JAFRON
OVERSEA CLINICAL CASES COLLECTION

2020.12
Foreword

This cases collection follows the relevant regulations and policies of the Jafron CREAT project, and is intended to promote the clinical experience sharing, discussion and application education of hemoperfusion.

We thank the clinicians’ valuable sharing and their continuous attentions to this project with their creative thinking and exploration in the field of hemoperfusion during clinical practice.
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I. CLINICAL CASES COLLECTION
HA-130 Hemoperfusion Cartridge in the Treatment of Cast Nephropathy in a 58-year-old Male with Multiple Myeloma: A Case Report

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This report highlights the use of hemoperfusion using HA 130 cartridge in combination with chemotherapy using Bortezomib in reducing free light chain levels in a 58-year-old male that developed renal failure secondary to cast nephropathy. Patient was able to achieve reduction in free light chain levels, improvement in renal function and eventually independence from hemodialysis four weeks after the last hemoperfusion treatment.

CASE REPORT

In this case report we describe the use of HA 130 hemoperfusion cartridge in the treatment of cast nephropathy in Multiple Myeloma. A 58-year-old male, diabetic, non-hypertensive came in for 5-day history of generalized body weakness, associated with myalgia, lumbar pain and undocumented fever, with 1-day history of loose stools and vomiting which prompted consult. After admission he was diagnosed with Acute Renal Failure and Multiple Myeloma. Medical tests revealed that he had multiple lytic bone lesions, high levels of serum B2-MG and free kappa light chains, and monoclonal gammopathy. The patient received combined hemodialysis with hemoperfusion were done using HA 130 filter and high flux dialyzer for 2.5 hours then hemodialysis for three times a week. He was also started on chemotherapy using Bortezomib with Dexamethasone for 2 cycles.

Totally he received 14 sessions of combined hemoperfusion with hemodialysis, then free kappa light chains reduced remarkably. Patient was maintained on hemodialysis three times a week and was discharged after 55 hospital days. With the outpatient hemodialysis, the patient showed renal recovery and was eventually off hemodialysis four weeks after the last hemoperfusion treatment.

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<th>Post-HP</th>
<th>2 Weeks Post-HP</th>
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<td>Hb (g/dL)</td>
<td>7.8</td>
<td>10.3</td>
<td>7.7</td>
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<tr>
<td>Hct (%)</td>
<td>23.4</td>
<td>31.4</td>
<td>25.4</td>
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<tr>
<td>WBC (mm³)</td>
<td>19,040</td>
<td>13,000</td>
<td>8,040</td>
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<td>Neutrophils (%)</td>
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<td>94</td>
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<td>Lymphocytes (R)</td>
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<td>Platelet (mm³)</td>
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<td>146,000</td>
<td>696,000</td>
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<td>Creatinine (mg/dL)</td>
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<td>4.78</td>
<td>2.1</td>
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<td>BUN (mg/dL)</td>
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<td>Sodium (mmol/L)</td>
<td>139</td>
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<td>137</td>
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<td>Potassium (mmol/L)</td>
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<td>4.5</td>
<td>4.3</td>
</tr>
<tr>
<td>I onized Calcium (mmol/L)</td>
<td>1.21</td>
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<td>Total Protein (g/dL)</td>
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<td>AVG Rnpp</td>
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BACKGROUND

Multiple myeloma is a plasma cell neoplasm that results in the production of monoclonal immunoglobulin. Renal failure is a common complication of multiple myeloma, occurring in approximately one-half of patients on initial presentation and is associated with increased mortality. Among patients who develop renal failure, progression to end stage kidney disease is common and is associated with decreased patient survival [1-3]. Cast nephropathy in particular, is considered to be one of the major mechanisms of renal failure in multiple myeloma, and is characterized by precipitation of free light chains in the distal nephron, leading to intratubular obstruction, leading to inflammation and fibrosis [4].

Recent studies have demonstrated the use of extracorporeal methods such as plasmapheresis and high-cutoff membrane dialysis[5] as an adjunctive therapy to chemotherapy in the management of cast nephropathy, however currently there are no existing guidelines in the use of extracorporeal therapies in the management of complications of multiple myeloma [6]. Hemoperfusion is an extracorporeal treatment technique which utilizes adsorption in the removal of specific toxins. In a cohort study in 2017 and a case report in 2019, the use of adsorption cartridges in patients with myeloma cast nephropathy showed higher rates of survival and renal recovery [7-8]. The HA 130 cartridge in particular has a resin pore size distribution of 500-40 KDa and is able to remove molecules at 5-30kDa [9-10].

CASE PRESENTATION

A 58-year-old male, diabetic, non-hypertensive came in for 5-day history of generalized body weakness, associated with myalgia, lumbar pain and undocumented fever, with 1-day history of loose stools and vomiting which prompted consult. Upon admission blood tests done revealed anemia with a hemoglobin of 7.8g/dl, creatinine of 9.97mg/dL and potassium of 5.5mmol/L. He was diagnosed with acute renal failure and underwent hemodialysis on the second hospital day. On workup he had lytic bone lesions in the spine, pelvis and cranium on CT scan and X-ray. Serum beta 2 macroglobulin and free kappa light chains were both elevated at 12,618ng/dl and 19,250mg/L, respectively, with Serum Protein Electrophoresis (SPEP) and Serum Free Light Chain (sFLC) tests showing a monoclonal gammopathy. Bone marrow biopsy was done with findings of markedly hypercellular marrow with 80% plasma cells confirming the diagnosis of Multiple Myeloma. Combined hemodialysis with hemoperfusion were done using HA 130 filter and high flux dialyzer for 2.5 hours then hemodialysis for three times a week. Patient was also started on chemotherapy using Bortezomib with Dexamethasone for 2 cycles.

Patient had a total of 14 sessions of combined hemoperfusion with hemodialysis, and on repeat free kappa and lambda light chains decreased to 212.5mg/L and 41.0mg/L, respectively. Patient was maintained on hemodialysis three times a week and was discharged after 55 hospital days. Outpatient hemodialysis was continued three times a week, and after 2 weeks, patient showed signs of renal recovery with a repeat creatinine of 2.1. Four weeks after discharge patient was independent of hemodialysis with a repeat creatinine of 1.3mg/dL and had completed cycle three of chemotherapy.
DISCUSSION

In this report we describe a case of multiple myeloma initially presenting with symptoms of weakness, fever and bone pain. Severe acute kidney injury was evident in the onset of presentation, as the patient had a creatinine of 9.97mg/dl on admission with symptoms of uremia. The mechanisms of renal injury in multiple myeloma in this case may have been a combination of factors, which include light chain cast nephropathy, intravascular volume depletion and exposure to nephrotoxic agent. The patient had a history of intake of nonsteroidal anti-inflammatory drugs (Mefenamic acid) 5 days prior to admission, which may have aggravated renal vasoconstriction, in the setting of a volume depleted state from gastrointestinal losses. Indications for hemodialysis for this patient was increasing azotemia with hyperkalemia and beginning signs of uremia.

Early identification and treatment of cast nephropathy was vital for this patient in improving renal function and achieving independence from dialysis. The mechanism of cast nephropathy involves tubular obstruction from the precipitation of monoclonal serum free light chains. Rapid reduction of circulating free light chains was important in order to decrease further inflammation and tubular damage and fibrosis and based on several studies, is associated with renal recovery [11].

At present, there are no existing guidelines regarding extracorporeal methods in the management of multiple myeloma. In this case, we utilized hemoperfusion using HA 130 cartridge, that can remove molecules at 5-30kDa in order to rapidly remove free light chains. Serum kappa free light chains measure approximately 25kDa and is within the range that can be effectively removed by this filter. A total of 14 sessions of hemoperfusion with hemodialysis was done for this patient during the admission prior to being discharged. This case is significant, that it demonstrated hemoperfusion using HA 130 filter with chemotherapy using bortezomib resulted in reduction in free light chain concentrations, and in this case resulted in improvement in renal function. This patient continued to show signs of renal recovery and was able to achieve independence from hemodialysis 4 weeks after discharge.

CONCLUSIONS

This report highlights the use of hemoperfusion using HA 130 cartridge in combination with chemotherapy using Bortezomib in reducing free light chain levels in a 58-year-old male that developed renal failure secondary to cast nephropathy. Patient was able to achieve reduction in free light chain levels, improvement in renal function and eventually independence from hemodialysis four weeks after the last hemoperfusion treatment.

RECOMMENDATIONS

Further studies using a randomized control trial on the use of hemoperfusion in directly reducing serum free light chain levels is recommended. The value of hemoperfusion on the rate of independence from hemodialysis as well as survival rates among patients with renal failure secondary to multiple myeloma may also be worth investigating using larger studies.
References


EFFECTIVENESS OF HEMOPERFUSION BY RESIN HA330 IN SUPPORTIVE TREATMENT OF SEVERE ACUTE PANCREATITIC PATIENTS

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* Hanoi Medical University, ** Bach Mai Hospital

ABSTRACT

Objectives
The aim of this study is to describe the results of HA330 resin - directed hemoperfusion therapy in treatment of patients with severe acute pancreatitis in the early stage of the disease.

Methods
HA330 resin directed hemoperfusion therapy was applied in 22 patients diagnosed with acute pancreatitis (according to Alanta 2012 criteria) and severe acute pancreatitis (according to American Society of Pancreas 2007 criteria) within the first 5 day of disease at Emergency Department – Bach Mai Hospital and who accepted the therapy from April 2019 to August 2019. These patients were treated with hemoadsorption once a day in 3 consecutive days and in 4 hours session. We evaluated clinical and paraclinical variables over time: at admission (T0), 24 hours (T1), 48 hours (T2) and 72 hours after hospitalization (T3).

Results
The results showed that, intra-abdominal pressure in patients with hemoperfusion at T3 decreased compared to that at T0 and 24-hour urine output at T3 increased compared with that at T1, the difference was statistical significant. For inflammatory biomarkers, serum interleukin-6 concentration was not a standard variable (p <0.05). This concentration at T3 decreased than that at time T0, the difference was statistically significant (p <0.05).

Conclusions
This study showed that HA330 resin hemoperfusion was effective in the treatment of patients with severe acute pancreatitis in the early stages of the disease.

Figure 1. Changes in intra-abdominal pressure
Figure 2. Changes in serum interleukin-6 level
INTRODUCTION

Acute pancreatitis is an acute pancreatic damage caused by activation of pancreatic enzymes right inside the gland causing pancreatic organ necrosis, complicated progression from a mild local manifestation to a severe degree with multi-organ failure with high mortality rates. Regarding the pathogenesis of acute pancreatitis, the central role was due to inflammatory mediators. When pancreatic necrotizes of any cause, the damaged tissue will release inflammatory mediators into the blood including many cytokines such as IL-1, IL-6, IL-8, TNFα ... This substance continues to enhance the inflammatory response not only in the pancreas but also in other organs such as the heart, lungs, liver, kidneys. In severe acute pancreatitis, cytokines will be produced very quickly and abundantly within the first week of onset of illness causing a "cytokine storm" [1-2]. The disease progression will be through three stages: local lesions, systemic inflammatory response and multiple organ failure [3].

The treatment of acute pancreatitis is basically the treatment of the cause (if any: gallstones, pancreatic stones); symptomatic treatment and treatment of complications if any. A number of supportive treatments in recent years aimed at reducing cytokine levels in patients with severe acute pancreatitis have been shown to be effective. Intravenous-venous dialysis (CVVH) has been shown to remove cytokines, stopped the vicious cycle causing multiple organ failure, and significantly reduce SOFA scores and mortality [4]. Recently, in one study in China in 2012, Lu-yi Liu et al., demonstrated that in the context of multi-organ failure, hemoperfusion by resin based adsorbent in combination with CVVH has significantly reduced cytokine levels compared to CVVH filtration alone [5]. However, in Vietnam, there has not been any research on the application of this adsorption therapy in patients with severe acute pancreatitis as well as the complications during the implementation of this technique. Therefore, we conducted this study to describe the results of adsorption therapy by HA330 resin column in combination therapy for severe acute pancreatitis.

METHODS

1. Patient selection
   1) Inclusion criteria
      (1) Patients with diagnosis of acute pancreatitis based on revised 2012 ALANTA criteria
      (2) Onset ≤ 5 days
      (3) Patients with diagnosis of severe acute pancreatitis within 1 week based on the American Pancreatitis Association 2007: at least 1 organ failure (SOFA score for individual organ ≥ 2) without prior underlying diseases and/or inflammatory diseases
      (4) Patients and/or family agreed study consent

   2) Exclusion criteria
      (1) From patients side
         • Acute pancreatitis due to mechanical obstruction in which surgery was indicated
         • Immunocompromise or under immunotherapy
         • Secondary pancreatitis due to septic shock and multiple organ failure
      (2) For indication for hemoperfusion
      Mean arterial pressure could not obtain 65 mmHg even with aggressive fluid resuscitation and vasopressor
2. Methods
(1) A prospective, observatory study which had been carried out at the Emergency Department of Bach Mai hospital from April 2019 to August 2019.
(2) Sample size: all patients met inclusion criteria

3. Study protocol
Patients recruited in this study should be hemodynamic stable or under control, airway under control, central venous catheter placement, circulatory fluid supplemented, femoral venous catheter placement. Blood test had been carried out on admission (T0), then hemoperfusion was performed on JK machine with blood pumping speed of 80-160 ml / min, treatment duration of 4 hours. After 24 hours from admission (T1), clinical evaluation and blood test had been done. Conducting 2nd session 24 hours after 1st session, clinical assessment and blood collection after 48 hours of admission (T2) and 3rd session had been carried out 24 hours after 2nd session, clinical evaluation and blood test collected after 72 hours of admission (T3). After the end of hemoperfusion, additional follow-up tests will be taken daily (Ttd1, Ttd2). Data collection had been done at time intervals including variables and indicators.

4. Data analysis
The data was processed statistically by SPSS 16.0 software. Calibration of standard variables by Kolmogorov test. Standard variables are described as mean ± standard deviation, variables that do not follow the standard rule described by Box-plot graphs. For pairing comparison, if it is a standard variable using Paired - Sample T Test, if it is a non-standard variable using Wilcoxon test. The difference was statistically significant when p <0.05.

5. Ethical issues
Family members of patients agreed to participate in the study. Medical records and photos are confidential. The research topic has been approved by the Science and Medical Ethical Committee of Bach Mai Hospital and Hanoi Medical University.

RESULTS

1. Changes in organ function
1) Changes in 24 hours urine output
The 24-hour amount of urine was the standard variable (p> 0.05). The number of 24-hour urine at the time of T1 was 852 ± 553 ml, at the time of T3 was 1507 ± 1095 ml. Compared to admission, the 24-hour urine output increased after 3 sessions of hemoperfusion, the difference is statistically significant (p <0.05).

2) Changes in intraabdominal pressure
Intra-abdominal pressure was not the standard variable (p <0.05). Intra-abdominal pressure at T3 decreased compared to that at T0, the difference was statistically significant (p <0.05).

2. Changes in serum interleukin – 6 level
Serum interleukin - 6 concentration was not a standard variable (p <0.05). This concentration at T3 decreased than that at time T0, the difference was statistically significant (p <0.05).
CONCLUSIONS

In patients with severe acute pancreatitis in the early stages, HA330 resin filter adsorption technology helps to significantly reduce the concentration of Interleukin-6 in serum and can reduce the complication of multi-organ failure.

REFERENCES

[2] Rohit Makhija and Andrew N. Kingsnorth. Cytokine storm in acute pancreatitis. University of Plymouth, Level 07, Derriford Hospital, Derriford Road, Plymouth, PL6 8DH, UK
New therapeutic approach to reduce methotrexate toxicity after high-dose chemotherapy in a child with acute lymphocytic leukemia: efficacy and safety of hemoadsorption with HA-230 adsorber

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Abstract

A recent publication describes the various cartridges in the HA series, including the HA-230 adsorber (Jafron, Zhuhai City, China), which are increasingly being used worldwide. Studies suggest their effectiveness in the different clinical settings where adsorption therapy may be recommended. Here, we report a successful implementation of HA-230 hemoadsorption single procedure to remove MTX and reduce its toxicity in a child with ALL after HDMTX, as well as discussed relevant literature.

The HA-230 adsorber (Jafron, Zhuhai City, China) was installed after the hemofilter. During the four hours procedure, the blood samples were collected from the extracorporeal circuit at different time points, and blood sampling was done on three different points of the system. This is a first successful implementation of HA-230 adsorber to remove blood methotrexate level and to reduce its toxicity due to delayed elimination in a pediatric patient with ALL after high dose chemotherapy. Our results, with the reduction rate of -85.27\%, showed that even single four hours procedure of hemoadsorption would significantly improve the patient’s condition. At the same time, we do not see any major changes in erythrocyte, hemoglobin, albumin levels.

Table 1. Methotrexate levels obtained from different points of combined CVVHDF-Hemoadsorbsion system during the procedure.

<table>
<thead>
<tr>
<th>The time of sampling</th>
<th>Point 1 (before dialyzer-filter)</th>
<th>Point 2 (between dialyzer-filter and HA-230 adsorber)</th>
<th>% of reduction between P1 and P2</th>
<th>Point 3 (after HA-230 adsorber)</th>
<th>% of reduction between P2 and P3</th>
<th>% of reduction between P1 and P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0h</td>
<td>540.70 µmol/l</td>
<td>522.34 µmol/l</td>
<td>-3.39%</td>
<td>415.22 µmol/l</td>
<td>-20.5%</td>
<td>-23.21%</td>
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<tr>
<td>2h</td>
<td>199.43 µmol/l</td>
<td>191.62 µmol/l</td>
<td>-3.91%</td>
<td>142.03 µmol/l</td>
<td>-25.8%</td>
<td>-28.78%</td>
</tr>
<tr>
<td>4h</td>
<td>86.52 µmol/l</td>
<td>83.82 µmol/l</td>
<td>-3.12%</td>
<td>79.60 µmol/l</td>
<td>-5.03%</td>
<td>-7.99%</td>
</tr>
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<td>Reduction rate from 0h point-1 to 4h point-3 (from 540.7 to 79.6 µmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-85.27%</td>
</tr>
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Note: Sampling - Point 1 – before filter, Point 2 – after filter, before adsorber, Point 3 – after adsorber
BACKGROUND

Acute lymphoblastic leukemia (ALL) is a rapidly progressive and the most common malignancy in children aged 3–7 years [1]. The absence of proper treatment within 5-10 days can lead to death [2], whereas the treatment in a high-risk patients started in time has good prognoses and reaches a total survival rate of up to 50% [3].

High dose methotrexate (HDMTX) has proven an effect and still playing a significant role in the treatment of different type malignances in children, including ALL, non-Hodgkin lymphoma, osteosarcoma and others [4]. However, HDMTX is very likely to cause a number of side effects and manifest itself as hepatotoxicity, nephrotoxicity, mucositis, and neurotoxicity. MTX is eliminated by renal excretion involving passive glomerular filtration and active tubular reabsorption and secretion [5]. A number of studies have been published demonstrating the use of extracorporeal detoxification methods for the treatment of MTX delayed clearance (DMC): plasma exchange (PE), hemodialysis (HD), hemodialysis filtration (HDF), and hemoperfusion (HP) using an activated carbon absorption column [6]. However, for various reasons, none of the methods is universally safe and effective.

The protein-binding rate for MTX is 50%, and for this reason, plasma exchange could be efficient, still has potential serious side effects, including infection, deficiency of coagulation factors, hypoalbuminemia. Using of HD alone or HDF alone requires repeated sessions, as methotrexate levels in the blood increasing again since the procedure finished. In a recent study, good results showed a combination of HD and HP, with the reduction rate of 57.9% (± 10.6%) [6].

A recent publication describes the various cartridges in the HA series, including the HA-230 adsorber (Jafron, Zhuhai City, China), which are increasingly being used worldwide. Studies suggest their effectiveness in the different clinical settings where adsorption therapy may be recommended [7]. Despite following the treatment protocol and maintenance therapy to avoid side effects (intravenous hydration, leucovorin rescue, and proper monitoring of serum creatinine and methotrexate levels), we face the problem of DMC. We hypothesized that, given the molecular weight of methotrexate 454 Da, the HA-230 adsorber is potentially more efficient and safe for methotrexate elevation in children, comparing other extracorporeal detoxification methods. Here, we report a successful implementation of HA-230 hemoadsorption single procedure to remove MTX and reduce its toxicity in a child with ALL after HDMTX, as well as discussed relevant literature.

MATERIAL AND METHODS

An eight-year child (Weight: 18 kg, S: 0.79m²) was admitted to the department of hematology “University Medical Center” with the diagnosis of acute lymphocytic leukemia FabL2, T – IV type, high risk group, neuro-leukemia. The patient has been ill since April 2020, when the diagnosis was verified, and treatment was carried out according to protocol (ALL BFM IC 2002 Block HR1) [3]. An unstable remission has been achieved for a short period and the patient was hospitalized again in July 2020. Taking into account clinical and laboratory data, HDMTX (in a dose of 5 grams per m2) was started and plasma-MTX (p-MTX) at the end of the 24 hours MTX-infusion reached 669 µmol/l.
That is why, according to the protocol, the patient was receiving intravenous hydration, leucovorin rescue (in a dose of 75 mg/m²). However, conventional treatment during next 12 hours (36 hours after the HDMTX was started) had resulted in no positive change in patient condition and the child has developed acute kidney injury in combination with DMC, which was reason to transfer patient in to the intensive care unit (ICU).

Acute kidney injury led to the initiation of pediatric (continuous veno-venous hemodiafiltration) CVVHDF with the "Prismaflex" device (Baxter, US) with the following prescription parameters: both predilution and post-dilution -400 ml/h, ultrafiltration - 50ml/h, prolonged heparinization 5-30 IU/kg/hour, effluent 1600 ml/h, dialysate fluid - 800 ml/h. A hemodialysis catheter was inserted into the right subclavian vein as appropriate according to children size. As a part of pilot study with obtained approval from the Clinical Research Ethics Committee of “University Medical Center” (No. 5, June 30, 2020) and signed informed consent by parents. The HA-230 adsorber (Jafron, Zhuhai City, China) was initiated and maintained for the next 4 hours.

The HA-230 adsorber was installed after the hemofilter (Supplemental Figure 1). During the four hours procedure, the blood samples were collected from the extracorporeal circuit at the following time points: after 5 minute of initiation (0h), two hours later (2h) and just before the timing of procedure (4h). Blood sampling was done on three different points of the system. The first point (P1) – before the filter, second point (P2) – between the filter and adsorber, and the last one (P3) – after the adsorber HA-230.

A single procedure of CVVHDF combined with HA-230 adsorption resulted in reduction of methotrexate level from 540.7 to 79.60 μmol/l immediately (reduction rate is -85.27%) during the four hours (Table 1). The methotrexate level was 49.04 μmol/l 12 hours after the procedure. Later the patient received leucovorin and hydration (after the acute kidney injury was resolved) and after 24 hours, the MTX level reached 28.32 μmol/l. The patient was transferred from ICU to the hematological unit and 48 hours after the procedure the level of methotrexate reduced to 14.60 μmol/l. The routine blood biochemistry and hematologic parameters improved (Table 2), as well clinical condition. During the entire procedure, the patient continued to receive the leucovorin rescue protocol.

**DISCUSSION**

To the best of our knowledge, this is a first successful implementation of HA-230 adsorber to remove blood methotrexate level and to reduce its toxicity due to delayed elimination in a pediatric patient with ALL after high dose chemotherapy. A single four hours procedure of HA-230 adsorption coupled to CVVHDF significantly reduced the blood methotrexate level for 85.27%.

HDMTX is still a method of choice in the treatment of malignancies in children. And in the case of DMC, many side effects can be fatal, which in 80% of cases is associated with bone marrow suppression [8]. For this reason, the methotrexate level should be monitored as well, as the signs of toxic effect. If the protocol is followed and conventional treatment is ineffective, the patient should be transferred to extracorporeal methods. A few existing methods allowing the eliminating of methotrexate from the body and reducing the toxic effects have been reported in the literature. Fujikura, E., et al describe four cases and each of them uses one of the existing methods [6]. Hemodialysis allowed achieving a reduction rate of 58.3% ±6.17. And this method is one of the available ones. However, it has a number of known side effects, including but not limited to:
intolerability of procedure, hypotension, anemia, chest pain, headache, vomiting, gastrointestinal bleeding, as well as limitations to conduct hemodialysis in a low weight pediatric patients. Furthermore, repeated sessions of hemodialysis might be required due to the peculiarities of distribution methotrexate [9]. Hemodiafiltration is another option; however, limited removal rate (40.0 ± 5.63%) may also require continuous and repeated procedure. The combination of hemodialysis and hemoperfusion is probably one of the most promising and has made it possible to achieve the rate of reduction 57.9 ± 10.6% [6]. A combined hemodialysis and plasma exchange have also demonstrated the 45.7 ± 14.7% removal rate of MTX level [10]. However, this method requires a large amount of donor plasma transfusion, which undoubtedly increases the risk of infection.

The technique of using various adsorbers, including the removal of endotoxins and exotoxins is used in different fields of medicine [11]. Despite the fact that the HA-230 adsorber has been well studied in patients with paraquat poisoning [12] and organophosphorus poisoning [13], the method shows promising results in the case of DMC. At the same time, using the HA-230 adsorber has proven to be a safe and effective in a pediatric patient. In addition, a recent study has shown that HA-230 adsorber carry an optimal level of biocompatibility and their use in HP is not associated with adverse reactions or signs of cytotoxicity [14]. Our results, with the reduction rate of -85.27%, showed that even single four hours procedure of hemoadsorption would significantly improve the patient’s condition. At the same time, we do not see any major changes in erythrocyte, hemoglobin, albumin levels.

Another option to treat the child with delayed methotrexate clearance is glucarpidase (Carboxypeptidase G2). Glucarpidase hydrolyzes methotrexate to inactive metabolites and was approved by the US FDA in January 2012 for the treatment in patients with delayed methotrexate clearance due to impaired renal function [15]. The study done exclusively for the pediatric patients with ALL confirms that glucarpidase treatment do result in a rapid decrease of MTX concentration [16]. Currently, this drug is still not approved in many countries, including Kazakhstan. But the use of glucarpidase both independently and in combination with the leucovorin does not give complete confidence that it will be possible to avoid the extracorporeal detoxification methods [17][18] [19].

Despite the significant effect in our case, we would like to note some limitations. There are currently no other reports that would support our opinion in using HA-230 for methotrexate elimination. In addition, our study is limited to one case only. We also suggesting that in some cases it may be necessary to repeat the session of hemoadsorption. At the same time, we may encounter complications common to extracorporeal methods: catheter bleeding and infection, side effects of heparinization, platelet reduction. However, the advantage of this method is that the short procedure time reduces the above risks.

**CONCLUSION**

Timely detection of an increase in methotrexate levels and initiation of treatment will avoid serious, sometimes irreversible, consequences. Management of methotrexate toxicity using the HA-230 adsorber in case of delayed methotrexate clearance showed 85.27% reduction rate during the single 4 hours procedure and well tolerated in a pediatric patient with ALL. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients.
Supplemental Figure 1.
The demonstration of HA-230 hemoadsorber integration with CVVHDF procedure.

Table 2. Baseline hematologic parameters and its change after the single procedure

<table>
<thead>
<tr>
<th>The main parameters</th>
<th>Before HDMTX</th>
<th>Before the procedure</th>
<th>24 hours after the procedure</th>
<th>Reference levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes</td>
<td>2.75*10^9/L</td>
<td>30.19*10^9/L</td>
<td>13.01*10^9/L</td>
<td>4.50 – 13.50*10^9/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>115 g/l</td>
<td>136 g/l</td>
<td>128 g/l</td>
<td>115 – 150 g/l</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>203*10^9/L</td>
<td>50.0*10^9/L</td>
<td>52.0*10^9/L</td>
<td>150.0 – 400.0*10^9/L</td>
</tr>
<tr>
<td>CRP</td>
<td>0.24 mg/mL</td>
<td>84.03 mg/mL</td>
<td>60.95 mg/mL</td>
<td>0.00 – 5.00 mg/mL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>26.0 μmol/L</td>
<td>111.93 μmol/L</td>
<td>69.94 μmol/L</td>
<td>35.0 – 53.0 μmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>2.50 mmol/L</td>
<td>12.33 mmol/L</td>
<td>9.01 mmol/L</td>
<td>2.78 – 8.07 mmol/L</td>
</tr>
<tr>
<td>Bilirubin (direct, indirect)</td>
<td>7.70 μmol/L</td>
<td>35.50 μmol/L</td>
<td>9.69 μmol/L</td>
<td>1.7 – 21.00 μmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>47.0 g/l</td>
<td>30.40 g/l</td>
<td>32.49 g/l</td>
<td>38.00 – 54.00 g/l</td>
</tr>
<tr>
<td>Na</td>
<td>137 mmol/L</td>
<td>132 mmol/L</td>
<td>134 mmol/L</td>
<td>136.0 – 146.0 mmol/L</td>
</tr>
<tr>
<td>K</td>
<td>4.7 mmol/L</td>
<td>4.5 mmol/L</td>
<td>4.0 mmol/L</td>
<td>3.5 – 5.1 mmol/L</td>
</tr>
<tr>
<td>Ca</td>
<td>1.33 mmol/L</td>
<td>1.10 mmol/L</td>
<td>1.06 mmol/L</td>
<td>1.11 – 1.31 mmol/L</td>
</tr>
<tr>
<td>pH</td>
<td>7.34</td>
<td>7.342</td>
<td>7.327</td>
<td>7.35 – 7.45</td>
</tr>
<tr>
<td>cBase(Ecf),c</td>
<td>1 mmol/L</td>
<td>-5 mmol/L</td>
<td>-3.9 mmol/L</td>
<td>-2 to +2 mEq/L</td>
</tr>
<tr>
<td>cHCO3-(P, st),c</td>
<td>19.8 mmol/L</td>
<td>20.1 mmol/L</td>
<td>20.6 mmol/L</td>
<td>22 – 26 mmol/L</td>
</tr>
<tr>
<td>pCO₂</td>
<td>38.1 mmHg</td>
<td>37.3 mmHg</td>
<td>41.3 mmHg</td>
<td>35 – 45 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>41.0 mmHg</td>
<td>53.8 mmHg</td>
<td>42.3 mmHg</td>
<td>30 – 40 mmHg</td>
</tr>
</tbody>
</table>

Abbreviations: CRP – C-reactive protein; Na – sodium; K – potassium; Ca – Calcium
Early application of extracorporeal hemadsorption methods to patients after transplantation

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Sepsis is one of the most urgent problems of modern cardiac surgery and is one of the most common causes of death of stationed patients. In particular, after heart and lung transplantation, such factors as the widespread use of various invasive procedures in the post-transplant period, the effect of specific homeostasis disorders, and constant immunosuppressive therapy create conditions for secondary immunodeficiency lead to the development of sepsis. The aim of the study was to evaluate the effectiveness of early use of the hemadsorption method in sepsis after heart and lung transplantation.

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CASE REPORT

A 41-years-old patient, who's main disease is chronic heart disease, has peri-membranous defect of the interventricular septum and one of the main complication is Eisenmenger's Syndrome. He received operation (Bilateral lung transplantation, plastic surgery of peri-membranous DMJ with a patch from the auto-pericardium in ECMO conditions from 18.05.2020.)

On the 2nd day after the operation, acute renal injury (AKI), stage 3 (KDIGO, 2018), a violation of hemodynamics that required high doses of vasopressors, leukocytosis - 24,81x10 9/l, procalcitonin - 2.59 PG/ml, presepsin – 856pg/ml, lactate – 9.4 mmol/l) was diagnosed. Signs of SPON on the SOFA scale-14 points, the risk of death is 50%. Bacteremia was not detected. Taking into account the patient's condition, septic shock, renal failure, extended continuous hemofiltration + hemoadsorption with HA 330 was initiated (Jafron Biomedical, China).

The first procedure due to a high risk of bleeding was performed without heparin. A two-light dialysis catheter was used as vascular access. Blood flow rate at the level of 160-180 ml/min, perfusion time of 1 HA330 cartridge for 6 hours, then the extended hemofiltration procedure was continued until the next connection of the HA330 cartridge , three HA330 procedures were performed for 6 hours with further continuation of extended hemofiltration with minimal heparinization, according to indications until 26.05.2020.

As a result of complex treatment, positive dynamics were observed in the form of: recovery of diuresis, relative stabilization of hemodynamics, reduction on the SOFA scale, the risk of death is less than 10%. decrease in leukocytosis, CRP, procalcitonin, presepsin, 01.06.20 g the patient was transferred to the specialized Department.
BACKGROUND

Sepsis is one of the most urgent problems of modern cardiac surgery and is one of the most common causes of death of stationed patients. In particular, after heart and lung transplantation, such factors as the widespread use of various invasive procedures in the post-transplant period, the effect of specific homeostasis disorders, and constant immunosuppressive therapy create conditions for secondary immunodeficiency lead to the development of sepsis. Improving the results of sepsis treatment is achievable by optimizing the schemes of antibacterial prevention and therapy, introducing a set of new methods of extracorporeal hemocorrection.

MATERIAL AND METHODS

The aim of the study was to evaluate the effectiveness of early use of the hemadsorption method in sepsis after heart and lung transplantation.

Indications for the beginning of hemadsorption: there are signs of multiple organ failure (SOFA scale ≥ 2 points), the presence of reperfusion syndrome against the background of intensive infusion therapy, signs of intoxication (leukocytosis, a pronounced shift to the left of rod-shaped neutrophils, the appearance of young forms). Indications for early use: the crucial importance is the timeliness and validity of the start of extracorporeal procedures. The maximum effect can be achieved if extracorporeal treatment is performed in the early stages of the appearance of clinical and laboratory manifestations of cytokine storm syndrome and SPON. Extrarenal indications for the use of renal replacement therapy in patients after transplantation, especially permanent or continuous, include: maintaining thermoregulation, correction of water-electrolyte and acid-base balance in hyperhydration, right ventricular failure, acute respiratory distress syndrome in the absence of the effect of conservative therapy.

Applied selective hemadsorption technologies: hemadsorbent HA 330 (Jafron Biomedical, China). Jafron disposable cartridges are filled with an adsorbent material - a styrene-divinylbenzene copolymer. The adsorbing material of different models of cartridges of the "HA" series has different porosity of granules. Due to this, as well as hydrophobic and ion interaction, the target molecules - toxins, cytokines, bilirubin and others-are removed from the bloodstream.

CASE PRESENTATION

This is a 41-years-old patient, who's main disease is chronic heart disease. Perimembranous defect of the interventricular septum. Complication of the main one: Eisenmenger's Syndrome. FC 3 (WHO). Concomitant diseases: Type 2 diabetes mellitus, subcompensation. Dyscirculatory encephalopathy of stage 2, Consequences of onsc (2016) of ischemic type in the left hemisphere of the cerebellum. Hysteromyoma. Cyst of the right breast. Operation: Bilateral lung transplantation, plastic surgery of perimembranous dmj with a patch from the autopericardium in ECMO conditions from 18.05.2020. On the 2nd day after the operation, acute renal injury (AKI), stage 3 (KDIGO, 2018), a violation of hemodynamics that required high doses of vasopressors, leukocytosis - 24,81x10⁹/l, procalcitonin - 2.59 PG/ml, presespin – 856pg/ml, lactate – 9.4 mmol/l) was diagnosed. Signs of SPON on the SOFA scale-14 points, the risk of death is 50%. Bacteremia was not detected. Taking into account the patient's condition, septic shock, renal failure, extended continuous hemofiltration + hemadsorption with HA 330 was initiated (Jafron Biomedical, China).
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As a result of complex treatment, positive dynamics were observed in the form of: recovery of diuresis, relative stabilization of hemodynamics, reduction on the SOFA scale-1 point, the risk of death is less than 10%. decrease in leukocytosis (see Fig2.1), CRP (see Fig2.2), procalcitonin (see Fig2.3), presepsin (see Fig2.4), 01.06.20 g the patient was transferred to the specialized Department.

Figure 2.1

Figure 2.2

Figure 2.3
CONCLUSION

In these clinical cases, early use of selective hemoadsorption in patients with sepsis led to a decrease in the level of endogenous intoxication and indicators of systemic inflammation, as well as selective adsorption.

REFERENCES

Severe Leptospirosis with Multiple Organ Failure Treated with Renal Replacement Therapy, ECMO and Hemoperfusion using HA 330: A Case Series

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National Kidney and Transplant Institute, Philippines

BACKGROUND
Leptospirosis is an endemic zoonosis in the Philippines precipitated by disasters and extreme weather events. It emerged as an important cause of pulmonary hemorrhage and acute kidney injury. This case series aimed to describe the use of hemoperfusion therapy using HA 330 cartridge in patients with severe leptospirosis who were on extracorporeal membrane oxygenation (ECMO) together with renal replacement therapy (RRT).

METHODS
We included patients with severe leptospirosis who acute respiratory distress syndrome and acute renal failure. All patients received a minimum of 3 hemoperfusion treatments using HA 330 cartridge for 3 hours for 3 days and underwent additional treatments depending on their hemodynamic status. Blood flow rates were kept between 150-200mL/minute. Sequential organ failure assessment (SOFA) score, demand for inotropes to achieve a MAP 65 (µg/h*mmHg-1), HsCRP and Procalcitonin were collected at the baseline until after the last hemoperfusion therapy. Renal and patient survival were also noted.

RESULTS
There were 19 patients who were included in this case series. Fourteen patients survived and all patients recovered their pulmonary and renal function. Five patients died.

CONCLUSION
There was a decrease of Procalcitonin, HsCRP levels, SOFA scores, and decrease of inotropes after the first hemoperfusion, allowing adequate blood pressure support to do the ECMO and renal replacement therapy. It stabilized the hemodynamic status of the patient.
Clinical Outcomes of Hemoperfusion Using HA330 Cartridge Among Patients with Sepsis in St. Luke’s Medical Center

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INTRODUCTION

Hemoperfusion is among the extracorporeal blood purification therapies proposed to improve outcomes in sepsis by removing inflammatory mediators from the blood. Results of earlier studies are conflicting hence this study aimed to determine the clinical outcomes of hemoperfusion using sepsis (Jafron HA330) filter among patients with sepsis.

METHODS

We retrospectively investigated 41 patients and reviewed their demographic data, routine biochemistry, microbiological data, site of infection, APACHE II score, procalcitonin level, inotropic score, duration of mechanical ventilation, ICU stay, and ICU and 28-day mortality rate. We compared the characteristics of patients who survived and did not survive after 28 days of observation and their mean arterial pressure (MAP), inotropic score, creatinine, APACHE II score, procalcitonin before and after hemoperfusion treatment.

RESULTS

The ICU mortality rate and 28-day mortality rate were 46.34% and 41.6% respectively which are lower than the predicted mortality rate of 49.70% based on the APACHE II score before hemoperfusion treatment and 54% among patients with septic shock. There is a significant difference between the non-survivors and the survivors in terms of duration of ICU stay (P=0.006), duration of mechanical ventilation (p=0.029), number of hemoperfusion treatment (p=0.007) and timing of hemoperfusion (p=0.006). Early hemoperfusion treatment (within 48 hours) has significant effect on the duration of ICU stay (p=0.008) and duration of mechanical ventilation.

CONCLUSION

Hemoperfusion treatment results in lower ICU and 28-day mortality rate, shorter ICU stay and duration of mechanical ventilation. We recommended early hemoperfusion treatment as it reduces the duration of ICU stay and mechanical ventilation.
Comparison of efficacy between maintenance hemodialysis and their combination with hemoperfusion in patients undergoing chronic hemodialysis treatment

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University Clinical Centre Sarajevo, Clinic for Hemodialysis, Sarajevo, Bosnia and Herzegovina

BACKGROUND

The occurrence of mid- and long-term uremic complications is related to the low clearance rate of middle and large molecule uremic toxins when hemodialysis (HD) alone is adopted. As the uremic toxins and their corresponding bio-logical effects become increasingly clear, blood purification treatment that aims to remove these toxins, has developed from a stage of life-sustaining to improving the quality of life.

OBJECTIVE

The objective of this study was to evaluate demographic, clinical and laboratory data in patients who underwent the combination of maintenance hemodialysis with hemoperfusion (HP) and in those who received HD alone and to investigate whether this combination could improve the clearance rate of middle and large molecule uremic toxins.

METHOD

A total of 26 patients, who underwent routine hemodialysis, were assessed in this study. Those patients were randomly divided into three groups: Group I (7 patients) received combined treatment of HD with HP biweekly (HD 2 times a week with HD+HP once a week), whereas Group 2 (10 patients) was given HD with high-flux dialyzer and Group 3 (9 patients) was given HD with low flux dialyzer 3 times a week. This study was followed for 4 months. Before and after the observational period demo-graphic and clinical data were taken from the medical history and blood samples were taken for hemoglobin (Hb), iron (Fe), total iron binding capacity (TIBC), albumin (Alb), calcium (Ca), phosphorus (P04) and parathyroid hormone (PTH).

RESULTS

This study included 13 female and 13 male patients with a mean age of 41.62 ±11.12 and a mean dialysis duration of 62.78±53.33 months. When it comes to baseline characteristics, patients of the group 3 were significantly older than patients in other groups (p=0.001). At the end of the four months observation period, the same difference according to age was noticed (p=0.01). Also, HD+HP group had significantly higher values of TIBC (p=0.006) and significantly lower serum levels of P04 (p=0.001). EPO doses were very similar in group 1 and 2, but in group 3 there were noticeably lower than in those two groups but without a significant difference. The serum levels of albumin were higher in group 3 compared to the other two groups but also without statistical difference. No statistical difference between groups after the follow up period was observed in
terms of Hb, Fe, PTH, Ca, BMI, duration of dialysis treatment and vascular access. When groups are viewed individually, in the HD+HP group serum P04 levels were significantly lower after the 4 months off the follow up period than it was at the beginning (p=0.031) and also TIBC was significantly higher (p=0.018). In group 2 the values of TIBC were significantly lower after the follow up period than it was at the beginning (p=0.025). No significant difference was noticed in group 3 but serum PTH levels tends to decrease after 4 months compared to baseline measurement.

**CONCLUSION**

This Combination treatment of HD with HP was superior to HD in reducing levels of phosphorus. These findings suggests a potential role of reducing the risk of cardiovascular events in this population especially when it is known that hyperphosphatemia has been pointed out as the primary culprit in the process of cardiovascular calcification. Also, patients who underwent the Combined treatment showed higher values of TIBC but unfortunately no difference was noticed between Hb levels and EPO doses. These results eventually demonstrates their role in the improvement of renal dis-ease anemia, which opens up the possibility of further research on a larger sample and over a longer period of time.
Continues renal replacement therapy (CRRT) with disposable hemoperfusion cartridge: A promising option for severe COVID-19

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Cytokine release syndrome is prevalent in severe cases of COVID-19. In this syndrome, an uncontrolled response of immune system occurs. Extracorporeal blood purification has been proven to effectively remove the released inflammatory cytokines. Here, we reported a successful case to represent our experience of extracorporeal blood purification in a patient with severe COVID-19.

CASE REPORT

A 54-year-old man presented to the emergency department of Erfan Niyayesh Hospital, Tehran, Iran, with complains of high-grade fever, cough, and dyspnea for five days. At admission time, he had fever up to 38 °C. Peripheral oxygen saturation was 90% with a facemask. No abnormality was seen in laboratory results except positive C-reactive protein, lymphopenia with 570 cells/mL, and severe respiratory acidosis. The chest X-ray imaging revealed bilateral infiltration in both upper and lower lobes (Fig. 1a). The patient had no underlying diseases and history of medicine usage. Reverse transcription polymerase chain reaction (RT-PCR) sample for COVID-19 was reported positive and according to RT-PCR test and clinical symptoms, the diagnosis of COVID-19 was made for the patient. The therapeutic regimen included Hydroxychloroquine at a dose of 200 mg P.O. BID and lopinavir/ritonavir at a dose of 200/50 mg P.O.BID initiated for the patient. After four days, the clinical condition of the patient was deteriorated and he was subjected to intubation for invasive mechanical ventilation. The peripheral oxygen saturation decreased to 82%. The chest X-ray imaging showed the progressive infiltration (Fig. 1b) and the patient was categorized as a critically COVID-19 case with remarkable acute respiratory distress syndrome (ARDS). The plasma level of interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha were measured at this time. The results showed high levels of inflammatory cytokines. The urine output also decreased to 200 mL during the last 12 h and creatinine increased to 1.5 mg/dL. At this time, it is decided to start continuous renal replacement therapy (CRRT, Prismaflex, Baxter, IL, USA) with disposable hemoperfusion cartridge (HA 380 cartridge, Jaftron Biomedical Co., China) due to cytokine release storm and hypoxemia. A Shaldon catheter was inserted and CRRT was done for three sessions. The CRRT modality was continuous veno-venous hemofiltration (CVVH). The replacement fluid volume was removed by 35 mL/kg/h and the pump circulated blood by 250 mL/min. Priming of hemoperfusion was done with saline, and the cartridge was primed in a vertical position with the arterial side facing downward. A bolus dose of 2500 IU of heparin was administered into the arterial line, the cartridge was kept inlet side down, and blood flow through the cartridge was begun. Totally, 6000 IU was needed through the procedure. CRRT was started with a high ultrafiltration rate (200 mL/h). Each cartridge was replaced with a new cartridge after 6 h. The fluid removal rate was decreased to 50 mL/h after 8 h and then to zero mL/h during the last 8 h in the first 24 h. The second and the third sessions of CRRT were conducted by 0 mL/h fluid removal. A 24-h rest between sessions, was considered to avoid the probable coagulopathy and electrolyte abnormality.
After three sessions of CRRT plus hemoperfusion, the clinical condition of the patient was improved with the peripheral oxygen saturation of 95%. The creatinine also decreased to 1.1 mg/dL after the end of CRRT and urine output reached to 70 mL/h. No laboratory abnormality was seen during the CRRT. The chest X-ray revealed recovery of both lungs following the completion of 3 sessions of hemoperfusion (Fig. 1c). Also, the inflammatory cytokines were measured 48 h following the last session of hemoperfusion and showed a remarkable decrease. IL-1, and IL-6 were decreased from 523.3 pg/mL to 38.25 pg/mL, and 226.35 pg/mL to 210.18 pg/mL, respectively. The measurements also showed the decrease in IL-8 from 886.5 pg/mL to 482.4 pg/mL. Tumor necrosis factor alpha level decreased from 49.5 pg/mL to 47.3 pg/mL at the end of 3 sessions of hemoperfusion. The patient was finally transferred to the ward with an acceptable clinical condition. The “cytokine cascade” in patients with new coronavirus (COVID-19) is a leading cause of death in critically ill patients [1]. A variety of blood purification technology treatment methods such as CRRT plus hemoperfusion seem to be effective in certain cases. Cytokine release storm is the probable Phenomenon in severe COVID-19 cases [2]. Extracorporeal organ support can not only support vital organ functions such as the heart, lungs, kidneys, and liver but also avoid organ damage by removing excess inflammatory mediators [3]. Extracorporeal blood purification technology has been proven to effectively eliminate inflammatory cytokines such as CRP, IL-1, IL-6, etc. [4]. Here, we reported a successful case to represent our experience of extracorporeal blood purification in a patient with confirmed COVID-19. In this case, IL-6 was high and Tocilizumab, as an IL-6 antagonist, was another potential agent. However, Tocilizumab therapy may be associated with adverse effects and the access to Tocilizumab is limited in Iran. Also, tocilizumab is effective only on IL-6 regarding its mechanism. Hemoperfusion can have impact on more than one cytokine and may be more effective. This case responded to hemoperfusion and CRRT without remarkable complication. Hence, hemoperfusion with a disposable cartridge may be a promising option to decrease the inflammatory cytokines in COVID-19 induced ARDS. However, it is necessary to conduct clinical trials to find the efficacy and safety of this strategy.

References

Early Hemoperfusion for Cytokine Removal May Contribute to Prevention of Intubation in Patients Infected with COVID-19

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Hemoperfusion (HP) was helpful to prevent the development and progression of ARDS, AKI, liver failure, and septic shock by removing cytokines and other inflammatory mediators and ultimately preventing progression toward multiple organ failure.

ABSTRACT

A 54-year-old man diagnosed with COVID-19 was hospitalized in the intensive care unit. The patient’s O2 saturation was 80% using an oxygen mask, which was gradually declining. After 4 sessions of HP/continuous renal replacement therapies (CRRT), O2 saturation reached to 95%, and the patient was transferred to the general ward. Performing HP/CRRT at the early stages of ARDS can obviate the need for intubating patients with COVID-19. Punctual and early use of HP and CRRT in the treatment of ARDS in patients with COVID-19 prevented the progression of ARDS and patient intubation, reduced respiratory distress and the patient’s dependence on oxygen, prevented other complications such as AKI and septic shock in the patient, and reduced mortality and hospital length of stay.
CASE REPORT AND PRESENTATION

A 54-year-old male with cough and dyspnea was referred to the emergency department 2 days ago. The patient received antiviral (chloroquine, colta, and siltamivir), antibacterial (meropenem and vancomycin), and anticoagulant (heparin 10 U/kg/h) drugs. Due to the history of hypertension and diabetes mellitus, the patient also received antihypertensive and diabetes medications.

The patient treated in the present report was diagnosed with COVID-19 for SOB, a decrease in O2 saturation (80% with the reservoir bag mask), and transferred to the ICU. The patient had oliguria and a high level of BUN and creatinine before ICU admission (creatinine 2.7 and BUN 70). The patient was heavily dependent on oxygen O2 saturation, and it was rapidly decreasing to <70% upon mask removal.

HP (HA cartridge, Jafron Biomedical Co., Zhuhai, China) in combination with CRRT was initiated. The patient had acute renal failure, and the patient had a history of diabetes and high blood pressure. Before the onset of HP-CRRT, the patient has oliguria (urine <400 cm3 in 24 h). After HP-CRRT, the patient’s urine output reached 1,100 cm3 in 24 h. CRRT mode used was as follows: CVVH pre-dilution and post-dilution every 2 h, blood flow: 200–250 mL/min, substitution flow: 25 cm3/kg/h, UF rate: 20 cm3/h, heparin: 10 U/kg/h, patient weight: 70 kg. The HP cartridge was added to the CRRT circuit simultaneously with the start of CRRT, and HP and CRRT were started simultaneously. After 6 h, the HP cartridge was removed from the CRRT circuit, and CRRT was continued. After 20 h, the second HP cartridge was added to the CRRT circuit, and it was used for 6 h and then removed. The fluid balance was maintained neutral.

The O2 saturation of the patient gradually increased after the first hour of HP/CRRT, reaching 95 and 100% after several hours. Figure 2 shows the patient's chest X-ray after the second HP cartridge application. After 24 h, the patient's clinical condition was significantly improved. CRRT was then stopped. After about 10 h from discontinuation, O2 saturation gradually declined and after 20 h reached about 90%, and CRRT/HP was started again. Two HP sessions were performed within the following 24 h in conjunction with CRRT, and the O2 saturation climbed above 95% again. CRRT continued for another 12 h, and the O2 saturation was still above 95% using a mask with a reservoir bag. The patient's creatinine and BUN levels also decreased significantly (creatinine 0.7 and BUN 30). The patient's dependence on oxygen decreased, and he could remove the mask for a few minutes. The patient was monitored for loss of O2 saturation, but O2 saturation had stabilized, and there was no decrease in the following 24 h. After 5 days, the patient was finally discharged from the ICU.

Table 1. Inflammatory and biochemical parameters before and after HP-CRRT

<table>
<thead>
<tr>
<th>Test</th>
<th>Before HP</th>
<th>After 4 sessions of HP-CRRT</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/mL</td>
<td>103</td>
<td>12</td>
<td>0–3</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>52</td>
<td>15</td>
<td>1–13</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>450</td>
<td>260</td>
<td>200–400</td>
</tr>
<tr>
<td>PCT, ng/mL</td>
<td>0.22</td>
<td>0.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D-dimer, ng/mL</td>
<td>750</td>
<td>120</td>
<td>&lt;250</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>500</td>
<td>112</td>
<td>140–280</td>
</tr>
<tr>
<td>IL6, pg/mL</td>
<td>265</td>
<td>10</td>
<td>0–7</td>
</tr>
<tr>
<td>WBC, 10^3/mm^3</td>
<td>8,300</td>
<td>6,700</td>
<td>4.5–11</td>
</tr>
<tr>
<td>RBC, 10^6/mm^3</td>
<td>5,500</td>
<td>4,300</td>
<td>4.3–5.9</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>14.5</td>
<td>12.8</td>
<td>13.5–17.5</td>
</tr>
<tr>
<td>Platelets, 10^3/μL</td>
<td>257</td>
<td>19</td>
<td>150–450</td>
</tr>
<tr>
<td>Neutrophil, 1.70–7.00 × 10^9/L</td>
<td>85</td>
<td>73</td>
<td>40–60%</td>
</tr>
<tr>
<td>Lymphocyte, 0.90–2.90 × 10^9/L</td>
<td>6%</td>
<td>17%</td>
<td>20–40%</td>
</tr>
<tr>
<td>Monocyte, 0.30–0.90 × 10^9/L</td>
<td>10</td>
<td>16</td>
<td>2–8%</td>
</tr>
<tr>
<td>Cr, mg/dL</td>
<td>2.7</td>
<td>0.8</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>70</td>
<td>35</td>
<td>10–20</td>
</tr>
</tbody>
</table>
DISSCUSSION AND CONCLUSION

ARDS is the most common cause of intubation in patients with COVID-19 and admission in the ICUs. Subsequently, septic shock, elevated liver enzymes and renal markers, acute hepatic and renal failure, and multiple organ failure occurred and resulted in death for the patient. Cytokine storm is addressed as one of the contributing factors to ARDS.

Applying HP/CRRT with a mechanism of adsorption appears to capture and harvest cytokines from the blood, prevents them from lying on the wall of the alveoli and pulmonary arteries, and ultimately prevents the incidence of ARDS and/or its progress [1-3]. Thus, we consider that there is a rationale for early application of HP/CRRT before the patient’s clinical condition becomes so severe to require invasive mechanical ventilation. This is especially true in the absence of pharmacological remedies for the COVID-19 infection. Indications and duration of HP/CRRT should respond to specific criteria in order to be consistent in the application of this rescue treatment. High level of inflammatory markers and cytokines, the severe tendency to hypoxia, clinical signs of hemodynamic instability, and need for vasopressor support may represent a trigger for early application of HP/CRRT. Further studies are needed to confirm this hypothesis, but recent data are promising.

In conclusion, with clinical experiences we have shown that the application of CRRT/HP in the early stages of ARDS, when the O2 saturation of the patient’s blood with a reservoir oxygen mask is <90%, prevented the progression of the disease to moderate-to-severe ARDS, stabilized the O2 saturation, and gradually led to increased O2 saturation, prevention of intubation, improved clinical conditions, reduced dependence on oxygen, discharge from ICUs, and ultimately discharge from the hospital.

References

HA330 Hemoperfusion combined with CRRT for severe COVID-19 with sepsis, cases from Malaysia

* Edited from clinical data

Cytokine storm was common seen among COVID-19 patients, in patients with bacterial co-infection, sepsis/septic shock was observed and with worse outcomes. Here we presenting with three cases treated with HA 330 hemoperfusion combined with CRRT from Malaysia. Results showed that patients’ organ function such as renal, liver or lung function was improved in degrees. Meanwhile, the hemoperfusion combining with CRRT could help control patients’ inflammatory status.

CASE REPORT - 1

A 62-year-old male patient with fever for 2 days, accompanied with short of breath was admitted to Hospital Raja Permaisuri Bainun, HRPB. Medical evaluation showed that he was with multi-organ injury with Murray score of 3.8 on March 23, 2020, MELD score was 24 and APACHE II score was 32. CXR revealed bilateral infiltrates (Right > Left) on March 26, 2020.

He was diagnosed with COVID-19 infection, AKI(AKIN stage), ARDS, and septic shock which is secondary to cytokine releasing syndrome. He received pharmaceutical therapy such as Kaletra, hydroxychloroquine, Azithromycin, cefepime, interferon, etc. He was under invasive mechanical ventilation as for respiratory support. Hemoperfusion was conducted with CRRT. Totally 3 treatments of hemoperfusion (HA330) were conducted in 2 days, each treatment duration was 8 hours. For the CRRT, its was the CVVHDF mode lasted for over 72 hours duration. Heparin was used as anticoagulant (first dose 800U, with additional dose 80 U/h).

After the treatment, patient showed an improvement in liver and kidney function that we can see a decrease in ALT/AST, BUN and creatine. Additionally, there was a decrease in of WBC count. Moreover, with the improvement of hemodynamic status and respiratory function, the patient was able to get rid of vasopressor/inotropic and weaning mechanical ventilation.
A 72-year-old male patient with fever, lethargy intubated because of worsening type-1 respiratory failure. He was admitted to ICU required CRRT in view of worsening kidney function with poor heart condition. Medical evaluation showed that he was with multi-organ injury with MELD score of 29, SOFA score was high and SAPS II score was 52.87%, PCT kept increasing to 11.66 ng/ml on May 4, 2020.

He was diagnosed with COVID-19 infection, AKI(Stage 3, KDIGO), ARDS, and sepsis. He received pharmaceutical therapy and was under invasive mechanical ventilation as for respiratory support. Other supportive symptomatic treatment such as DVT and stress ulcer prophylaxis were performed as well. Hemoperfusion was conducted with CRRT. Totally 3 treatments of hemoperfusion (HA330) were conducted in 3 days, each treatment duration was 6 hours. Clexane was used as anticoagulant (Dose was 60mg OD).

After the treatment, patient showed an improvement in oxygenation that we can see an increase in PaO2/FiO2 and O2 Saturation. Additionally, there was a decrease in CRP. The doctor was satisfied with the hemoperfusion efficacy in this case especially for the significant reduction of inflammatory biomarker, and regards the HA330 hemoperfusion played a potential role in cytokines clearance.
A 26-year-old male patient was admitted to hospital with hyperglycemic symptoms and was diagnosed as DM HPT (He was on insulin and one type of anti-HPT therapy) 2 weeks ago. Then he presented with worsening SOB, rhinorrhea, cough and sore throat for 3 days, but he denied fever at home. He was brought into Emergency Department on April 24, 2020 with GCS 9/15 (E2V2M5) and got intubated. Medical evaluation showed that he was with multi-organ injury. Murray Score was 3.5, MELD score was 28 and APACHE II score was 29. CXR revealed progressive bilateral infiltrates, and blood culture on April 25, 2020 revealed Gram-negative bocilli infection.

He was diagnosed with COVID-19 infection, AKI(Stage 3, AKIN), ARDS, septic shock and liver injury. He received pharmaceutical therapy such IV Meropenem 1g TDS, IV Fluconazole 400mg OD, IV Clindamycin 900mg TDS, etc. He was under SIMV ve 500ml, rate 20, PEEP 12, P1512, Fio2 0.8, and prone position as for respiratory support. Additionally, he received inotropic support with IVI Noradrenalin 0.9mcg/kg/min, IVI vasopressin 0.03unit/min, and IVI dobutamine 1mcg/kg/min. Hemoperfusion was conducted with CRRT. Totally 4 treatments of hemoperfusion (HA330) were conducted in 3 days, each treatment duration was 8 hours. For the CRRT, its was the CVVHDF mode lasted for 72 hours duration.

Right few hours after the treatment, patient showed an improvement in kidney function that we can see a decrease in BUN and creatine. Additionally, there was a decrease in of WBC count and CRP. Moreover, with the improvement of hemodynamic status and respiratory function, the patient required lower inotropic support and ventilator setting, such as FiO2 down to 0.04. Doctors were satisfied with the hemoperfusion efficacy in this case.
HA330 hemoperfusion combined with CRRT for a 75-Year-Old Man with Covid-19 and Acute Kidney Injury, case from Ecuador

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Currently there are 56,432 confirmed cases in Ecuador and 7,931 cases in the province of Pichincha. The COVID-19 infection has shown a significant contagion capacity and severe multi-organ involvement with disastrous results. In this report, a 75-year-old man with COVID-19 and Acute Kidney Injury treated with hemoperfusion combined with CRRT which was aimed to manage the cytokine storm with satisfactory outcomes was presented.

ABSTRACT

Since December 2019 we have seen how we quickly went from spectators to actors in almost all the countries of our planet and we had to face a pandemic that has forced, like no other, to paralyze the world and us health professionals to face to a great challenge, a new virus that has shown a significant contagion capacity and severe multi-organ involvement with disastrous results. Currently there are 56,432 confirmed cases in Ecuador and 7,931 cases in our province of Pichincha [1-2]. We present one of our 10 cases COVID-19 positive patients in which we used hemoperfusion with macro-adsorbent resin (Jafron HA330 cartridge) as part of the treatment in the presence of cytokine storm, with satisfactory results in the proposed treatment objectives.
A 75-year-old man was admitted to the Emergency Department, and after 7 days of illness onset, without significant history, he developed a compatible picture with COVID-19 in outpatient management with Azithromycin and NSAIDs.

On examination, the temperature was 37.8 °C, the blood pressure was 130/70 mmHg, the heart rate was 110 beats per minute, and the respiratory rate was 25 breaths per minute. The patient had diffuse coarse crackles at the lungs. The remainder of the physical examination was normal. Oxygen saturation was 50%, and the patient had severe increased shortness of breathing, dyspnea, tachypnea, and orthopnea (SAFI: 83, PAFI 133), qSOFA score > 2, requiring vasoactive amines and mechanical ventilation. Meanwhile, patient was oliguric with serum creatinine at 1.86 mg/dl, leukocyte values at 14,520 cel/ml, lymphocytes 857 cel/ml, platelets 381000 cel/ml, LDH 331 U/L, D-dimer 621 ng/ml, ferritin 940 ng/mL, CPK 80 U/L, ultrasensitive Troponin 47.94 ng/L, IL-6 361 pg/ml. PCR-RT for SARS-Cov-2 was positive. CT of the chest reveals peripheral and central frosted glass opacities, bilateral (Fig 1-2). The patient was transferred to the intensive care unit (ICU) and Azithromycin and Hydroxychloroquine for 5 days, Lopinavir/Ritonavir for 3 days, Tocilizumab 500 mg every 12 hours for 3 doses, anticoagulation with low molecular weight heparin were administered.

On the 8th day of hospitalization, patient was reported with refractory hypoxemia, increased vasoactive support and creatinine elevation, it was decided to prone the patient and start continuous renal replacement therapy (CRRT) in the modality of continuous veno-venous hemodiafiltration (CVVHDF) dose of 30 ml/kg/h (Multifiltrate Machine, AV1000S filter) and Hemoperfusion (HA330 Jafron cartridge) (Fig 3). The hemoperfusion was developed with 2-1-1 protocol (4 sessions, the first day 1 each 12 h, and then 1 each 24 h for 2 days). The hemoperfusion duration was 4 hours each treatment.

Before the start of CRRT, IL-6 was measured with levels > 5000 pg/ml, at the end of the therapy, it had IL-6 of 1277 pg/ml. On the 12th day, the mechanical ventilation parameters were lowered (PAFI 280 and SAFI 265), with a subsequent decrease in vasoactive drugs and renal function recovery. The patient was ICU discharged and full recovery to home. Laboratory evolution is displayed in table 1.
The incidence of acute kidney failure from 3% to 9%[3], however recent reports show higher incidences. Renal abnormalities reported have been massive albuminuria (34%), hematuria (26.7%) on the day of admission (34%), 63% developed proteinuria during the hospital stay, blood urea nitrogen was elevated in 27% of cases and in 2/3 of the patients who died, elevated serum creatinine 15.5% and Renal CT showed reduced density about inflammation and edema[4-5]. The exact pathophysiological mechanism of renal compromise is unclear, however, the most acceptable pathophysiology is that of a sepsis-like syndrome induced by high levels of circulating cytokines (the so-called cytokine storm) or direct cell injury from the virus. The coronavirus is linked to receptors such as the ACE-2 that is present in the epithelium of the lung, small intestine, colon and biliary tract[6], with a clinical picture that initially implies lung involvement in addition to kidney, liver and multiple organ dysfunction [7]. Regarding the treatment of Acute Kidney Failure (AKF) in the context of a COVID-19 patient, this should include general support management similar to AKF secondary to sepsis and renal replacement therapy, which, given the evidence and experience of other countries, we have adopted an early behavior-oriented more to water overload of >3kg, independent of serum creatinine value and the preferred modality is convective with Continuous Renal Replacement Therapy (CRRT) combined with Hemoperfusion (adsorptive). So, base on pathophysiological derangement observed in these kinds of patients, a rationale emerges for extracorporeal therapies to remove inflammatory mediators and support different organ systems [8].

In our case report, we have been able to demonstrate the efficacy of extracorporeal therapies and mainly hemoperfusion to combat cytokine storm and we have correlated the results of the therapy with clinical improvement of the patient, decreased vasoactive drug requirements, ventilatory weaning and adequate control of the systemic inflammatory response syndrome, in addition to rapid recovery of kidney function Finally, the “2-1-1” hemoperfusion scheme with Jaftron HA 330 filter can be recommended as an effective therapy in the management of COVID-19 patients with a clinical picture of cytokine storm and multi-organ compromise.

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>Hospital Day 8 (CRRT + HP start)</th>
<th>Hospital Day post CRRT + HP treatment</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cells (cel/ml)</td>
<td>14520</td>
<td>9430</td>
<td>7030</td>
<td>3740</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2937</td>
<td>7836</td>
<td>4773</td>
<td>1560</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>857</td>
<td>613</td>
<td>1069</td>
<td>1141</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>1652</td>
<td>1142</td>
<td>1074</td>
<td>604</td>
</tr>
<tr>
<td>D-Dimer (ng/ml)</td>
<td>621</td>
<td>2286</td>
<td>2481</td>
<td>1873</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>361</td>
<td>&gt;5000</td>
<td>1257</td>
<td>109</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>32</td>
<td>226</td>
<td>76</td>
<td>22</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.8</td>
<td>4.4</td>
<td>1.7</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion & Conclusion**

The incidence of acute kidney failure from 3% to 9%[3], however recent reports show higher incidences. Renal abnormalities reported have been massive albuminuria (34%), hematuria (26.7%) on the day of admission (34%), 63% developed proteinuria during the hospital stay, blood urea nitrogen was elevated in 27% of cases and in 2/3 of the patients who died, elevated serum creatinine 15.5% and Renal CT showed reduced density about inflammation and edema[4-5]. The exact pathophysiological mechanism of renal compromise is unclear, however, the most acceptable pathophysiology is that of a sepsis-like syndrome induced by high levels of circulating cytokines (the so-called cytokine storm) or direct cell injury from the virus. The coronavirus is linked to receptors such as the ACE-2 that is present in the epithelium of the lung, small intestine, colon and biliary tract[6], with a clinical picture that initially implies lung involvement in addition to kidney, liver and multiple organ dysfunction [7]. Regarding the treatment of Acute Kidney Failure (AKF) in the context of a COVID-19 patient, this should include general support management similar to AKF secondary to sepsis and renal replacement therapy, which, given the evidence and experience of other countries, we have adopted an early behavior-oriented more to water overload of > 3kg, independent of serum creatinine value and the preferred modality is convective with Continuous Renal Replacement Therapy (CRRT) combined with Hemoperfusion (adsorptive). So, base on pathophysiological derangement observed in these kinds of patients, a rationale emerges for extracorporeal therapies to remove inflammatory mediators and support different organ systems [8].

In our case report, we have been able to demonstrate the efficacy of extracorporeal therapies and mainly hemoperfusion to combat cytokine storm and we have correlated the results of the therapy with clinical improvement of the patient, decreased vasoactive drug requirements, ventilatory weaning and adequate control of the systemic inflammatory response syndrome, in addition to rapid recovery of kidney function Finally, the “2-1-1” hemoperfusion scheme with Jaftron HA 330 filter can be recommended as an effective therapy in the management of COVID-19 patients with a clinical picture of cytokine storm and multi-organ compromise.
References


Combined extracorporeal blood purification by means of cytokine sorption and selective plasma exchange in patients with severe COVID-19 — clinical case series, from Russia

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National Medical Research Center of Cardiology, Ministry of Healthcare Russian Federation

ABSTRACT

New coronavirus infection can be life-threatening. Cytokine storm is an essential pathophysiological element in severe COVID-19 cases. Existing methods of the cytokine storm treatment can be divided into two categories: pharmacological therapy and extracorporeal blood purification (EBP). Multiple modes of EBP have been used in clinical studies in patients with bacterial sepsis and septic shock, the pathogenetic mechanisms of which are also centered around hypercytokinemia. Although poor data shows an improvement of prognosis in this group of patients, effective lowering of concentrations of proinflammatory cytokines was demonstrated, as well as reaching of several secondary endpoints, when cytokine sorption (CS) and selective plasma exchange (SPE) were used. Due to a different mechanism of cytokine hyperproduction in COVID-19 compared to sepsis, EBP may have additional benefits and improve outcomes even better. Therefore, these methods are extensively investigated in the COVID-19 pandemic setting. A combination of CS and SPE in patients with severe COVID-19 may be more effective than each method when used separately.

CASE PRESENTATION

CASE ONE

A 59-years-old male was admitted to an ICU with COVID-19. To treat hyperinflammatory state, the decision was made to start combined extracorporeal blood purification by means of consequent cytokine sorption and selective plasma exchange (SPE). Extracorporeal blood purification was initiated approximately on the day 3 from the onset of cytokine storm. Due to multorgan failure syndrome, SPE was chosen as the initial procedure. Later, stable improvements were observed, with the progressive decrease in the levels of inflammatory markers. The patient was discharged from the ICU on the 3rd day after the last extracorporeal blood purification procedure. On Day 7 after the last procedure, the patient was weaned of the oxygen therapy. On Day 14, the patient was discharged in satisfactory condition, with SpO2 98% while breathing ambient air.

CASE TWO

A 44-years-old female was admitted to a COVID-19 line department with dry cough, dyspnea and fever 39°C. Considering the cytokine storm resistant to conservative therapy, including IL-antagonists, respiratory failure requiring invasive ventilation, a procedure of cytokine sorption was initiated. The procedure was performed on Day 2 from the onset of cytokine storm. The cytokine sorption was performed using HA330 column for 2 hours, with perfusion volume 30 l, flow rate 240 ml/min. In the morning after the procedure (4 hours after its completion), body temperature normalization was observed.
INTRODUCTION

Currently, there is no causal treatment of COVID-19 with proven efficacy. For this reason, studying pathogenetic methods of treatment for patients with new coronavirus infection is a priority.

Cytokine storm is one of the key elements in severe COVID-19 pathogenesis [1,2]. Activation of macrophages, monocytes, and dendritic cells in response to viral invasion leads to innate immunity stimulation with hyperproduction of proinflammatory cytokines, including IL-1, IL-6, IL-8, IL-17, IFN-γ, TNF-α [3]. Following activation of neutrophils, monocytes, T- and B-cells, along with the release of higher quantities of inflammatory mediators, results in progressive increase in immune signaling, mainly through the JAK-STAT pathway [3]. This leads to an increase in microvascular permeability, micro- and macro- thromboses, eventually culminating in the injury of lungs, kidneys, liver, heart, and other vital organs [3]. Progression of this condition results in advanced multiorgan failure and fatal outcome.

Existing methods of cytokine storm treatment can be subdivided into pharmacological therapy and EBP. Main medications used to decrease cytokine production and activity include corticosteroids, IL-6 and IL-1 antagonists, JAK kinase inhibitors, colchicine, as well as several other drugs. Currently, pharmacological treatment of cytokine storm has some limitations, although it is actively used in clinical practice. As of today, only for corticosteroids convincing evidence has been obtained demonstrating improved outcomes in COVID-19 patients.

In clinical practice, some patients show resistance or have contraindications to pharmacological treatment. In such cases, EBP methods may be promising, as they permit to eliminate large quantities of multiple inflammatory mediators and pathogen/damage-associated molecular patterns (PAMPs, DAMPs) [4, 5].

It has been demonstrated that such EBP methods as plasmapheresis, hemofiltration, and cytokine sorption, may have positive effects in patient with sepsis and septic shock, i.e. in the conditions which also involve hypercytokinemia [4, 6, 7]. Among all EBP methods, published data regarding COVID-19 patients involve only cytokine adsorption. The existing experience is mostly presented by clinical cases of successful use of Cytokine adsorption cartridges, where EBP had beneficial effects on cytokine clearance, pulmonary function, vasopressor requirements and respiratory support needs [8].

Comparative studies are currently limited and represented by preprinted articles only. The only prospective randomized trial by Liang Yu et al. using HA330 sorption device in 47 patients (n=26 in the EBP group) with severe COVID-19 is presented in the form of drafting manuscript [9]. According to the presented preliminary data, this study has demonstrated statistically significant outcome improvement after 72 hours, not only for secondary outcomes (p=0.026 for the oxygenation index, p=0.004 for APACHE II index), but also for mortality (47.6% vs. 15.4% in the intervention group, p=0.025). As of today, several RCTs of cytokine sorption in COVID-19 patients have been initiated; their results will permit to evaluate the significance of the efficacy of this method [10, 11, 12, 13, 14, 15, 16]. Based on the available promising data, experts from multiple countries (China, Italy, Russia) have included cytokine sorption into the temporary guidelines on COVID-19 patients with marked inflammatory reaction [17,18,19]. UK NICE has authorized the use of the hemoperfusion cartridge Jafron HA330 for cytokine sorption in COVID-19 [8]. ERA-EDTA permits use of the hemoperfusion cartridges for cytokine adsorption in severe COVID-19 patients with acute kidney injury requiring renal replacement therapy [20].
The use of SPE also appears to be well justified in the view of COVID-19 pathogenesis, as this method eliminates all molecules with the weight below 60 kDa from blood by means of convection through a highly permeable super high-flux and high cut-off membrane. In the treatment of sepsis, combined methods are being used, including options of coupled plasma filtration and adsorption (CPFA) [21]. Nevertheless, there is no published data on combined methods of treatment for COVID-19, but their use may be justified in severe disease.

We have used a combination of cytokine sorption with the HA-330 cartridges (Jafron, China) and SPE with the Evaclio 2C20 plasma separators (Kawasumi Laboratories Inc., Japan) in 8 patients with severe COVID-19. In this article, we present 2 most exemplary clinical cases and a description of our EBP clinical protocol.

CASE PRESENTATION

CASE ONE

Patient A., 59 years old, male, was admitted on the May 2, 2020, to an intensive care unit (ICU) in COVID-19 center with symptoms of dyspnea, dry cough, fever of up to 38.5°C. The disease had presumably started 7 days prior to the admission, when dry cough and fever developed. The day before the hospitalization, respiratory failure signs started (dyspnea, shortness of breath). Computer tomography (CT) scan was performed on an outpatient basis; it showed diffuse thickening of pulmonary tissue, with ground-glass opacities, polysegmental interstitial pneumonia, presumably of viral origin. The area of pulmonary tissue involvement reached 75% (Figure 1).

Figure 1. CT scan of Patient A

His comorbidities included grade 2 hypertension. On admission the patient had evidence of respiratory failure: tachypnea (respiratory rate (RR) 30 per minute) with significant respiratory effort, SpO2 77% while breathing ambient air. Body temperature 38.6°C. Hemodynamic parameters were stable, blood pressure (BP) 150/82 mmHg, sinus rhythm, heart rate (HR) 115 beats per minute (bpm). High-flow oxygen supply was initiated, with the flow 60 l/min, FiO2 55-60%. The patient was transferred to prone position, conscious. To decrease the respiratory distress, promedol 200 mg and paracetamol 1000 mg were administrated. On the background of this therapy, SpO2 increased to 90-92%, but tachypnea (up to 24 per minute) and marked respiratory effort continued. Arterial blood gases showed decompensated respiratory alkalosis (pH 7.5, PaCO2 20 Hg mm, BE -3.7 mM).
Laboratory data showed neutrophilic leukocytosis up to 11.4x109/l (neutrophils 9.6x109/l, lymphocytes 0.9x109/l), moderate increase in liver enzymes (ALT 52 UI, AST 72 UI, bilirubin level was normal). There was an increase in inflammatory marker levels: CRP 371 mg/dl, procalcitonin 0.72 pg/ml. Polymerase chain reaction (PCR) demonstrated SARS-CoV-2 RNA in the oropharyngeal smear. Therefore, the patient had severe COVID-associated viral pneumonia complicated by respiratory failure, with evidence of bacterial infection.

The following treatment was started: hydroxychloroquine 400 mg BID followed by 200 mg BID during 7 days; lopinavir/ritonavir 200+50, 2 tablets BID for 5 days; antimicrobial therapy: azithromycin 500 mg daily, amoxicillin/clavulanic acid 1000+200 mg BID; enoxaparin sodium in therapeutic dose of 80 mg BID; intravenous (iv) dexamethasone 12 mg daily; antihypertensive treatment: losartan 100 mg daily, amlodipine 5 mg daily. Subsequently respiratory failure progressed. Non-invasive ventilation (NIV) was initiated by means of facial mask with the following working parameters: PEEP 8 cmH2O, P (supp.) 5 cmH2O, FiO2 50%. P/F ratio during the initiation of NIV was 114 mmHg. In addition, laboratory tests showed liver injury progression (ALT increase to 174 UI, AST 219 UI) along with the signs of acute kidney injury (serum creatinine more than triple increase, up to 294 μM, decrease in GFR (by CKD-EPI) to 19 ml/min/1.73 m2). The diuresis rate also decreased. High level of inflammatory markers persisted. White blood cells 13.1x109/l, IL-6 222.7 U/ml, CRP 348 mg/dl, ferritin 7819 ng/ml. These symptoms were interpreted as cytokine storm with macrophage activation syndrome. To treat hyperinflammatory state, the decision was made to start combined extracorporeal blood purification by means of consequent cytokine sorption and selective plasma exchange (SPE). Extracorporeal blood purification was initiated approximately on the day 3 from the onset of cytokine storm. Due to multiorgan failure syndrome, SPE was chosen as the initial procedure.

SPE was performed by means of Evaclo 2C filter on the renal replacement therapy machine (Aquarius, Nikkiso Medical, Japan) for 5 hours, with the perfusion volume 2 liters, blood flow rate 240 ml/min. The procedure was terminated early due to a blood collection line issue. In the morning after the procedure (4-5 hours after its completion), body temperature normalized; CRP level decreased more than twice, to 164 ng/ml; some decrease in hepatic transaminases was seen (ALT 115 UI, AST 88 UI), creatinine level was the same (287 μM/l). The patient was transferred to oxygen insufflation through nasal cannulas, with the rate of 14 l/min in prone position. On this background, the SpO2 grew to 90%, but episodes of desaturation to 85% continued. As a second procedure, cytokine sorption with HA330 adsorption column on the Hemma (PlasmoFilter, Russia) machine was initiated 10-11 hours after the end of SPE. The duration of the procedure was 4 hours, perfusion volume 20 l, flow rate 140-150 ml/min. 1 to 2 hours after the end of CS, the IL-6 level decreased by 3.5 times compared to baseline, to 65.9 U/ml. The morning blood test (12-13 hours later) showed CRP level 134.8 mg/dl, creatinine 220 μM, ALT 114 UI, AST 63 UI, white blood cells number was normalized. Regarding the clinical picture, marked positive dynamics of respiratory function was seen, which included decrease in respiratory rate to 20 per minute, decrease in the oxygen requirement (stable SpO2 96% during the oxygen insufflation with the rate of 8 l/min). Later, stable improvements were observed, with the progressive decrease in the levels of inflammatory markers. The patient was discharged from the ICU on the 3rd day after the last extracorporeal blood purification procedure. On Day 7 after the last procedure, the patient was weaned of the oxygen therapy. On Day 14, the patient was discharged in satisfactory condition, with SpO2 98% while breathing ambient air.

**CASE TWO**

Patient B., 44 years old, female, was admitted on the May 20, 2020, to a COVID-19 line department with dry cough, dyspnea and fever 39°C. The disease had presumably started 3 days prior to the admission, when dry cough and weakness appeared. The day before the hospitalization, dyspnea and shortness of breath started. CT scan was performed on an outpatient basis; it showed polysegmental interstitial pneumonia, presumably of viral origin. The area of pulmonary tissue involvement reached 40%. His comorbidities included cerebral palsy since childhood, with left eye blindness and ambulation disorder. On admission, the patient was demonstrating moderate dyspnea with tachypnea to 24 per minute, SpO2 97% while breathing ambient air. Body temperature 38.1°C. BP 140/90 mmHg, sinus rhythm, HR 110 beats per minute (bpm).
Laboratory data showed neutrophilic leukocytosis up to 16.4x10^9/l (neutrophils 13.9x10^9/l, lymphocytes 1.7x10^9/l), increase in CRP level (44.5 mg/dl), procalcitonin 0.58 ng/ml, D-dimer 305 ng/ml, LDH 260 U/l. PCR showed SARS-CoV-2 RNA in the oropharyngeal smear. The following treatment was started: hydroxychloroquine 400 mg BID followed by 200 mg BID for 7 days; azithromycin 500 mg daily, cefoperazone/sulbactam 1+1 g BID. On the 3rd day of hospitalization, tocilizumab 400 mg was administered due to persistent fever and high CRP level. With the treatment delivered, after tocilizumab administration, CRP level decreased to 7.8 mg/l, procalcitonin 0.36 ng/ml, but leukocytosis persisted (13.4x10^9/l), D-dimer level grew to 2862 ng/ml, ALT 84U/l, AST 70 U/l, LDH 1025 U/l, IL-6 2641 pg/ml, ferritin 258 µg/l. Nevertheless, during the delivered treatment febrile fever persisted, despite the use of antipyretics. On the 6th day of hospitalization, the patient had marked progression of respiratory failure and required oxygen; during the oxygen insufflation with the rate 10 l/min, the SpO2 was 80% in prone position, respiratory rate 26 per minute, signs of increased respiratory effort. During the transportation to MSCT in the supine position, the patient desaturated to 45% on the background of O2 insufflation with the rate 15 l/min and was transported to the ICU. NIV was initiated with the following working parameters: PEEP 10 mmH2O, P (supp.) 4 mmH2O, FiO2 60%; tocilizumab 400 mg i.v. was administered again. Despite NIV in the prone position, the oxygen requirement progressed (FiO2 80%). SpO2 maintained at 80%, respiratory rate 30 per minute. Invasive ventilation was started; a recruitment maneuver was performed with a positive effect; ventilation continued in the PC-CMV mode with the following parameters: PEEP 20 cmH2O, P (insp.) 35 cmH2O, FiO2 60%, respiratory rate 18 per minute, tidal volume 300-350 ml. The measured compliance of respiratory system was 32 ml/cmH2O. Arterial blood gases were consistent with decompensated respiratory acidosis (pH 7.32, PCO2 50 mmHg, paO2 86, P/F ratio 143 Hg mm). CT-angiopulmonography was performed; acute pulmonary embolism (PE) was excluded; polysegmental interstitial pneumonia without clear consolidation areas was observed, presumably of viral origin. The area of pulmonary tissue involvement reached 90%. Considering the disease severity, dexamethasone 12 mg daily, and enoxaparin 120 mg daily were added to the treatment.

Considering the cytokine storm resistant to conservative therapy, including IL-antagonists, respiratory failure requiring invasive ventilation, a procedure of cytokine sorption was initiated. The procedure was performed on Day 2 from the onset of cytokine storm. The cytokine sorption was performed using HA330 column for 2 hours, with perfusion volume 30 l, flow rate 240 ml/min. In the morning after the procedure (4 hours after its completion), body temperature normalization was observed. Laboratory tests showed a decrease in IL-6 to 938.9 pg/ml, ferritin 196 µg/l, LDH 918 U/l, CRP 1.5 mg/l, white blood cells 12.1x10^9/l, procalcitonin 0.11 ng/ml. Nevertheless, hepatic enzyme levels continued to increase: ALT 118 U/l, AST 110 U/l, D-dimer level increase to 7371 ng/ml. Respiratory function did not change. SPE with Evaclio 2C filter was initiated 10 hours after the end of cytokine sorption. The duration of the procedure was 5 hours, perfusion volume 10 l, flow rate 150-180 ml/min. Twelve hours after the end of the procedure, D-dimer level decreased to 5284 ng/ml, LDH 775 U/l, ALT increase up to 169 U/l, AST 142 U/l, white blood cells 16.7x10^9/l. In addition, positive clinical dynamics was seen, with a decrease in respiratory support parameters: PEEP decreased to 12 cmH2O, P (insp.) to 25 cmH2O, FiO2 to 40% in the prone position. On the background of the decrease of the respiratory support, the SpO2 was 96%. The respiratory system compliance was 39 ml/cmH2O. Arterial blood gases test showed no abnormalities in acid-base balance; P/F ratio 155 mmHg. In 17 hours after the SPE, a second SC on HA330 column was initiated, with the duration of 2.5 hours, perfusion volume 30 l, perfusion rate 100-200 ml/min. In the morning after the procedure (16 hours after its completion), IL-6 level decreased to 809 pg/ml, procalcitonin to 0.08 ng/ml, D-dimer to 4471 ng/ml, white blood cells to 12.3x10^9/l. Positive clinical
dynamics was observed, which included an improvement of respiratory function with an increase of P/F ratio to 196 mmHg. After that, a series of laboratory tests showed progressive decrease in levels of inflammatory mediators: IL-6 level was 154.2 pg/ml after 3 days and 29.2 pg/ml after 9 days; ferritin level was 69 μg/l after 6 days. After the last procedure of extracorporeal blood purification, progressive increase in hepatic transaminases levels was observed, to the maximum levels of 610 U/l for ALT and 402 U/l for AST; this was followed by spontaneous decrease to the normal levels during 3 to 4 days. The antimicrobial therapy was corrected due to discovery of polyresistant Acinetobacter baumannii in tracheal aspirate; tigecycline monotherapy was prescribed for 6 days until the respiratory tract sanitation. On the 6th day after the last procedure of EBP (11th day of hospitalization in ICU), the patient was extubated. On the 11th day after the last procedure (18th day of staying in ICU), the patient was discharged for outpatient follow-up.

**DISCUSSION**

EBP methods, in particular cytokine sorption and selective plasma filtration, look promising in the COVID-19 treatment. Nevertheless, currently there is no consensus opinion on the indications for the initiation of such therapy and its timing; all protocols are local and differ significantly from each other. In addition, there are several discussion questions regarding the technique of the cytokine sorption procedure. From our point of view, combination of this method with the selective plasma exchange may have advantages in patients with severe COVID-19, which has been demonstrated by our experience with the patients described above. This approach in ICU patients with COVID-19 has not been described.

- **Which COVID-19 patients have indications for EBP?**
  In the protocols of many clinics, laboratory markers are being used to assess the indications for the initiation of the cytokine sorption in severe COVID-19 patients; they include IL-6, IL-10, IL-8, CRP, ferritin, lactate dehydrogenase, D-dimer [3]. Many experts agree that early initiation of cytokine sorption has advantages in COVID-19 patients. Thus, in our opinion, in the definition of the indications for EBP starting in these patients, complex of laboratory and clinical parameters should be assessed. Among them, most important are the progression of respiratory failure and early signs of multiorgan failure on the background of high or increasing levels of proinflammatory cytokines. Early identification of an organ dysfunction, when the level of inflammatory markers is not yet very high but tends to be increasing, provides rationale to include patients in the EBP protocol and expect higher efficacy in comparison to the delayed strategy, which involves waiting for formal laboratory indications. So, in our opinion, a certain threshold level of an inflammatory marker should not be a basis for defining the indications for EBP in COVID-19 patients, as this may result in a delay of potentially life-saving therapy.

Both clinical situations described above had quite high baseline levels of proinflammatory cytokines, along with the progressive organ/multiorgan failure. In the case of patient 1, significantly increased ferritin level suggested macrophage activation syndrome associated with severe COVID-19; on Day 3 of the observation in ICU, respiratory function impairment and hepatic and renal dysfunction signs were seen. Concomitant bacterial infection precluded administration of IL-antagonists. EBP done at the moment of early multiorgan failure, when NIV was effective, with a significant decrease in proinflammatory cytokine levels, in our opinion, permitted to stop the organ damage and avoid invasive ventilation requirement. In patient 2, effective decrease in cytokine levels was also observed after the procedure and during the follow-up. Timely initiation of EBP after the ineffective conservative treatment, including with IL-6 antagonists, permitted to stop the progressive pulmonary injury and shorted the expected duration of the invasive ventilation.

- **What kind of procedure is optimal in COVID-19?**
  Due to the lack of a sound evidence for COVID-19 patients, our choice of EBP methods was based on theoretical data of the range of molecules to be eliminated. The sorption method is the best studied regarding cytokine elimination, especially in COVID-19 patients. For this procedure, we used HA330 cartridge in all patients; its efficacy has been shown in several works. In our opinion, the use of this method in combination with selective plasma exchange offered additional benefits, as this technique had further advantages, at the same time widening the spectrum of eliminated cytokines (additional elimination of the TNF-alpha trimer). Comparative characteristics are shown in the Table 1.
Table 1. Comparative characteristics of extracorporeal blood purification methods: cytokine sorption and selective plasma exchange

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hemoperfusion</th>
<th>Selective plasma exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of removed molecules</td>
<td>10-60 kDa</td>
<td>&lt;65 kDa</td>
</tr>
<tr>
<td>Solubility of removed molecules</td>
<td>Both</td>
<td>Predominately hydrophilic</td>
</tr>
<tr>
<td>Albumin loss</td>
<td>&lt;5%</td>
<td>30%</td>
</tr>
<tr>
<td>Effect on electrolyte balance</td>
<td>No</td>
<td>Substitution of plasma electrolytes with a polyionic solution</td>
</tr>
<tr>
<td>Endotoxin removal</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ig, coagulation system proteins, IL-antagonists removal</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

From our point of view, SPE should be considered for the following patient groups: patients with a concomitant bacterial infection or/and signs of multiorgan failure, especially renal and hepatic. In patient 1, SPE was chosen as the first procedure followed by the cytokine sorption. In our opinion, in case of a sequential cytokine sorption without the SPE, we could expect an increase in toxic substances to a critical level due to a progressive injury of liver and kidneys. Our protocol allowed us to continue support hepatic and renal function during the same procedure, from the first minutes of EBP, while eliminating cytokines at the same time. The SPE procedure was followed by a significant decrease in the levels of ALT and AST, no significant creatinine level increase, as well as an effective decrease in CRP level, white blood cells count, febrile fever resolution. After the CS, ongoing reduction in inflammatory markers levels and improvement of the clinical picture was observed. Two methods can also be used in the framework of a single procedure where 2 filters work in one contour, sequentially or in CPFA mode which involves plasma separation before the blood is transferred to the sorption column [21, 22]. This option has several advantages including shortening of the total duration of the procedure and, at the same time, an increase in efficacy and longer duration of effective work of both columns. Sequential connection of 2 types of cartridges was used in other patients in our ICU. But the requirement in more aggressive anticoagulation significantly limited the compliance to this method, as local anticoagulation with citrate was unavailable. In addition to the type of the procedure, an important consideration is the quantity of EBP sessions. For the HA330 cartridge, the official manufacturer’s protocol is 2+1+1, i.e. 2 cartridges during the first 24 hours and 1 cartridge during each of the following 2 days. Nevertheless, this protocol is only one of many possible, and it requires further validation [4]. Considering lack of a protocol for combined EBP, we decided to base our strategy on clinical and laboratory response in each individual patient. The number of cytokine sorption and/or SPE sessions in 8 patients varied from 1 to 4, with the median of 2 procedures.

CONCLUSION

Anti-cytokine therapy by means of reasonable and timely EBP is a powerful instrument to prevent adverse outcomes of cytokine storm, by neutralizing the main damaging factors. The pandemic of a new coronavirus infection triggered the development of these methods and the initiation of evidence base formation. Availability, technical feasibility, and good safety profile of these techniques permit to use EBP in the conditions of ICU even during a pandemic, when there is a high workload in these units. We can suggest that after the end of the pandemic, methods of cytokine sorption, selective plasma exchange, as well as combined methods, will become common in routine ICU practice. Larger trials are needed to establish an optimal protocol of extracorporeal blood purification for COVID-19 patients as well as in other clinical settings.
REFERENCES

Patients suffered from COVID-19 would develop the Cytokine Release Syndrome and multiple organ failure. During the COVID-19, lots of Clinical trials were developed. We also developed one investigation with the aims to determine death risks and odds ratio in patients with COVID-19 with cytokine adsorption (HA-330 adsorber) versus conservative therapy, and to evaluate the dynamics of laboratory parameters (PCT, IL-6 and CRP) during the treatment with cytokine adsorption (HA-330 adsorber).

ABSTRACT

Objectives
To determine death risks and odds ratio in patients with COVID-19 with cytokine adsorption (HA-330 adsorber) versus conservative therapy, and to evaluate the dynamics of laboratory parameters (PCT, IL-6 and CRP) during the treatment with cytokine adsorption (HA-330 adsorber).

Methods
The patients are divided into two groups, the hemoadsorption (HA) + CRRT group (N=16) and CRRT group (N=14). There were no significant different between two groups in patients’ characteristics such as PCT and IL-6 level (P > 0.05). The hemoadsorption therapy (HA-330 adsorber) was conducted for three procedures with a 12-hours interval between procedures. For each treatment, the duration was 6 hours, the blood flow was 200 ml/h and the anticoagulant were heparin.

Results
The Death Risk Assessment in group of patients treated with ha-330 hemoadsorption and group with conservative treatment and CRRT revealed that, the absolute risk of HA-330 was lower that comparison group (0.29 vs 0.56), with the odds ratio as 3.2. 2) Comparison Dynamics of Indicators Before and After Cytokine Adsorption in Patients with Covid-19 reveals that, both the PCT and IL-6 level showed significant difference before and after the HA-330 hemoadsorption therapy.

Conclusions
1) Patients treated with cytokine adsorber + CRRT and patients receiving conservative therapy and CRRT had comparable death risk.
2) Therapy with the cytokine adsorber HA-330 showed statistically significant decrease of procalcitonin and interleukin-6 levels in dynamics after the second procedure HA-330 hemoadsorption.
3) Patients are not homogenous in terms of their inflammatory phenotype and have widely varying levels of cytokines in their blood (e.g. IL-6 can range from <6 to >1 million pg/ml) [Ref. Claudio Ronco et al, Blood Purification 05/2020]
Haemoperfusion by HA-330-II in severe acute pancreatitis

**Short title: HA-330-II in severe acute pancreatitis**

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Key words: Haemoperfusion, Acute pancreatitis, Cytokine, HA-330

**Abstract:** Acute pancreatitis occurs when there is inflammation of the pancreas secondary to the autodigestion of pancreatic parenchyma, which is initiated by the abnormal release of activated digestive enzymes. Severe acute pancreatitis is often associated with cytokine dysregulation leading to systemic inflammation and multiple organ dysfunction. The exact pathogenesis of acute pancreatitis is not clearly elucidated but there is growing evidence suggesting that the damage-associated molecular pattern molecules (DAMPs) from cell necrosis are the main culprits that initiate the inflammatory cascades with cytokine release. Extracorporeal removal of inflammatory mediators like DAMPs and cytokines is a novel concept in treating acute pancreatitis and we would like to share our experience by using haemoperfusion (HA-330-II cartridge, Jafron) with concurrent renal replacement therapy on a patient diagnosed with severe acute pancreatitis and multiple organ failure. There is an improvement of SOFA score with blood parameters in parallel with his clinical status after 3 sessions of haemoperfusion.

**Introduction**

Acute pancreatitis occurs when there is inflammation of the pancreas secondary to the autodigestion of pancreatic parenchyma, which is initiated by the abnormal release of activated digestive enzymes. The common etiologies of acute pancreatitis comprise gallstones, alcohol, hypertriglyceridemia, medication and infection. The annual incidence of acute pancreatitis ranges from 13 to 45 per 100 000 people in the United States and the mortality rate is staggering with severe acute pancreatitis(1). Severe acute pancreatitis is often associated with cytokine dysregulation leading to systemic inflammation and multiple organ dysfunction(2). The exact pathogenesis of acute pancreatitis is not clearly elucidated but there is growing evidence suggesting that the damage-associated molecular pattern molecules (DAMPs) from cell necrosis are the main culprits that initiate the inflammatory cascades with cytokine release(3).

Supportive therapy like fluid resuscitation, antimicrobial agents and symptomatic treatment (pain control, oxygen and surgical drainage) are the mainstay of treatment. Extracorporeal removal of inflammatory mediators like DAMPs and cytokines is a novel concept in treating acute pancreatitis and there is a case series displaying the positive outcome of using CytoSorb® Haemoadsorbent(4). Herein we would like to share our experience by using haemoperfusion (HA-330-II cartridge, Jafron) with concurrent renal replacement therapy on a patient diagnosed with severe acute pancreatitis and multiple organ failure.
**Case Presentation**

A 63-year-old man was admitted to the hospital with a history of fever, vomiting and abdominal pain for 10 days which manifested after heavy alcohol drinking. His past medical history is notable for diabetes mellitus and hypertension and he had cholecystectomy 2 years back. Upon arrival in hospital, inotropic support was started as he was hypotensive despite boluses of intravenous fluid resuscitation. He was tachypneic and required non-invasive ventilatory support with high oxygen concentration as the blood gas showed type 1 respiratory failure. Examination demonstrated generalised tenderness in the abdomen with no guarding. Blood investigation revealed elevated serum amylase level, deranged liver profile, acute kidney injury and severe metabolic acidosis (blood parameters are shown in the table below). Contrast computed tomography (CT) of the abdomen confirmed the diagnosis of acute pancreatitis as evidenced by diffuse swelling of the pancreas with peripancreatic fluid while chest radiograph showed right sided pleural effusion. He was monitored closely in the intensive care unit (ICU) and intravenous meropenem was administered empirically to cover for infection. The sequential organ failure assessment (SOFA) score and Ranson’s score was 13 and 8 respectively upon admission into ICU.

We resorted to renal replacement therapy as he became oliguric with refractory metabolic acidosis. Continuous veno-venous haemofiltration (CVVH) with haemoperfusion (HA-330-II cartridge, Jaftron) was commenced. We switched to sustained low efficiency dialysis (SLED) with haemoperfusion on the subsequent treatment as his haemodynamic status improved. After three haemoperfusion therapy, we could taper off his inotropic support and NIV. Antibiotic was stopped after 10 days with good recovery of septic markers. He required intermittent dialysis for 2 weeks during the hospital stay. Unfortunately, he developed clostridium difficile infection on day 19 of admission and was treated with oral vancomycin. The repeated contrast CT abdomen on day 24 showed extensive peripancreatic fluid collection in which the surgical team had managed conservatively. His serum creatinine normalised prior to the discharge and he was scheduled to visit the nephrology clinic for further monitoring.

**Table 1: Laboratory investigation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre RRT+HP</th>
<th>Post RRT+HP</th>
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<tbody>
<tr>
<td>C-Reactive Protein (mg/dl)</td>
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<td>Lactate (mmol/l)</td>
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<tr>
<td>Sequential organ failure assessment (SOFA) score</td>
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<td>8</td>
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</table>

Diagram 1. Set-up of continuous veno-venous haemofiltration with haemoperfusion
Discussion

Mortality rate of acute pancreatitis is parallel with the severity of the presentation and it is as high as 20% in severe cases. Almost half of the mortality occurs during the first 2 weeks of hospitalization due to multiple organ involvement while the late deaths are secondary to the infected pancreatic necrosis or hospital acquired sepsis(5). It's postulated that cytokine storms orchestrate the disorganised inflammation leading to multiple organ failure in the early stage of acute pancreatitis. Literature has stated that the worsening of the organ failure in the first week give rise to a higher mortality rate(6).

Hence, supportive therapy during the early presentation is the cornerstone of management. Todate, there is no specific treatment for acute pancreatitis and haemoperfusion is one of the novel therapies that can be employed as adjunct therapy. HA-330-II haemoperfusion cartridge contains resin absorbing beads that can remove protein bound and middle uremic toxin, inflammatory mediators like cytokines, liver toxin like ammonia and bilirubin(7). Haemoperfusion is reported to be beneficial in improving the septic markers and inotropic supports in the case of severe acute pancreatitis(4). We had noticed a similar outcome from our case whereby patient improved after 3 consecutive sessions of haemoperfusion with concurrent renal replacement therapy (RRT) (1 CVVH and 2 PIRRT). The improvement of septic markers correspond to clinical recovery with rapid tapering of the inotropic and ventilatory support. We also observed a downtrending of the liver enzymes and serum bilirubin level. The SOFA score improves from 13 to 8 after the haemoperfusion which is against the findings from aforementioned case series(4). We believe that the early initiation of haemoperfusion is one of the main contributing factors in our case.

After 2 sessions of haemoperfusion, he developed thrombocytopenia but without any hypotension and bleeding tendency. We managed conservatively and the platelet counts normalise after the termination of haemoperfusion. Thrombocytopenia was one of the reported adverse effects from Huang et al.(8) However, We do not think that there is a direct linkage between pseudomembranous colitis and haemoperfusion as the patient was exposed to antibiotic prior to that. Moreover, we do not find any similar occurrence from the existing literature.

According to Huang et al, 3 days of consecutive treatment is sufficient to sustain the anti-inflammatory effect.(8) Hence we adopted the similar strategy and we had witnessed positive outcomes from the therapy. Nevertheless, the optimal duration of the haemoperfusion is unknown but it is recommended around 2 - 2.5 hours as there is a concern of reduced efficiency due to saturation of the sorbent material. Our HA-330-II cartridge was running for 6 hours each session with the concurrent renal replacement therapy.

Conclusion

Extracorporeal removal of inflammatory mediators like cytokines remains one of the research areas with a knowledge gap. Our case report has illustrated a successful experience of using HA-330-II in a patient with severe acute pancreatitis with multi organs failure (lungs, liver and kidney). Undoubtedly, more larger randomised controlled trials are warranted to assess the efficacy and potential adverse effects of haemoperfusion. Meanwhile, haemoperfusion might be considered as one of the adjunct treatments on top of standard of care in managing acute pancreatitis.
References
IMMUNOMODULATORY EFFECTS OF DOUBLE PLASMA MOLECULAR ABSORPTION SYSTEM IN PATIENT WITH DECOMPENSATED LIVER FAILURE

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Introduction

Recently, Double plasma molecular absorption system (DPMAS) was proved to be equally effective with total plasmapheresis (TPE) in bilirubin reduction and mortality rate. However, the immunomodulatory effects of DPMAS have not been explored. We reported improvement of immunomodulatory effects in a case of decompensated liver disease who received DPMAS therapy.

Case Description

A case of 65-year-old Thai male who presented with progressive jaundice for 3 days. He had underlying disease of HBV cirrhosis, Child–Turcotte–Pugh score (CTP) class B. After admission, he developed hepatic encephalopathy (HE) grade 3 and hepatorenal syndrome requiring renal replacement therapy. His conditions failed to improve with standard treatments consisted of laxative, albumin infusion and antiviral medication. DPMAS therapy was done one session per day for three consecutive days. The circuit consisted of bilirubin adsorbent hemoperfusion cartridge (BS330; Jafron, Zhuhai City, China) and the resin adsorbent hemoperfusion cartridge (HA330-II; Jafron, Zhuhai City, China). We used blood flow rate of 150 ml/min and plasma flow rate of 30 ml/min without anticoagulant (Figure 1). After third session of DPMAS, HE was improved from grade 3 to grade 2. Serum total bilirubin and IL-6 levels were reduced from 34.9 mg/dL to 20.1 mg/dL and 425 to 243.7 pg/mL, respectively (Table 1). We found improvement of monocyte human leukocyte antigen (mHLA-DR) expression from 28.7 percent (prior to first session of therapy) to 50.3 percent (after third session of therapy). CD11b expression was decrease from 16.7 percent to 11.9 percent (Table 2).
We demonstrated that DPMAS was effectively reduce HE grading, total bilirubin, and IL-6 level. We are the first to show an improvement of mHLA-DR and CD11b expressions after DPMAS therapy of decompensated liver disease patient. From this finding, we can imply that DPMAS had an immunomodulatory effect in this patient. However, a randomized controlled trial is required to prove this concept.

### Acknowledgments

We would like to thank the staff, fellows, nurses, and research coordinators from the Excellence Center for Critical Care Nephrology (EC-CCN), Faculty of Medicine, Chulalongkorn University. We also thank Miss Sasipha Tachaboon, MSc medical technologist, for laboratory procedures.

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**Table 1.** Serum laboratory values during DPMAS sessions and day 7 after the first session.

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>Before 1st session</th>
<th>After 1st session</th>
<th>Before 2nd session</th>
<th>After 2nd session</th>
<th>Before 3rd session</th>
<th>After 3rd session</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>34.9</td>
<td>27.9</td>
<td>30.3</td>
<td>21.0</td>
<td>28.5</td>
<td>20.1</td>
<td>41.0</td>
</tr>
<tr>
<td>Direct bilirubin, mg/dL</td>
<td>22.4</td>
<td>19</td>
<td>19.9</td>
<td>12.7</td>
<td>18.3</td>
<td>12.5</td>
<td>27.4</td>
</tr>
<tr>
<td>SGOT, U/L</td>
<td>811</td>
<td>751</td>
<td>449</td>
<td>444</td>
<td>342</td>
<td>342</td>
<td>222</td>
</tr>
<tr>
<td>SGPT, U/L</td>
<td>1150</td>
<td>1050</td>
<td>621</td>
<td>618</td>
<td>483</td>
<td>483</td>
<td>106</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>161</td>
<td>162</td>
<td>124</td>
<td>138</td>
<td>149</td>
<td>129</td>
<td>148</td>
</tr>
<tr>
<td>Ammonia, mcg/dL</td>
<td>148</td>
<td>148</td>
<td>153</td>
<td>130</td>
<td>128</td>
<td>125</td>
<td>115</td>
</tr>
<tr>
<td>PT</td>
<td>29.3</td>
<td>37.2</td>
<td>34.1</td>
<td>32.8</td>
<td>38.6</td>
<td>64</td>
<td>33.3</td>
</tr>
<tr>
<td>INR</td>
<td>2.62</td>
<td>3.35</td>
<td>3.06</td>
<td>2.94</td>
<td>3.5</td>
<td>5.9</td>
<td>2.99</td>
</tr>
<tr>
<td>APTT</td>
<td>29.3</td>
<td>61.5</td>
<td>65.5</td>
<td>59.7</td>
<td>65.9</td>
<td>140.1</td>
<td>69.8</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>11027</td>
<td>11373</td>
<td>7553</td>
<td>7304</td>
<td>5541</td>
<td>5556</td>
<td>-</td>
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<tr>
<td>Interleukin-6, pg/mL</td>
<td>425</td>
<td>523</td>
<td>305</td>
<td>358.8</td>
<td>242.7</td>
<td>243.7</td>
<td>175</td>
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<tr>
<td>hs-CRP</td>
<td>116</td>
<td>92.2</td>
<td>84.6</td>
<td>60.1</td>
<td>78.3</td>
<td>56.3</td>
<td>-</td>
</tr>
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</table>

**Table 2.** Immunomodulatory effect of DPMAS during and after DPMAS sessions

<table>
<thead>
<tr>
<th>CD11b (%)</th>
<th>Before 1st session</th>
<th>Before 2nd session</th>
<th>Before 3rd session</th>
<th>After 3rd session</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.7</td>
<td>18.0</td>
<td>13.4</td>
<td>12.0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CD11b (MF)</th>
<th>10093.1</th>
<th>1572</th>
<th>7270.2</th>
<th>3361.3</th>
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</table>

<table>
<thead>
<tr>
<th>mHLA-DR expression (%)</th>
<th>Before 1st session</th>
<th>After 1st session</th>
<th>Before 2nd session</th>
<th>After 2nd session</th>
<th>Before 3rd session</th>
<th>After 3rd session</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.7</td>
<td>22.2</td>
<td>41.4</td>
<td>50.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mHLA-DR expression (MF)</th>
<th>Before 1st session</th>
<th>After 1st session</th>
<th>Before 2nd session</th>
<th>After 2nd session</th>
<th>Before 3rd session</th>
<th>After 3rd session</th>
</tr>
</thead>
<tbody>
<tr>
<td>3233.9</td>
<td>1507.8</td>
<td>1549.3</td>
<td>3073.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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INTRODUCTION

Cytokine storm had been proposed as one of the main driven mechanisms in severe COVID-19 pneumonia. Such patients had high mortality rate despite receiving standard treatment. The roles of cytokines adsorbent therapy in these patients are still unclear.

OBJECTIVE

To explore the roles of cytokines adsorbant therapy in severe COVID-19 pneumonia.

METHODS

We conducted a retrospective case series of HA-330 cytokine adsorbent therapy in severe COVID-19 patients who received cytokines removal therapy in King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between 13th March and 17th April 2020.
The clinical course and laboratory data were obtained retrospectively. Thirteen different types of cytokines levels were obtained prior to therapy, after therapy, and at day 7 after the first session of therapy.

**Results**

During study period, there were three severe COVID-19 pneumonia patients who received cytokine adsorbant therapy. All patients received one session of HA-330 (Jafron, Zhuhai City, China, Figure 1) hemoadsorbant therapy per day for two consecutive days. Initial PaO2/FiO2 ratio were ranging from 117 to 293 and two patients were intubated prior to the first session of therapy. At day 7 after therapy, all patients had survived, had increased PaO2/FiO2 ratio and were free from mechanical ventilation (Figure 2). Serum IL-6 levels (pg/mL) of three patients decreased from 100.7 to 74.1, 12.6 to 3.41, and 41.8 to 12.2. Serum IL-10, TNF-α, and MCP-1 levels were also decreased in all patients (Table 1).

**Conclusions**

We successfully demonstrated the use of HA-330 cytokine adsorbant therapy in severe COVID-19 pneumonia patients. We showed reduction of both important pro-inflammatory cytokines and anti-inflammatory cytokines. Although all patients showed favorable outcomes, large randomized controlled trials are still required.

**Acknowledgments:** We would like to thank the staff, fellows, nurses, and research coordinators from the Excellence Center for Critical Care Nephrology (EC-CCN) and Emerging Infectious Disease (EID) unit, Faculty of Medicine, Chulalongkorn University. We also thank Miss Sasipha Tachaboon, MSc medical technologist, for laboratory procedures.

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Clinical outcomes of artificial liver support treatments for critically ill patients with liver failure

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Background

• Liver failure is a high mortality condition in intensive care unit (ICU). Artificial liver support (ALS) devices have been developed for bridging to liver recovery or transplantation.
• Some recent studies reported that ALS might be benefit in more severe patients\(^1\)-\(^3\). However, there’s no certain recommendation on when to start ALS treatments\(^4\)-\(^5\).
• ALS treatment in appropriately selected patients may improve survival outcome.

Objective

• To determine the clinical outcomes of critically ill patients with liver failure using ALS treatments compared with standard medical treatment (SMT) in selected criteria.

Method

• A retrospective study was conducted in medical ICU at Siriraj Hospital, Thailand between January 2017 and September 2020.
• Included critically ill patients who diagnosed
  ▪ Acute liver failure (ALF) as EASL 2017\(^4\) and determined with King’s College criteria
  ▪ Acute on chronic liver failure (ACLF) as APASL 2019\(^5\) and MELD score ≥ 30 or AARC score ≥ 8
• Exclusion criteria: poor prognostic coexisting disease, uncontrolled bleeding or infection, uncontrolled hemodynamic instability, HIV infection
• Primary outcome: 28-day survival.

Result

• Total 26 patients including 8 (30.8%) ALF and 18 (69.2%) ACLF
• ALS group received total 29 sessions included
  ▪ 16 Double plasma molecular adsorption system (DPMAS) (55.2%)
  ▪ 4 Plasma exchange (PE) (13.8%)
  ▪ 9 DPMAS with sequential PE (31.0%)
• RRT was initiated for 90.9% in ALS group and 33.3% in SMT group.

<table>
<thead>
<tr>
<th></th>
<th>SMT (n=15)</th>
<th>ALS (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>44.1 ±14.5</td>
<td>47.7 ±14.3</td>
<td>0.54</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (60.0)</td>
<td>5 (45.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>24.5 ±5.9</td>
<td>26.9 ±5.9</td>
<td>0.32</td>
</tr>
<tr>
<td>HBV infection, n (%)</td>
<td>5 (33.3)</td>
<td>5 (45.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>APACHE-II</td>
<td>18.8 ±8.0</td>
<td>19.6 ±5.5</td>
<td>0.76</td>
</tr>
<tr>
<td>SOFA score</td>
<td>11.9 ±3.7</td>
<td>14.8 ±2.6</td>
<td>0.029</td>
</tr>
<tr>
<td>MELD score, median (IQR)</td>
<td>37 (32-40)</td>
<td>40 (33-40)</td>
<td>0.24</td>
</tr>
<tr>
<td>HE grade 4, n (%)</td>
<td>4 (26.7)</td>
<td>4 (36.4)</td>
<td>1.08</td>
</tr>
<tr>
<td>TBIL, mg/dL</td>
<td>22.9 ±12.0</td>
<td>32.7 ±11.4</td>
<td>0.046</td>
</tr>
</tbody>
</table>
• The 28-day survival was 18.2% in ALS and 30.8% in SMT, respectively (95%CI, 0.07-3.45, p=0.649).

• Length of ICU stay was longer in ALS group (10 vs 4 days, p=0.006).
• Reduction rate of TBIL on day 5 was significantly higher in ALS group (26.9% vs 0.3%, p=0.041).
• Among ALS patients, median TBIL was significantly decreased after ALS treatment; Pre-ALS 28.3 vs Post-ALS 24.3 (p=0.014).

• Of all, only 2/11 patients (18.2%) in ALS and 3/15 in SMT (20.0%) could proceed to liver transplantation (p = ns).

Conclusions

This small study showed no improvement in survival in ALS over SMT in moderate to severe liver failure patients. However, ALS significantly decreased TBIL levels. Liver transplantation may still be the mainstay treatment of these patients.

References
Early Cytokine Removal in Critical COVID-19 Patients with Extracorporeal Therapies (HA-380 plus High Volume Hemofiltration) May Prevent Progression of Acute Respiratory Distress Syndrome: Case Report

Gonzalo Ramírez-Guerrero, Vicente Torres Cifuentes, Romyna Baghetti Hernández, Francisco Villagrán Cortés, Simón Rojas Doll, Rocio Oliva Alarcón, Cristian Lucero Córdova, Pablo Flores Fernandez, Osvaldo Garay Coloma

Keywords
COVID-19 · Acute respiratory distress syndrome · Cytokine release syndrome · Hemadsorption.

Abstract
We present the case of a patient who suffered from acute respiratory distress syndrome caused by pneumonia associated with COVID-19 and cytokine release syndrome. This patient received a high-volume hemofiltration plus adsorption, solving the hemodynamic deterioration, pulmonary infiltrates, and gas exchange. Our clinical case proposes that the extracorporeal therapies can have a role in the management of severe COVID-19.

Introduction
The extracorporeal therapies for COVID-19 have the role of removing the proinflammatory molecules for patients that suffer from severe pulmonary involvement and cytokine release syndrome (CRS) [1, 2]. Clinical studies in different scenarios and HVHF plus adsorption have shown that its premature use is associated with a decrease of cytokines, improvement of PaO2/FIO2, better result in severity scores (APACHE II and SOFA), accomplishing the reduction of the sepsis’s incidence, days of mechanical ventilation, and mortality [3–5]. Our group proposes that the premature use of extracorporeal therapies for immunomodulation could have a role, modifying the natural history of severe COVID-19.

Case Presentation
A 59-year-old man presented without comorbidities and 15 days of respiratory symptoms. The chest CT is shown in Figure 1. Upon admission, the data were as follows: PaO2/FIO2 134, C-reactive protein 132 mg/dL, ferritin 1,278 µg/L, LDH 632 UI/L, and absolute lymphocyte count 376 cell/µL. He was admitted in the critical care unit, developing gas exchange deterioration (PaFiO2 69) requiring mechanical ventilation, recruitment maneuver, neuromuscular blockade, and prone position with improvement of PaO2/FIO2 to 124. The patient develops persistent fever, circulatory instability
(noradrenaline 0.14 µg/kg/min), a rise of the inflammatory parameters (C-reactive protein >320 mg/dL, ferritin 2,411 µg/L, and LDH 629 U/L), renal markers (Cr 1.8; [TIMP-2 × IGFBP7] 1.8 (ng/mL)/2/1,000; severe hyperkalemia 6.6) with a negative microbiological study, deterioration of ventilatory mechanics, and PaO2/FiO2 114. CT shows a significant progression. Due to the CRS context, HVHF plus adsorption and corticoids therapy was proposed. A hemoperfusion (HP) of 10 h (HA-380 cartridge, Jafron Biomedical Co.) was performed combined with HVHF in Prismaflex monitor (Baxter) with 250 mL/min blood flow and 70 mL/kg/h effluent dose, with prefiltre replacement and heparin. The HP cartridge was installed postfilter. According to local protocol, after 24 h, an 8 h HVHF was performed, maintaining parameters. There were no adverse events associated with the performed process. Normalization of the temperature and discontinuation of vasoactive drugs during the first hour was accomplished. After that, we can highlight the significant improvement of the ventilatory mechanics and gas exchange in supine position (PaO2/FiO2 192) (Fig. 1), without making any changes in the parameters of the mechanical ventilator. Significant regression of CT images was observed. After the described procedure, it was maintained in the intensive unit, evolving with an infection caused by Enterococcus faecalis, dying weeks later.

<table>
<thead>
<tr>
<th>Report</th>
<th>Ventilation</th>
<th>Mechanics</th>
<th>PaFiO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass that involves all lobes of symmetrical distribution with a discrete apic basal gradient</td>
<td>Spontaneous, supine</td>
<td>RR 27, FiO2 50%, SpO2 92%</td>
<td>134</td>
</tr>
<tr>
<td>Ground glass progression. Foci of consolidation in both lung bases</td>
<td>ACV prone</td>
<td>VT 6 mL/kg PEEP 12 FiO2 65% cest 30 plateau 30 driving pressure 16</td>
<td>117</td>
</tr>
<tr>
<td>Resolution of the consolidation areas in both lung bases, persisting ground glass with lower density</td>
<td>ACV supine</td>
<td>VT 6 mL/kg PEEP 10 FiO2 60 cest 35 plateau 24 driving pressure 12</td>
<td>192</td>
</tr>
</tbody>
</table>

**Fig. 1.** Imaging of evolution of patient. HP, hemoperfusion.
Discussion and Conclusion
The hemadsorption was proposed as a rescue therapy in a COVID-19 patient with severe ARDS in spite of the protective mechanical ventilation according to the modern concepts and in which we demonstrated the regression of pulmonary images associated to the improvement in gas exchange and ventilatory mechanics. Unfortunately, it evolves unfavorably due to complications not associated with the procedure. The CRS and ARDS are phenomena that are related in their pathophysiology, contributing to increase in COVID-19 mortality. Recently a case was reported, in which the intubation’s prevention through extracorporeal therapies was achieved [2]. Our team presented this case in which we could avoid the progression of ADRS with HVHF/HP as adjuvant therapy [6].

Acknowledgements
The authors wish to thank the ICU staff at Carlos Van Buren Hospital. Statement of Ethics Biochemical and clinical parameters were collected under the approval of the scientific Ethics Committee of the health service of Valparaiso – San Antonio. Written informed consent was obtained from the patient’s daughter for publication of this case report and any accompanying images. The consent document was authorized and reviewed by the local Ethics Committee.

Conflict of Interest Statement
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding Sources
There was no funding for the study.

Author Contributions
G.R.G., R.B.H., V.T.C., and F.V.C. designed the work; G.R.G., R.B.H., and F.V.C. collected and analyzed the data; G.R.G., R.B.H., V.T.C., F.V.C., S.R.D., P.F.F., C.L.C., R.O.A., and O.G.C. drafted the work or substantively revised it; and all authors read and approved the final manuscript.

Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

References
Suspected heparin-induced thrombocytopenia in a COVID-19 patient on extracorporeal membrane oxygenation support: a case report

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²Department of Hematology, Cho Ray Hospital, 201B Nguyen Chi Thanh Street, Ward 12, District 5, Ho Chi Minh City, Vietnam

Abstract

**Background:** Extracorporeal membrane oxygenation (ECMO) support can be life-saving in critically ill COVID-19 patients. However, there are many complications associated with this procedure, including Heparin-induced thrombocytopenia (HIT). Despite its rarity in ECMO cases, HIT can lead to devastating consequences and is difficult to manage.

**Case presentation:** In this report, we present a case of a COVID-19 patient on ECMO support who was diagnosed with HIT and required intensive treatment. Initially, HIT was only suspected due to newly-developed thrombocytopenia and oxygenator dysfunction, with thrombi observed later. Regarding his treatment, since there was no recommended replacement to heparin available to us at the time of diagnosis, we decided to use rivaroxaban temporarily. No adverse events were recorded during that period. The patient was able to make a full recovery.

**Conclusion:** HIT may jeopardize patient’s care during ECMO. As COVID-19 may bring about a surge in the number of patients requiring ECMO support, we need consented guidance to optimize treatment in this specific situation.

**Keywords:** HIT, ECMO, Extracorporeal, COVID-19, Thrombocytopenia patients with severe COVID-19 may be more effective than each method when used separately.

**Background**

Coronavirus disease 2019 (COVID-19), the disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is an ongoing medical problem worldwide [1]. Patients may have different severity levels, ranging from mild dyspnea or coughing to multiorgan failure [1]. For those with lifethreatening complications, intensive interventions may be requisite. Extracorporeal membrane oxygenation (ECMO) is a potentially life-saving procedure, in which the patient's blood is circulated through an oxygenator to provide oxygen to vital organs [2]. In ECMO, the tubing system is usually coated with heparin to reduce to risk of thrombosis due to widespread coagulation activation throughout the set [2]. However, this practice gives rise to an increased risk of Heparin-induced thrombocytopenia (HIT), a condition in which platelets are incessantly activated by anti-PF4/Heparin antibodies, leading to catastrophic thrombotic events [2]. In this report, we describe a case of a COVID-19 patient on ECMO with suspected HIT who was particularly difficult to manage due to our lack of resources.
Case report

A 43-year-old Caucasian male patient was admitted to the Hospital for Tropical Diseases in Ho Chi Minh City due to fatigue, mild fever, dry coughing and shortness of breath. He was diagnosed with SARS-CoV2 infection after his positive PCR result and was transferred to the isolation room. He was also given subcutaneous enoxaparin for venous thrombosis prophylaxis as part of COVID-19 treatment. After 4 days of enoxaparin administration, his condition quickly worsened and he required intubation and mechanical ventilation 2 weeks after admission, and veno-venous extracorporeal membrane oxygenation (ECMO) using ROTAFLOW pump (Maquet, Germany) and PLS-I oxygenator (Maquet, Germany), together with continuous renal replacement therapy (CRRT) 1 day later. Enoxaparin was stopped and unfractionated heparin (UFH) was given as a bolus dose of 8000 units, then 1200–1700 units/hour to maintain an activated partial thromboplastin time (aPTT) of 60–80 s. After the start of ECMO, he was routinely monitored by complete blood count (CBC) every 12–24 h, which revealed a drop in his platelet count to 44 × 109/l one day after ECMO start, necessitating platelet transfusion. For the next few days, his platelet count continued to fluctuate. Furthermore, the patient required 2 oxygenator exchanges within 4 days after the start of ECMO due to increased transmembrane pressure. After the second exchange, several tests were performed to clarify his hypercoagulable status, including D-Dimer, antithrombin level, anti-β2-glycoprotein, anti-Cardiolipin, anti-PF4/ Heparin antibodies, plasminogen, plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin quantification assays, as well as routine tests like aPTT, PT and fibrinogen level. All the assays were within normal ranges or negative, except for the anti PF4/Heparin antibody test (HemosIL® HIT-Ab, Instrumentation Laboratory, Bedford, MA,) which showed a high antibody titer of 2.9 U/ml (normal range 0.0–1.0 U/ml), an elevated D-Dimer of 5.594 μg/ml and a prolonged aPTT of 53.1 s. One day later, there was a sudden drop in the flow volume from the outflow cannulae, noises of obstruction coming from the ECMO pump and thrombi were observed in the tubing by attending physicians. Coagulation assays were reassessed, showing a prolonged aPTT (87.7 s,) a normal fibrinogen level (3.65 g/L,) a high D-Dimer value of 6.050 μg/ml and a rising anti-PF4/Heparin antibody titer of 4.0 U/ml. As a result, HIT was suspected and UFH was stopped. However, we did not have access to other intravenous anticoagulants and the non-heparin coated disposables for ECMO at that moment. Therefore, we decided to start rivaroxaban given through the patient’s nasogastric tube at 15 mg twice daily and continued using the current ECMO set. An anti-Xa based assay (HemosIL Liquid anti Xa, Instrumentation Laboratory, Bedford, MA) was also performed 4 times per day to monitor the trough and peak rivaroxaban levels. At the same time, we added an HA280 immunoadsorption column (Jaftron Biomedical Co., Ltd., China) to the CRRT system to filter out the antibodies. Anti PF4- Heparin antibody titer was undetectable 48 h after the start of rivaroxaban and we removed the hemoperfusion cartridge. The patient’s platelet count started to bounce back after 4 days of rivaroxaban use and fully recovered (> 150 × 109/l) after 7 days. However, D-Dimer remained consistently high at 5.067–6.538 μg/ml throughout rivaroxaban administration. Nevertheless, no thrombotic event, including unexpected oxygenator exchange (besides fortnightly replacements recommended by the manufacturer,) was recorded during rivaroxaban use. After 10 days, we managed to get argatroban and switched to such anticoagulant. The patient required ECMO support with argatroban infusion for 42 more days. Throughout this period, his platelet count remained > 150 × 109/l. Meanwhile, his D-Dimer was initially high at 5.0–7.0 μg/ml, with occasional peaks of > 10.0 μg/ml, usually accompanied by sudden increases in his interleukin-6 level, but then dropped to about 2.0–3.0 μg/ml when his overall condition improved. No thrombotic or hemorrhagic events were recorded during argatroban use.
He was able to wean off ECMO and other mechanical supports and made a full recovery, with D-Dimer returning to normal 2 weeks after ECMO weaning. He was discharged on oral rivaroxaban for venous thrombosis prophylaxis, after more than 3 months of hospitalization. Key events in the patient's treatment course and laboratory results are summarized in Fig. 1.

**Discussion and conclusion**

Current reports have highlighted the hypercoagulable state of COVID-19 patients and its implication in the patients' prognosis [1]. Consequently, the International Society on Thrombosis and Hemostasis (ISTH) have issued guidelines that recommend prophylactic Lowmolecular-weight heparin for almost all COVID-19 patients [3]. However, this routine use of heparin may precipitate an increased risk of HIT, a potentially catastrophic thrombotic event, especially in critically ill patients. In patients on ECMO support, the incidence of HIT is reported to be 0.36% [2]. In critically ill COVID-19 patients, only a few cases have been described, with devastating consequences [4].
To evaluate the probability of HIT, physicians normally use a clinical assessment tool, such as the 4Ts Scoring system [2]. Our patient had a 4Ts score of 5 (Platelet count fall > 50% and nadir ≥20 × 109/l; 2 points, consistent fall between 5 and 10 days, but unclear: 1 point, suspected thrombosis: 1 point, possible other causes of thrombocytopenia: 1 point,) suggesting an intermediate probability of HIT [5]. Nevertheless, the 4Ts score may be of little value in COVID-19, since there are many factors affecting its credibility. For example, in COVID-19, thrombocytopenia is a common finding and is linked to a plethora of etiologies [6]. To further complicate matters, thrombocytopenia can also be caused by other ECMO-related etiologies such as platelet activation and aggregation in the ECMO circuit, as well as multi-organ failure while on ECMO support [7]. The first drastic drop in our patient’s clinical course may be related to these issues, besides the presence of HIT antibodies, since his platelet count recovered after transfusion, without any clear sign of thrombus formation [7]. However, we should be aware that thrombosis may prove difficult to detect, partly due to the isolation requirements. Indeed, only 1 in the first 3 reported COVID-19 patients with HIT had typical clinical manifestations [4]. In our patient, a drop in platelet count which only improved after UFH cessation and oxygenator dysfunction were the initial signs of HIT. Actually, several reports have shown that thrombocytopenia and associated oxygenator dysfunction should prompt the suspicion of HIT in patients on ECMO support [8, 9]. To make a definitive diagnosis of HIT, an immunologic assay and a functional assay are required [10]. However, functional assays like the serotoninreleasing assay are time-consuming, difficult to perform and, as we encountered in our case, are not always available [10]. Immunologic tests are generally very sensitive and easy to perform, but not very specific [10]. Our patient had 2 separate positive results for anti-PF4/Heparin antibodies and matching clinical manifestations, thus his HIT diagnosis is highly likely. However, without results from a functional test, other hypercoagulable disorders could not be ruled out definitely. One possible differential diagnosis is sepsis-related disseminated intravascular coagulation (DIC.) Elevated D-Dimer, thrombocytopenia and thrombosis are common findings in DIC. However, D-Dimer are usually high in ECMO patients, [11] and can also be observed in cytokine release syndrome, a common complication of severe SARS-CoV-2 infection [12], while prolonged coagulation times are associated with anticoagulant use. Moreover, PAI-1, plasminogen, α2- antiplasmin, which are usually abnormal in sepsis-related DIC [13, 14], were within normal ranges. Therefore, DIC was unlikely in our patient. While establishing the diagnosis of HIT in this patient was difficult, managing his condition was even more challenging. Firstly, it is recommended that when HIT is suspected, heparinoids should be stopped immediately and switching to another type of anticoagulants is warranted [2]. In ECMO, the preferred alternatives are intravenous anticoagulants such as bivalirudin, danaparoid, argatroban and fondaparinux [2, 15]. Unfortunately, none of the mentioned drugs was available to us at the time of HIT diagnosis. Consequently, we decided to start oral rivaroxaban, a factor Xa direct inhibitor. Although there have been reports regarding the efficacy and safety of rivaroxaban in patients with HIT [2], there is very little data about its use in the ECMO setting. From our experience, rivaroxaban was seemingly effective and safe, as we observed no thrombotic or bleeding events during our obligatory use of such drug. Besides the use of rivaroxaban, we also used an immunoadsorption column normally used in patients with autoimmune disorders to filter out antibodies, [16] in the hope that it can quickly remove the anti-PF4/Heparin antibodies from the patient’s circulation. Immunoabsorption has been used in various autoimmune disorders, usually in acute, lifethreatening cases as it can rapidly remove harmful autoantibodies from the patient’s circulation [17, 18]. In HIT, this practice has not widely been described, except for a single case report, in which immunoadsorption helped remove the antibodies after just 3 days [19], while normally antibodies will only completely disappear about 3 months after heparin cessation [20].
In our case, after 2 days of immunoadsorption, the HIT antibody titer became undetectable. Therefore, immunoadsorption seems to be effective in HIT, especially when rapid removal of antibodies is required. Nevertheless, further studies are necessary to clarify the role of this promising therapy in HIT. Another aspect of HIT management is whether to change the ECMO circuit or not. There are currently commercially available non-heparin coated tubing sets intent to use in HIT cases [9]. Nevertheless, many reports have showed that changing the ECMO circuit has no impact on the patients’ survival, since heparin in the tubing set cannot diffuse into the patients’ blood [15]. In our case, we did not, and admittedly could not, change the ECMO circuit, as there was no available alternative. However, we encountered no complication with continuous use of the heparin-coated tubing set. The patient presented in this report is arguably the most complex COVID-19 case treated in Vietnam up to this date. His treatment was complicated by many affecting factors, most notably HIT. In general, management of HIT in patients on ECMO support is still difficult, as there is a lack of well-designed trials to clarify the importance of various practices in this setting. Our case highlights the need for consented guidelines in this specific situation, especially when COVID-19 is causing more and more patients to require life-saving ECMO support.

**Abbreviations**

aPTT: Activated partial thromboplastin time; CBC: Complete blood count; COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; DIC: Disseminated intravascular coagulation; ECMO: Extracorporeal membrane oxygenation; HIT: Heparin-induced thrombocytopenia; ISTH: International Society on Thrombosis and Hemostasis; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; UFH: Unfractionated heparin

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**Consent for publication**

The patient gave written consent for the publication of this article. Competing interests The authors declare that they have no conflict of interest.

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II. VICENZA COURSE POSTERS
Objective
Evaluate the hemo-adsorption treatment method for patients with septic shock including
- feasibility and safety
- efficacy for disease’s severity improvement
- impact on parameters related with sepsis severity or outcome

Method
6 septic patients all with over 2 organ failure, average SOFA score 14
- Adsorber: HA330 Disposable Hemoperfusion Cartridge (Jafroon Biomedical)
- Treatment: 6 patients under CRRT + 1 session of HA/day (duration of each session 2h),
  for 3 consecutive days (3 sessions per patient)
- Observation: 7 days monitoring period with indicators of SOFAm, oxygenation, needs of
  vasoactive drugs, CRP and CTP changes and 7 and 28 days mortality and ICU mortality
  (compared with an historical control group of 12 similar patients in our ICU).

Results
CRP and PCT values decreased in all patients during and after the 3 sessions
SOFA score decreased due to respiratory and cardiovascular improvement
7 days, 30 days and ICU mortality compared with an historical control group of 12 patients

Conclusion
Hemoadsorption (HA330) for septic patients
- Relatively simple, feasible, compatible with most CRRT devices in our ICU
- No complications and no major events were attributed to the HA sessions
- Improvement of respiratory and cardiovascular performance and of hemodynamic status
- Significant sepsis severity reduction (decrease of SOFA score)
- Hypothesis: can be used as a treatment to decrease or at least delay organ failures and
  therefore to “buy crucial time” within which disease reversibility may be possible with
  appropriate etiological treatment

38th Vicenza Course on AKI&CRRT
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2-6 November 2020
EFFECT OF EXTRACORPOREAL HEMOPERFUSION REMOVAL OF INFLAMMATORY MEDIATORS AND SURVIVAL IN END STAGE LIVER DISEASE PATIENTS WITH SEPTIC SHOCK

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Objective: To study the effects of HA330 resin cartridge in patients with end stage liver disease presenting to critical care unit with septic shock, with regards to hemodynamic stability, lactate levels, levels of inflammatory mediators, requirement of other organ support and the length of ICU stay.

Inclusion criteria: Adult patients presenting within 24 hours of onset septic shock with noradrenaline requirement of more than 10 microgram /min, serum lactate >4mmol/L, APACHE-II SCORE <30.

Exclusion criteria: Age <18 yrs, severe cardiovascular and craniocerebral disease, severe coagulopathy, severe anemia, active bleeding, long term immunosuppressant therapy, noradrenaline requirement > 0.5mcg/kg/min or requirement of multiple vasopressors.

Methods: Three adult cirrhotic patients admitted to ICU with septic shock matching the inclusion criteria were subjected to hemoperfusion using HA 330 resin cartridge for a duration of 2-4 hrs for three consecutive days. HA 330 filter was applied to all three patients using regular dialysis machine. There was no indication for renal replacement therapy in all three patients. Serum levels of IL-6, TNF-α, lactate, dose of vasopressors, APACHE-II score before and after hemoperfusion were measured.

Results: All three patients were weaned off vasopressor dose by day 4 and discharged from ICU by day 5. The IL6, TNF alpha and lactate values decreased following third session of filter. None of the three patients required ventilator support or renal replacement therapy during their ICU stay. Patient 1 had neutropenia and so third filter was not initiated. No other complications were seen as part of hemadsorption cartridge use. All three patients had gram negative bacterial growth in their blood cultures which was treated with appropriate antibiotics.

Conclusion: HA330 filter effectively removed inflammatory mediators in adult cirrhotic patients with septic shock thereby improving the organ dysfunction and hemodynamic stability and decreased the ICU stay.
Cytokine Removal Therapy in Sepsis with neutral-macroporous sorbent– Case Report

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Case presentation:

A 79 years-old male admitted to the ICU from the OR after emergent surgery due to suture dehiscence and diagnosed of fecaloid peritonitis and septic shock with MODS. He was hemodynamically unstable, with unresponsiveness to fluids and received high doses of vasopressors (up to 1.7 µg/kg/min of noradrenaline), peripheral hypoperfusion, increase in lactate (3.5 mmol/L) and low urine output.

Lab tests showed lactic acidosis, low white blood cell (2.59x10^3/µL with neutrophil 62.6%). PaO₂/FI₂ 158 mmHg. The C-reactive protein (CRP) level was 495.13 mg/L (nv<10 mg/L), procalcitonin levels were high (5.25 ng/ml, nv<0.5 ng/ml) IL-6 >5000 pg/mL (nv <40 pg/mL). SOFA score 11 points. SAPS III 88 points (predicted mortality 83%). He received meropenem (continuous perfusion) and linezolid. CVVHDF (Baxter Prismaflex) with RCA and three times Hemoperfusion (Jafron HA380) were conducted. Changes of inflammatory mediators, blood pressure, doses of vasopressor, diuresis were monitored. Favorable clinical progression. No major complications related to HP. On day 4 of admission RRT was stopped, on day 5 he was weaned from mechanical ventilation and on day 8 he was transferred to Surgery ward.

Conclusion:

- Cytokine removal therapy should be considered in unresponsiveness septic shock.
- Potential role of HP (isolated or associated with CRRT) for:
  - Decrease cytokines and inflammatory mediators
  - Stabilize hemodynamic with decrease in requirements for vasopressors
- Safe technique with close and correct monitoring.

Reference:
THERAPEUTICAL APPROACH OF HA330 ABSORBER IN CASE OF SEPSIS IN CHILDREN


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ABSTRACT

Background. Sepsis is one of the most common causes of hospitalizations and deaths in the world and defined as life-threatening organ dysfunction caused by a dysregulated host response to infections. The final event of this dysregulated and intense inflammatory response is a cytokine storm mainly, which leads to multiple organ dysfunctions if it cannot be controlled by the medical management. Material and Methods. New therapeutic resources are under investigation in order to further improve the prognosis of the most severe patients affected with sepsis. One of those therapies is the extracorporeal blood purification therapy with hemoadsorption device HA330 (Jafron Biomedical Co., Ltd, China), which aims to eliminate endo- and exotoxins from the blood during the most severe inflammatory conditions [1]. So far this therapeutical approach was successfully used in a few adult septic patients. Here, we describe and discuss three ALL children who developed severe sepsis and underwent extracorporeal blood purification using HA330 filter. Results and Conclusion. We applied the HA330 hemoadsorption in a three pediatric patients hospitalized in the PICU and diagnosed with septic shock. The treatment was associated with hemodynamic stabilization and a reduction of procalcitonin, IL6, C-reactive protein. In one case due to “second hit” episode another session with HA330 was run. We also noted that early initiation of therapy leads to faster and more sustainable results. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infections. In general, sepsis treatment is mainly based on the broad-spectrum antibiotic administration to fight the ongoing infection, but additional and supportive therapies are usually and variably required according to sepsis severity and clinical background. Unfortunately, patients with severe sepsis may not respond to the usual antimicrobial and supportive therapies. Therefore, new therapeutic resources are under investigations in order to further improve the prognosis of the most severe patients affected with sepsis. One of those therapies is the extracorporeal blood purification therapy with hemoadsorption device HA330 (Jafron Biomedical Co., Ltd, China), which aims to eliminate endo- and exotoxins from the blood during the most severe inflammatory conditions [1]. So far this therapeutical approach was successfully used in a few adult septic patients. Here, we describe and discuss three ALL children who developed severe sepsis and underwent extracorporeal blood purification using HA330 filter.

MATERIAL AND METHODS

Case 1: is a 6 months old girl with confirmed diagnosis of pure red aplasia, presented with fever, general weakness, malaise, anuria, progressive dense maroon-purple spots on anterior abdominal wall, back, inguinal and buttock areas, with areas of necrosis on the left buttock. Due to drastic increase in azotemia (BUN, creatinine) and inflammatory markers (CRP, procalcitonin, IL6) the decision was made to perform continuous veno-venous hemofiltration (CVVHF), Prismaflex, M60, Baxter, USA) with disposible hemofusion cartridge HA 330 (Jafron Biomedical Co., Ltd, China) for 4 hrs. After the 1st session there was drastic improvement in all investigated parameters. Patient’s respiratory system was gradually discontinued. Similarly, inflammatory markers dropped significantly (CRP 517.09 to 138.62 mg/l, PRC 20.28 to 4.27 mg/l, IL6 839.00 to 67.74 pg/ml). Patient also improved her metabolic status (creatinine 92.59 to 32.27 μmol/L; BUN 36.14 to 11.67 mmol/l; diuresis 0.6 to 7.053; pCO2 106 to 45 839.00 to 67.74 pg/ml). Patient also improved her metabolic status and diuresis. Patient’s respiratory system required much less oxygen (FiO2 – 72% to 0.3). Patient’s general condition improved significantly, with notable decrease in azotemia. Patient’s blood pressure didn’t show any result. In order to decrease the inflammatory markers in the blood the decision was made to perform CVVHDF with hemoperfusion cartridge HA330 for 4 hrs. After the procedure, patient’s general condition improved significantly, with notable decrease of inflammatory markers (CRP and Procalcitonin decreasing to 150.03 mg/l and 49.60 ng/L respectively). Patient’s blood pressure stabilized, and vaspressors requirement decreased twice. Patient’s renal function also improved with increased clearance of the BUN and creatinine, and increased diuresis.

DISCUSSION AND CONCLUSION

The technique of using various adsorbers, including the removal of endotoxins and exotoxins is used in different fields of medicine [2]. To the best of our knowledge, this is a first successful implementation of HA-330 adsorber in pediatric patients with sepsis. A four hours procedure of HA-330 adsorption coupled to CVVHDF significantly reduced the markers of inflammation. The reduction rate of leukocytes in average was 71.78%, for CRP – 71.79%, Procalcitonin and IL-6 level – 89.4% and 79.4% respectively. At the same time, using the HA-330 adsorber has proven to be a safe and effective in a pediatric patient. In addition, a recent study has shown that HA series adsorbers carry an optimal level of biocompatibility and their use in HP is not associated with adverse reactions or signs of cytotoxicity [3]. Despite the significant effect in our case, we would like to note some limitations. There are currently no other reports that would support our opinion in using HA-330 in septic children. In addition, our study is limited to three cases only. We also suggesting that in some cases it may be necessary to repeat the session of hemoadsorption. At the same time, we may encounter complications common to extracorporeal methods: catheter bleeding and infection, side effects of heparinization, platelet reduction. However, the advantage of this method is that the short procedure time reduces the above risks.

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References:
HEMOPERFUSION AS AN ADJUVANT THERAPY IN SEVERE COVID-19 IN HEMODIALYSIS PATIENTS: EXPERIENCE FROM FATMAWATI GENERAL HOSPITAL


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ABSTRACT

Background. Mortality rate among maintenance hemodialysis (HD) patients with COVID-19 is alarmingly high. Hemoperfusion (HP) is a blood purification therapy used to remove cytokines and inflammatory mediators to prevent ARDS and organ failure. Hemoperfusion was performed in HD patients whom have not developed to severe ARDS. Methods. We report three cases of COVID-19 in maintenance HD patients. HD and HP were performed in two consecutive days when patient developed early ARDS as indicated by inflammatory markers elevations. HD was performed by using high-flux dialyzer and neutral macroporous resin cartridge HA-330, respectively, for 4 hours. All patients received standard care of i.e. anti-viral agent, unfracticated heparin, empirical antibiotic, acetylcysteine, glucocorticoids, vitamin C, and caillitiz. Result. All three ARDS patients who had HP were subsequently managed without intubation. Case 2 was on high flow nasal cannula while case 1 and 3 were on non-rebreathing oxygen mask. After HP, C-reactive protein (CRP) PaO2/FiO2 ratio and chest X-ray were improved. Case 1 and 2 had less dependency to oxygen supplementation and were discharged from the hospital. Case 3 also had improvement after HP but then developed septic shock due bacterial infection few days afterwards and succumbed to the disease. Conclusion. Improvement in CRP levels, PaO2/FiO2 ratio and chest X-ray were noted in all patients except for the third patient. Based on our clinical experience, timing of HP delivery is crucial and should be performed in early phase of ARDS with early increase of inflammatory marker. This measure may prevent the requirement for intubation in patients with severe COVID-19. Combination use of HP-HD on maintenance HD patients with COVID-19 is promising that merits further investigations.

Keywords: hemodialysis, hemoperfusion, hemadsorption, COVID-19, resist, cytokine storm

INTRODUCTION

Mortality rate among maintenance hemodialysis (HD) patients with COVID-19 is alarmingly high. Hemoperfusion (HP) is a blood purification therapy used to remove cytokines and inflammatory mediators. In our hospital, HP was performed in HD patients with severe COVID-19 when clinical condition worsened. Severity of the disease was assessed by room air SpO2, PaO2/FiO2 ratio and C-reactive protein (CRP). HD and HP were conducted for 4 hours by using high-flux dialyzer and neutral macroporous resin cartridge HA-330 (Jaftron Biomedical Company, China), respectively. All patients received standard care of i.e. anti-viral agent, unfractionated heparin, empirical antibiotic, acetylcysteine, glucocorticoids and vitamin C.

CASES

Case 1. Female, 42 years old came with shortness of breath and fever 1 day before admission. She was on maintenance hemodialysis for 2 years. She came with Modified Sequential Organ Failure Assessment (mSOFA) score of 7 and PaO2/FiO2 ratio 155. Laboratory studies showed leukocytosis 8100/µl, absolute lymphocyte count (ALC) 729/µl, neutrophil-lymphocyte ratio (NLR) 9.3, CRP 30.7 mg/dl, procalcitonin 5.4 ng/ml, LDH 919 u/l, lactate 1.2 mmol/l, Ferritin 9,555 ng/ml, d-dimer 3,040 mg/ml, and positive PCR SARS-CoV-2. She was on HD thrice weekly and her clinical condition was improved. On day 5, 7 and 11 CRP were decreased to 33.2 mg/dl, 28.6 mg/dl and 4 mg/dl, respectively. On day 17, she developed severe shortness of breath with room air SpO2 85%, PaO2/FiO2 114 and CRP elevation (19.8 mg/dl). HD and HP were then initiated on day 18 and 19. After the first HP-HD, CRP decreased to 12.4 mg/dl and PaO2/FiO2 increased to 163. Following the second HP, CRP and PaO2/FiO2 were further improved to 7 mg/dl and 178, respectively (graph 1). The next day CRP decreased to 3.3 mg/dl, room air SpO2 was 95%, and chest X-ray (Figure 1) also improved. Patient was then discharged on day 35.

Case 2. Female, 44 years old presented with cough and shortness of breath 2 days before admission. She was a maintenance hemodialysis patient for 5 years. She came with mSOFA score of 8 and PaO2/FiO2 ratio 150. Laboratory studies demonstrated leukocytosis 1,100/µl, ALC 88/µl, NLR 10.5, CRP 2.1 mg/dl, procalcitonin >32 ng/ml, LDH 447 u/l, lactate 1.0 mmol/l, ferritin 1,614 ng/ml, d-dimer 850 mg/ml and positive PCR SARS-CoV-2. On day 5, she’s shortness of breath progressed, room air SpO2 88%, PaO2/FiO2 ratio 130, CRP elevated to 32 mg/dl. High flow nasal cannula with FiO2 70% was administered. HD were then performed on day 6 and 7. After the first and second HP-HD, CRP, PaO2/FiO2 ratio, and chest X-ray were improved. She was subsequently stepped down to general ward in day 15, and later was discharged on day 20.

Case 3. Male, 67 years old presented with shortness of breath for 12 hours before admission. He had hypertension and was on maintenance hemodialysis for 8 months. Initially, he had mSOFA score of 7, PaO2/FiO2 ratio 206. Laboratory studies showed leukocytosis 1,0300/µl, ALC 1,030/µl, NLR 8.7, CRP 3 mg/dl, procalcitonin 4.11 ng/ml, LDH 520 u/l, lactate 1.4 mmol/l, d-dimer 3,814 ng/ml, and positive PCR SARS-CoV-2. He had regular HD on alternating days. On day 5, his respiratory condition deteriorated with room air SpO2 83%, PaO2/FiO2 141 and elevated CRP 26.9 mg/dl. HD and HP were performed on day 5 and 6. After the first and second HP, CRP PaO2/FiO2 ratio, and chest X-ray were improved. Kibesilbo pneumoniae was found in his blood culture. Despite antibiotic escalation, his clinical condition was worsened on day 15. His clinical condition progressed into septic shock while procalcitonin level remained high. Ultimately, he succumbed to the disease on day 17.

DISCUSSION

Hemoperfusion was reported to be beneficial when conducted with HP machine or combined with CRRT in severe COVID-19.15.16 Due to limitation in number of CRRT machines in our hospital and stable hemodynamic condition of these patients, we initiated HP with HD machine. Timing for HP is critical to yield an optimal outcome. HP elevation and deterioration of clinical condition in case 1 appeared later than case 2 and 3. This finding suggests systemic cytokine release can appear in different timing between patients. Inflammatory marker close observation along with clinical condition is crucial hence facilitating early detection of deterioration that requires prompt treatment. HP was suggested to be performed in 2-1-1 order. Due to limitation of cartridges in our hospital, we modified the protocol by assessing the requirement of HP for individual patient. We found improvement in PaO2/FiO2 ratio, CRP level, and chest X-ray after second HP and we did not continue to third HP.

CONCLUSION

Improvement in CRP levels, PaO2/FiO2 ratio and chest-X ray were observed after two sessions of HP-HD. Based on our clinical experience, timing of HP delivery is crucial and should be performed in early phase of ARDS with early increase of inflammatory marker. This measure may prevent the requirement for intubation in patients with severe COVID-19.

Figure 1. Chest X-ray pre and post hemoperfusion a, c, e, CRP pre-HP; b, d, f CRRT post-HP.

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Clinical Outcomes Of COVID-19 Patients Who Underwent Hemoadsorption Therapy

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Background

COVID-19 is an infectious disease caused by the novel coronavirus SARS-CoV-2. Majority of the patients experience mild to moderate disease. Approximately 14% of the patients experience severe disease and 5% develop respiratory failure or multi-organ failure\(^1\). No therapy has been shown to conclusively reduce mortality in the critically ill patients.

Methods:

• A total of 41 COVID-19 patients were admitted to the ICU and 14 (34.1%) patients received hemoadsorption therapy.

Results:

• Ten (71.4%) of the patients who underwent hemoadsorption therapy were successfully extubated and discharged from the critical care unit.
• Three out of the four patients who succumbed had a delay in initiating the hemoadsorption therapy due to delayed consent.
• One patient who succumbed had progressed well after the hemoadsorption therapy but had a sudden cardiac arrest following an arrhythmia.

Discussions

• Hemoadsorption therapy using HA-330 cartridges is a promising therapeutic option for the treatment of severe disease. It works by removal of all cytokines during the cytokine storm which is postulated to cause severe disease and multi-organ dysfunction.

Conclusions

• Hemoadsorption is a promising modality of treatment for COVID-19 pneumonia with severe acute respiratory distress syndrome.
• HP has to be initiated early to get good clinical outcomes
• More definitive conclusions from RCTs are needed

Bibliography

1. Wu Z et al, JAMA 2020; 323:1239
**Hemoperfusion EXPERIENCE IN SARS-COV-2 PATIENTS**

Jiménez Darío*, Jiménez Fernando, Portilla Andrea, Torres Germán, Barahona Diego, Montalvo Miryam, Trujillo Freddy.

Address: dxjimenezmd@gmail.com Critical Nephrology Department, DIALNEF. Nephrology Department and Critical Care Unit, Hospital de los Valles. Quito, Ecuador.

Objective: Demostrate that Hemoperfusion (HP) is effective to relieve the covid-19 Hyperinflammatory syndrome (cHIS). To assess the role of convective and adsorptive therapies as organ support in COVID-19 patients. Compare the effectiveness of continuous (CHP) vs intermittent (IHP).

Method: Cohort prospective study in 24n COVID-19 critical ill patients. IHP (JAFRON HA 330 cartridge) 2-1-1 scheme was used and CHP scheme consisted of 48h treatment (CYTOSORB cartridge), 24h each one. The outcomes were IL-6, ferritin, LDH, D-Dimmer, lymphocyte seric levels pre and post intervention and finally mortality. T-student test was developed for median difference. Therefore length of ICU stay, ventilation mechanical and vasoactive drugs dependence were analyzed. In AKI patients who start continuous renal replacement therapy (CRRT), the dialytic modality and prescribed dose was continuous venovenous hemodiafiltration (CVVHDF) 35 ml / kg / h with HP on series.

Results: Age mean 65y, MCI 30,21 (SD 4,5) CALL score 9,96 (SD 2,25), SOFA mean 11,7 (SD 1,8), Mellitus Diabetes 25%, Cardiovascular disease 41,7%, Chronic Respiratory Diseases 4%, Neoplasy 4%. Comparing IHP group vs CHP the IL-6 mean decrease 60% vs 29% (p=0,003), Ferritin decrease 33% vs 29%; LDH 32% vs 2%. All patients met criteria for cHIS, The total mortality was 42,8% (IHP 38%) (CHP 50%)

Conclusion: Based on SARS-CoV-2 pathophysiology, a rationale emerges for HP in order to remove inflammatory mediators; The HP efficacy to combat cytokine storm is better evidenced with intermittent HP than continuous HP. The mortality is understandably high in critically ill patients with severe mortality scores. However the results are encouraging and apparently show more efficiency in Intermittent HP technique.
Introduction: We report two cases of middle aged patients with ARDS related Covid-19 that needed EC MO support. Both received standard therapy (sedation, curarization, enteral nutrition and positive mechanical ventilation); antibiotics pr ophylaxis w ith piperacillin/tazobactam and azithromycin were prescribed. If CD4+ count was lower than 500 cell/microliter, sulfamethoxazole/trimethoprim was added.

Case 1: The first case is an obese, 54 years-old man, without comorbidities. After pronation and iNO, he required VV-ECMO (on day 11). We administered 2 doses of convalescent plasma (day 4 and 23) also. However, severe septic shock occurred and we shifted to VAV-ECMO (day 28). In this context, we performed 2 sessions of HP with Jaffron HA330, directly connected to ECMO circuit (Figure I). Immediately after the sessions hemodynamic parameters, lactate levels and procalcitonin improved; all cytokines decreased. After 6 days, we noted an improvement of innate immune response (Table, patient 1). Unfortunately, a second septic shock due to coinfection of Candida Parapsilosis and Acinetobacter Baumanii resulted in MOF and death, 20 days later.

Case 2: The second case describes the case of an obese middle age man (51 years-old) with no comorbidities. In addition to standard therapy, remdesivir had been administered for 14 days. VV-ECMO was started on day 4. Two sessions of HP (Jaffron H A330) were performed (days 4 and day 5), combining ECMO and CRRT device. After HP, procalcitonin, RCP, hemodynamic parameters and lactate improved. We measured an improvement of the CD4+, CD 8+ and NK counts, again (Table, patient 2). In one session, we evaluated the extraction ratio of the cartridge, which decreased over time except for IL-10 (data confirmed by plasma measurements).

Conclusion: In summary, we speculated two indications of HP in Covid-19 patients: to modulate the unbalanced inflammatory response and when the immune paralysis promotes a co-infection.
COMBINED EXTRACORPOREAL BLOOD PURIFICATION IN A PATIENT WITH SEVERE COVID-19 AND SEPTIC SHOCK

Avetisyan EA, Merkulova IA, Pevsner DV, Pokrovskiy SN

Background: The effective lowering of proinflammatory cytokines' concentration by cytokine sorption (CS) and selective plasma exchange (SPE) was demonstrated in sepsis. Taking into account the different mechanism of cytokine hyperproduction in COVID-19 compared to sepsis, EBP may have additional benefits and even improve outcomes. A combination of CS and SPE in patients with severe COVID-19 may be more effective than each method when used separately. Our experience of successful treating severe COVID-19 with cytokine storm, complicated by sepsis and septic shock is demonstrated in this case.

Method/Case Presentation: A 69-year-old lady admitted with COVID-19 and deteriorated on day 3 of hospital stay. Cytokine storm with respiratory and circulatory failure was diagnosed with CRP level of 298 mg/l and COVID-19 pneumonia with 90% lung tissue involvement on CT. She was transferred to an ICU where NIV, infusion therapy and tocilizumab were started. After 2 days she was intubated because of the respiratory failure progression and cerebral dysfunction. Septic shock was diagnosed soon with PCT level of 2.2 ng/ml, hypercytokinemia with IL-6 of 2491 pg/ml, ferritin of 4642 mcg/l and acute renal, liver and circulatory failure. SPE with Evaclio 2C20 was followed by three consecutive CS’s with two Jafron HA330 cartridges attached simultaneously during the first procedure and one cartridge for the each next session. There were circulatory, renal and liver failure resolution, complete weaning from vasopressors after the first CS procedure. She was switched to spontaneous breathing in 2 days after the last CS and decrease of IL-6 level to 161 pg/ml, ferritin of 35 mcg/l. PCT of 0.24 ng/ml was seen. She was rehabilitated and discharged on day 39 of hospital stay.

Conclusion: CS in combination with SPE can be effective in treating patients with severe COVID-19, complicated by bacterial co-infection with sepsis and septic shock.

Objective: to evaluate the dynamics of procalcitonin, IL-6 and CRP during the treatment with cytokine adsorption.

Methods. The investigation included COVID-19 patients with multiple organ failure, subtotal lung injury with ARDS and received CRRT due to acute kidney injury. Patients were categorized into 2 groups according to extracorporeal hemocorrection treatment regimen. The 1st group received conservative therapy, CRRT and 3 hemoadsorption (HA) with cytokine adsorber HA-330. The indication for starting HA was sepsis. The second group received conservative therapy and CRRT. HA regimen with cytokine removal Hemoadsorber – HA-330: duration 6 hours with interval between procedures 12 hours.

Results:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before HA, Median [25 %’s-75 %’s]</th>
<th>HA1, Median [25 %’s-75 %’s]</th>
<th>HA2, Median [25 %’s-75 %’s]</th>
<th>HA3, Median [25 %’s-75 %’s]</th>
<th>P-value (Friedman ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin (normal range 0.0-0.5 ng/ml)</td>
<td>3.6 [1.65-33.3]</td>
<td>4.61 [1.38-11.61]</td>
<td>2.33 [1.15-4.2]</td>
<td>0.493 [0.15-1.44]</td>
<td>0.029</td>
</tr>
<tr>
<td>IL-6 (normal range 0.0-6.4 pg/ml)</td>
<td>417 [166-980]</td>
<td>155.4 [97.74-2816]</td>
<td>63.14 [17.61-127]</td>
<td>73.16 [21.96-224.9]</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Comparison of these indicators by Friedman ANOVA showed statistically significant decrease in procalcitonin and IL-6 levels after the 2d HA. After the 3d HA IL-6 slightly increased again. Then 4 groups were compared with each other by Wilcoxon test, which revealed statistically significant decrease in the levels of procalcitonin (p=0.04) and interleukin after 2 hemoadsorption procedures (p=0.04). Changes in the CRP level in both cases remained statistically insignificant.

Conclusions: Therapy with the cytokine adsorber HA-330 showed statistically significant decrease of procalcitonin and IL-6 levels in dynamics after the second procedure. So, it is necessary to consider the issue of continuous cytokine adsorption for the 1st 24 hours or more, possibly in combination with CRRT, since one of the indications for CRRT is an acute respiratory distress syndrome in adults.
HEMOPERFUSION IN ERC5D PATIENT WITH SEPSIS PICTURE DUE TO ACUTE INTERSTITIAL PNEUMONIA SECONDARY TO SARS COV2 (COVID19) INFECTION

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OBJECTIVE: evaluate the impact of haemoperfusion in SIRS secondary to secondary sepsis SARS COV2

METHOD: A case of a 66-year-old CKD5D woman is reported secondary to diabetic nephropathy presenting with symptoms of acute respiratory failure associated with fever and SIRS with rapid IgM (+) test for COVID 19 and tomographic findings compatible with atypical interstitial pneumonia. SCORE APACHE II and SOFA are calculated, establishing criteria for sepsis and mortality of around 15%. It was decided to undergo conventional hemodialysis therapy with a polyethersulfone (PES) filter plus hemoperfusion with a HA330 Disposable Hepmoperfusion Cartridge filter.

RESULTS: Baseline values: ECG: 10 / 15 pts, APACHE II 18 pts, SOFA 6, PaFiO2: 240 mmHg, procalcitonin 10ng / ml, CRP 3.1mg / L, leukocytes 9290 cells / mm3. The patient received only 2 hemoperfusion sessions applied on consecutive days, each lasting 3 hours, after which the following were observed: ECG: 13/15 pts, APACHE II 16, SOFA 5, PaFiO2: 342 mmHg, procalcitonin 0.3ng / ml, CRP 0.1mg / L, leukocytes 5200 cells / mm3

CONCLUSION: There was clinical and laboratory improvement after the application of the haemoperfusion sessions, which suggests that their use benefits the evolution and prognosis of septic symptoms secondary to atypical respiratory infection.
COMPARISON OF DEATH ODDS RATIO IN PATIENTS WITH COVID-19 IN GROUPS WITH CONSERVATIVE THERAPY AND AFTER CYTOKINE ADSORPTION

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Objective: to determine death risks and odds ratio in patients with COVID-19, multiple organ failure on CRRT and conservative therapy versus treatment by cytokine hemoabsorption (HA).

Methods. The investigation included COVID-19 patients with multiple organ failure, subtotal lung injury with ARDS and received CRRT due to acute kidney injury. Patients with ESRD, oncological and severe somatic pathology in history were excluded from the study. Patients were categorized into 2 groups: group 1 received conservative therapy, CRRT and 3 HA with cytokine adsorber HA-330; group 2 received only conservative therapy and CRRT. There is no statistically significant differences in age, interleukin six and CRP levels in comparing these groups. The indication for starting HA was sepsis. Absolute and relative risks, odds ratio and Fisher exact p (one-tailed, two-tailed) were calculated using 2x2 table.

Results.

<table>
<thead>
<tr>
<th>Investigated groups</th>
<th>Death</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-330 treatment, n=16</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Comparison group, n=14</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

HA-330 vs comparison groups: absolute death risk = 0.29, relative risk = 1.9 and odds ratio = 3.2, Fisher exact p = 0.12 (one-tailed) и 0.16 (two-tailed).
The odds ratio shows that the risk of death is higher in the 2d group compared with the HA group, however obtained data are not statistically significant for this groups.

CONCLUSIONS:
So, patients treated with cytokine adsorber and CRRT and patients receiving conservative therapy and CRRT had comparable death risk. As obtained data are not statistically significant for this groups, because of small number of patients. More observations are needed to clarify effects of HA on death risk and to for it’s prevention it is necessary: 1) to develop acute respiratory distress syndrome risk scale, 2) to determine criteria for the earlier start cytokine hemoabsorption in view of the inflammatory phenotype of the patient, 3) explore HA influence on wider cytokine profile.
USE OF HEMOADSORPTION IN CARDIAC SURGERY. CASE PRESENTATION.

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Background

• The contact of blood with the foreign surface of CPB → SIRS → MODS
• Cytokine adsorbers → ↓ SIRS → ↓ MODS
• Case presentation: redo cardiac surgery - hemoadsorption intra- and postop.

Methods:

• 64-year-old female - dysfunction of mitral and aortic prosthesis + aortic aneurysm pulmonary hypertension
• Intraoperative hemoperfusion with HA330 (Jafron Biomedical LTD) cytokine filter during the CPB + Postoperative hemoadsorption - because of SIRS.

Results:

• Aortic and mitral prosthesis replacement + ascending aortic recalibration
• CPB time: 277 minutes.

<table>
<thead>
<tr>
<th></th>
<th>Preop.</th>
<th>Postop. day 1</th>
<th>Postop. day 2</th>
<th>Postop. day 3</th>
<th>Postop. day 5</th>
<th>Postop. day 7</th>
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</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>36.2</td>
<td>36.5</td>
<td>38.7</td>
<td>36.3</td>
<td>37.9</td>
<td>36.7</td>
</tr>
<tr>
<td>Leucocyte nr. (/μl)</td>
<td>8070</td>
<td>7200</td>
<td>17700</td>
<td>9730</td>
<td>13130</td>
<td>8500</td>
</tr>
<tr>
<td>PCT (ng/L)</td>
<td>0.8</td>
<td>9.8</td>
<td>2.3</td>
<td>6.7</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.8</td>
<td>30.8</td>
<td>10.6</td>
<td>24.7</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>80</td>
<td>70</td>
<td>55</td>
<td>85</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Vasoactive-inotropic score</td>
<td>0</td>
<td>46</td>
<td>57</td>
<td>33.5</td>
<td>43</td>
<td>20.5</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.9</td>
<td>6.4</td>
<td>16.5</td>
<td>5.6</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>APACHE II</td>
<td>8</td>
<td>20</td>
<td>19</td>
<td>9</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>SOFA</td>
<td>1</td>
<td>13</td>
<td>14</td>
<td>11</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>SAPS</td>
<td>20</td>
<td>40</td>
<td>38</td>
<td>27</td>
<td>32</td>
<td>21</td>
</tr>
</tbody>
</table>

• Respiratory dysfunction (paO₂/FiO₂: 140), coagulation disorders (thrombocytopenia)
• Day 9 – transferred to surgical ward
• Day 16 – discharged from hospital

Discussions

• Removal of cytokines → ↓ SIRS → ↓ MODS
• Low CO → SIRS → MODS

Conclusions

• cytokine adsorber ↓ severity of SIRS + improve hemodynamic condition

Bibliography

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Hemoperfusion in Triple Valve Endocarditis Surgery

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Background
Inflammatory response due to the cascade of blood expose to CBP circuit has been extensively discussed [1]. The better outcomes of inflammatory modulation by cytokine scavenger in septic patients has been led to the rationale of using hemoperfusion for same purpose during and after cardiopulmonary bypass procedures [2].

Methods:
- 27 - years old male with sepsis, pancarditis, AR 4+, MR 4+, TR 4+, severe PHT, significant pericardial and pleural effusions, cardiac cirrhosis, MOF, NYHA IV
- CPB time 224 min, Haemoperfusion (HA330) time 220 min.

Results:
- Patient was weaned from CPB successfully
- Patient was extubated 1 POD, mobilisation 1 POD
- Chest tubes removal on the 1st and 2nd POD
- Lab findings (CRP, total bilirubin, AST and ALT) show improvement
- X-Ray and phisical findings on lungs satisfactory, saturation SpO2 99%
- Haemodynamic: systemic tension was 105/76 mmHg (inotrops – low dose) with sinus rhythm and HR 100/min
- Control TEE showed improvement in LVEF without any other pathological findings
- Discharge to Clinic for Infective Diseases on 8th postop day.
- Lab findings before discharge hospital were within the range

Discussions
- Oxygenation improvement and rapid extubating when using HP + CPB
- Hemodynamic stability, better lab findings and low inotrope use when adding HP

Conclusions
- HP + CPB could mediate the inflammation and improve the hemodynamic status

Bibliography

38th Vicenza Course on AKI&CRRT
a week of virtual meetings
2-6 November 2020
Does removal of inflammatory factors during bypass improve outcome in high-risk patient undergoing cardiac surgery?

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Objective: To investigate whether removal of proinflammatory factors during cardiopulmonary bypass (CPB) improves the postoperative outcomes for the high-risk patients undergoing cardiac surgery.

Method: This is a prospective, randomized, controlled study. Patients over 18 years and scheduled for cardiac or vascular surgery under CPB were eligible. The inclusion criteria were EuroSCORE II > 2 and TNF-a over 8.0 pg/mL. Patients who were pregnant, or had long-term glucocorticoid use, or with immune system diseases (such as HIV infection), or without informed consent were excluded. The patients were randomly divided into HA380 group and Control group. In the former group, an adsorber (HA380 haemoperfusion cartridge, Jafron Biomedical Co., China) was used continuously during CPB. The perfusionist was aware of the grouping, while the staffs for follow-up and the statisticians were blinded. The primary outcome were composite events, including all-cause mortality in 30-day, permanent or transient neurological dysfunction, new onset myocardial infarction or low cardiac output, renal failure, acute respiratory disease syndrome, intestinal bleeding or ischemia, and prolonged intubation time (> 24-hours). The secondary outcomes were hospitalization time, blood product consumption and chest drainage. Pre- and Post-operative TNF-a levels and white blood cell counts were also obtained.

Results: A total of 40 patients were included into the study (20 in each group). Their demographic characteristics were comparable between groups. There were no significant difference between control group and HA380 group regarding the preoperative complications, EuroScore II, surgical types, CPB time, and cross-clamp time. The composite events occurred in 4 (20%) patients in HA380 group, and in 7 (35%) patients in control group (p=0.48).

Both hospitalization time and blood product consumption were similar between groups, but the chest drainage after 4 hours were slightly lower in HA380 group (median: 75 mL) than that in control group (median: 150 mL) (p=0.19). Although there were no significant differences regarding to peak plasma levels of creatinine, bilirubin, transaminase, troponin between groups (all p>0.1), TNF-a levels (28 ± 12 pg/mL vs. 30 ± 17 pg/mL, p=0.78), counts of leukocyte (median: 7.5 *10^9/L vs 10.9*10^9/L, p=0.08), neutrophil (5.9 *10^9/L vs 8.3*10^9/L p=0.11) and monocyte (0.36 *10^9/L vs 0.64 *10^9/L, p=0.02) were slightly lower in HA380 group than control group.

Conclusion: This prospective, randomized, controlled study showed that removal of inflammatory factors during cardiopulmonary bypass may help to attenuate the systemic inflammation for the high-risk patients undergoing cardiac surgery on CPB. Whether it improves outcomes for these population needs further studies with larger sample size.
A Case of Acute Renal Injury After Arteriosclerosis Obliterans Operation Treated by Blood Purification

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Objective: To evaluate the efficacy of blood purification therapy in patients with acute kidney injury (AKI) after recanalization of lower limb arteriosclerosis obliterans.

Method: A 55-year-old male presented with intermittent claudication of both lower limbs for 20 years, aggravated for more than 2 months, and was diagnosed with lower limb arteriosclerosis obliterans (ASO). On June 24, the patient underwent "abdominal aortofemoral artery bypass + femoral arterioplasty + lower limb arteriography" under general anesthesia, and was given blood purification treatment due to acute renal impairment caused by ischemia-reperfusion injury after operation. The decision was made to perform a hemoperfusion and hemofiltration treatment, JaFron HA380 of hemoperfutor and Baxter M150 of hemofilter. The changes of myoglobin, creatinine, urine volume, urine color and inflammatory factors before and after treatment were recorded and compared.

Results: On the first postoperative day, Mb > 2000 ug/l; urine output: 30-50ml/h; urine color was normal; Cre: 248 mmol/l. After 6 hours of hemoperfusion (HP) treatment, Mb: 1800 ug/l, urine volume: 50-80 ml/h. On the second postoperative day, Mb > 2000 ug/l; urine output: 30 – 50 ml/h, dark urine with soy sauce color (Figure A), Cre: 340 mmol/l. Blood purification was continued, which was stopped after 6 hours of perfusion, followed by filtration therapy, HP once daily for 6 hours, until myoglobin was less than 2000 ug/l and creatinine was no longer elevated. On July 1, the patient had normal hemogram, decreased inflammatory factors (Figure C), Mb: 1700 ug/l, urine volume > 200 ml/d, normal urine color (Figure B), Cre < 200 mmol/l. Blood purification treatment was stopped.

Conclusion: 1. The damage of ischemia-reperfusion to distant organs should be fully assessed, and staged surgery can be considered for chronic ischemia to reduce the risk of AKI; 2. Postoperative urine volume, urine color, myoglobin and other indicators should be closely monitored, once every 4-6 hours, early intervention should be performed to prevent further progression of the disease; 3. Once the occurrence of AKI is determined, blood purification treatment should be performed as soon as possible to remove harmful substances and prevent irreversible renal impairment; 4. Appropriately increase the frequency of hemoperfusion according to the patient's condition and be long in time.

38th Vicenza Course on AKI&CRRT
a week of virtual meetings
2-6 November 2020
Comparison Of maintenance Hemodialysis And Their Combination With Hemoperfusion In Patients Undergoing Chronic Hemodialysis Treatment

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Email: amutevelic@yahoo.com

Background
The occurrence of uremic complications is related to the low clearance rate of middle and large molecule uremic toxins when haemodialysis (HD) alone is adopted. As the uremic toxins and their corresponding biological effects become increasingly clear, blood purification treatment that aims to remove these toxins, has developed from a stage of life-sustaining to improving the quality of life.

Method:
• A total of 36 haemodialysis patients were randomly divided into three groups.
• Group 1 (n=17): received HD + HP (HA130), (HD 3times/week + HP biweekly).
• Group 2 (n=10): given HD with high flux dialyzer 3 times/week.
• Group 3 (n=9): given HD with low flux dialyzer 3 times/week.
• The study was followed for 4 months.
• Before and after the observational period blood samples were taken for haemoglobin (Hb), iron (Fe), total iron binding capacity (TIBC), albumin (Alb), calcium (Ca), phosphorus (PO4) and parathyroid hormone (PTH).

Results:
• At the end of the four months observation period:
  • Group 1 had significantly higher values of TIBC (p<0.05) and significant lower levels of PO4 (p<0.01), there was no significant differences of EPO doses, PTH and albumin levels between the 3 groups after the follow up period.
  • In the group 1, serum PO4 levels were significantly lower (p<0.05) and TIBC was significantly higher ((p<0.05) after the 4 months of the follow up period than it was at the beginning.
  • In group 2 the values of TIBC were significantly lower after the follow up period than it was at the beginning (p<0.05).

Discussion:
The combination treatment of HD with HP was superior to HD in reducing of phosphorus levels, these findings suggest a potential role of reducing the risk of cardiovascular events. The results also demonstrated significant high levels of TIBC in HP group which demonstrate the role in the improvement of renal disease anaemia, however researches on a larger sample size are needed.

Conclusion:
The combination of HD+HP is a promising therapy in reducing the cardiovascular events and renal disease anaemia in dialysis patients.
EFFECTIVENESS OF DPMAS IN SUPPORTING TREATMENT FOR ACUTE LIVER FAILURE PATIENTS IN VIETNAM

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2Hanoi Medical University
3Poison Control Center, Bach Mai Hospital

Objective: to evaluate the clinical and subclinical results of double plasma molecular absorption system (DPMAS) as a supporting treatment for patients with acute liver failure.

Patients and method: a prospective non-controlled interventional study was carried out on 27 patients diagnosed acute liver failure (ALF) or acute-on-chronic liver failure (ACLF) from June 2019 to August 2020 with 51 DPMAS episodes at Emergency Department, Bach Mai Hospital. Clinical and subclinical parameters were recorded at admission, before and after each DPMAS episode, mortality rate was collected within 30 days.

Results: Among 27 patients, the male accounted for 88.9%, the mean age was 52.3 ± 14.1, the number of patients diagnosed with ALF and ACLF was 44.6%, 55.6%, respectively.

Figure 1: Etiologies of ALF and ACLF

Table 1: Severity at hospital admission

<table>
<thead>
<tr>
<th>Severity score</th>
<th>General Mean±SD</th>
<th>ALF group Mean±SD</th>
<th>ACLF group Mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>26.85±8.14</td>
<td>28.33±7.9</td>
<td>25.67±8.41</td>
<td>0.408</td>
</tr>
<tr>
<td>SOFA</td>
<td>8.19 ± 3.63</td>
<td>8.83 ± 4.41</td>
<td>7.67±2.92</td>
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<td>Glasgow</td>
<td>12.67 ± 2.99</td>
<td>12.83 ± 2.55</td>
<td>12.53 ± 3.39</td>
<td>0.801</td>
</tr>
<tr>
<td>APACHE II</td>
<td>14.00 ± 7.7</td>
<td>13.50±8.34</td>
<td>14.40±7.41</td>
<td>0.769</td>
</tr>
</tbody>
</table>

Table 2: Mortality rate at 30 days

<table>
<thead>
<tr>
<th>Mortality</th>
<th>General N(%)</th>
<th>ALF group N(%)</th>
<th>ACLF group N(%)</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>15(55.6%)</td>
<td>8(66.7%)</td>
<td>7(46.7%)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Conclusion: DPMAS effectively reduced level of total bilirubin, direct bilirubin, AST, and ALT.

38th Vicenza Course on AKI&CRRT
a week of virtual meetings
2-6 November 2020

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RE-EXPLORE THE ROLE OF ARTIFICIAL LIVER SUPPORT SYSTEM (ALSS) DURING COVID-19 PANDEMIC

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Background:
Coronavirus Disease-19 (COVID-19) had been declared as pandemic since 11 March 2020 and there was an exponential increase of cases in Malaysia since mid-March 2020.1 The outbreak had inflicted major disruption in the healthcare service and transplantation had been suspended temporarily due to logistic reasons and scarcity of resources. To date, liver transplantation is the only effective therapeutic option with proven survival benefits in irreversible acute liver failure (ALF). The role of ALSS in ALF is controversial but it provides an alternative to remove the endogenous toxin and inflammatory mediators while waiting for the definitive treatment. We would like to report the application of ALSS as bridging therapy in 2 patients with ALF during the interruption of transplantation service due to the pandemic.

Method/Case Presentation:

Case 1:
A 24-year-old lady was admitted for ALF due to anti-tuberculosis agents which were started for tuberculous lymphadenitis. She was intubated for airway protection as encephalopathy ensued with multiple episodes of seizures. Her MELD score was 37 and we could not facilitate the liver transplantation from the other centre due to the pandemic. Haemoperfusion (Jafron HA330-II) was initiated and showed biochemical improvement but nothing from the clinical aspect (Bilirubin 312 to 240 μmol/l, Interleukin-6 (IL-6) 208.5 to 92.3 pg/ml). Subsequently, single pass albumin dialysis (albumin 2% with dialysate flow rate of 700mL/hour for 6 hours) was attempted but was withdrawn due to severe coagulopathy and she succumbed secondary to hospital acquired infection.

Case 2:
A 26-year-old Indian citizen was admitted for ALF secondary to alcoholic hepatitis with a MELD Score of 40. He was monitored closely while the family was arranging for the medevac service back to India for liver transplantation. The transfer required intricate legal documentation during the pandemic and we had started 3 cycles of haemoperfusion to buy time. We were able to wean off his inotropic support (Intravenous infusion of noradrenaline 0.6 mcg/kg/hour) with stabilization of liver parameters before his transfer (Bilirubin 619 to 461 μmol/l, Ammonia 92 to 57 μmol/l).

Table 1.
Comparison of blood parameter before and after haemoperfusion

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre HP</td>
<td>Post HP</td>
</tr>
<tr>
<td>Ammonia (μmol/l)</td>
<td>73</td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>312</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>208.5</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>99</td>
</tr>
</tbody>
</table>

Conclusion:
ALSS involves extracorporeal blood purification technique and this includes molecular adsorbent recirculating system (MARS), SPAD, plasma exchange and haemoperfusion. It can be considered as one of the therapeutic options as bridging therapy while waiting for liver transplantation especially during this pandemic. Jafron HA330 II is effective in removing serum ammonia, cytokines and bilirubin in Hepatitis B patients from a retrospective study.2 However, our case series are unable to conclude due to the limited number of patients. Nevertheless, patient selection, the appropriate timing for initiation and the frequency of treatment warrants future study.

References:
1) WHO Director-General’s opening remarks at the media briefing on COVID-19 on 11 March 2020.

Diagram 1. High flux haemofilter with Jafron HA 330-II

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HEMOADSORPTION WITH HA 230 ADSORBER IN CASE OF ACUTE DELAYED METHOTREXATE CLEARATION IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA AFTER HIGH-DOSE CHEMOTHERAPY

Vitaliy Sazonov, Askhat Saparov, Zaure Tobilyboeva, Bolatbek Jubanyazov, Samat Issakov, Abu Zhappar Gaidy

University Medical Center, Nur-Sultan, Kazakhstan

ABSTRACT

Background. High dose methotrexate (HDMTX) is very likely to cause a number of side effects and manifest itself as hepatotoxicity, nephrotoxicity, mucositis, and neurotoxicity. A several studies demonstrated the efficacy of extracorporeal detoxification methods such as plasma exchange, hemodialysis, hemofiltration, and hemoperfusion for the treatment of MTX delayed clearance. However, none of the existing methods as effective as expected and limited for general implementation due to procedure related complications. Material and Methods. Here we report a successful implementation of HA-230 hemoadsorption procedure to remove cumulated MTX from the body and reduce its toxicity in a child with acute lymphocytic leukemia (AAL) after high-dose chemotherapy. Based on our results single-hemoadsorption procedure with the HA-230 adsorber in case of delayed methotrexate clearance was safe and well-tolerated in a pediatric patient with ALL and would significantly improve the patient’s condition. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients.

INTRODUCTION

HDMTX has proven an effect and still playing a significant role in the treatment of different type malignances in children, including ALL, non-Hodgkin lymphoma, osteosarcoma and others [1]. However HDMTX is very likely to cause a number of side effects and manifest itself as hepatotoxicity, nephrotoxicity, mucositis, and neurotoxicity. MTX is eliminated by renal excretion involving passive glomerular filtration and active tubular reabsorption and secretion [2]. A number of studies have been published demonstrating the use of extracorporeal detoxification methods for the treatment of MTX delayed clearance: plasma exchange (PE), hemodialysis (HD), hemofiltration (HF), hemoperfusion (HP) using an activated carbon absorption column [3]. However, for various reasons, none of the methods is universally safe and effective.

MATERIAL AND METHODS

An eight-year-old child (weight – 18 kg, S-0.792m²) was admitted to the Department of hematology with the diagnosis of ALL Fab2, 1 – IV type, high risk group, neuroleukemia. Taking into account clinical and laboratory data, HDMTX (in a dose of 5 grams per m²) was started. Later on, according to the protocol, the patient was receiving intravenous hydration, leucovorin rescue. However, conservative treatment had resulted in no positive change in patient condition and the child has developed acute kidney injury in combination with delayed methotrexate clearance, which was reason to transfer patient to the intensive care unit (ICU). Acute kidney injury led to the initiation of pediatric (continuous veno-venous hemodialfiltration) CVVHD with the “Prismaflex” device (Baxter, US). As a part of pilot study with obtained approval from the Clinical Research Ethics Committee of “University Medical Center” (No. 5, June 30, 2020) and signed informed consent by parents. The HA-230 adsorber (Jafron, Zhuhai City, China) was initiated and maintained for the next 4 hours. The HA-230 adsorber was installed after the hemofilter. During the four hours procedure, the blood samples were collected from the extracorporeal circuit at the following time points: after 5 minute of initiation (0h), two hours later (2h) and just before the timing of procedure (4h). Blood sampling was done on three different points of the system. The first point (P1) – before the filter, second point (P2) – between the filter and adsorber, and the last one (P3) – after the adsorbent HA-230. A single procedure of CVVHD combined with HA-230 adsorption resulted in reduction of methotrexate level 54.07 to 79.60 μmol/l (immediately reduction rate is -85.27%) during the four hours (Table 1). The MTX level was 49.04 μmol/l 12 hours after the procedure. Later the patient received leucovorin and hydration (after the acute kidney injury was resolved) and after 24 hours, the MTX level reached 28.32 μmol/l. The patient was transferred from ICU to the hematological unit and 48 hours after the procedure the level of methotrexate reduced to 14.60 μmol/l. The routine blood biochemistry and hematologic parameters improved as well clinical condition.

DISCUSSION

To the best of our knowledge, this is a first successful implementation of HA-230 adsorber to remove blood methotrexate level and to reduce its toxicity due to delayed elimination in a pediatric patient with AAL after high dose chemotherapy. A single four hours procedure of HA-230 adsorption coupled to CVVHD significantly reduced the blood methotrexate level for 85.27%. A few existing methods allowing the eliminating of MTX from the body and reducing the toxic effects have been reported in the literature. Fujikura, E., et al. describe four cases and each of them uses one of the existing methods [3]. Hemodialfiltration allowed achieving a reduction rate of 58.3% ±6.17. And this method is one of the available ones. However, it has a number of known side effects as well as limitations to conduct hemodialfiltration in a low weight pediatric patients. Hemodialfiltration is another option; however, limited removal rate (40.0 ± 5.63%) may also require continuous and repeated procedure. The combination of hemodialfiltration and hemoperfusion is probably one of the most promising and has made it possible to achieve the rate of reduction 57.9 ±10.6% [3]. A combined hemodialfiltration and plasma exchange have also demonstrated the 45.7 ± 14.7% removal rate of MTX level [4]. However, this method requires a large amount of donor plasma transfusion, which undoubtedly increases the risk of infection.

CONCLUSION

Timely detection of an increase in methotrexate levels and initiation of treatment will avoid serious, sometimes irreversible, consequences. Management of methotrexate toxicity using the HA-230 adsorber in case of delayed methotrexate clearance showed 85.27% reduction rate during the single 4 hours procedure and well tolerated in a pediatric patient with ALL. Further studies needs to demonstrate its safety and efficacy in a large number of pediatric patients.

Acknowledgement

The authors express their special gratitude to all those involved in the treatment and care of the patient in this difficult time: parents, doctors, nurses, and clinic staff.

Table 1. Methotrexate levels obtained from different points of combined CVVHD-Hemoadsorption system during the procedure.

<table>
<thead>
<tr>
<th>Time of sampling</th>
<th>Point 1</th>
<th>Point 2</th>
<th>% of reduction between P1 and P2</th>
<th>Point 3</th>
<th>% of reduction between P2 and P3</th>
<th>% of reduction between P1 and P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h</td>
<td>540.70</td>
<td>3.39%</td>
<td>191.62</td>
<td>25.8%</td>
<td>415.22</td>
<td>85.27%</td>
</tr>
<tr>
<td>2h</td>
<td>191.62</td>
<td>3.39%</td>
<td>3.91%</td>
<td>25.8%</td>
<td>142.03</td>
<td>85.27%</td>
</tr>
<tr>
<td>4h</td>
<td>86.52</td>
<td>23.21%</td>
<td>3.12%</td>
<td>25.8%</td>
<td>58.53</td>
<td>88.74%</td>
</tr>
</tbody>
</table>

The reduction rate from point 1 to point 4h is 85.27% ± 9.6%.
BACKGROUND: Digoxin is a non-dialyzable drug that is part of a drug class called cardiac glycosides. These medications work by inhibiting the Na-K-ATPase within the cardiac myocytes thereby causing shifts in the intracellular sodium gradient within the muscle. This increase in sodium gradient increases intracellular calcium ions allowing for increased contractility of the myocytes [1]. Additionally, digoxin affects vagal tone, these actions of digoxin can easily cause arrhythmias in patients especially if digoxin levels are at toxic levels [10]. Having a narrow therapeutic range (0.5-1.0 ng/ml) [11], digoxin can easily result in toxic or sub-therapeutic levels, hence doses must be adjusted to cater to an individual’s renal function [20]. In patients with End Stage Renal Disease, digoxin use is associated with increased risk for toxicity and subsequently mortality [7].

Hemoperfusion refers to the circulation of anticoagulated blood into an extracorporeal circuit utilizing adsorbent cartridges [10]. Having a narrow therapeutic range (0.5-1.0 ng/ml) [11], digoxin can easily result in toxic or sub-therapeutic levels, hence doses must be adjusted to cater to an individual’s renal function [20]. In patients with End Stage Renal Disease, digoxin use is associated with increased risk for toxicity and subsequently mortality [7].

CASE PRESENTATION: A 67-year-old male, diabetic, hypertensive with heart failure on digoxin, and ESRD on renal replacement therapy and hemodialysis 3x/week came in due to 1 episode of vomiting few hours prior to admission. He reported feeling nauseated during the hemodialysis, which led to an episode of vomiting after the session. This prompted laboratories and ECG to be done revealing normal blood chemistry however ECG revealed sinus bradycardia with poor P wave progression on leads V1-V3 and a mobitz type II heart block. Patient was immediately brought to our institution for observation and evaluation.

At the ER, physical exam revealed ronchi on both lower lung fields and Grade II bipedal pitting edema. Patient was admitted at the ICU for close monitoring and observation. ECG done at the ER (Fig. 1) noted findings of atrial fibrillation in controlled ventricular response with occasional ventricular ectopic complexes, suspecting digoxin toxicity hence, a digoxin serum assay was done.

![Fig 2. (ECG post hemoperfusion)](image)

**Fig 2.** (ECG post hemoperfusion: sinus rhythm, First Degree AV block to inferolateral ischemia)

**DISCUSSION:** In the case above, Digoxin Toxicity was confirmed by the elevated serum digoxin assay of 2.7 ng/ml and evidenced by ECG changes and patient’s symptoms (nausea, vomiting, bradycardia).

Treatment for patients with digoxin toxicity involves the use of Digitalis immune Fab, this a digoxin specific antibody and a first line drug that specifically binds to digoxin in the body preventing it from binding to its binding site, and allowing the kidney to expel it [17]. However in this patient’s case we utilized hemodialysis as well as hemoperfusion using the HA-230 cartridge. The HA-230 is a hemoperfusion cartridge specific for its use on poisoning. It utilizes the adsorptive capability of neumonacoroporous resin to remove toxins in the blood. [2,4]

After undergoing hemoperfusion, patient’s condition notably improved documented by the ECG, digitalis assay as well as the patient’s symptoms.

Shi et al. (2012), studied the effects of hemoperfusion using the HA-230 in 85 patients with paraquat poisoning. In their study, they noted that the decline in paraquat concentration was greatest in the 1st hour of treatment than the succeeding hours and that higher level of the initial toxin equated to a better response to the treatment. With this they also recommended that frequent therapies might be more effective compared to a single prolonged session of hemoperfusion. This recommendation was echoed by a study done by Hui Dong Et al. (2017). In their study they utilized the use of standard therapy + hemodialysis + hemoperfusion in the treatment of organophosphate poisoning. Their findings showed that frequent therapy showed better cure rates, less atropine use, shorter time of recovery from coma compared to those that did one prolong hemoperfusion session.

**CONCLUSIONS:** This report highlights that use of HA-230 hemoperfusion cartridge in the treatment of a 67-year-old ESRD patient with digoxin toxicity. Patient underwent 1 session of hemoperfusion with HA-230 cartridge and has shown notable progress as evidenced by improvement of symptoms and normalization of ECG.

**RECOMMENDATIONS:** Further studies of the use of the HA-230 hemoperfusion cartridge is recommended since the utilization of this cartridge is neither widespread nor well documented in the Philippines.

**References:**
REPORT ON CASE SERIES OF ACETAMINOPHEN POISONING AT CHO RAY HOSPITAL: REVIEWING THE ROLE OF HEMOPERFUSION IN THE TREATMENT OF ACUTE POISONING

Author: Dr. Duong Toan Trung (Hemodialysis Department – Cho Ray Hospital)
Instructor: Dr. Nguyen Minh Tuan (Hemodialysis Department – Cho Ray Hospital)
Email: minhtuan2066@yahoo.com.vn

Abstract:
Nowadays, most cases of drug or chemical poisoning are treated primarily by intensive medical care. Intensive supportive measures such as hemodialysis or hemoperfusion may be helpful in patients with severe complications who need removing toxic agents. The factors influencing to the removal of toxins by hemodialysis and hemoperfusion are understood partly clearly. As a practical guide, drugs that can be eliminated with both techniques will be presented and updated periodically according to the development of techniques of producing filtration membrane.

Although nephrologists and emergency and critical care physicians usually deal with dialysis-related decisions in treatment for poisoning case because of their popularity, although, the mortality rate is not high. The role of hemodialysis and hemoperfusion in the treatment for poisoning is frequently discussed in the field of Resuscitation and Poison Control when mention to techniques used to treat poisoning patients such as hemofiltration, continuous dialysis (CAVH, CVVH), plasma plasmapheresis (PP) and blood transfusion. Chelation agents may require a combination of hemodialysis and hemoperfusion (HD and HP), for example, aluminum, iron, thallium, and mercury.

Objection and Method
Case series report

Result and Report Case Study

<table>
<thead>
<tr>
<th>Time from taking drug to admission</th>
<th>Dosage of APAP</th>
<th>Clinical findings</th>
<th>Laboratory features</th>
<th>Serum concentration of APAP (mg/l)</th>
<th>Level of poisoning</th>
<th>Treatment</th>
<th>Result</th>
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<tbody>
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<td>Not clear</td>
<td>-Coma</td>
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<td>Severe</td>
<td>NAC for 72 hours</td>
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<td>2</td>
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<td>3</td>
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<td>31,9</td>
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<td>Survive</td>
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<tr>
<td>8</td>
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Conclusion
- Patients admitted to hospital for serious conditions includes cognitive disorder, respiratory distress, acute liver failure, acute renal injury, metabolic acidosis, coagulation disorder.
- The first two patients diagnosed with severe paracetamol poisoning were treated with oral NAC regimen for 72 hours. These patients got worse.
- Other patients diagnosed with severe paracetamol poisoning were treated with oral NAC regimen for 72 hours. The fourth patient who was intolerable to NAC, was transferred to a 20-hour intravenous NAC regimen. Especially, these cases are treated with hemodialysis and the patient were completely recovered.
- Hemoperfusion has been used for many years about removing toxins from the body. Clinical studies show the effectiveness of this techniques in clinical practice. In the future, there should be more clinical trials with larger sample in multi-center to assess better the applicability of this techniques.
- In addition, there should be specific standards for initiating treatment, recommendations in the process of treatment and other applications of hemoperfusion in clinical practice.

Reference:

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