have facility to check real-time IL-6 at early phase of pandemic, we are only able to check IL-6 in 3 last cases. In those cases, IL-6 were decreased after first and second HP. This finding is in line with other case report, which also found improved levels of inflammatory parameters.[16]

All the patients except case 5 showed significant PaO_2/FiO_2 ratio improvements. Case 5 was the youngest of the 6 patients and had no other comorbidities, yet she did not survive. She developed severe ARDS when admitted and immediately received high-flow nasal cannula. She showed an improvement in SpO_2 until day 4 and worsened on day 5. Her CRP levels before HP were lower than in the other patients, and her improvement after HP was unlike that of the other patients. This may have been caused by the advanced stage of the disease as her symptoms had developed 10 days prior to hospital admission, and fibrosis had likely already occurred. She had the longest symptom onset and the highest modified sequential organ failure assessment (mSOFA) score among the patients. She developed respiratory failure and severe disseminated intravascular coagulation (DIC) before succumbing to the disease. Similarly, in one serial case report involving 4 COVID-19 patients in Iran, HP did not produce a significant therapeutic effect[18]. This could have been because HP was performed in the late stage of the disease as all the patients in the study had already been intubated. Performing HP in the late course of the disease may therefore result in a poor outcome even though it reduces CRP and IL-6 levels.

It has been suggested that HP be performed in a 2-1-1 order, that is, 2 cartridges in the first 24 hours and 1 cartridge for the following two days.[2] Due to the limited availability of cartridges in our hospital, we assessed the need for HP individually for each patient by evaluating the PaO_2/FiO_2 ratio and CRP level after each HP to determine the disease severity and inflammatory status. In most cases, we found improvements in PaO_2/FiO_2 ratios, CRP levels, and chest X-rays after the second HP, so we did not continue to third HP.

CONCLUSION

Improvements in CRP levels, PaO_2/FiO_2 ratios, and chest X-rays were observed after 2 sessions of HP in most of our patients. Based on our small clinical experience, the timing of HP delivery is critical and should be considered to be undertaken in the early phase of ARDS. We still need larger studies with control group to show best time of performing hemoperfusion, how many sessions are needed, and how its effect on mortality.

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