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Early Induction of PMX-DHP Improves Oxygenation in Severe Sepsis Patients with Acute Lung Injury

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ABSTRACT

Direct hemoperfusion with polymyxin B-immobilized fibers (PMX-DHP) has been widely regarded as a treatment modality for septic shock in Japan. Recently, it was reported that PMX significantly improved the P/F (PaO_2/FiO_2) ratio in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The aim of this study was to examine whether the phase of sepsis is related to the effects of PMX-DHP treatment on oxygenation in patients with ALI and ARDS. Thirty-four patients who had ALI or ARDS with severe sepsis were included in this study, and split into two groups: a high-risk for septic shock (H-R) group and a septic shock (S-S) group, based on the cut-off value at a mean arterial pressure of 60 mmHg. We analyzed the modified APACHE-II score, the sepsis-related organ failure assessment (SOFA) score, mean blood pressure (mBP), catecholamine index (CAI), P/F ratio, and 28 days mortality before and after PMX-DHP treatment. SOFA and modified APACHE-II scores showed no significant difference between the two groups. In both groups, mBP and CAI increased significantly following PMX-DHP. In the H-R group, P/F ratio increased from 194 ± 83 to 262 ± 113 after PMX-DHP treatment, with a statistical significance, whereas no difference was found in the S-S group. There was no difference in the 28 days survival rate between the groups. It was suggested that early introduction of PMX-DHP for severe sepsis may improve oxygenation.

Key words: *Polymyxin B-immobilized fiber, Acute lung injury (ALI), Acute respiratory distress syndrome (ARDS), Sepsis*

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) with infection. To this day, the prognosis of severe sepsis with multiple organ failure is dismal. In 2004, the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock were reported. These guidelines recommended the resuscitation of patients with severe sepsis and septic shock during the first 6 hours by what is called the early goal-directed therapy (EGDT)[2]. EGDT is the concept of stabilization of the circulatory status using fluid resuscitation, inotropic agents, and blood transfusion. On the other hand, in Japan, direct hemoperfusion (DHP) using a polymyxin B-immobilized fiber column (PMX; Toray Industries Inc., Tokyo, Japan) (PMX-DHP) has been widely used as a treatment modality for septic shock[14, 15].

PMX was released to remove endotoxin from blood in septic shock caused by Gram-negative bacteria in 1994[1]. A subsequent study showed that PMX-DHP inhibited not only lipopolysaccharide production by Gram-negative bacteria, but also lipoteichoic acid production by Gram-positive bacteria, as demonstrated in an experimental study[3, 4]. From the very beginning, PMX-DHP has been reported to be effective for patients with septic shock[1]. We reported that PMX-DHP in the early phase improved one of the SIRS items, the respiratory rate[12]. In addition, there have been a wide variety of reports on the effects of PMX-DHP. Recently, it was shown that introduction of PMX-DHP in the early phase was more effective for severe sepsis[7]. On the other hand, it was reported that PMX significantly improved the P/

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F (PaO_2 / FiO_2) ratio in patients with ALI (acute lung injury) or ARDS (acute respiratory distress syndrome)[7,9,13,16].

The aim of this study was to examine whether the phase of sepsis is related to the effect of PMX-DHP on oxygenation in patients with ALI and ARDS.

PATIENTS AND METHODS

This was a retrospective observational study. Informed consent was obtained from each patient or their family. Patients admitted to our center between April 2002 and March 2006 were included. The diagnostic criteria for ALI and ARDS were: acute onset of lung injury, diffuse bilateral infiltrates on chest X-ray film, P/F ratio not over 200 mmHg for ARDS and not over 300 mmHg for ALI, and no clinical evidence of congestive heart failure. The patients were split into two groups: a high-risk for septic shock (H-R) group, and a septic shock (S-S) group, with a cut-off value of a mean arterial pressure of 60 mmHg.

Blood access for PMX-DHP was obtained via a triple-lumen catheter inserted into the internal jugular vein or femoral vein using Seldinger's method.

We reviewed patients' charts with respect to monitored modified acute physiology and chronic health evaluation II (mAPACHE-II) score, sepsis-related organ failure assessment (SOFA) score, mean blood pressure (mBP), catecholamine index (CAI), and P/F ratio before and after PMX-DHP treatment in severe sepsis patients with ALI and ARDS. The mAPACHE II score was defined as APACHE II score without Glasgow Coma Scale and was employed to assess the severity of each patient's condition. CAI was defined as mBP (mmHg) / [dopamine (mcg/kg/min) + dobutamine (mcg / kg / min) + 10 norepinephrine (mcg / kg / min)]. Survival was defined at 28 days after PMX-DHP.

PMX-DHP was performed using a polymyxin B immobilized fiber column (PMX; Toray Industries Inc., Tokyo, Japan) which was covalently bound at a weight ratio of 0.5%. Direct hemoperfusion was carried out for approximately 2 hours at a flow rate of 100 ml/min. Nafamostat mesilate (Torii Pharma Co.Ltd., Tokyo, Japan) was used as an anticoagulant. Nafamostat mesilate is a serine protease inhibitor that exerts its anticoagulant effects primarily by inhibiting thrombin. The half-life of nafamostat mesilate is 8 min, and its anticoagulant effects are observed only in the extracorporeal circuit.

Statistical analysis

Values are expressed as mean ± standard deviation. Mann-Whitney's U test and Wilcoxon signed-ranks test were used to determine statistically significant differences. $p < 0.05$ was considered statistically significant.

RESULTS

Seventy-three patients with severe sepsis were treated using PMX-DHP during the study period. Of these, thirty-four had ALI or ARDS. PMX-DHP was performed for these 34 patients (23 men and 11 women), aged 24- 86 years old (mean 64.4 +/- 15.7years). As shown in Table 1, the patients had various underlying diseases. Appropriate antibiotic therapy was selected from a laboratory culture of microorganism. In the H-R group and S-S group the mAPACHE-II score was 16.4 ± 5.0 and 19.5 ± 5.5, respectively, which were not significantly different. SOFA scores showed no significant difference between the two groups (Fig.1). In both groups, the SOFA score showed no significant difference after PMX-DHP (Fig. 1). Regarding hemodynamical parameters, mBP and CAI increased significantly following PMX-DHP in both groups (Fig. 2, 3). In the H-R group, the P/F ratio increased from 193.7 ± 83.1 to 261.9 ± 113.1 after PMX-DHP (Fig. 4), with a statistical significance ($p=0.0019$). However no difference was found in the S-S group (Fig. 4). The survival rates were 35.3% (6/17) in both groups.

DISCUSSION

The present study showed that early introduction of PMX-DHP improved oxygenation in severe sepsis, although the mechanism of action was unclear.

Kushi and colleagues considered that once shock occurs and organ ischemia progresses, cellular dysfunction at the molecular level becomes severe, and this makes it difficult to assess the effect of PMX-DHP[7]. It has been suggested that the earlier PMX-DHP is started, the more effective it is to improve the clinical condition.

mAPACHE-II and SOFA scores

mAPACHE-II and SOFA scores before PMX-DHP showed no significant difference between the groups. In this study, although PMX-DHP improved P/F ratio and mBP in the H-R group, the SOFA score did not improve after PMX-DHP. The SOFA score comprises six items: respiration, coagulation, liver, cardiovascular, central nervous system and renal function. We speculated that the magnitude of changes of P/F, mBP did not affect the factors in SOFA. In addition we reported that the coagulation score deteriorated or did not improve following PMX-DHP[13].

Table 1. Demographic characteristics of patients included in the study

	Age	Sex	Disease	Survived or died
H-S group	70	M	pyelonephritis	survived
	53	M	liver abscess	survived
	73	M	diffuse peritonitis, strangulation ileus	survived
	75	M	diffuse peritonitis, rectal perforation	survived
	78	M	unknown, postoperative bacteremia	survived
	53	M	diffuse peritonitis, transverse colon perforation	survived
	65	M	strangulation ileus	survived
	56	M	diffuse peritonitis, perforated duodenal ulcer	survived
	74	M	traumatic small-bowel perforation	survived
	40	M	diffuse peritonitis, perforated duodenal ulcer	survived
	81	M	diffuse peritonitis, sigmoid colon perforation	survived
	60	M	unknown, acute abdomen	died
	85	M	diffuse peritonitis, colon perforation	died
	75	M	diffuse peritonitis, sigmoid colon perforation	died
	55	M	diffuse peritonitis, sigmoid colon perforation	died
	21	F	diffuse peritonitis, gastric perforation	died
	65	F	pneumonia	died
S-S group	50	M	unknown, postoperative bacteremia	survived
	79	M	unknown	survived
	68	M	pneumonia	survived
	60	M	unknown, postoperative bacteremia	survived
	82	M	diffuse peritonitis, intestinal perforation	survived
	71	F	diffuse peritonitis, sigmoid colon perforation	survived
	24	F	unknown, postoperative bacteremia	survived
	56	F	diffuse peritonitis, transverse colon perforation	survived
	54	F	diffuse peritonitis, gastric perforation	survived
	68	F	pneumonia	survived
	77	F	necrotic cholecystitis	survived
	65	M	aspiration pneumonia	died
	81	M	pneumonia	died
	86	M	unknown	died
	73	M	diffuse peritonitis, intestinal perforation	died
	70	F	descending necrotizing mediastinitis	died
	47	F	diffuse peritonitis, intestinal perforation	died

M, male; F, female; survived or died, survival at 28 days after initiating PMX-DHP.

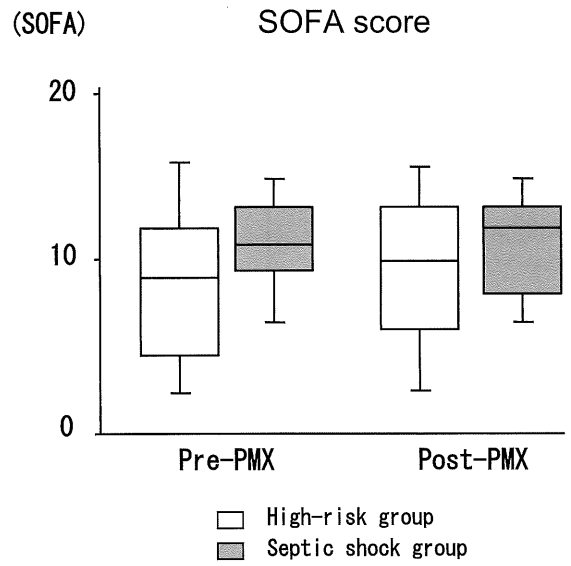

Fig. 1. SOFA score was measured before and after PMX-DHP in the high-risk group (white boxes, n=17) and septic shock group (black boxes, n=17).
There was no significant difference in SOFA score between the two groups.
In both groups, there was no significant change in SOFA score after PMX-DHP.

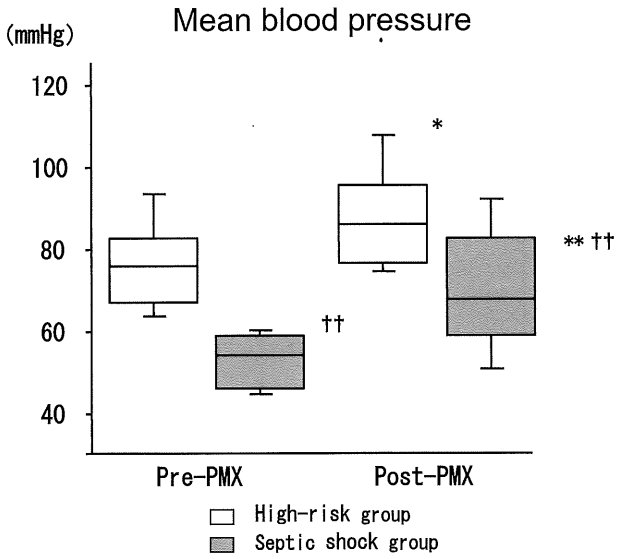

Fig. 2. Mean blood pressure (mBP) was measured before and after PMX-DHP treatment in the high-risk group (white boxes, n=17) and septic shock group (black boxes, n=17).
In both groups, mBP significantly increased after PMX-DHP.
There were significant differences in mBP between the groups.
*: p<0.05, **: p<0.01 pre-PMX vs. post-PMX, ††: p<0.01 high-risk group vs. septic shock group

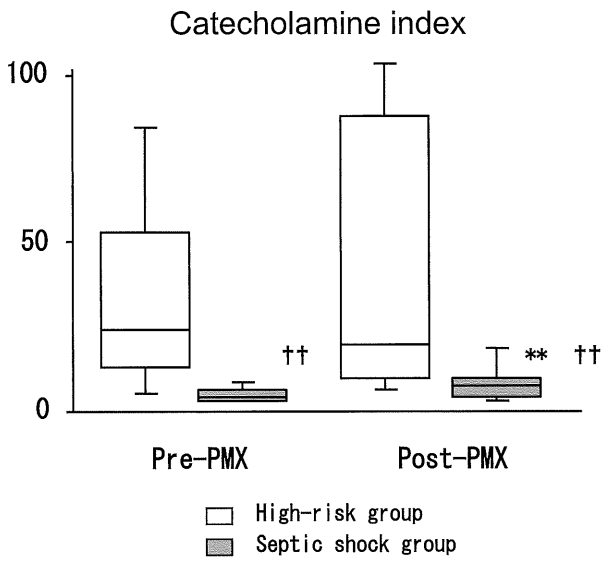

Fig. 3. Catecholamine index (CAI) was measured before and after PMX-DHP in the high-risk group (white boxes, n=17) and septic shock group (black boxes, n=17).
There was a significant difference in CAI between the groups, both before and after PMX-DHP.
There was a significant change in CAI in the septic shock group after PMX-DHP.
**: p<0.01 pre-PMX vs. post-PMX,††: p<0.01 high-risk group vs. septic shock group

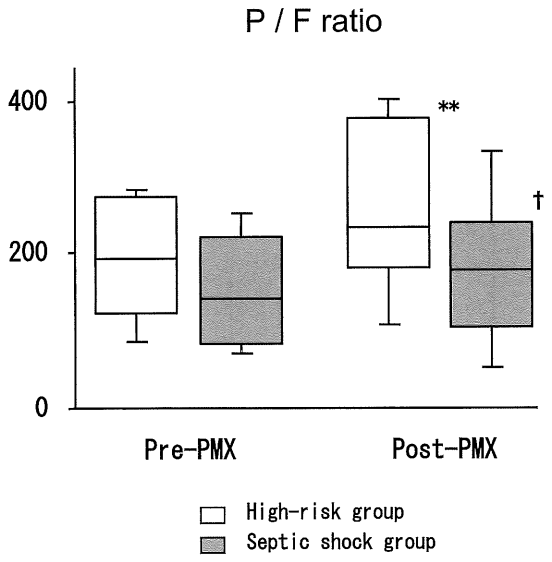

Fig. 4. PaO_2 / FIO_2 (P/F) ratio was measured before and after PMX-DHP in the high-risk group (white boxes, n=17) and septic shock group (black boxes, n=17).
In the high-risk group, there was a significant increase in P/F ratio after PMX-DHP, but not in the septic shock group.
After PMX-DHP, there was a significant difference in P/F ratio in both groups.
**: p<0.01 pre-PMX vs. post PMX, †: p<0.05 high-risk group vs. septic shock group

mBP and CAI

In this study, both groups showed an increase in mBP. This result is in agreement with previous reports[14, 15]. The theoretical effect of PMX-DHP to stabilize circulatory dynamics is through the removal of endotoxin produced by gram-negative bacteria. However, it has been subsequently shown that PMX-DHP was also effective in gram-positive sepsis in an experimental study[4]. More recently, the mechanisms of hemodynamical improvement by PMX-DHP were reported to be removal of substances such as anandamide[6]. In our study, several cases had gram-positive bacteria, not gram-negative bacteria.

P/F ratio

Tsushima and colleagues examined the effects of PMX-DHP on two processes, direct and indirect lung injury, which are known to lead to ARDS[16]. They reported that two groups, those with respiratory and non-respiratory disease, showed improved oxygenation and hemodynamics after PMX-DHP treatment[16]. They suggested that PMX-DHP treatment might directly or indirectly decrease extravascular lung water and production of pro-inflammatory cytokines by the removal not only of endotoxin but also of other substances in plasma[16].

Nakamura and colleagues showed that matrix metalloproteinase-9 (MMP-9) and tissue inhibitors of metalloproteinase-1 (TIMP-1) may play a role in the pathogenesis of ARDS, and that the circulatory disturbance in patients with ARDS caused by abnormal regulation of MMP-9 and TIMP-1 was alleviated by PMX-F treatment[9]. Recently, it was reported that MMP-9 may play an anti-fibroproliferative role in the pathogenesis of ARDS, by preventing the development of fibrosis by degrading the extracellular components synthesized by fibroblasts[8]. It has been reported that the intrapulmonary level of MMP-9 in sepsis increased first, followed by the plasma level. This indicates that a change in plasma MMP-9 level may not develop in the initial stages of sepsis [10].

Kushi et al demonstrated that PMX-DHP significantly decreased blood levels of plasminogen activator inhibitor-1 (PAI-1), neutrophil elastase (NE), and interloikin-8 (IL-8), and significantly improved P/F ratio[7]. They suggested that PMX-DHP improved pulmonary oxygenation through the elimination of humoral mediators[7]. Further studies will be required to elucidate the exact mechanisms of the effects of PMX-DHP on oxygenation in the early phase of severe sepsis.

Nafamostat mesilate which is used as an anticoagulant causes suppression of inflammation[5,11]. It has been suggested that nafamostat mesilate may reduce the pulmonary vascular injury as well as coagulation abnormalities induced by LPS. The former effect may be dependent on the inhibitory effect on activation of the complement system in rats administered LPS[17]. There might be a possibility that nafamostat mesilate used with PMX-DHP treatment may lead to an improvement of the oxygenation in sepsis patients with ALI or ARDS.

CONCLUSION

It is suggested that early introduction of PMX-DHP for severe sepsis may improve oxygenation.

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