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Direct Hemoperfusion Using a Polymyxin B Immobilized Column Improves Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is characterized by a high mortality rate. We have studied whether direct hemoperfusion using a polymyxin B immobilized fiber column (PMX-DHP) is effective for acute lung injury (ALI) and ARDS. Two ALI and eighteen ARDS patients were evaluated, four congestive heart failure (CHF) patients were evaluated as cardiogenic pulmonary edema, and we retrospectively compared the outcome with ten patients with ARDS who had been hospitalized between 1990 and 1998 as the untreated group. PMX-DHP was carried out twice at a rate of 80–100 ml/minute for 2 hours, with a time interval of approximately 24 hours. We monitored systolic blood pressure (BP), diastolic BP, and the PaO_2/FiO_2 (PF) ratio before and after PMX-DHP treatment. The mortality was classified if patients were alive at day 30 after initiating PMX-DHP. The mortality of ARDS patients was approximately 20%. Systolic BP increased significantly from 106 ± 20 to 135 ± 21 and to 125 ± 20 mmHg on the following day. Diastolic BP increased from 61 ± 16 to 78 ± 15, and to 72 ± 12 mmHg. The PF ratio increased significantly from 125 ± 54 to 153 ± 73, and 163 ± 78 Torr. CHF patients did not reveal improvement of systolic, diastolic BP, and PF ratio after PMX-DHP. Eight of ten patients in the untreated group died through exacerbated ARDS. In ARDS patients, PMX-DHP improved circulatory disturbance and oxygenation despite the underlying diseases. The mortality improved compared with that before induction of PMX-DHP. J. Clin. Apheresis 17:97–102, 2002. © 2002 Wiley-Liss, Inc.

Key words: PMX-DHP; ALI; ARDS; PaO_2/FiO_2 ratio

INTRODUCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [1] are characterized by severe acute hypoxemia caused by increased pulmonary capillary permeability. Although supportive therapies for ALI and ARDS, including positive end-expiratory pressure, have been performed, overall mortality from ARDS remains high at 50 to 90% [2]. Understanding the range of pathways that lead to organ system dysfunction after endotoxemia, bacteremia, and local infections permits classification of infected patients based on their underlying pathophysiology and permits inclusion of appropriate patients into therapeutic studies earlier in their clinical course, before organ dysfunction develops. In the case of ALI/ARDS, the consensus conference definition permits inclusion of a multiplicity of clinical entities. Many studies for ALI and ARDS, excluding autoimmune disorders, have shown no new pharmacological therapies, including agents that inhibit endotoxin [3] or cytokine [4]. Activated inflammatory cells, including peripheral monocytes and alveolar macrophages, leukocytes, and polymorphonuclear neutrophils, were suggested to play an essential role in the pathogenesis of ALI and ARDS [5]. Initial cytokine production occurs from peripheral monocytes and alveolar macrophages in the setting of ALI and ARDS. Recently, some studies have focused on endotoxin induced activated peripheral monocytes and alveolar macrophages, partly because of the discovery that the cells are chief sources of cytokines that amplify lung inflammation and injury [6]. Since peripheral monocytes increase in the lung during the resolution of inflammatory responses, some clinical evidence suggests that this phenomenon may also occur in the lungs of patients with ALI and ARDS [7]. The recent development of an endotoxin-removal column that contained polymyxin B immobilized fiber (PMX-DHP) has enabled the safe use of direct hemoperfusion (direct hemoper

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TABLE I. Characteristics

Group	A) Respiratory disease	B) Non-respiratory disease	C) CHF
Male	Eight cases	Six cases	Three cases
Female	Four cases	Two cases	One case
Mean age (years)	65 ± 16	62 ± 15	65 ± 10
APACHE II score	23.0 ± 5.8	21.5 ± 5.4	23.9 ± 9.0
Lung injury score	3.0 ± 0.6	2.9 ± 0.3	2.6 ± 0.8
PF ratio (Torr)	114 ± 52	141 ± 58	161 ± 81
MOF score	4.1 ± 0.8	4.2 ± 0.8	5.1 ± 1.2
Endotoxin <10 pg/ml	Eight cases	Four cases	Four cases
>10 pg/ml	Three cases	Three cases	—
Endotoxin level (pg/ml)	19.4 ± 7.5	16.5 ± 14.2	—

CHF, congestive heart failure; MOF, multiple organ failure; PF, PaO_2/FiO_2; data are mean ± SD. A) vs B), A) vs C), and B) vs C) were not significant, respectively.

fusion by using a PMX-DHP column; hereafter referred to as PMX-DHP treatment) procedure to treat septic shock [8]. Some clinical study groups reported that PMX-DHP treatment decreased the concentration of endotoxin and other substances as a result of treatment for septic shock and reduced mortality in a multicenter study [9]. Endotoxin was detected in 64% of the plasma samples obtained from patients with ARDS [10]. However, septic shock with ARDS is caused by not only Gram-negative rod bacteria but also Gram-positive cocci bacteria. The wall material of Gram-positive cocci bacteria could also activate peripheral monocytes via the toll-like receptor-2 [11]. Moreover, the toxicity of toxic shock syndrome toxin (TSST)-1 in staphylococcal infection increases by 50,000-fold in the presence of endotoxin [12]. PMX-DHP treatment cannot remove inflammatory cytokines such as tumor necrosis factor α, interleukin 1 and TSST-1 from plasma.

Anandamide, an endogenous cannabinoid, can be generated by activated macrophages during endotoxin shock and was suggested to be a paracrine contributor to hypotension [13]. Anandamide adsorbed in a PMX-DHP. The adsorption of anandamide by PMX-DHP may abolish the diverse effects of anandamide such as hypotension, immunosuppression, and cytotoxicity. In many cases, septic shock develops complications such as ARDS caused by inflammatory cytokines. Direct pulmonary injury results from causes as diverse as pneumonia, aspiration of gastric contents, or smoke inhalation to indirect pulmonary injury from bacteremia, endotoxicemia, or hemorrhage/trauma. We hypothesized that removing endotoxin or some mediators such as anandamide in plasma may permit resolution of ALI and ARDS. In the present study, we divided the underlying diseases into two groups: a respiratory disease group and a non-respiratory disease group. We tried to establish whether direct hemoperfusion using PMX-DHP was effective against ALI and ARDS induced by direct or indirect pulmonary injury.

MATERIALS AND METHODS

Patients

On enrollment, age, gender, clinical diagnosis at hospital admission, the initial PaO_2/FiO_2 (PF) ratio, and chest X-ray were recorded. The definitions of ALI and ARDS were briefly described at the American-European Consensus Conference [1]. The criteria for diagnosis of ALI and ARDS as set by American-European Consensus Conference were used and were as follows: acute onset of lung injury, diffuse bilateral infiltrates seen upon chest X-ray, a PF ratio < 200 mmHg for ARDS and a PF ratio < 300 mmHg for ALI, pulmonary artery occlusion pressure < 19 mmHg, or no clinical evidence of congestive heart failure. To rule out congestive heart failure, we performed echo cardiography for the 20 enrolled patients. PMX-DHP treatment was performed in 20 patients diagnosed as ARDS and ALI (14 males and 6 females) ages between 29 and 85 years. We divided patients into two groups according to the kind of underlying diseases: respiratory disease group (direct pulmonary injury) and non-respiratory disease group (indirect pulmonary injury) (Table I). In addition, no patients received nitric oxide, surfactant, or other experimental pharmacological intervention for either ALI or ARDS. The multiple organ failure (MOF) score was diagnosed according to Goris's criteria in all treated patients. The APACHE II scores and lung injury scores (LIS) were determined at the time of starting PMX-DHP treatment. The comparability of each group based on the statistical test was equivalent for mean ages, the APACHE II score, LIS, the PF ratio, and the MOF score. Previous studies have used 30 days mortality after an episode of ARDS [14]. Patients who die after these 30 days usually die for other reasons than the original ARDS. Therefore, we chose to compare the mortality of patients who survived greater than 30 days with that of patients who died within 30 days. We performed PMX-DHP treatment on four patients who were diagnosed as

congestive heart failure with bilateral infiltrate shadows on chest X-ray to explain that PMX-DHP treatment did not directly affect improvements in the circulation system. Moreover, we retrospectively compared the outcomes with those of ten patients with ARDS in hospitalization between 1990 and 1998 before induction of the PMX-DHP treatment. Ten patients (eight males and two females) between 49 and 81 years old (mean ± SD age, 67.0 ± 11.7 years) did not undergo PMX-DHP treatment. They belonged to the above respiratory disease group and to control groups without PMX-DHP treatment.

PMX Treatment

We performed PMX-DHP treatment (Toraymyxin, Toray Medical Co., Tokyo, Japan) in patients with ALI and ARDS, simultaneously with various conventional therapies including antibiotics and gamma globulin concurrently. PMX-DHP was produced by immobilizing polymyxin-B on 0.5% weight ratio polystyrene fiber by covalent bonding; examination confirmed a firm binding of polymyxin-B without it being released [15]. The holding blood volume of this column was 200 ml. The column for direct hemoperfusion was filled with 53 g PMX-DHP and physiological saline. Direct hemoperfusion was performed by using conventional equipment for hemoperfusion and a circuit for hemodialysis. The column was washed by perfusion with 4 liters of physiological saline. For venous access, a double-lumen catheter (Arrow International, Inc., Reading, PA) was inserted into the femoral vein using Seldinger's method. Direct hemoperfusion carried out at a flow rate of 80–100 ml/minute for 2 hours. PMX-DHP treatment was performed twice with a time interval of approximately 24 hours. Heparin, low molecular weight heparin, or nafamostat mesilate (Torii Pharma Co., Ltd, Tokyo, Japan) were used as anticoagulants. Nafamostat mesilate markedly inhibits trypsin, thrombin, plasmin, kallikrein, and the classical complement pathway. Nafamostat mesilate is a serine protease inhibitor that exerts its anticoagulatory effects primarily by inhibiting thrombin. The half-life of nafamostat mesilate is 8 minutes and anticoagulatory effects were observed only in the extracorporeal circuit.

Data Collection and Management

We recorded hemodynamic parameters such as systolic blood pressure (BP), diastolic BP, and heart rate (HR), and respiratory parameters such as arterial blood gases and F_IO_2. Chest X-rays were obtained at diagnosis, on day 3 and day 7, and then weekly. The fluid balance of intake and output were adjusted to zero balance by using diuretics daily. Arterial blood gases were obtained before and after PMX-DHP treatment and on the following day. To evaluate the effects of the PMX-DHP treatment, some parameters (systolic BP, diastolic BP, HR $PaCO_2$, and PF ratio) were also monitored before, after (2 hours after the start of PMX-DHP treatment), and on the day following PMX-DHP treatment (24 hours after the treatment).

Measurement of Endotoxin

The concentration of endotoxin in the peripheral blood was measured before and after the initiation of PMX-DHP treatment. We assayed the endotoxin levels by Endospecy with the new perchloric acid method [16]. The normal upper limit of endotoxin concentration was 10 pg/ml. Endotoxin reduction by PMX-DHP treatment was evaluated as the difference in the plasma endotoxin concentration before and after PMX-DHP treatment.

Statistics

Normal distribution values were presented as means ± SD. These data were analyzed using an analysis of variance repeated over time. A P value of 0.05 was used as the cut-off point for statistical significance.

RESULTS

No bacteria from sputa, urine, stool, or blood were detected in any patients. As shown in Table II, two patients with ALI survived. Fourteen of eighteen patients with ARDS survived at 30 days after the initiation of PMX-DHP treatment. Two of four patients died due to exacerbated ARDS, one of four patients died due to a worsening of an underlying disease, and the others died due to acute renal failure within 30 days. The total mortality at day 30 was approximately 20%. The respiratory disease group enrolled nine patients with pneumonia and three patients with aspiration pneumonia. The non-respiratory disease group enrolled five patients with postoperative complications (massive hemorrhage) of malignant diseases, one patient with liver abscess, and two patients with enterocolitis. In the respiratory disease group, three of twelve patients died, and in the non-respiratory disease group, one of eight patients died. The mortality of each group was 25% and 12.5%, respectively. PMX-DHP treatment showed no significant difference in the mortality between respiratory and non-respiratory groups ($P = 0.62$). In the

TABLE II. Outcome

Group	Respiratory disease (n = 12)	Non-respiratory disease (n = 8)
Alive at day 30	Nine cases including one ALI patient	Seven cases including one ALI patient
Death within 30 days	Three cases	One case
Alive at day 90	Eight cases	Three cases
	The period between onset and starting of PMX	
Within 48 hours (n = 12)		
Alive at day 30	Ten cases including two ALI patients	
Death within 30 days	Two cases	
Over 48 hours (n = 8)		
Alive at day 30	Five cases	
Death within 30 days	Three cases	

respiratory disease group the degree of improvement of patients with PMX-DHP treatment resulted in withdrawal from the mechanical ventilator within 30 days. In the non-respiratory disease group the degree of improvement resulted in withdrawal from the ventilator except for two patients with malignancy. The APACHE II scores, LIS, and the MOF score did not show significant decreases after PMX-DHP treatment. Twelve patients who underwent PMX-DHP treatment within 48 hours after being diagnosed ALI or ARDS showed low mortality of 17%. Eight patients who had PMX-DHP treatment induced over 48 hours showed mortality of 38%. However, there was no significant difference between and over 48 hours ($P = 0.35$).

Although not shown, the therapeutic effect of PMX-DHP treatment was independent of the presence of steroid therapy and mechanical ventilation. The ventilator mode was set as synchronized mechanical ventilation or mechanical ventilation with 6–10 ml/kg tidal volume and 10 cmH_2O of positive end-expiratory pressure. A consecutive chest X-ray finding retained the bilateral infiltrate shadow, considering the improvement in the PF ratio. As shown in Table III, systolic BP, diastolic BP, and the PF ratio increased significantly in the respiratory group and the non-respiratory group. The increased ratio of systolic BP, diastolic BP, HR, and the PF ratio did not show significant differences between the respiratory and non-respiratory groups. As an evaluation of the above findings, it is suggested that PMX-DHP treatment might have a similar effect between direct and indirect pulmonary injury. In ten patients whose blood pressure was maintained above 90 mmHg with an inotropic agent or a vasopresor, usually dopamine, dobutamine, or noradrenalin, the dosages of vasoactive agents could be reduced in all patients after PMX-DHP treatment. Two of five patients with ARDS whose PF ratio decreased on the day following PMX-DHP treatment were dead due to the exacerbation of ARDS. It appears that PMX-DHP treatment lessens the rate of respiratory failure completely independent of the improvement in circulatory disturbance, although no relation was shown between the PF ratio and systolic BP ($r = 0.14$).

The endotoxin levels were within normal ranges in 13 patients with ALI and ARDS. The endotoxin level showed no direct relations to response after PMX-DHP treatment.

In four patients with cardiogenic pulmonary edema, systolic BP, diastolic BP, and HR showed no significant difference from 129 ± 26, 69 ± 16 and 112 ± 18 to 133 ± 20, 64 ± 13 mmHg and 119 ± 20 per minute after PMX-DHP treatment, respectively. The PF ratio and $PaCO_2$ showed no significant difference from 161 ± 81 and 39 ± 13 to 128 ± 53 and 43 ± 9.1 Torr after PMX-DHP treatment, respectively. In all patients alive at day 30, oxygenation and pulmonary circulation improved after administration of diuretics but not PMX-DHP treatment. Therefore, it is

TABLE III. Results†

	Respiratory disease		Non-respiratory disease	
	Before PMX	After PMX	Before PMX	After PMX
SBP (mmHg)	101 ± 23	130 ± 17*	113 ± 15	142 ± 25*
DBP (mmHg)	58 ± 19	77 ± 17*	65 ± 10	80 ± 14*
HR (/minute)	90 ± 21	96 ± 27	99 ± 21	104 ± 24
PF ratio (Torr)	114 ± 52	140 ± 67*	141 ± 58	173 ± 82*
$PaCO_2$ (Torr)	39 ± 6.0	38 ± 5.3	34 ± 6.8	35 ± 5.1

†Data are mean ± SD.

*$P < 0.05$ before PMX versus after PMX.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PF, PaO_2/FiO_2; PMX, polymyxin B.

suggested that PMX-DHP treatment did not have a direct effect on cardiac pulmonary edema.

Eight of ten patients with untreated PMX-DHP treatment died due to exacerbated ARDS within 30 days. The mortality at day 30 was approximately 80% before induction of PMX-DHP treatment. The mortality of ARDS apparently improved because therapies excluding PMX-DHP treatment did not change.

DISCUSSION

A recent study [17] reported that in patients with ALI and ARDS, mechanical ventilation with a low tidal volume was a procedure that resulted in decreased mortality and increased number of days without use of ventilation. However, many other recent studies of patients with ALI and ARDS have shown no benefits using new pharmacological therapies. In the present study, PMX-DHP treatment markedly improve oxygenation and circulatory disturbance in patients with ALI and ARDS. The overall 30-day survival for this PMX-DHP treatment trial was approximately 80%. The induction of PMX-DHP treatment significantly improved 30-day mortality compared with our group's results between 1990 and 1998. The 6-month survival for the present study was 60%. There were four patients who died between 1 and 6 months after the PMX-DHP treatment. These four patients all appeared to have died from underlying disease and not directly as the result of their ARDS.

The causes of ARDS are multiple. In this study, we chose to study two processes known to lead to ARDS. The source of sepsis included the lung but occurred elsewhere in the body in over 60%. Patients who had pneumonia as the source of sepsis showed subsequent development of diffuse infiltrates and worsening hypoxemia. It is suggested that there is no significant difference in the inflammatory response of the lung for those patients with pneumonia vs. those with an alternative source for their sepsis. Therefore, we divided the present groups into respiratory and non-respiratory disease groups. In the results, some effects of PMX-DHP treatment showed no significant differences between the two groups, disregarding underlying diseases. However, a 20% mortality figure is almost too good compared with other clinical trials that have been reported. In comparison with the severity of the present patients with the outcomes of other intervention trials in ARDS, we did not measure the inflammatory cytokines in serum or bronchoalveolar lavage fluid. The severities of the present patients showed no significant differences among their APACHE II scores, LIS, or preceding organ dysfunction compared with a previous study [18]. Approximately, 20% of their patients died by day 30, but an extrapolation of this mortality to all patients with ARDS treated with PMX-DHP treatment would have to be determined in a properly randomized clinical trial.

This suggests that PMX-DHP treatment was effective against the compromised oxygenation and circulatory disturbance, although endotoxin levels were within normal ranges. In our previous study of endotoxemia in anesthetized sheep, PMX-DHP treatment improved and restored systemic pressure and arterial oxygen [19]. The intrapulmonary shunt ratio after PMX-DHP treatment increased immediately from 0.53 ± 0.11 at baseline to 0.87 ± 0.24 at 0.5 hours and returned to the baseline level at approximately 4 hours. However, the intrapulmonary shunt ratio without PMX-DHP treatment increased to 0.89 ± 0.04 at 1.5 hours and maintained that level. Thus, the intrapulmonary shunt ratio was significantly lower in PMX-DHP treated sheep than untreated sheep during endotoxemia. However, there are several factors that could affect the oxygenation during endotoxemia. The causes of hypoxemia on clinical ARDS are also due to complex interactions of air spaces and pulmonary circulation, including chemical mediators. A study on endotoxin infusion in humans has shown that endotoxin caused marked changes in blood pressure, cardiac index, and systemic vascular resistance [20]. Rothstein [21] showed marked potentiation of the effect of tumor necrosis factor with a small amount of endotoxin, and the lethal effects of their simultaneous presence even at less than lethal doses in mice. Small amounts of endotoxin may play a key role in the presence of other proinflammatory cytokines and mediators in the development of sepsis. A similar finding was observed in the interaction between endotoxin and toxic shock syndrome toxin-1 (TSST-1). The toxicity of TSST-1 in staphylococcal infection increases by 50,000-fold in the presence of endotoxin [12]. There is no available evidence to confirm or show that the endotoxin levels in responders of PMX-DHP treatment were lowered significantly more than the endotoxin levels in non-responders. Septic shock is induced by not only endotoxin but also by some other mediators. The measurement of endotoxin in plasma is based on the bacterial wall of Gram-negative rods alone. Unknown materials such as anandamide can be generated by activated macrophages during endotoxin shock. The adsorption of materials by PMX-DHP may abolish the diverse effects in the septic condition. In the present clinical study, it is suggested that PMX-DHP treatment might directly or indirectly decrease extravascular lung water and the production of proinflammatory cytokines by removal not only of endotoxin but some other factors in plasma and thus demonstrate clinical effects.

CONCLUSIONS

The PMX-DHP treatment improved the circulatory disturbance and oxygenation in patients with ALI and ARDS. The mortality of ARDS patients was approximately 20%. Further studies are necessary to clarify the effectiveness of PMX-DHP treatment in patients with ALI and ARDS.

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