Role of hemofilter with endotoxin adsorption capacity in management of septic shock

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Abstract

We reported an adolescent male with acute lymphoblastic leukemia who developed septic shock due to Klebsiella pneumoniae. Continuous renal replacement therapy using a hemofilter with endotoxin adsorption capacity was used to remove endotoxin and cytokines. The promising result suggested that this technique may be applied as an adjuvant therapy for treatment of septic shock.

Key word: CRRT, endotoxin adsorption, Gram-negative septicemia, adolescents.

History

An 18-year-old male patient with history of B-cell acute lymphoid leukemia had disease relapse one month after completion of chemotherapy requiring commencement of intensive chemotherapy according to the local relapse protocol (CCCG ALL - 2015 Study: Hong Kong). He developed neutropenic fever after starting the second block chemotherapy. Investigation showed hemoglobin level 8.7 g/dL, total white blood cell count $0.1x10^9$/L and platelet count $20x10^9$/L. He quickly deteriorated and developed septic shock with blood pressure 88/54 mmHg. He was then transferred to pediatric intensive care unit (PICU) for further management. He soon developed coma and required mechanical ventilator support. Dopamine, adrenaline and noradrenaline infusion were added to maintain his blood pressure. There was metabolic acidosis with blood gas showing pH 7.35, pCO2 3.5kPa, bicarbonate 14.0 mmol/L and base excess -9.7 mmol/L. His urea level was 5.2 mmol/L and creatinine level was 70 umol/L. Clotting profile showed disseminated intravascular coagulopathy (DIC) with international normalized ratio 1.71, activated partial thromboplastin time 48.2 s, D-dimer level >5000 ng/ml (normal: <500 ng/ml) and fibrinogen level 4.8 g/L (normal: 1.5-3.6 g/L). Vancomycin and meropenem were started empirically one hour after PICU admission. Acyclovir was added and prophylactic fluconazole was continued. Hydrocortisone was also started for relative cortisol insufficiency (random cortisol level was 367 nmol/L).

Despite all the treatment, his condition remained critical. C-reactive protein (CRP) level rose from 76 mg/L to 352 mg/L (normal: <5 mg/L) and procalcitonin level was 183.65 ng/ml (normal: <0.5 ng/ml). Serial renal function tests revealed a rising trend of serum creatinine to a peak level of 143 umol/L (2.9 times of baseline level with estimated glomerular filtration rate [eGFR] of 44 ml/min/1.73 m2; stage 2 acute kidney injury [AKI] by the KDIGO criteria). Blood culture showed Klebsiella pneumonia and was sensitive to meropenem as well as amikacin, hence amikacin was added.

At 35 hours after PICU admission, daily infusion of intravenous immunoglobulin (IVIG) at a dose of 21 g (~0.4 g/kg) was given for three consecutive days. Also continuous renal replacement therapy (CRRT) using an oXiris^{TM} filter (Gambro product), which is designed for cytokines removal and endotoxin adsorption, through the left femoral vein was started 39 hours after admission (**Figure 1**). The mode of CRRT was continuous veno-venous hemofiltration (CVVH) and the CRRT machine (Prismaflex) was primed with heparinized normal saline. No anticoagulation was given due to DIC.

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The urine output 24 hours prior to initiation of CRRT was 5.2 ml/kg/hour and the corresponding fluid overload percentage was -4.5%. The inotropes given at CRRT initiation included dopamine 20 ug/kg/min, adrenaline 0.12 ug/kg/min and noradrenaline 0.5 ug/kg/min. He received three sessions of CRRT using the oXiris™ filter. Except for mild hypocalcaemia requiring intravenous supplement of calcium, there was no major complication encountered.

Inotropic support could be reduced after initiation of the above treatment. Adrenaline infusion was stopped 1.5 hours after starting CRRT, noradrenaline infusion was reduced to lowest 0.07 ug/kg/min during CRRT and stopped 89 hours after initiating the treatment, and dopamine was reduced to lowest 6.8 ug/kg/min during CRRT and stopped 118hours after commencement of CRRT. The inflammatory markers also markedly decreased. CRP level dropped to 275 mg/L (39 hours after CRRT initiation, two days from first CRP). After the last CRRT session, blood tests showed creatinine 93 umol/L (eGFR of 67.9 ml/min/1.73 m2), CRP 120 mg/L and procalcitonin 25 ng/ml. Fever also subsided. Two days after stopping CRRT he was extubated. However two weeks after PICU admission, he succumbed due to an invasive fungal infection.

Discussion

Sepsis with acute kidney injury is commonly encountered among critically ill patients and CRRT has been increasing employed in this situation. Although earlier study has showed that higher CRRT dose resulted in better patient outcomes, (1) recent trials failed to reproduce such improvement. (2) As sepsis is now recognized as an inflammatory response involving a complex interplay of pro-inflammatory and anti-inflammatory cytokines triggered by endotoxin, (3) the use of CRRT with specially designed filter for endotoxin adsorption and cytokines removal has been increasingly explored.

Endotoxin is a lipopolysaccharide expressed at the outer membrane of Gram-negative bacteria, which activates the release of cytokines when recognized by immune cells. (4) As endotoxin plays an early role in inducing sepsis, removal of these molecules by means of extracorporeal therapy is a potential strategy for sepsis management. (5) Polymyxin B-immobilized cartridge is a hemoperfusion column for endotoxin removal and has been used for treatment of Gram-negative septicemia. (5) A recent meta-analysis has reported that hemoperfusion using polymixin B-immobilized cartridge reduced mortality (risk ratio [RR] 0.57 with 95% confidence interval [CI] 0.45-0.72), though most of the studies were carried out in Japan. (6) There was also survival benefit when hemofiltration was combined with hemoperfusion (RR 0.69 with 95% CI 0.55-0.87). (6)

It is therefore attractive to perform CRRT by a specific membrane coupling endotoxin adsorption as it combines both hemofiltration and endotoxin removal. In-vitro experiment using a septic porcine model has demonstrated a reduction of endotoxin level and improvement of hemodynamic parameters after a six-hour hemofiltration treatment using the membrane with endotoxin adsorption property compared to a standard membrane. (7) This specific filter is an AN69-base three-layered membrane. In addition to its cytokines removal capacity, the polycation on the membrane surface provides enhanced endotoxin adsorption property, which allows catching of endotoxins that are negatively charged. (7,8)

The application of this novel membrane in sepsis management is largely confined to adult patients. Shum et al reported six patients with AKI and septicemia due to Gram-negative bacteria infection treated with CRRT using this novel filter, and the Sequential Organ Failure Assessment score was significantly reduced in the six patients compared to the historical controls. (9)

Our case demonstrated that such filter can be considered as an adjunctive therapy in management of severe sepsis in pediatric patients. Several points of our case merit discussion. Firstly the optimal timing of CRRT initiation in patients with sepsis is still unknown. Early initiation of CRRT in management of AKI with fluid overload may potentially improve outcome as fluid overload contributes to mortality in critically ill patients. Patients with septicemia are commonly associated with AKI and/or fluid overload, and cytokines play an important role in initiation of sepsis, therefore it should be more beneficial, at least in theory, to start CRRT early in the course of septicemia. Whether earlier commencement of CRRT would impact on clinical outcome is important to the physicians at bedside. A retrospective study has found that late initiator of CRRT among patients with AKI had a higher mortality compared to early initiator. (10) However similar study in septicemia is lacking.

There is also no information on optimal number of sessions and dose of CRRT when employing this filter. This will be best addressed by a properly conducted clinical trial. We decided to use this specific hemofilter when the patient was unlikely

to wean down the inotropic support in short period of time despite fluid balance was not an immediate concern at that juncture. We gave three sessions of consecutive treatment for our patient, which was totally based on clinical judgment.

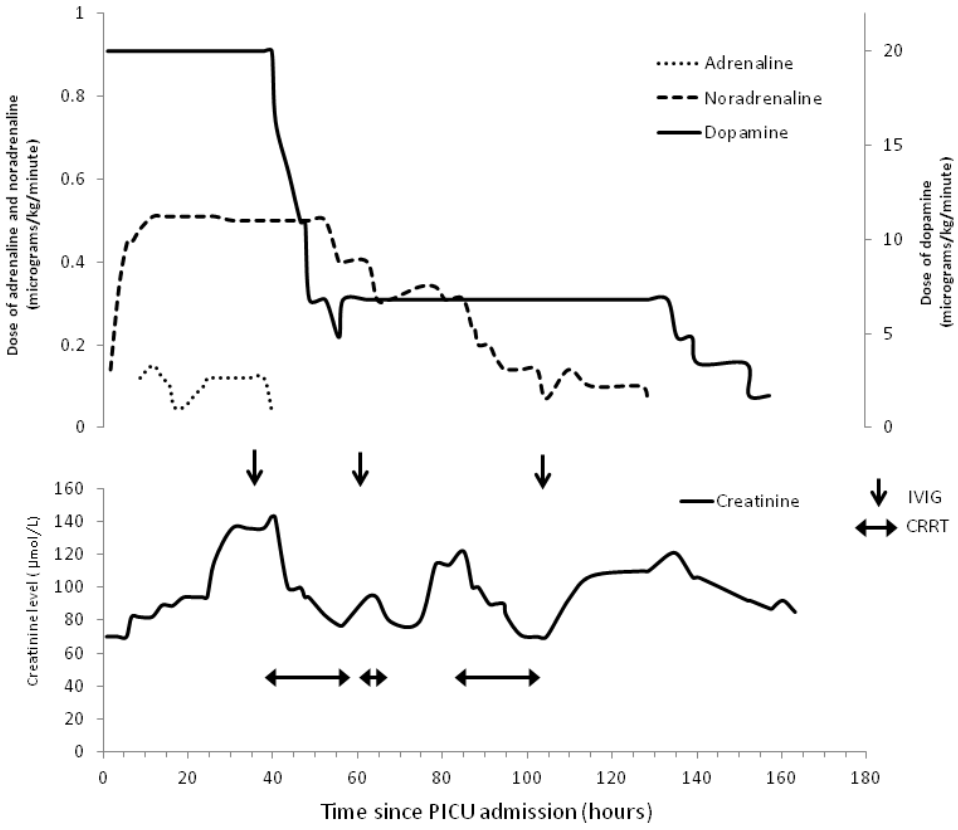
We did not manage to check his blood cytokines or endotoxin level as the tests were not available in our laboratory. However, based on the property of the filter, the marked improvement in clinical parameters and the reduction of levels of inflammatory markers, we believe that the cytokines and endotoxin have been removed and have contributed to his recovery in addition to all other supportive measures.

Another point of note is that the surface area of this filter is 1.5 m2 and this specific filter is suggested to use on patients >30 kg of weight, which certainly limits its application in smaller size pediatric patients. This may probably be one of the reasons for the paucity of clinical report using such technique in pediatric population as there is lack of suitable equipment for children in the market. More study regarding the optimal timing, dosing of such therapy and experience on its application in smaller children are still required to better define its role in management of sepsis.

Conclusion

The concomitant use of hemofilter with endotoxin adsorption capacity and other support measures can successfully and safely be applied in pediatric patients with septic shock.

Figure 1. Change of inotropes dosage and trend of serum creatinine level in relation to continuous renal replacement therapy



Legend: PICU=pediatric intensive care unit; IVIG=intravenous immunoglobulin; CRRT=continuous renal replacement therapy. Three doses of IVIG with CRRT using the specific hemofilter were started 35 hours and 39 hours after admission, respectively. The duration of each session was 18 hours 15 minutes, 5 hours and 20 hours 12 minutes, respectively (using three filters). The blood flow rate was set at 3.1 ml/kg/min (150 ml/min), and the replacement flow was set at 40.7 ml/kg/hour (2189.9 ml/hour/1.73 m2). Replacement solution contained sodium 140 mmol/L, bicarbonate 32 mmol/L and calcium 1.75 mmol/L, and 14.9% potassium chloride solution was added to the solution as required based on the serum potassium level. There was dramatic reduction in the required dose of inotropes. Adrenaline infusion was taken off 1.5 hours after starting first session of therapy. Noradrenaline infusion was reduced from 0.5 ug/kg/min to 0.07 ug/kg/min and dopamine infusion was reduced from 20 ug/kg/min to 6.8 ug/kg/min during CRRT. Two days after stopping CRRT, the patient was successfully extubated and weaned off inotropes.

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