Jafron HA330/HA380 Hemoperfusion Cartridge for COVID-19 with Acute Kidney Injure

1. Rational use of hemoperfusion for COVID-19 with AKI

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).

- 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.*

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

1) *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.*

2) *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.

- An article published (Jean Louis Vincent et al, The LANCENT) suggested that new extracorporeal organ support therapies including haemoadsorption and haemoperfusion, with new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered in the management of cytokine storm in patients with COVID-19. A comment (Ronco et al, Nature Reviews, Nephrology) 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.

2. 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.

- **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)

- **Timing and Application Suggestion**

a) 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.*

b) 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.

- **Clinical Evidence for COVID-19 with/before AKI**

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)
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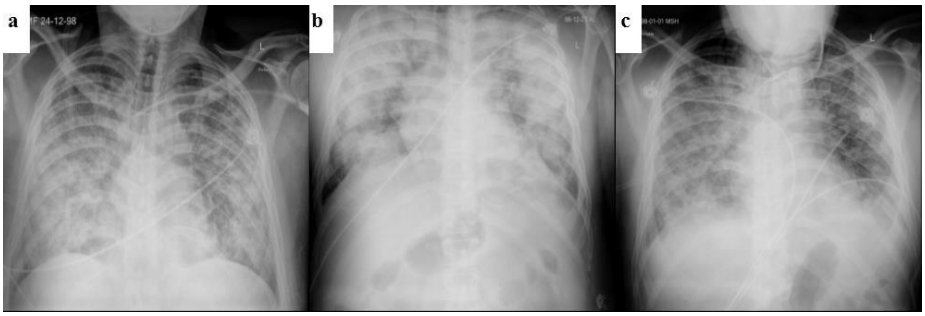
Figure 2. The chest X-ray of the patient during hospitalization

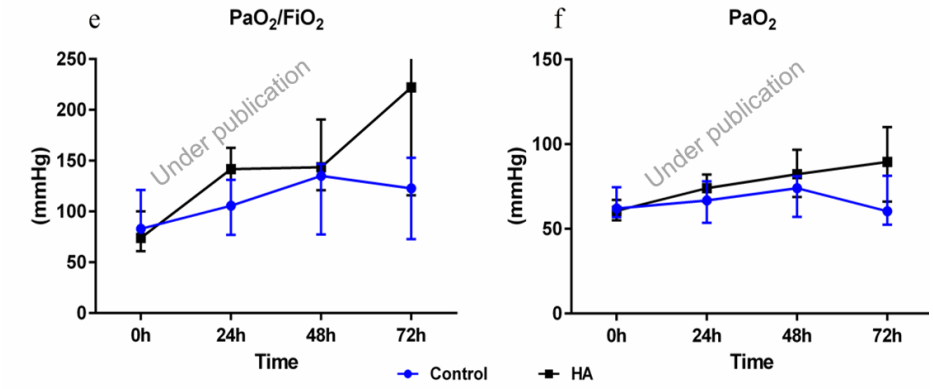
(a; admission time, b; before hemoperfusion, c; after hemoperfusion)



- 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.
  (http://www.chictr.org.cn/hvshowproject.aspx?id=23111)

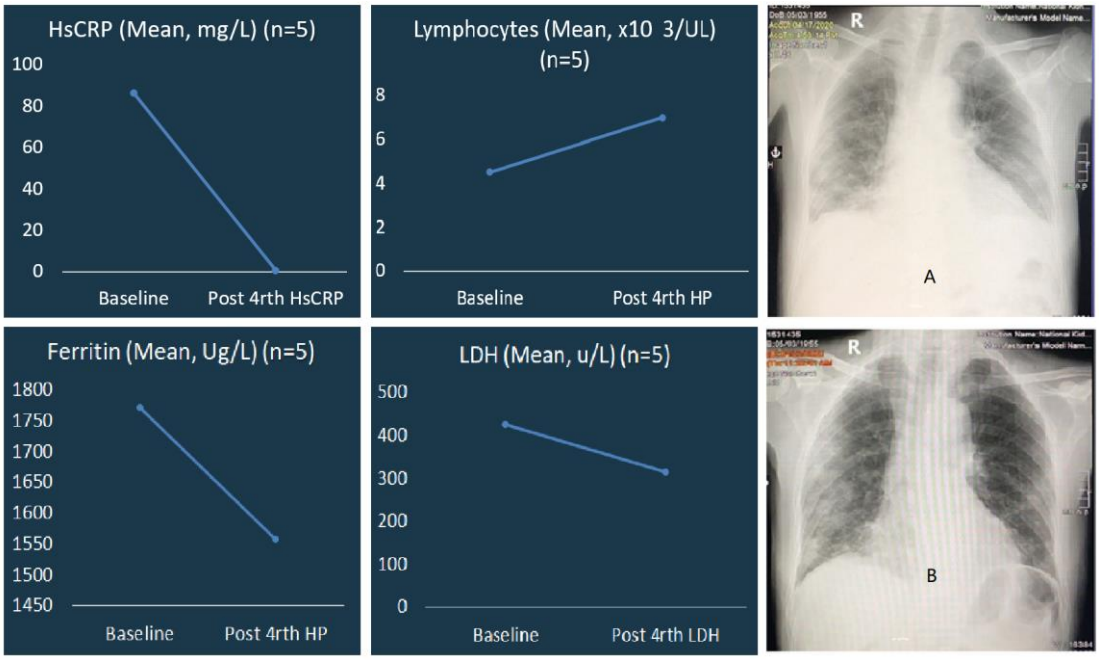
Figure 3. Comparison of PaO2/FiO2 ratio and PaO2
prior and after the intervention between HA group and control group



- 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 4)

Figure 4. The changes of patients before and after hemoperfusion

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



- **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

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