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A LONGER DURATION OF POLYMYXIN B–IMMOBILIZED FIBER COLUMN HEMOPERFUSION IMPROVES PULMONARY OXYGENATION IN PATIENTS WITH SEPTIC SHOCK

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ABSTRACT—Endotoxin plays an important role in the pathogenesis of septic shock. Exposure of endothelial cells to endotoxin activates endothelial cells and increases the surface expression of adhesion molecules, markers of endothelial damage in organ dysfunction. Endotoxin adsorption therapy by polymyxin B–immobilized fiber column (PMX) hemoperfusion has been used for the treatment of septic shock patients. In this study, we measured plasma concentrations of endotoxin and soluble adhesion molecules in septic shock patients before and after the PMX treatment then observed on the relationships between actual duration of use and various outcomes. Sixteen patients with septic shock were studied. The 28-day mortality rate was 50%. The elevated plasma concentrations of endotoxin decreased after the PMX treatment in the survivors but not in the nonsurvivors. The norepinephrine dose and plasma concentrations of soluble endothelial leukocyte adhesion molecule 1 and soluble intercellular adhesion molecule 1 significantly ($P < 0.05$) decreased in the PMX greater-than-2-h (prolonged) group than in the PMX 2-h (conventional) group (-17.8 ± 14.6 vs. -1.8 ± 2.7 μg/min, -143.0 ± 111.0 vs. 0 ± 2.8 ng/mL, and -126.2 ± 144.9 vs. 16.5 ± 108.1 ng/mL, respectively). Changes in the Pa_{O_2}-F_{IO_2} ratio and the Sequential Organ Failure Assessment score were significantly ($P < 0.05$) more improved in the PMX greater-than-2-h group than in the PMX 2-h group (75.4 ± 80.7 vs. 1.2 ± 49.2 and -0.8 ± 1.8 vs. 2.2 ± 1.9 torr, respectively). We thus suggest that a longer duration of PMX treatment may improve the pulmonary oxygenation associated with decreased adhesion molecules in septic shock.

KEYWORDS—Adhesion molecules, endotoxin, endothelial damage, organ dysfunction, polymyxin B, pulmonary oxygenation, septic shock

INTRODUCTION

Septic shock has a high risk of mortality despite the availability of various treatments using antibiotics, fluids, or vasopressive/inotropic approaches. Endotoxin, an outer membrane component of Gram-negative bacteria, plays an important role in the pathogenesis of septic shock. The actions of endotoxin on macrophages and other leukocytes induce an excessive generation of cytokines, which in turn increases systemic inflammatory response and leads to endothelial dysfunction (1). Endotoxin adsorption therapy by polymyxin B–immobilized fiber column (PMX) hemoperfusion has been widely used in patients with septic shock in Japan. Polymyxin B–immobilized fiber column treatment is based on the binding property of polymyxin B to lipid A of endotoxin. The covalent binding of polymyxin B onto the surface of the polystyrene-based carrier fiber in PMX inactivates the endotoxin in the blood without exerting toxicity (2, 3). Polymyxin B–immobilized fiber column reduces the plasma concentrations of endotoxin and inflammatory cytokines (4, 5), but the mechanisms by which it does so remain unclear.

Exposure of endothelial cells to endotoxin or inflammatory cytokines activates the endothelial cells and increases the surface expression of several adhesion molecules, including three with a confirmed involvement in leukocyte rolling and leukocyte adhesion: endothelial leukocyte adhesion molecule 1 (ELAM-1), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) (1, 6). Plasma concentrations of soluble adhesion molecules correlate well with the severity of inflammation and outcome (6), suggesting that these adhesion molecules are markers of endothelial damage in organ dysfunction.

There have been no previous reports on PMX treatment administered for longer than 2 h, the standard duration of PMX treatment for patients with septic shock. Our group hypothesized that a longer duration of PMX treatment for patients with septic shock would bring about greater reduction in the plasma concentrations of endotoxin, plasma concentrations of soluble adhesion molecules, and endothelial damage compared with PMX of the standard duration (2 h). To test this hypothesis, we measured the plasma concentrations of endotoxin and soluble adhesion molecules of patients with septic shock before and after the PMX treatment then observed on the relationship between actual duration of use and various outcomes.

MATERIALS AND METHODS

Sixteen patients with septic shock, as defined by the Consensus Conference of American College Physician/Society of Critical Care Medicine criteria (7), were studied. This study was approved by the institutional review board of Tokyo Medical and Dental University. Informed consent was obtained from the families of the patients before the PMX treatment. Demographic data, routine biochemistry, microbiological data, infection focus, the Acute Physiology and Chronic Health Evaluation (APACHE) II score (8), the Sequential Organ Failure Assessment (SOFA) score (9), and 28-day mortality were recorded.

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TABLE 1. **Patients' characteristics at baseline**

	Overall (n = 16)	PMX 2 h (n = 5)	PMX > 2 h (n = 11)	*P*
Age, yr	65 ± 17	71 ± 10	62 ± 19	*P* = 0.358
Sex, male/female	11/5	3/2	8/3	
Body temperature, degrees	38.1 ± 1.8	37.7 ± 2.5	38.2 ± 1.4	*P* = 0.621
Heart rate, bpm	131.8 ± 15.6	146.0 ± 18.5	125.5 ± 9.1	*P* = 0.009
Respiratory rate, breaths/min	30.1 ± 8.2	28.4 ± 6.5	30.9 ± 9.1	*P* = 0.592
MAP, mmHg	53.4 ± 15.1	51.4 ± 26.8	53.5 ± 8.1	*P* = 0.814
Pao_2-Fio_2 ratio, torr	148 ± 95	126 ± 76	159 ± 105	*P* = 0.543
White blood cells/μL	11138 ± 12791	5500 ± 4186	13700 ± 14672	*P* = 0.248
APACHE II score	23.3 ± 6.5	27.0 ± 10.2	21.5 ± 3.3	*P* = 0.122
SOFA score	11.7 ± 3.8	9.6 ± 2.1	12.6 ± 4.1	*P* = 0.145
Infection site				
Abdomen	n = 7	n = 3	n = 4	
Blood	n = 6	n = 1	n = 5	
Urinary tract	n = 2	n = 1	n = 1	
Lung	n = 1	n = 0	n = 1	
Bacteriology				
Mixed	n = 1	n = 1	n = 0	
Gram-negative only	n = 12	n = 3	n = 9	
Gram-positive only	n = 2	n = 1	n = 1	
Use of vasopressive/ inotropic agents				
Norepinephrine	n = 13	n = 4	n = 9	
Dopamine	n = 14	n = 5	n = 9	
Dobutamine	n = 10	n = 3	n = 7	

n = number of patients, mean ± SD, *P* value; PMX 2 vs. PMX > 2 h.

The PMX treatment was administered by the following method. A Toraymyxin 20-R (Toray Industries, Tokyo, Japan) was washed by perfusion with 4 L of physiological saline. After inserting a double-lumen catheter into a central vein, blood was drawn from the proximal port, perfused through Toraymyxin 20-R, and returned to the vein through the distal port of the catheter (V-V method). The perfusion was performed at a rate of 80 to 100 mL/min using protease inhibitor nafamostat mesilate (Torii Pharmaceuticals, Co., Ltd., Tokyo, Japan) as an anticoagulant. The PMX treatment was commenced within 24 h after diagnosis of septic shock. We observed two groups: the PMX 2-h (conventional) group, who received the PMX treatment for 2 h, and the PMX greater-than-2-h (prolonged) group, for whom the PMX treatment was extended for as long as possible beyond 2 h. The duration of PMX treatment was decided on by the conference of attending physicians, intensivists, and nephrologists. It depended on the time of start and arrangements of staff in the Department of Blood Purification. The end point for the PMX greater-than-2-h group was improvement of MAP and/or decrease in doses of vasopressive/inotropic agents.

Plasma concentrations of endotoxin, soluble ELAM-1, soluble ICAM-1, and soluble VCAM-1 were measured before and after PMX treatment. The assay for endotoxin was performed with separated plasma from heparinized whole blood samples centrifuged at 3,000 rpm for 40 s. The high-sensitivity assay was performed by kinetic turbidimetric Limulus assay using a MT-358 Toxinometer (Wako Pure Chemical Industries, Ltd, Osaka, Japan) (10, 11), a device theoretically capable of measuring with as accuracy up to 0.01 pg/mL. This Limulus assay test is specific to endotoxin and has no cross-reaction to β-glucan as previously described (12). The cutoff endotoxin level for the diagnosis of sepsis is 1.1 pg/mL (11). Plasma concentrations of soluble ELAM-1, soluble ICAM-1, and soluble VCAM-1 were measured using the quantitative sandwich enzyme immunoassay according to the manufacturer's protocol (Parameter human sE-selectin, Parameter human sICAM-1, and Quantikine human sVCAM-1, respectively; R & D Systems, Inc., Minneapolis, Minn).

Changes in the heart rate, MAP, body temperature, and Pao_2-Fio_2 ratio were also evaluated.

Statistical analysis

Data are expressed as mean ± SD. Statistical analyses between two groups were performed using Student *t*-tests or chi-square tests. Correlations between two parameters were evaluated using simple regression tests. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The patients' characteristics at baseline and causative bacteria are shown in Tables 1 and 2, respectively. The mean duration of the PMX treatment in the PMX greater-than-2-h (prolonged) group was 16.9 ± 7.0 h (6–27 h). The 28-day mortality rate for the whole study population was 50%. Of 5 patients, 3 died in the PMX 2-h group, and 5 of 11 patients died in the PMX greater-than-2-h group. There was no significant difference in mortality rate between the two groups. The PMX treatment significantly ($P < 0.01$) increased the MAP from 53.4 ± 15.1 to 74.3 ± 19.3 mmHg, significantly ($P < 0.05$) decreased the heart rate from 131.8 ± 15.6 to 113.1 ± 18.5 bpm, and significantly ($P < 0.05$) decreased the body temperature from 38.1 ± 1.8 to 36.7 ± 0.8 degrees. The PMX treatment did not significantly change the white blood cell counts. The norepinephrine dose fell significantly ($P < 0.05$) in the PMX greater-than-2-h group than in the PMX 2-h group (−17.8 ± 14.6 vs. –1.8 ± 2.7 μg/min), and the doses of dopamine and dobutamine tended to fall to lower levels in the PMX greater-than-2-h group than in the PMX 2-h group (Fig. 1). Relationships between duration of PMX treatment and changes in doses of vasopressive/inotropic agents are shown in Figure 2. There was a significant ($P < 0.01$) correlation between duration of PMX treatment and change in norepinephrine dose (Fig. 2). There were no significant differences between the two groups in the changes of MAP, heart rate, body temperature, or white blood cell counts. The elevated plasma concentrations of endotoxin decreased after the PMX treatment in the survivors

TABLE 2. **Causative bacteria in patients with septic shock**

Bacteria	n
Gram-negative bacteria	
Escherichia coli	5
Pseudomonas aeruginosa	4
Enterobacter cloacae	3
Klebsiella pneumoniae	2
Serratia marcescens	1
Haemophilus influenzae	1
Citrobacter freundii	1
Aeromonas sp.	1
Xanthomonas maltophilia	1
Acinetobacter calcoaceticus	1
Gram-positive bacteria	
Methicillin-resistant *S. aureus*	3
Enterococcus faecalis	2

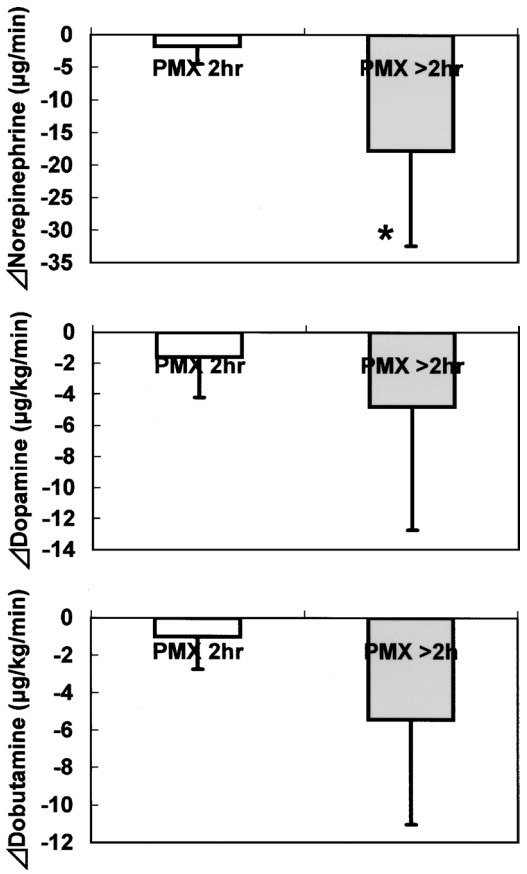

FIG. 1. **Changes in doses of norepinephrine, dopamine, and dobutamine before and after the PMX treatment in patients with septic shock**. White columns represent the PMX 2-h group, and gray columns represent the PMX greater-than-2-h group. Each column with bar represents mean and SD. *$P < 0.05$ vs. the PMX 2-h group.

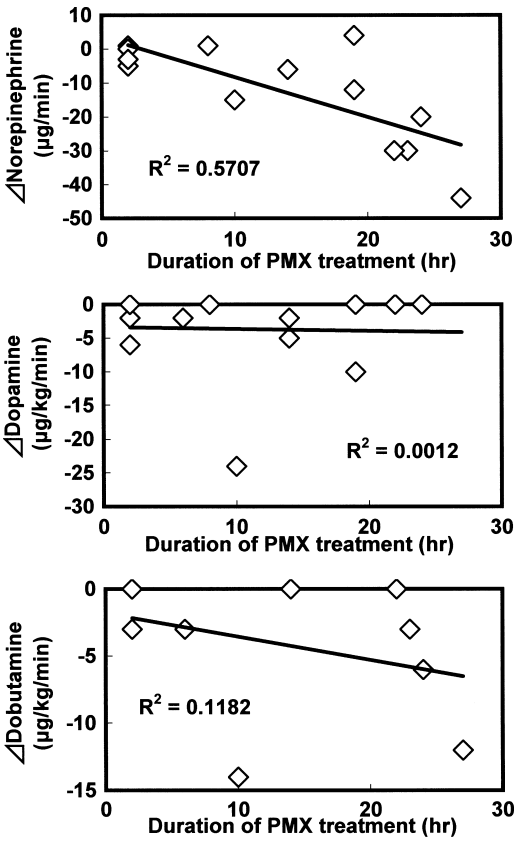

FIG. 2. **Relationships between duration of PMX treatment and changes in doses of norepinephrine, dopamine, and dobutamine before and after the PMX treatment in patients with septic shock.**

but not in the nonsurvivors (Fig. 3). Plasma concentrations of endotoxin were almost same or increased after the PMX treatment especially in four nonsurvivors. Causes of septic shock in these patients were 1) toxic epidermal necrolysis, 2) perforation of small intestine, 3) graft-versus-host disease after bone marrow transplantation, and 4) lung abscess after hepatic segmentectomy. The plasma concentrations of soluble ELAM-1, soluble ICAM-1, and soluble ICAM-1 in our subjects were markedly elevated (370.1 ± 408.5, 795.6 ± 437.5, and 2,508.8 ± 890.1 ng/mL, respectively) at baseline. The plasma concentrations of soluble ELAM-1 and soluble ICAM-1 fell significantly ($P < 0.05$) in the PMX greater-than-2-h group than in the PMX 2-h group (−143.0 ± 111.0 vs. 0 ± 2.8 and −126.2 ± 144.9 vs. 16.5 ± 108.1 ng/mL, respectively). Plasma concentrations of endotoxin and soluble VCAM-1 tended to fall to lower levels in the PMX greater-than-2-h group than in the PMX 2-h group (Fig. 4). Changes in the Pao_2-Fio_2 ratio and the SOFA score were significantly ($P < 0.05$) improved in the PMX greater-than-2-h group than in the PMX 2-h group (75.4 ± 80.7 vs. 1.2 ± 49.2 and −0.8 ± 1.8 vs. 2.2 ± 1.9 torr, respectively) (Fig. 5). Duration of PMX treatment significantly ($P < 0.05$) correlated with change in SOFA score but not with decreased plasma concentrations of endotoxin or change in APACHE II score (Fig. 6). Decreased plasma concentrations of endotoxin did not correlate with changes in plasma concentrations of adhesion molecules, MAP, heart rate, Pao_2-Fio_2 ratio, or body temperature.

DISCUSSION

This study showed that the PMX treatment improved the hemodynamics of the patients with septic shock, and that a

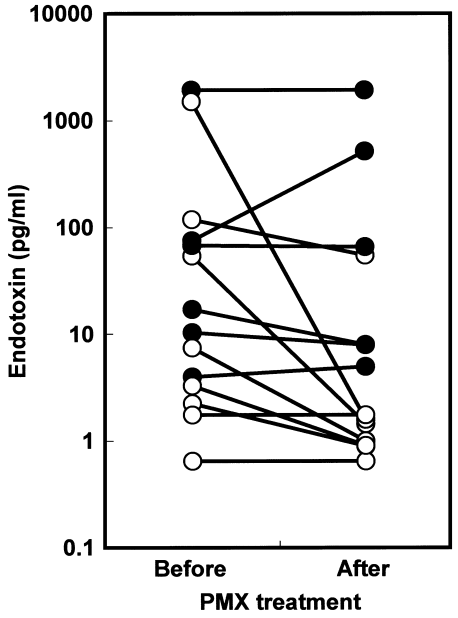

FIG. 3. **Changes in plasma endotoxin concentrations before and after the PMX treatment in patients with septic shock**. Open circles represent survivors, and closed circles represent nonsurvivors.

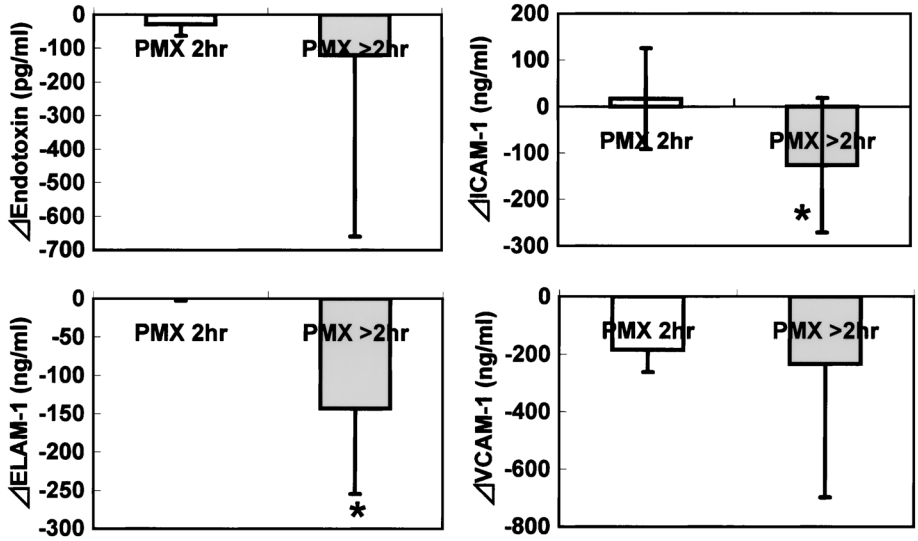

FIG. 4. **Changes in plasma endotoxin, soluble ELAM 1, soluble ICAM 1, and soluble VCAM-1 before and after the PMX treatment in patients with septic shock**. White columns represent the PMX 2-h group, and gray columns represent the PMX greater-than-2-h group. Each column with bar represents mean and SD. *$P < 0.05$ vs. the PMX 2-h group.

longer duration of the treatment was more effective in decreasing the dose of norepinephrine and increasing the Pao_2-FIO_2 ratio and the SOFA score. Polymyxin B–immobilized fiber column treatment has been shown to improve hemodynamic parameters such as the arterial pressure, cardiac index, left ventricular stroke work index, and oxygen delivery index in patients with septic shock (11, 13). Although the precise mechanisms behind these hemodynamic improvements remain unknown, the PMX-induced decrease of endotoxin in plasma may play a role. Polymyxin B–immobilized fiber column has been shown to inhibit endotoxin activity by removing endotoxin via *in vitro* hemoperfusion of human plasma (14) and in a piglet sepsis model (15). Endotoxin initiates a cascade of inflammatory mediators and activates various inflammatory responses.

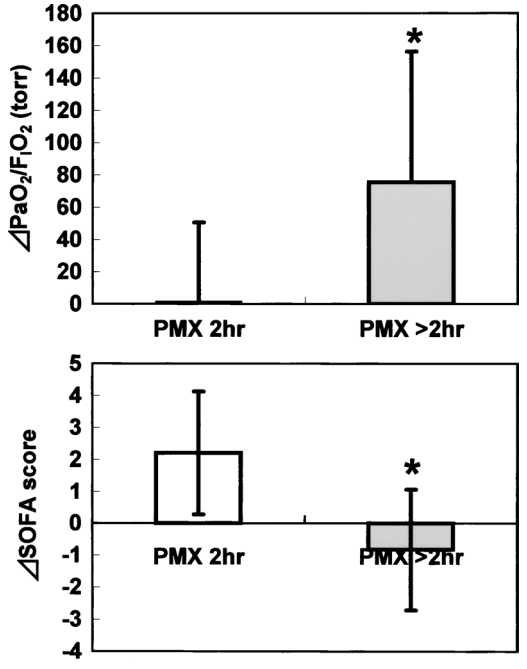

FIG. 5. **Changes in Pao_2-FIO_2 ratio and SOFA score before and after the PMX treatment in patients with septic shock**. White columns represent the PMX 2-h group, and gray columns represent the PMX greater-than-2-h group. Each column with bar represents mean and SD. *$P < 0.05$ vs. the PMX 2-h group.

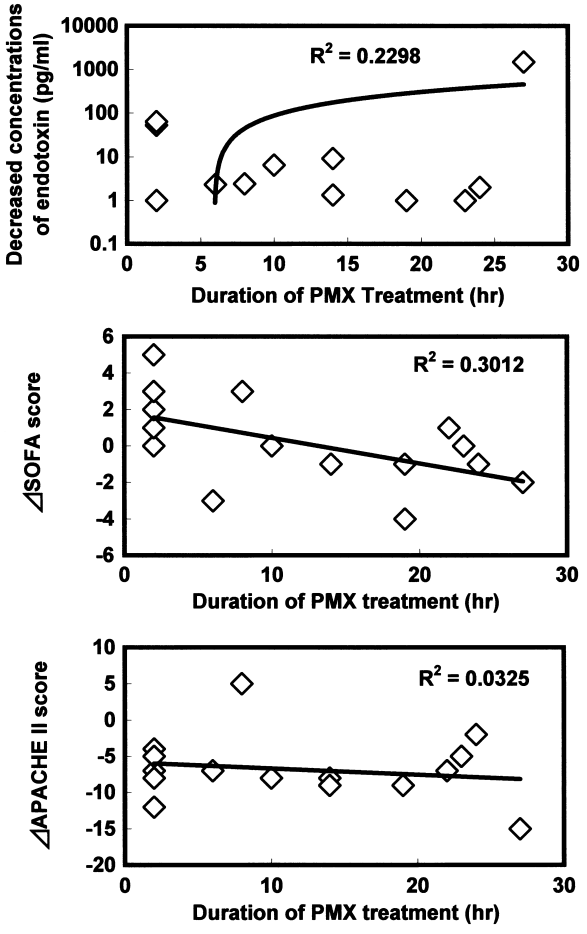

FIG. 6. **Relationships between duration of PMX treatment and decreased concentrations of endotoxin, changes in SOFA score, and APACHE II score before and after the PMX treatment in patients with septic shock**. Two nonsurvivors, whose plasma concentrations of endotoxin increased after the PMX treatment, were excluded in the top panel.

Endotoxin-induced inflammatory cytokines activate nuclear factor–κB, a central transcriptional activator of many proinflammatory genes, and regulates the transcription of adhesion molecules and immunoreceptors (1). Plasma concentrations of endotoxin decreased after the PMX treatment in the survivors in our study but not in the nonsurvivors. Plasma concentrations of endotoxin were almost the same or increased after the PMX treatment especially in four nonsurvivors. We speculated the reason why plasma concentrations of endotoxin did not decrease in these patients. 1) In the patient with toxic epidermal necrolysis, although the infectious regions were removed by debridement, infection might spread out systemically through blood. 2) In the patient with perforation of small intestine, endotoxin absorption from the gut would be increased after operation. 3) In the patient with graft-versus-host disease after bone marrow transplantation, injury of intestinal mucosa might induce bacterial translocation that continuously absorbed endotoxin. 4) In the patient who underwent hepatic segmentectomy, we could not determine lung abscess until autopsy. Therefore, we supposed that the source of infection was not adequately controlled in these patients. We thus conclude that the endotoxin adsorptive effect of PMX was sufficient to reduce inflammatory mediators in the survivors, whereas the rate of endotoxin production may have exceeded the rate of endotoxin removal by PMX in the nonsurvivors.

Adhesion molecules play a central role in the interaction of neutrophils with vascular endothelium during inflammation. Exposure of endothelial cells to endotoxin or proinflammatory cytokines activates the endothelial cells and increases the surface expression of ELAM-1, ICAM-1, and VCAM-1 (1, 6). Patients with sepsis have exhibited marked elevation in the plasma concentrations of soluble ELAM-1, soluble ICAM-1, and soluble VCAM-1 (16–19). Given that plasma concentrations of soluble adhesion molecules correlate with the severity of inflammation and outcome (6, 18, 19), generalized activation of adhesion molecules may be implicated in endothelial damage and multiple organ dysfunction syndrome associated with septic shock. The plasma concentrations of soluble adhesion molecules in our subjects were markedly elevated at baseline, and the plasma concentrations of soluble ELAM-1 and ICAM-1 decreased to significantly lower levels in the PMX greater-than-2-h group than in the PMX 2-h group. In experimental studies, ELAM-1 has been shown to cause neutrophil-mediated lung injury and pulmonary edema (20, 21). Inhibition of ICAM-1 has also been found to prevent alveolocapillary membrane damage, improve gas exchange, and reduce mortality in a rabbit model of acute lung injury (22). Therefore, the decrease in the plasma concentrations of soluble ELAM-1 and soluble ICAM-1 by the longer duration of PMX treatment may have contributed to improved pulmonary oxygenation in the present study. We do not know whether the PMX treatment removed adhesion molecules directly or whether it weakened their concentration by reducing the stimulation of endothelial cells via its effect in absorbing pathogenic toxins.

Three of the patients in our study were infected with methicillin-resistant *Staphylococcus aureus*. The MAPs of these patients increased after the PMX treatment, although none of three survived. Polymyxin B–immobilized fiber column removed TNF-α during an *in vitro* hemoperfusion of human plasma containing *S. aureus* challenge (23), suggesting that the PMX treatment is also effective in reducing inflammatory cytokines in patients with Gram-positive bacteria infection. The PMX treatment is also reported to improve hemodynamics by reducing the level of anandamide, an endogenous cannabinoid (24), and reducing the level of high-mobility group box 1, a late mediator in endotoxemia (25). These findings suggest that the elimination of various mediators by the PMX treatment might also improve hemodynamics in patients with septic shock.

CONCLUSIONS

The PMX treatment improved hemodynamics in patients with septic shock, and a longer duration of this therapy effectively decreased the norepinephrine dose and plasma concentrations of soluble ELAM-1 and soluble ICAM-1. In addition, the longer duration of therapy brought about greater improvement in the Pa_{O_2}-F_{IO_2} ratio and the SOFA score. These findings suggest that PMX treatment during a longer duration may improve the pulmonary oxygenation associated with decreased adhesion molecules in septic shock.

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