Jafron HA330/HA380 Hemoperfusion Cartridge for COVID-19 Cytokine Storm Management

Summary

HA330/HA380 Disposable Hemoperfusion Cartridge has a specific and important role for patients infected with COVID-19 especially for the cytokine storm management that can damage organs resulting in multiorgan failure and possible death of COVID-19 patients. The clinical evidence shows that the HA330/HA380 hemoperfusion cartridge is effective for severe COVID-19 patients. By removing excessive cytokines, it takes part in cytokine storm management to regulate body immunity, hemodynamics, and improving organ function and ICU outcomes as well.

1. General Information of severe COVID-19

According to an article in China, most coronavirus patients have a good prognosis. About 5% of infected population requires intensive care. Among those critically ill patients, the mortality rate is 49%. [1] Severe patient can rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure. [2] Meanwhile, in a retrospective cohort study[3] on the Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China, showed that about 20% of the analyzed 191 patients developed into septic shock, with onset of 17% acute cardiac injury, 15% acute kidney injury. In particular, older age, d-dimer levels greater than 1 μg/L, and higher SOFA score on admission were associated with higher odds of in-hospital death. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, and lactate dehydrogenase and lymphopenia were more commonly seen in severe COVID-19 illness.

2. Cytokine Storm in COVID-19 patients

Cytokine Release Syndrome (CRS) induced by excessive cytokines is considered to be an important pathophysiological basis for COVID-19, from acute lung injury or AKI to multiple organ dysfunction syndromes (MODS).

- Ronco et al[1] demonstrated the potential mechanism of the sepsis-like syndrome induced by high level of circulating cytokines. In such circumstances, while pulmonary exchanges are compromised and dominate the clinical scenario, acute kidney injury and heart and liver dysfunction may also become evident. Cytokine storm may be induced by a superimposed septic syndrome or by the direct effect of the virus on the infected host.
- The China National Guideline for COVID-19[2] points out that, t*he severe patients can rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, bleeding and coagulation dysfunction and multiple organ failure*. Also, *critical cases should be treated in ICU as early as possible. On the basis of symptomatic treatment, to actively prevent and treat complications, underlying diseases, secondary infection, and support organ function timely, the blood purification system includes plasma exchange, adsorption, hemoperfusion, blood/plasma filtration, etc., which can remove inflammatory factors and block the "Cytokine Storm", thereby reducing the damage to the body caused by the inflammatory response. It can be used for severe and critically ill patients during the early to middle stages of Cytokine Storm management.*

3. Cytokine Storm Management with Jafron HA330/HA380 Hemoperfusion

Jafron HA hemoperfusion has been used clinically in China since 1999 and it has been used globally since 2015. The Jafron's hemoperfusion adsorption device

HA330/HA380 is the CE certified hemoperfusion product and has been applied in more than 50 countries with more than 30,000 clinical cases annually. HA330/HA380 is an extracorporeal technique involving the passage of blood through a cartridge. By using the neutral macro-porous resin, the cartridge showed high bio-compatibility and no cytotoxic effect reported in the study from Italy[4, 5]. The porosity structure of the adsorbing beads allows the cartridges to absorb excessive cytokines, which cannot be removed by hemodialysis.

In vivo, HA330/HA380 showed efficacy to help with cytokine storm management, regulate body immunity and hemodynamics. Additionally, there are previous publications of Jafron hemoperfusion demonstrated the beneficial for indications such as sepsis, acute pancreatitis, multiple organ dysfunction etc. with the following outcomes:

1. Improvement of hyper-inflammatory:

- Reduce the level of IL-6[9-10, 17, 21]、IL-8[9, 17, 21] 、TNF-a[8-10] 、IL-1[8, 9, 21] 、IL-2[9]、IL-10 [9, 21] 、PCT [12], and CRP [12-14]

2. Stable hemodynamic condition

- Decreasing need for vasopressors[8, 12, 17]
- Stabilization of arterial blood gas, PH[21], HCO3[21]

3. Improvement of organ function

- Decreasing in BUN [4, 10, 18, 21], Scr [10, 16, 18, 21]
- Improvement in ALT, AST, MAP, PaO2/FiO2 [8, 9, 17]
- Improvement in SOFA score [8-9, 13] and APACHE II score [7-9, 12, 16, 18].
- No further increase of ventilator support requirement [8, 19]

4. Benefits in ICU length of stay[8,10] and length of hospital stay [10, 15, 17]

4. Rational use of Hemoperfusion for COVID-19

1) From China Guideline and Experts Consensus

- The China National Guideline for COVID-19 mentioned that, *the blood purification system includes plasma exchange, adsorption, hemoperfusion, blood/plasma filtration, etc., which can remove inflammatory factors and block the "Cytokine Storm", thereby reducing the damage to the body caused by the inflammatory response. It can be used for severe and critically ill patients during the early to middle stages of Cytokine Storm management.*

- The use of blood purification for severe and critical novel coronavirus pneumonia (CHINA EXPERTS CONSENSUS) mentioned that:

  a) *"It is suggested that blood/plasma adsorption should be started at the early stage of inflammation and the predominance of pro-inflammatory cytokines in COVID-19."*

  b) *"When patients present with pro-inflammatory cytokines, blood/plasma adsorption therapy is recommended: 1) Persistent inflammatory fever, which cannot be controlled by glucocorticoid therapy; 2) A progressive increase in that ratio of IL-6/IL-10, or a persistent increase in the level of pro-inflammatory cytokines such as IL-6."*

  c) *"In the early stage of treatment, when the level of cytokines is high, adsorption therapy can be carried out every 12 hours, and gradually reduced to every 24 hours with the improvement of inflammatory response. When the body temperature gradually dropped to normal and the ratio of IL-6/IL-10 decreased progressively, indicating that the anti-inflammatory cytokines will gradually replace the pro-inflammatory cytokines to occupy a dominant position,*

cytokine adsorption therapy should be stopped. Because a certain amount of albumin is lost during cytokine adsorption therapy, albumin supplementation after cytokine adsorption therapy is recommended."

- Diagnosis and treatment of acute kidney injury associated with novel coronavirus infection (CHINA EXPERTS CONSENSUS) mentioned that:

  a) *It is very important to carry out blood purification and other renal replacement therapy in time for patients with severe coronavirus pneumonia complicated with AKI, SIRS, MODS, and CSS and so on. Blood purifications include plasma exchange, plasma adsorption, hemoadsorption/hemoperfusion, hemofiltration, especially continuous renal replacement therapy (CRRT). It has played an important role in the rescue and treatment of SARS, MERS and other sepsis in the past.*

  b) *We believe that SIRS, ARDS, CSS are associated with the release of a great number of cytokines, and the clinical processes are under critical conditions, which come be an important mechanism of disease progression. According to the principle of blood purification technology, early active start to remove cytokines with the use of plasma exchange, hemoadsorption or CRRT may be of great significance to rescue some severe patients, which is worth exploring in clinical practice.*

2) From International Expert Insights

- An article published (Jean Louis Vincent et al, The LANCENT[22]) stating that for COVID-19 patients a sepsis-like syndrome might occur frequently due to the virus itself or to a superimposed bacterial infection and in this case, since pharmacological approaches have shown poor results, new extracorporeal organ support therapies including haemoadsorption and haemoperfusion, with new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered.

- A comment (Ronco et al, Nature Reviews, Nephrology[23]) discussed about the potential mechanisms of kidney damage and the rationale of using hemoperfusion for COVID-19. Direct hemoperfusion using a neutro-macroporous resin can be used to remove cytokine in such patients, which might contribute to prevent multiple organ dysfunctions and other severe disease.

- The article Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum pointed out the suggested mechanism is the nonspecific removal of the peaks of the circulating cytokines both in the pro- and in the anti-inflammatory side, so as consistent with the "peak concentration hypothesis" from Prof. Claudio Ronco. The reasonable approach is to promote a nonspecific removal assuming that those cytokines with the highest concentration will be removed in higher amount, while with inability to obtain instantaneous monitoring of biological levels of cytokines[1]. (See Figure 1, a,b)

Figure 1. The mechanism of cytokine removal with Hemoperfusion

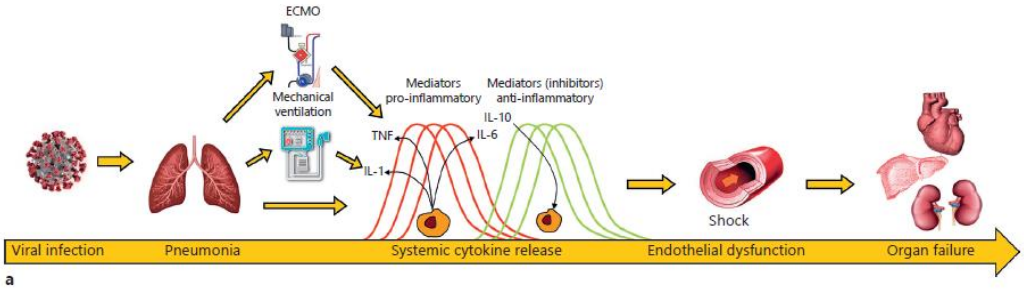


Figure 1-a. *After a viral infection, a percentage of patients suffer from severe pneumonia. Such patients may have a systemic cytokine release due to the illness itself, to the mechanical ventilation-associated lung injury, and to the extracorporeal membrane oxygenation. This will induce endothelial dysfunction and consequent organ failure.*

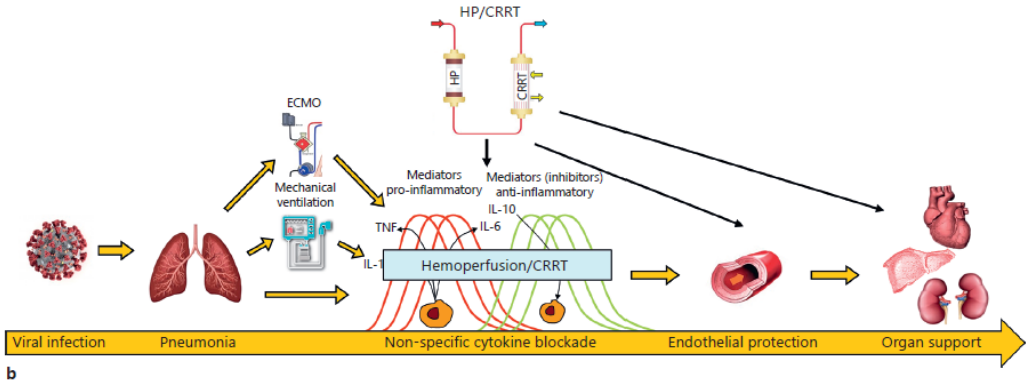


Figure 1-b. *The application of HP may contribute to reduce the burden of cytokines cutting the peaks in a nonspecific way, restoring at least in part immune-homeostasis. When hemoperfusion is combined with continuous renal replacement therapies (HP/CRRT), the effect can be further amplified and the additional task of organ support can be accomplished. TNF, tumor necrosis factor; IL, interleukin; HP, hemoperfusion; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.*

5. Jafron HA330/HA380 Hemoperfusion for COVID-19

Recently, Jafron Disposable Hemoperfusion Cartridge has been commonly used on approximately 1000 COVID-19 patients in China, Italy, Germany, UK, Turkey, Greece, Romania, France, Spain, Hungary, Russia, Thailand, India, Philippines, Malaysia, Indonesia, Vietnam, etc. In the publication *Coronavirus epidemic and extracorporeal therapies in intensive care: si vis pacem para bellum*, the author points out the 2-1-1 therapy recommendation for the severe COVID-19 patients; this means 2 times of hemoperfusion treatment per first 24 hours, followed by once each day for two days. Meanwhile, it was recommended to maintain the HA330/HA380 for COVID-19 patients for 2-6 hours, and in some cases, it can be up to 12 hours. This is also included some recommendation and regional protocol such as, in *the Acute renal failure and COVID-19 SMN recommendations (March 26, 2020 Morocco)*, which stated that, *the adsorptive modalities are used for the elimination of cytokines; to start if IL 6> 200-500 pg/ml (reference in China) or > 1000 pg/ml (reference in Europe); IL6 level*

*monitoring is required. Protocol of "2-1-1 therapy" for 3 days, using HA380 cartridges:1) Day1: Two sessions of 2 to 6 hours (2 HA380 cartridges per 24 hours); 2) Day2: One session of 2 to 6 hours (1 HA380 cartridge per 24 hours); 3) Day3: One session of 2 to 6 hours (1 HA380 cartridge per 24 hours); i*n *Critical Care Management of Severe COVID-19 (April 1st, 2020 Thailand)* it claimed that *in case of significant signs of inflammation/cytokine storm syndrome (high IL-6, high CRP, high ferritin, high LDH), consider hemoperfusion with cytokine absorber such as HA330.*

- **Patient Selection**

The HA330/HA380 device is aimed to treat patients 18 years of age or older with confirmed COVID-19 admitted to the ICU with any one of the following conditions:

1) Early acute lung injury (ALI)/early ARDS; or severe disease, defined as:

a) Dyspnea（ RR ≥ 30/min)

b) Hypoxemia (SpO2 ≤ 92%)

d) 100 < PaO2/FiO2 < 300, and/or

e) Lung infiltrates > 50% within 24 to 48 hours;

2) Life-threatening disease, defined as:

a) Respiratory failure (Before/when mechanical ventilation is needed)

b) Shock or septic shock (When vasopressor support is needed), and/or

c) Before or combined with impending organ dysfunction or failure. (Such as before AKI or at AKI Stage-I)

- **Recommended biomarkers to evaluate the cytokine status of inflammation**

➢ Lymphocyte Count < 0.8 Billion/L

- Cytokines > 5 folds of normal level, or elevates > 1 folds within 24h (IL-6, TNF-α, and IFN-γ, etc.)
- Lactate Dehydrogenase (LDH) > 245 U/L
- D-Dimer > 0.8ug/ml (or 1000-1500ng/mL)
- Serum Ferritin > 500 ug/L
- C-Reactive Protein (CRP) > 40mg/L
- Lactate level > 1.6 mmol/L
- Creatine Kinase > 190U/L (Male) or >155U/L (Female)
- PCT is low or normal, elevation may due to multiple infections
- Others

- **Duration**

It was recommended to maintain the HA330/HA380 for COVID-19 patients for 2-6 hours, and in some cases, it can be up to 12 hours when combined with CRRT. The 2-1-1 therapy recommendation for the severe COVID-19 patients is, 2 times of hemoperfusion treatment per first 24 hours, followed by once each day for two days.

- **Anticoagulation**

Anticoagulants for COVID-19 patients during hemoperfusion can be heparin, citrate, and others such as argatroban. For those under the hyper-coagulation situation, heparin seems to be a favored option. And topical citrate anticoagulation is recommended for severe COVID-19 patients with active bleeding who require hemoperfusion on CRRT. If heparin-induced thrombocytopenia occurs in severe COVID-19 patients, the anticoagulant argatroban/bivalirudin is recommended.

- **Operation mode**

HA330/HA380 cartridge can be conducted singly or with other treatment methods such as HD, HDF, CVVH, CPB, ECMO, and SLED. Physicians can adjust the treatment method and parameter according to patient's medical condition.

It can be added on CRRT machine and other blood purification machines. Therefore, in the case of ICU is overwhelmed by sudden flux of patients, the operation of HA330/HA380 is quite flexible.

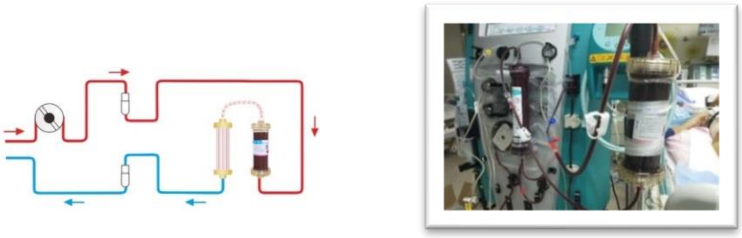


Figure 2. HA330/HA380 + CVVH

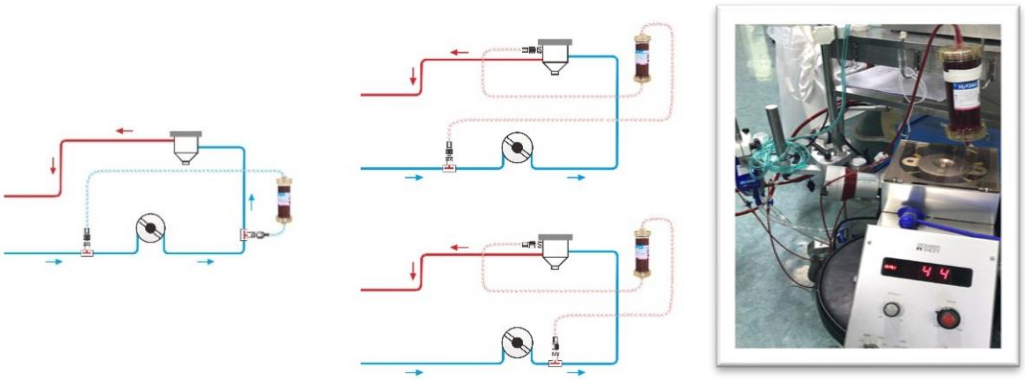


Figure 3. HA330/HA380 + ECMO

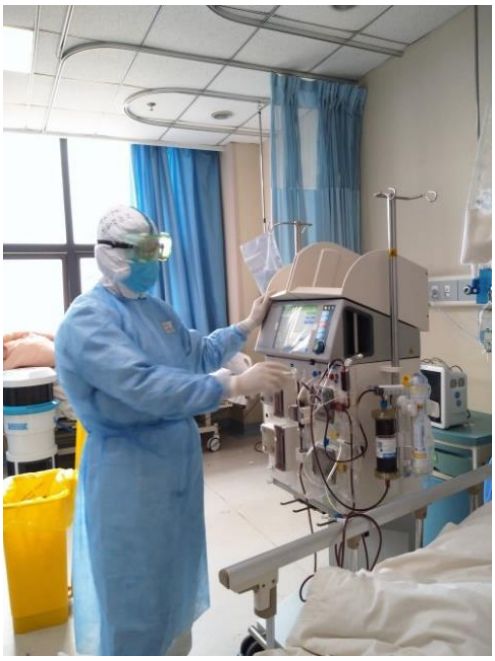


Figure 4. The clinical application of HA380 for severe COVID-19 patient.

Figure 5. An operation method (HP+CRRT) in clinical practice with HA330

- **Relative contraindications**

Generally speaking, there are several considerations that we don't recommend hemoperfusion for patients when they have been under long-term use of immunosuppressant or with immune deficiency, have severe anemia (hemoglobin ≤ 60g/L) without correct, have a malignant tumor, have very low chance to survive.

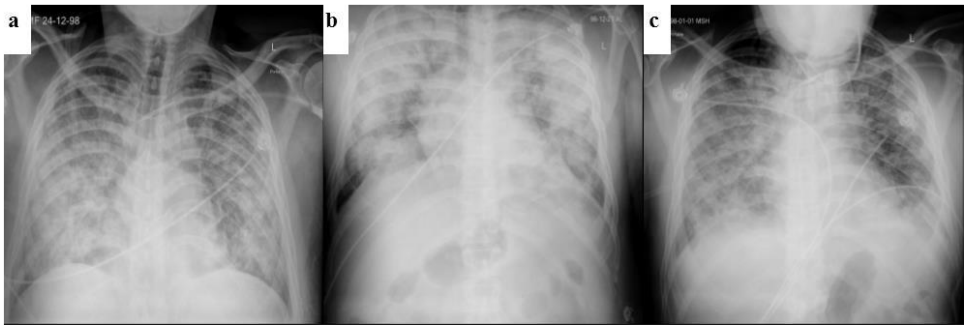
6. Clinical Evidence for COVID-19

Due to the extraordinary and emergency circumstances, some countries that are overwhelmed by COVID-19 pandemic, during which we have collected data in COVID-19 patients treated with HA330/HA380 Disposable Hemoperfusion Cartridge as follows:

- A Case report in press (https://doi.org/10.1016/j.jgar.2020.04.024) from **Iran**: *Continues Renal Replacement Therapy (CRRT) With Disposable Hemoperfusion Cartridge: A Promising Option for Severe COVID-19* described a critically COVID-19 case was treated with CRRT plus hemoperfusion using Jafron HA380 Disposable Hemoperfusion Cartridge, for hyperinflammation, hypoxemia and AKI. The decreasing of cytokines level (IL-1, IL-6, IL-8 and TNF-a), improving of Sat O2, CXR and kidney function reveal that hemoperfusion may be a promising option to decrease the inflammatory cytokines in COVID-19 induced ARDS. (Hashemian et al, Iran)

Figure 6. The chest X-ray of the patient during hospitalization

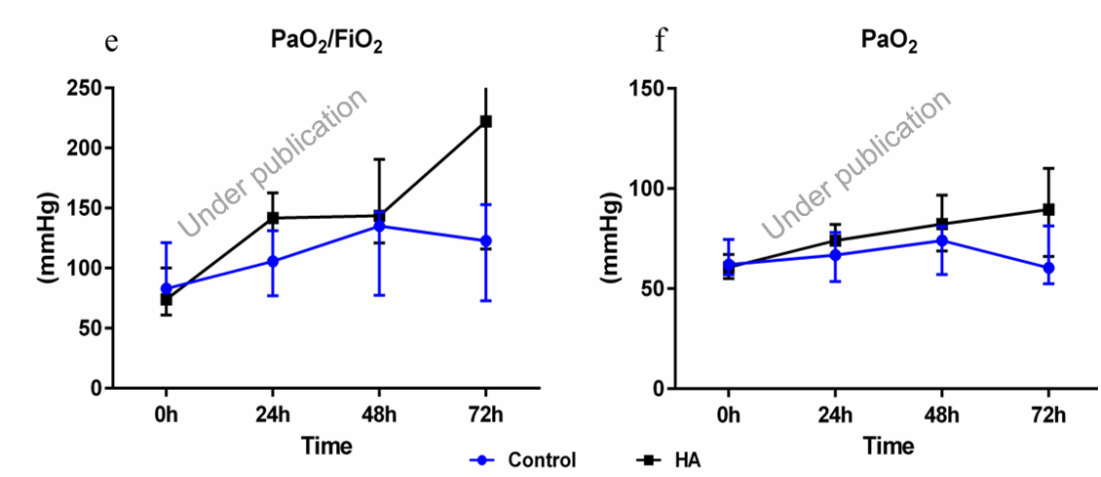
(a; admission time, b; before hemoperfusion, c; after hemoperfusion)



- The data collected from **Italy**'s clinical usage among 12 patients with extracorporeal therapies. 6 patients started HA380 hemoperfusion when AKI was absent or only at Stage 1, and the experience seems to corroborate the early use of hemoperfusion as a preventive protective measure in patients with Cytokine release syndrome. The results displayed a progressive decrease in inflammatory parameters and an improvement of hemodynamic conditions with withdrawal of vasopressor support after the first or second session of hemoperfusion. They all survived. Meanwhile, 6 patients who did not receive hemoperfusion in the early stage, subsequently developed AKI with oliguria and rise in serum creatinine such to require CRRT. One of these patients died for multiple organ failure. (Ronco et al, Italy)

- The data collected from **China**'s clinical usage: On Health Technology Wales, it published a Topic Exploration Report demonstrating that based on an unpublished draft manuscript: a Chinese prospective cohort study investigating extracorporeal blood purification therapy using haemoadsorption-type haemoperfusion in critically ill people with COVID-19. A total of 47 patients with severe COVID-19 were included: 26 COVID-19 patients (55.3%) received hemoadsorption treatment by Jafron Disposable Hemoperfusion Cartridge. At 72 hours, serum cytokines were decreased. The oxygen supply in the haemoadsorption group improved, with a significant increase in the ratio of arterial oxygen partial pressure to fractional inspired oxygen compared with that in the control group (who received conventional treatment). The mortality at day 28 in the haemoadsorption group (15.4%) was significantly lower than that in the control group (47.6%) and was concurrent with significantly shorter intensive care unit (ICU) days compared with that in the control. (Liang et al, China) (http://www.chictr.org.cn/hvshowproject.aspx?id=23111)

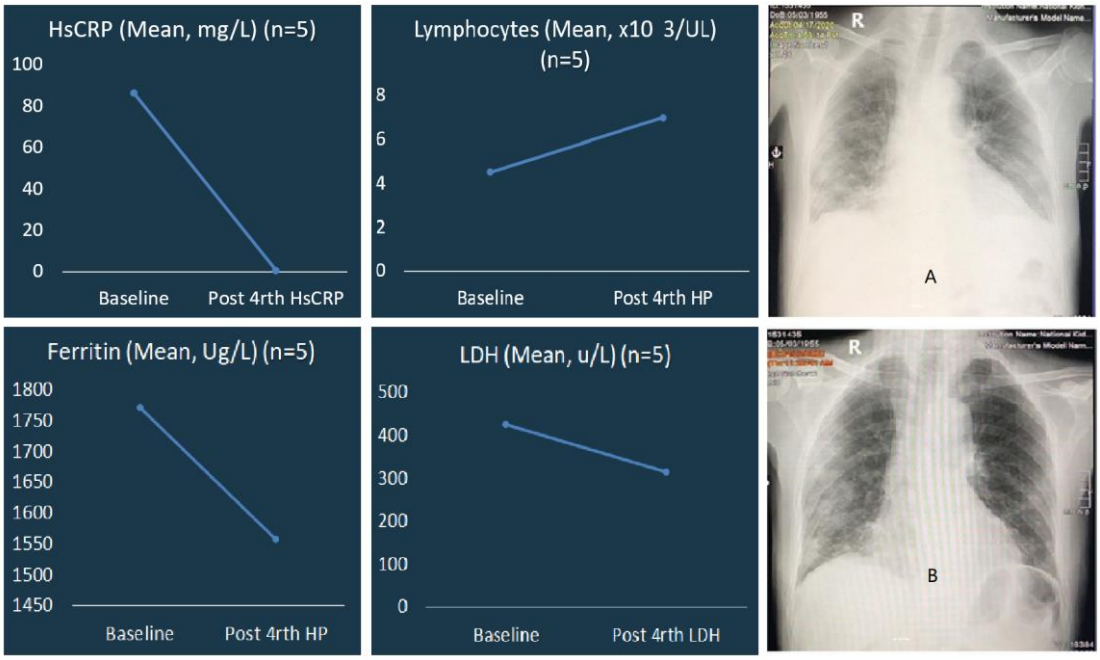
Figure 7. Comparison of PaO2/FiO2 ratio and PaO2
prior and after the intervention between HA group and control group



- A collection of case reports from **China, Thailand, Philippines** via the Webinar:
  1) Three cases using HA380 Haemoperfusion cartridge in combination with ECMO showed that, inflammatory biomarker, C-reactive protein (CRP), cytokines IL-6, IL-8 and IL-10 were reduced in all patients after HA380 haemoperfusion cartridge combined with and ECMO therapy. Biomarkers reflecting lung function and oxygenation also improved. (Peng et al, China)
  2) Five patients were treated with HA330 haemoperfusion cartridge at two sites in Thailand. Of the 5 cases, 4 showed lung function improvements and one did not. CRP levels were reported for 2 of the cases, both showed reduced levels of CRP after treatment. (Srisawat et al., Ratanarat et al. Thailand)
  3) Outcomes of five ESRD patients with COVID-19 infection received HA330 hemoperfusion showed that HsCRP, ferritin, and LDH decreased and lymphocytes increased after the 4 cartridges hemoperfusion therapy. CXR improvements were observed in both single hemoperfusion and hemoperfusion combined with tocilizumab cases. (Danguilan et al, Philippines, See Figure 8)

Figure 8. The changes of patients before and after hemoperfusion

(A. Baseline CXR of one case; B. CXR after 1st hemoperfusion of the same case)



7. Recent and ongoing studies of HA330/HA380

Treatment of COVID-19-induced cytokine storm with filter Haemoperfusion HA330

Trials identifier: IRCT20200317046797N5

Status: recruiting.

Indication: COVID-19, Severe Cytokine Storm, ARDS.

Devices: HA330.

Country: Iran

Sponsor: Dr Mohammad Samiei

Efficacy of HA330 Haemoperfusion in Critically Ill Patients with Severe COVID-19 (HA-COVID19)

Trials identifier: TCTR20200409006

Status: pending (not yet recruiting).

Indication: COVID-19, ARDS.

Devices: HA330

Country: Thailand

Contact Name: Nattachai Srisawat

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