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■ Case Report ■

Polymyxin B Immobilized Fiber Hemoperfusion in Refractory Intra-abdominal Septic Shock

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The effects of direct hemoperfusion with polymyxin B immobilized fiber (PMX) treatment for septic shock have been recently reported. However, little evidence of a true benefit on clinical outcomes, including mortality, is available. Herein, we report three cases of intra-abdominal infection associated with refractory septic shock Case 1 was *Escherichia coli* peritonitis after a colectomy. PMX treatment improved the hemodynamic parameters and lactic acid levels of the patient. In case 2, secondary peritonitis was associated with septic or cardiogenic shock. Septic cardiomyopathy was assumed to be the cause of shock. 24 hours after the use of PMX, cardiac contractility assessed by echocardiography returned to baseline. In case 3, a patient with Burkitt's lymphoma and neutropenia was found to be gastroenteritis and *Klebsiella pneumoniae* bacteremia. Intravenous meropenem was administered for 3 days. Hemodynamic parameters improve after the twice use of PMXOverall, the change of serial sequential organ failure assessment score (SOFA) was more significant in surgical cases as compared to the medical case at 72 hours after PMX administration. All patients were discharged from the hospital. In addition to early resuscitation efforts and infection source control, PMX treatment may be beneficial to patients with refractory intra-abdominal infection associated with septic shock.

Key Words: hemoperfusion, intra-abdominal infection, polymyxin B, septic shock.

Since it was first used in Japan two decades ago, polymyxin B immobilized fiber column hemoperfusion (PMX) has emerged worldwide as a novel endotoxin removal therapy for septic shock that is associated with gram-negative infection.[1] Endotoxin, a component of the outer membrane of gram-negative bacteria, has the key role of triggering immune and inflammatory responses in hosts, and exaggerated responses could cause cardiovascular collapse and multi-organ failure in septic patients. Preliminary studies supported the beneficial effect of PMX treatment on clinical outcomes in a targeted population with severe sepsis or septic shock from intra-abdominal gram-negative infections.[2-4] However, other studies found that there was no direct benefit of PMX treatment in terms of survival.[5,6] We tried to examine the effects of PMX treatment in the cases of three intra-abdominal infection associated with septic shock. We here report the detailed clinical courses of PMX treatment in patients with septic shock and discuss the decision-making process for this novel technique.

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Case Report

Case 1

A 50-year-old woman was referred to our hospital for emergency colorectal surgery. She was diagnosed with sigmoid colon cancer with multiple metastases, including lung and liver,

approximately one year ago, and she had been treated with palliative chemotherapy. She had a history of stent insertion in the colon three months earlier. Her abdominal tenderness was assessed by physical examination, and free air found on an abdominal CT suggested bowel perforation. Her vital sign was stable except tachycardia of 132/min. Her lactic acid level was 3.4 mmol/L, and white blood cell (WBC) count was 1.9 x10^3/ μL. Cefotaxime and metronidazole were given empirically. Two hours after admission to our hospital emergency room, surgery was performed. The operative field was filled with bowel contents, while tumor masses invaded the adjacent bladder, ovary and adnexa. Thus, she underwent total colectomy, radical cystectomy, and oophorectomy. Postoperatively, percutaneous nephrostomy catheters were inserted bilaterally. She was admitted to the intensive care unit (ICU). Piperacillin/tazobactam was given instead of cefotaxime, for broad spectrum antibacterial coverage. Her hemodynamic status progressively deteriorated, even after adequate fluid resuscitation and vasopressor support with norepinephrine. Arterial blood gas analysis revealed severe metabolic acidosis with respiratory compensation. The lactic acid level was over 24 mmol/L, and WBC was over 70 x10^3 /μL. The prothrombin time-international normalized ratio (PT-INR) was markedly increased at 4.51. All of the above findings manifested as septic shock. Finally, her heart rate increased to over 170/min, and the maximum dose of norepinephrine and epinephrine with a continuous infusion of bicarbonate was used to maintain the mean arterial blood pressure over 60 mmHg. Her peripheral skin was cold and had pallor. The noninvasive arterial blood pressure could not be measured properly. Her mental status abruptly changed to non-responsive. Twelve hours after conventional septic shock management, we initiated continuous venovenous hemodiafiltration (CVVHDF). However, the patient continued to need a high dose of vasopressor to maintain the mean arterial blood pressure above 60 mmHg after 4 hours of CVVHDF. Our intensive care unit staff discussed the use of PMX treatment in this case. It would be the first time that PMX treatment would be used in our institution. Previously, we had no experience with this relatively new technique, which demonstrated some evidence of efficacy in lowering the mortality rate in gram-negative infections associated with sepsis. The blood culture results were negative until that time, but this might have resulted f10xin 20-R cartridge (Toraymyxin®, Toray Medical Inc., Tokyo, Japan) was washed with 4 L of normal saline (Fig. 1). Blood was drawn from the proximal port of the double lumen hemodialysis catheter located in a central vein. The blood was combined with Toraymyxin 20-R and returned through the distal port of catheter. The blood was infused at a rate of 100 ml/min. The circuit was anticoagulated with nafamostat mesilate (Futhan®, Torii Pharmaceuticals Co., Tokyo, Japan). We performed the hemoperfusion over 2 hours, as indicated by the manufacturer's guideline. Afterwards, the used circuit was discarded, and additional CVVHDF was continued for more than 40 hours. As shown in Fig. 2, the mean arterial pressure started to increase during PMX treatment, and it continued to increase progressively after the PMX treatment compared with the value prior to treatment. The heart rate gradually decreased to approximately 100/min at 48 hours after the PMX. The dose of vasopressor was significantly reduced during the PMX treatment. At 12 hours after the hemoperfusion, the lactic acid level, the biomarker of tissue perfusion, gradually decreased and returned to a normal value within 48 hours. The WBC count decreased (Fig. 3).

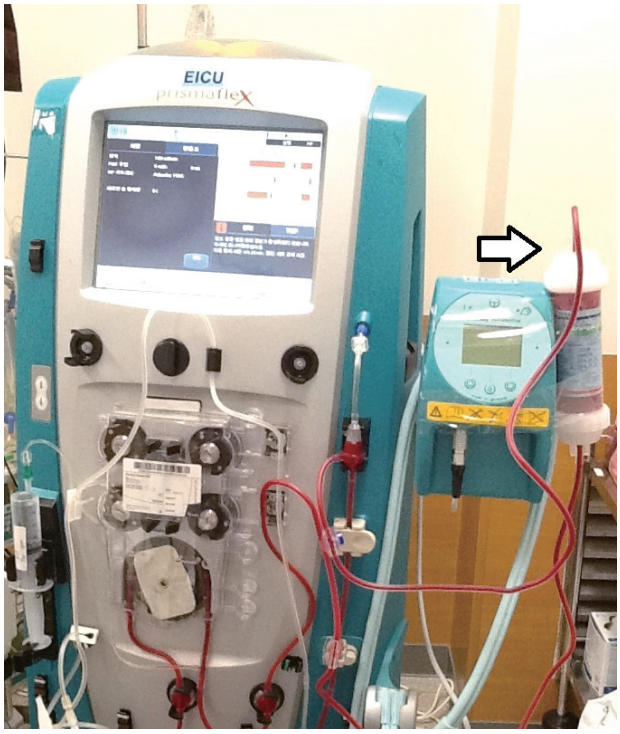

Fig. 1. Continuous renal replacement therapy machine connected to the Toraymyxin® cartridge (arrow) and tubing after flushing.

The serial sequential organ failure (SOFA) scores improved following the PMX (Table 1). Her delta-SOFA (differences between subsequent scores) at 72 hours after the PMX was 5. The prothrombin time (PT) and activated partial prothrombin time (aPTT) values decreased, and the fibrinogen level increased after the PMX treatment. However, the platelet count did not improve (Table 2). She was successfully weaned from mechanical ventilation on the 3rd day of ICU stay. Later, *Escherichia coli* grew in cultures from the operative specimens and the abdominal drainage tubes, consistently, and the strain was susceptible to cefotaxime, ceftazidime, and piperacillin/tazobactam. The piperacillin/tazobactam was maintained for 2 weeks. Subsequent blood cultures remained negative. She was transferred to a general

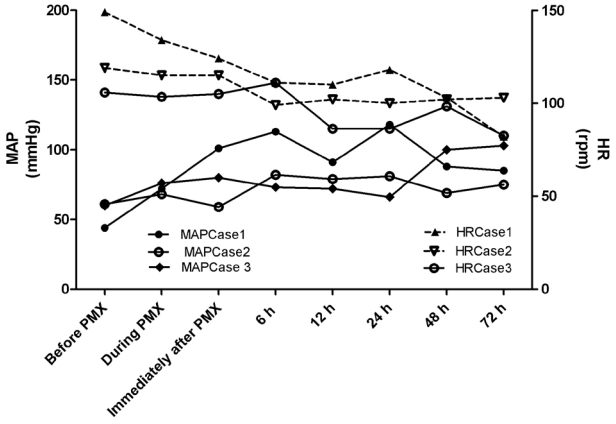

Fig. 2. Graphs show serial changes in the mean arterial blood pressure (MAP) and heart rate (HR) after polymyxin B immobilized fiber hemoperfusion (PMX) treatment.

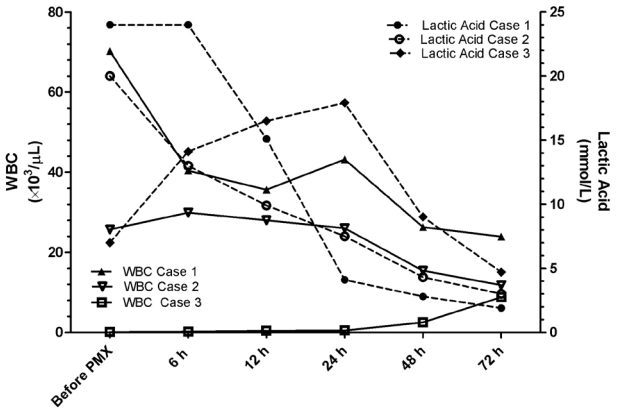

Fig. 3. Graphs show the serial change in lactic acid and white blood cell count after polymyxin B immobilized fiber hemoperfusion (PMX) treatment.

Table 1. Sequential organ failure assessment (SOFA) score of the patients

Variables	Case 1				Case 2				Case 3			
	T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
PaO_2/FiO_2 mmHg	490†	466.7†	406.7†	676.2	84.8†	113.9†	99.6†	315.8†	95.7†	134.8†	196.3†	284†
Respiratory	0	0	0	0	4	3	4	2	4	3	3	2
Platelets × 10^3/ μL	142	55	39	48	47	40	36	35	43	53	48	23
Coagulation	1	2	3	3	3	3	3	3	3	2	3	3
Bilirubin mg/dL	1.7	2.9	3.8	6.1	1.9	4.6	5.5	6.5	1.8	2.8	5.9	12.3
Liver	1	2	2	3	1	2	2	3	1	2	2	4
Vasopressor	Epi>0.2‡	Norepi <0.1‡	0	0	Epi>0.1, Dop>15‡	Dop>5, Norepi<0.1‡	Dop<5‡	0	Epi>0.2 Dopa>20	Norepi>0.2 Dopa>15	Norpei>0.2 Dopa>5	Norepi<0.1 Dopa>5
Cardiovascular	4	3	0	0	4	3	2	0	4	4	4	3
Glasgow coma scale	7	15	15	15	7	13	14	14	14	12	12	14
Central nervous system	3	0	0	0	3	1	0	0	1	2	2	1
Creatinine, mg/dL	2.46	0.75	0.56	0.52	1.06	0.65	0.68	0.6	2.77	1.87	1.70	1.37
Renal	2	0	0	0	0	0	0	0	2	1	1	1
Total SOFA	11	7	5	6	15	12	12	8	15	14	15	14

*Epi indicates epinephrine, Norepi indicates norepinephrine, Dop indicates Dopamine, FiO_2 indicates fraction of inspired oxygen, and PMX indicates polymyxin B immobilized fiber column hemoperfusion.

†Values are with respiratory support.

‡Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

T0: before PMX hemoperfusion, T1: 24 hours after PMX hemoperfusion, T2: 48 hours after PMX hemoperfusion, T3: 72 hours after PMX hemoperfusoin.

Table 2. Coagulation profiles and transfusion history in T patients

	Case 1				Case 2				Case 3			
	T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
PT- INR	4.51	1.96	1.73	1.36	4.36	2.41	2.45	2.04	2.01	3.2	1.96	1.93
PT (sec)	41.5	21.7	19.7	16.4	40.4	25.5	25.8	22.4	22.2	31.8	21.7	21.5
aPTT (sec)	111.2	57.1	57.1	44.4	74.3	52.2	51.1	49.1	61.2	52.2	39.3	38
Fibrinogen (mg/dL)	222	274	ns	ns	129	195	254	246	287	499	344	266

PT-INR: prothrombin time international normalized ratio; PT: prothrombin time; aPTT: activated partial thrombin time.
T0: before PMX hemoperfusion, T1: 24 hours after PMX hemoperfusion, T2: 48 hours after PMX hemoperfusion, T3: 72 hours after PMX hemoperfusoin.

ward after 5 days of stay in the ICU and discharged to home alive.

Case 2

An 80-year-old woman underwent an emergency subtotal colectomy due to colon rupture that occurred during a fluoroscopic guided stent insertion. She was diagnosed with advanced gallbladder cancer with lung metastasis. She had a medical history of three vessel coronary disease and had coronary artery graft surgery 15 years ago and percutaneous coronary intervention in the right circumflex artery 8 years ago. Before operation, vital signs showed blood pressure of 157/91 mmHg, heart rate of 116/min, respiratory rate of 24/min, and body temperature of 37°C. Her lactic acid level was 2.6 mmol/L, and WBC count was 2.8×10^3 / μL. 7 L of crystalloid fluid and 1 unit of packed red blood cell were given while estimated blood loss was 1.5 L in the operating room. She was hypotensive even after use of continuous norepinephrine and multiple bolus doses of phenylephrine. Her urine output was only 45 mL during 4 hour of operation. Postoperatively, she was admitted to the ICU with mechanical ventilation; cardiac arrest subsequently occurred. Restoration of spontaneous circulation (ROSC) occurred after 22 minutes of cardiopulmonary resuscitation with the use of 4 mg of epinephrine. Echocardiography revealed severe global hypokinesia. Immediately after ROSC, the patient was transferred to the coronary intervention unit to evaluate the graft patency in her coronary vessels because acute coronary syndrome was suspected as the cause of cardiac arrest. However, coronary angiography showed no stenosis, and the cause of shock was assumed to be stress induced or septic cardiomyopathy. Intra-aortic balloon pump (IABP) was performed by an interventional cardiologist. The patient was readmitted to the ICU after the procedure. High doses of dopamine and norepinephrine were used to support hemodynamics, despite the use of IABP. Arterial blood gas analysis showed severe hypoxemia. The PaO_2/FiO_2 (fraction of inspired oxygen) ratio was 84.8 mmHg. After 10 hours of IABP use, we started PMX treatment as described above. We performed 2 hours of PMX treatment before CVVDFH. Then, conventional CVVDHF continued for 14 days. The dose of vasopressor was gradually decreased, as shown in Table 1. Portable echocardiography showed improved cardiac contractility 24 hours after the PMX treatment. The IABP was removed at 26 hours after the PMX treatment. The mean arterial pressure was maintained above 80 mmHg when dopamine was administered at less than 5 mcg/min/kg 48 hours after the PMX treatment. The duration of vasopressor therapy was 72 hours after the PMX treatment. The lactic acid level and WBC count also gradually decreased (Fig 3). The PaO_2/FiO_2 ratio gradually increased and was higher than 300 mmHg at 72 hours after the PMX treatment (Table 1). She was successfully weaned from mechanical ventilation after 7 days. Her delta SOFA at 72 hours was 7 (Table 1). Her coagulation profiles gradually improved after the PMX (Table 2). She was treated with piperacillin/tazobactam for 4 days before obtaining results of culture and antibiotic susceptibility test from the laboratories. Her blood cultures drawn on admission were negative. Following initial antibiotic treatments, *Enterococcus faecium* was identified from her abdominal fluid in operative filed, and drainage tubes, consecutively. The strain was resistant to ampicillin, but sensitive to vancomycin. Therefore, the antibiotic prescription was changed to vancomycin, and it was maintained for 2 weeks afterwards. Repeated blood cultures remained negative. She was discharged to a local hospital after 25 days of stay in the ICU.

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Case 3

40-year-old woman who had stage IV burkitt's lymphoma with involvement of liver, kidney, bone, and bone marrow, was admitted for her fourth cycle of chemotherapy. During chemotherapy, she complained abdominal pain, vomiting diarrhea, and generalized myalgia, and clostridium difficile was identified on her stool culture. Her blood exam on 7 days after chemotherapy showed that Hb 8.7g/dL, WBC 0.38 $x10^3$/μL, platelet 39 $x10^3$/ μL, and absolute neutrophil count 238/ μL. It was suspected for acute gastroenteritis associated with neutropenia. Oral metronidazole and intravenous piperacillin-tazobactam was given empirically. On vital sign examination, the blood pressure was 82/32 mmHg, the pulse 142/min, the respiratory rate 26/min, and body temperature 40°C. Aggressive intravenous fluid replacement and vasopressor therapy was initiated. High dose norepinephrine, dopamine, vasopressin, and epinephrine were administered to support her hemodynamics. Intubation and mechanical ventilation were performed. PMX hemoperfusion was performed twice with a 20-hour interval between treatments. Abdominal ultrasound revealed edematous intestinal wall and ascites. In the meantime, gram staining of blood cultures revealed gram negative rods. Intra-abdominal infection might be the cause of gram negative sepsis. Intravenous meropenem was started. Non-extended-spectrum beta-lactamases (ESBL) producing *Klebsiella pneumoniae* was identified in blood culture after three days of administration of meropenem. Antibiotic therapy switched to cefepime and anidualfungin and it were maintained for next 5 days. Following PMX and antibiotic therapy, her hemodynamic and respiratory parameters gradually improved (Table 1). Lactic acid level was gradually decreased (Fig. 3). Coagulation profiles recovered (Table 2).After granulocyte infusions, neutrophil count was recovered. Mechanical ventilation support was maintained for 5 days. Vasopressor was used for 7 days. Conventional CVVDHF continued for 12 days. The patient was clinically resolved from septic shock and discharged to general ward on the 21 days of stay of ICU.

Discussion

Recently, several blood purification techniques including hemoperfusion, plasma exchange, and hemofiltration were reported as beneficial tools for decreasing mortality in patients with sepsis,[7] even though the 2012 sepsis campaign guidelines do not include extracorporeal therapy in the treatment of sepsis and or septic shock. Overall, the previous studies demonstrate that most of the remarkable outcomes result from treatment with polymyxin B hemoperfusion. In the first and second case, the beneficial effects of PMX treatment in refractory intra-abdominal septic shock associated with colon perforation were found. Though the bowel perforation was spontaneous in first case and iatrogenic in second case, in both cases, emergent surgical treatment was performed before the patients demonstrated the clinical features of septic shock. However, conventional supportive therapy seemed to be ineffective in these patients.

In the last case, we could not confirm intra-abdominal infection was the source of gram negative bacteremia because we did not perform microbiologic test from the abdominal source. However, *Klebsiella pneumoniae* was demonstrated in the blood culture, so PMX treatment may be appropriate choice for this patient. We only did abdominal ultrasound exam for evaluation of the infection focus because there were no further growths in the blood cultures after the treatment with meropenem and PMX .

The main mechanism of PMX treatment in septic shock is the direct absorption of endotoxin from the patient's blood. Originally recognized in the 1970s, polymyxin B is a cyclic cationic polypeptide antibiotic derived from Bacillus polymyxa that has the ability to bind and neutralize endotoxins. However, the systemic use of polymyxin B can cause nephrotoxicity and neurotoxicity in humans.[8] To prevent this, Tani and coworkers [1] developed the column containing polymyxin B tightly bound to the polystyrene fiber, named "Toraymyxin™", which was used clinically in the early 1990s in Japan. Since then, much clinical research has been done, mainly in Japan, and several randomized controlled studies have been conducted in Europe since 1998. Meanwhile, a North America study group recently published the procedures of ongoing multi-center trials.[9] To decrease the study sample size in this RCT, the participants were chosen if they had a high endotoxin level, as confirmed by an endotoxin activity assay at the bedside.

The role of endotoxin or lipopolysaccharide (LPS) is well described in the abundant medical literature. The gram-negative bacterial wall is composed of LPS. Increased amounts

of circulating LPS from bacteria trigger an inflammatory reaction, cascades of complement, and the coagulation system in hosts. Consequently, there is an increase in pro-inflammatory cytokines such as TNF-α, Interleukin 6, and Interleukin 8 in the blood. In addition to endotoxin, the plasma levels of a number of other mediators in septic patients decreased after the PMX treatment. These included procalcitonin, IL-6, IL-10, IL-18, TNF-a, metalloproteinase-9, plasminogen activator inhibitor-1, neutrophil elastase, platelet factor-4, β- thromboglobulin, soluble P selectin, endogenous cannabanoids such as anandamide, von villibrand factor, and thrombomodulin.[3,10] Therefore, we speculate that PMX treatment could reduce endotoxin and related inflammatory mediators and, as a result, could prevent an exaggerated inflammatory reaction and prevent adverse outcomes.

We found hemodynamic improvements in our cases, which were consistent findings reported in a number of studies using PMX.[2,3,5,11] The mechanism of the increase of blood pressure by PMX treatment was not clearly elucidated, but several mediators related to sepsis were suggested. High mobility group box-1 protein (HBGB 1) could be one of the candidates.[12] Moreover, we found improved cardiac contractility and ejection fraction measured by echocardiography at 24 hours after the PMX in case 2. Vincent et al found that left ventricular cardiac index, left ventricular stroke work index, and oxygen delivery was increased after the PMX treatment in same population as our cases.[5]

We also found significantly reduced lactic acid levels, which indicates adequacy of response to resuscitation and increase of end organ perfusion. We also found reduced levels of WBCs and some improved coagulation profiles. Ishizuka et al.[13] reported that only a PT-INR cut off value of 2.05 was associated with the survival of patients with septic shock who had received PMX treatment. It was suggested that preventing DIC progression might be an important clinical pathway affecting the prognosis and survival of severe sepsis and/or septic shock. However, low platelet counts associated with septic shock in our case, did not improve effectively even after platelet transfusion. The fibrinogen level was increased, but not to the baseline level in the patients.

Finally, we found an increase in the delta SOFA score, which is the change in the degree of organ dysfunction between baseline and 72 hours, indicating improvement in overall organ dysfunction in two patients undergoing colectomy. Respiratory, cardiovascular, neurologic and renal SOFA scores improved. A change in the cardiovascular component was the most prominent, as mentioned above. Additionally, we found improvement in the respiratory component in the patients at 72 hours after PMX. Improving oxygenation was reported in several investigations in animal and human studies in lung injury.[10,14]

Cruz et al.[2] revealed that the 28-day mortality was 32% (11/34 patients) in intra-abdominal septic patients receiving PMX compared with 53% (16/30 patients) in patients receiving conventional therapy alone. However, those authors did not measure the endotoxin level.

In similar populations, Shimizu et al.[15] found that the plasma endotoxin level was higher when the outcome was fatal compared with those levels in survivors and that it was markedly reduced after PMX therapy, even with a long duration use.

According to recent meta-analysis of 28 trials of PMX use for severe sepsis and septic shock, the mortality rates of patients were 61.5% in the conventional medical therapy group and 33.5% in the PMX treatment group.[16] However, the overall quality of the study was suboptimal, and none of the studies were double blind. Contrary to these results, in a recent retrospective matched cohort study of 60 patients with gram-negative septic shock who were treated with PMX or vasopressin, it was found that vasopressin was superior to PMX in terms of 90-day mortality.[17] Using a Japanese nationwide database, another retrospective propensity-matched cohort of 1,180 patients undergoing open abdominal surgery due to perforation of the lower intestinal tract who were administered vasopressor found that PMX hemoperfusion did not show any survival benefit for the overall study population.[6] Thus, the results of a large, randomized controlled trial that is being conducted in North America are important.[9]

Considering the high cost of the cartridge, the candidate must be adequate for the therapy. The shock must be refractory to conventional medical treatment, but the time to initiation must be early, i.e., within 24 hours of septic shock. In these cases, the actual PMX treatment was initiated at 12-16 hours from the start of resuscitation for septic shock. A previous study suggests that the early timing of PMX is associated with a short duration of ventilator and vasopressor requirement.[11] Therefore, the main cause of favorable

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outcomes could be the early use of PMX. The cause of shock must be infection related. As in the event of cardiac arrest in second case, acute coronary syndrome should be excluded as the cause of shock. The subsequent negative coronary angiography findings, together with the reversible change of myocardial function after PMX hemoperfusion, suggested myocardial dysfunction associated with severe sepsis, or septic cardiomyopathy. Frequently observed echocardiographic findings of septic cardiomyopathy include biventricular dilatation and a reduced ejection fraction.[18]

In conclusion, we tried to examine effects of PMX hemoperfusion in three cases of refractory intra-abdominal septic shock. Although the efficacy of PMX treatment is limited without removal of the infection focus and appropriate antibiotic therapy, PMX treatment may be a valuable treatment option for refractory septic shock, including septic cardiomyopathy, to improve hemodynamics and oxygenation during the life-threatening period in critically ill patients.

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