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Evaluation of Different Perfusion Durations in Direct Hemoperfusion with Polymyxin B-Immobilized Fiber Column Therapy for Acute Exacerbation of Interstitial Pneumonias

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Key Words
Acute exacerbation · Idiopathic pulmonary fibrosis · Interstitial pneumonia · PMX-DHP

Abstract
Background: Recently, the potential therapeutic effect of direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) has been reported for acute exacerbation of interstitial pneumonia (AE-IP), a highly morbid clinical event; however, there is no consensus on the appropriate procedure for PMX-DHP. We examined the appropriate perfusion duration of PMX-DHP for AE-IP. ***Methods:*** AE-IP patients receiving PMX-DHP were divided into two groups: short-duration group (≤6 h) (n = 5) and long-duration group (12 h) (n = 12). ***Results:*** The Pao_2/Fio_2 (P/F) ratio increased immediately after PMX-DHP in the two groups. In the long-duration group, the P/F ratio continued to increase over the following 7 days, while, in the short-duration group, the P/F ratio declined again 3 days after therapy. The survival rate 30 days after PMX-DHP was significantly higher in the long-duration group than in the short-duration group. ***Conclusions:*** A long perfusion duration of PMX-DHP is more efficacious for AE-IP than a short perfusion duration.

Introduction

Acute exacerbation of idiopathic pulmonary fibrosis (IPF) has been recognized as a highly morbid clinical event [1–6]. Acute exacerbation has been also reported in other interstitial pneumonias, such as idiopathic nonspecific interstitial pneumonia, interstitial pneumonia with collagen vascular disease (CVD-IP), and chronic hypersensitivity pneumonitis (CHP) [7–11]. This condition is generally resistant to intensive therapy, such as high-dose corticosteroids plus immunosuppressive agents, and the prognosis of acute exacerbation of interstitial pneumonia (AE-IP) has been reported to be extremely poor. Because an effective therapy for AE-IP has not been established, a new therapy with high efficacy is currently desired.

Direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) has been recently developed for the treatment of sepsis to remove endotoxin, which is produced by Gram-negative bacteria [12]. More recently, PMX-DHP has been shown to be an efficacious therapy for acute lung injury/acute respiratory distress syndrome despite their etiology [13–16]. Interestingly, several recent studies have demonstrated the possibility

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that PMX-DHP is also useful for the treatment of AE-IP [17–20]. We previously reported 5 patients with AE-IP treated with PMX-DHP, and found that pulmonary oxygenation was significantly improved in all patients, 2 of which survived more than 30 days after PMX-DHP [17]. In both surviving patients, PMX-DHP was performed for 12 h. In contrast, the other patients, who died within 30 days after PMX-DHP, were treated with PMX-DHP for less than 6 h. These observations suggest that a better outcome is associated with a long perfusion duration of PMX-DHP in patients with AE-IP. To date, however, there is no consensus on the appropriate duration of PMX-DHP for the treatment of AE-IP. In the present study, to determine the appropriate duration of PMX-DHP in AE-IP, we retrospectively reviewed our patients with AE-IP who received PMX-DHP, and investigated the association between the durations of hemoperfusion and its clinical efficacy.

Patients and Methods

Patients

The study population included 17 patients with AE-IP, who were treated with PMX-DHP from 2005 to 2009. Among 17 patients, 5 were included in our previous study [17]. Patients with idiopathic interstitial pneumonias (IIPs) were diagnosed according to the international consensus classification of the American Thoracic Society/European Respiratory Society [21]; 8 patients had IPF and 5 had non-IPF IIP. In IPF patients, 6 were diagnosed by surgical lung biopsy (SLB), and the other 2 were diagnosed clinically. In non-IPF IIP patients, 1 had a histological diagnosis of fibrotic non-specific interstitial pneumonia by SLB. The other 4 non-IPF IIP patients had biopsy-unproven interstitial pneumonia of unknown etiology, but did not meet the clinical diagnostic criteria for IPF on the consensus classification. Two patients had CVD-IP. One patient had rheumatoid arthritis and the other had dermatomyositis. They were diagnosed based on established criteria [22, 23] and neither underwent SLB. Two patients had CHP. The diagnosis of CHP was made according to previously described criteria [24, 25]. Both CHP patients had a history of exposure to birds, and their SLB specimens were compatible with CHP.

The study protocol was approved by the Ethical Committee of the Hamamatsu University School of Medicine and informed consent was obtained from each patient.

Diagnostic Criteria of Acute Exacerbation

Acute exacerbation was defined using the criteria proposed by IPF net [6], with slight modifications for adaptation to interstitial pneumonias other than IPF: (1) previous or concurrent diagnosis of interstitial pneumonia; (2) unexplained worsening or development of dyspnea within 30 days; (3) high-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern; (4) no evidence of pulmonary infection by negative respiratory culture and serological test results for respiratory pathogens, and (5) exclusion of alternative causes, such as left heart failure, pulmonary embolism, and identifiable cause of acute lung injury.

PMX-DHP Therapy

As described in our previous report, PMX-DHP therapy using a PMX column (Toray Medical, Tokyo, Japan) was performed [17]. Briefly, a double-lumen catheter was inserted into a femoral vein. Hemoperfusion was performed at a flow rate of 80–100 ml/min, with 2–3 cycles with a time interval of approximately 24 h through the catheter. Nafamostat mesilate and/or heparin sodium were used as anticoagulants. Initially, PMX-DHP therapy was performed for 2–6 h in the first consecutive 4 patients; however, we attempted to perform PMX-DHP for 12 h if possible in the following consecutive patients, because our previous study suggested that extended hemoperfusion was associated with a favorable outcome. In patients with AE-IP, the short-duration group was defined as undergoing PMX-DHP for $\leq$6 h, and the long-duration group was for 12 h. We compared the clinical effects between the two groups in terms of the improvement of PaO_2/FiO_2 (P/F) ratio and the survival rate at 30 days after PMX-DHP, and evaluated the usefulness of the expanded perfusion duration of PMX-DHP.

Statistical Analysis

For statistical analysis, the χ^2 test, Wilcoxon rank-sum test, and paired t test were used. For the change in the P/F ratio until 7 days after PMX-DHP between two groups, the repeated ANOVA test was used. The cumulative survival rate was calculated using the Kaplan-Meier test; the log-rank test was also used to compare the survival of patients between two groups. Data analyses were performed using JMP Start Statistics (SAS Institute, Inc., Cary, N.C., USA). Data are expressed as the mean $\pm$ SD. For all statistical analyses, a p value <0.05 was considered significant.

Results

Clinical Characteristics

The clinical characteristics of the patients with AE-IP are shown in table 1. Among 17 patients, the short-duration group included 5 patients (4 men and 1 woman, age 67.6 $\pm$ 12.2 years), and the long-duration group consisted of 12 patients (12 men, age 68.5 $\pm$ 8.5 years). Clinical diagnosis was as follows: 2 IPF patients, 2 non-IPF IIP, and 1 CVD-IP associated with dermatomyositis in the short-duration group, and 6 IPF patients, 3 non-IPF IIP, 1 CVD-IP associated with rheumatoid arthritis, and 2 CHP in the long-duration group. There was no significant difference in age, sex, smoking status, clinical diagnosis, previous therapy, and the duration to PMX-DHP from acute symptoms or the initial treatment between the two groups.

Immediately after diagnosis of AE-IP, all patients were treated with high-dose corticosteroid pulse therapy (methylprednisolone, 1,000 mg/day) for 3 days followed

Table 1. Clinical characteristics

	Short-duration group	Long-duration group	p value
Cases, n	5	12	
Age, years	67.6 ± 12.2	68.5 ± 8.5	0.95
Male/female	4/1	12/0	0.11
Smoking status			
Current/ex-smoker/never	0/3/2	0/11/1	0.11
Clinical diagnosis, n			
IPF	2	6	0.66
Non-IPF IIP	2	3	
CVD-IP	1	1	
CHP	0	2	
Previous therapy, n			
No therapy	3	4	0.22
PSL only	0	5	
PSL+ISA	2	3	
Duration to PMX-DHP, days			
From acute symptoms	12.8 ± 11.1	11.5 ± 9.9	0.83
From mPSL pulse	1.8 ± 2.1	0.41 ± 0.9	0.22

IPF = Idiopathic pulmonary fibrosis; IIP = idiopathic interstitial pneumonitis; CVD-IP = collagen vascular disease-interstitial pneumonia; CHP = chronic hypersensitivity pneumonia; PSL = prednisolone; ISA = immunosuppressive agents.

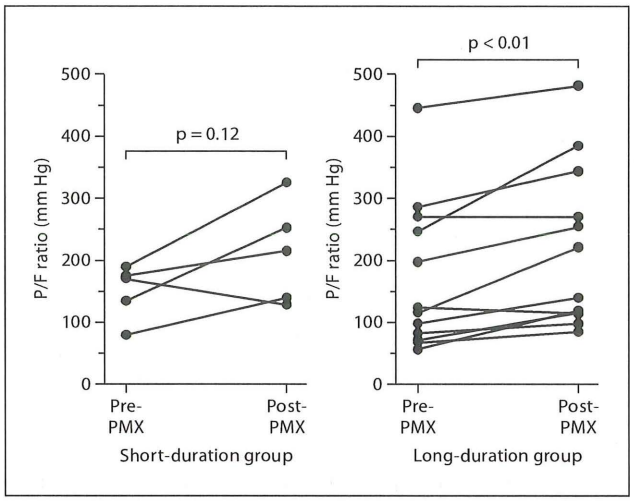

Fig. 1. Change of P/F ratio between before and after PMX-DHP in each individual. Most patients had an improved P/F ratio after PMX-DHP, regardless of the duration time, but the P/F ratio was significantly improved in the long-duration group ($p < 0.01$). However, the change of P/F ratio between before and after PMX-DHP was not statistically different between the two groups ($p = 0.60$).

Table 2. Treatment for acute exacerbation of interstitial pneumonia

	Short-duration group	Long-duration group	p value
Combination therapy			
mPSL pulse, n	5 (100%)	12 (100%)	1.00
CPA pulse, n	4 (80%)	5 (42%)	0.08
Mechanical ventilation, n	3 (60%)	5 (42%)	0.49
Cycles of PMX-DHP, n			
2 cycles/3 cycles	5/0	10/2	0.33

mPSL pulse = Methylprednisolone pulse; CPA pulse = cyclophosphamide pulse.

by tapering doses of prednisolone (table 2). When the effect of the initial treatment was insufficient, cyclophosphamide pulse therapy (500 mg/m^2) was added for 4 and 5 patients in the short- and long-duration groups, respectively. One patient with CHP in the long-duration group received cyclosporin A, and 1 patient with dermatomyositis in the short-duration group was given intravenous immunoglobulin therapy (400 mg/kg) for 5 days. All patients, except 2 in the long-duration group, had two cycles of PMX-DHP. There was no significant difference in the treatment, other than the perfusion duration, for AE-IP between the two groups.

No significant difference was found in any laboratory data, although the serum SP-D levels tended to be lower in the short-duration group than the long-duration group (table 3). Serum levels of endotoxin were within the normal range in all patients. There was also no significant difference in P/F ratios between the two groups. The amounts of the fluid balance varied widely among the patents, and no significant difference was found between the two groups ($p = 0.76$) (–72 ± 1,074 ml in the short-duration group, –534 ± 1,721 ml in the long-duration group).

Clinical Effects of PMX-DHP

The change in parameters after PMX-DHP is shown in table 3, and figures 1 and 2. In the long-duration group, the P/F ratio significantly improved from 170.0 ± 119.4 to 217.1 ± 129.6 just after PMX-DHP ($p < 0.01$) (table 3; fig. 1). In the short-duration group, the P/F ratio was increased from 148.9 ± 44.5 to 210.3 ± 81.1, but this improvement was not statistically significant ($p = 0.12$) (table 3; fig. 1).

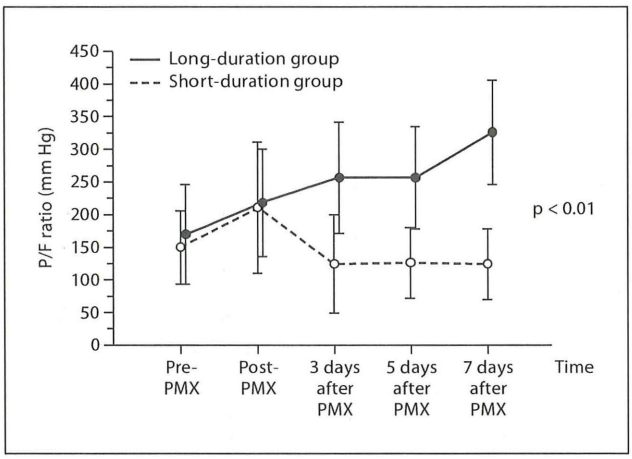

Fig. 2. Change of P/F ratio until 7 days after PMX-DHP. The P/F ratio was significantly improved in the long-duration group ($p < 0.01$).

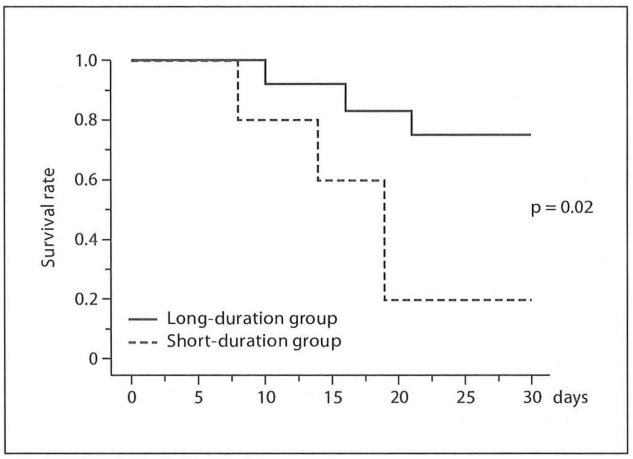

Fig. 3. Survival curves: survival was significantly higher in the long-duration group 30 days after PMX-DHP ($p = 0.02$).

Table 3. Laboratory findings before and after PMX-DHP

	Short-duration group		Long-duration group	
	pre-PMX-DHP	post-PMX-DHP	pre-PMX-DHP	post-PMX-DHP
White blood cells/μl	12,500 ± 6,658	12,460 ± 3,824	12,075 ± 3,654	9,008 ± 4,041*
Neutrophils/μl	11,653 ± 6,772	10,537 ± 3,510	8,922 ± 4,607	6,092 ± 2,280
Lactate dehydrogenase, IU/l	352 ± 62	472 ± 169	426 ± 148	439 ± 263
C-reactive protein, mg/dl	6.1 ± 4.7	7.4 ± 8.9	7.3 ± 6.4	4.15 ± 3.24
Hemoglobin, g/dl	10.9 ± 2.9	10.6 ± 3.4	13.3 ± 2.2	12.5 ± 1.9*
Platelets, $\times 10^4/\mu l$	23.3 ± 8.4	15.2 ± 6.7	23.2 ± 6.3	18.5 ± 7.5**
KL-6, U/ml	1,519 ± 633	–	2,107 ± 1,519	–
SP-D, ng/ml	191 ± 162	–	411 ± 263	–
Endotoxin, pg/ml	<0.8	–	<0.8	–
PaO_2/FiO_2 ratio, mm Hg	148.9 ± 44.5	210.3 ± 81.1	170.0 ± 119.4	217.1 ± 129.6**

* $p < 0.05$, pre- vs. post-PMX-DHP in the long-duration group.
** $p < 0.01$, pre- vs. post-PMX-DHP in the long-duration group.

Figure 2 shows the kinetics of the P/F ratio over the subsequent 7 days after PMX-DHP. In the long-duration group, the improved P/F ratio after PMX-DHP continued to increase over the following 7 days. In contrast, in the short-duration group, the P/F ratio increased just after PMX-DHP, but the ratio then declined to the levels before PMX-DHP 3 days after therapy. The change in the P/F ratio until 7 days after PMX-DHP was significantly larger in the long-duration group than in the short-duration group ($p < 0.01$).

Outcome

The survival curve is shown in figure 3. Four patients (80%) in the short-duration group and 3 patients (25%) in the long-duration group died within 30 days after PMX-DHP. The survival rate was significantly higher in the long-duration group than in the short-duration group ($p = 0.02$). The causes of death included respiratory failure due to AE-IP (n = 2), pulmonary infection (n = 1), and bleeding of a gastric ulcer due to disseminated intravascular coagulation (n = 1) in the short-duration group, and respiratory failure due to AE-IP (n = 2) and pulmonary

infection (n = 1) in the long-duration group. Among 8 patients who required mechanical ventilation (table 2), the long-duration group had longer ventilator-free days at 30 days than the short-duration group (11.2 ± 10.9 vs. 0 ± 0 days, respectively), but the difference was not statistically significant (p = 0.12).

Adverse Events

The red cells and platelets were significantly decreased after PMX-DHP in the long-duration group, but not in the short-duration group (table 3); however, no serious adverse events, such as bleeding during PMX-DHP, were found and the levels recovered spontaneously. No patients required platelet transfusion. There were no other adverse effects associated with PMX-DHP.

Discussion

AE-IP is currently defined as a distinct condition with acute, often fatal, deterioration of the respiratory status in several types of interstitial pneumonias [1–11]. Patients with AE-IP showed an extremely poor prognosis, and no efficacious therapy has been established so far. Interestingly, several recent studies, including ours, have demonstrated the therapeutic potential of PMX-DHP to improve oxygenation and prognosis in a small population of patients with AE-IP [17–20]. In the present study, we further confirmed these observations in more patients, and also found that the long duration (12 h) of PMX-DHP significantly improved the survival of patients with AE-IP, compared with the short duration (≤6 h).

In the treatment of sepsis, PMX-DHP is performed usually for 2 h. A meta-analytic review showed that 2-hour PMX-DHP has favorable effects on hemodynamics, pulmonary oxygenation, and mortality in sepsis [12]. PMX-DHP was performed for 2–3 h in the acute lung injury/acute respiratory distress syndrome, and these reports have also shown that PMX-DHP improved circulating disturbance and pulmonary oxygenation [13–16]. In patients with more severe conditions or with no efficacy of 2-hour PMX-DHP, however, recent studies recommended a longer duration of PMX-DHP, which significantly improved pulmonary oxygenation and hemodynamics with a reduction of required catecholamine [26, 27]. PMX-DHP is originally designed to be applied for 2 h, but Yamashita and coworkers [26, 27] demonstrated that the columns can be used for 6–24 h without loss of efficacy. They assumed that the high efficacy of long-duration PMX-DHP in patients with severe sepsis was associated with an increased absorption of inflammatory mediators as well as endotoxin. Indeed, Yamashita and Takasaki [26] reported that column-absorbed amounts of endogenous cannabinoids, including anandamide and 2-arachidonylglycerol, which are responsible for sepsis-induced hypotension, was increased 3.5- and 24-fold in 24-hour PMX-DHP, respectively, when compared with 2-hour PMX-DHP. In the treatment of AE-IP, however, there has been no report comparing the effectiveness of PMX-DHP between short and long durations. With this regard, the present study demonstrated that long-duration (12 h) PMX-DHP produced more marked and prolonged improvement of oxygenation, leading to significantly better survival than short-duration PMX-DHP in patients with AE-IP. Between the two groups, there were no significant differences in patient characteristics, baseline clinical data, or concomitant therapies. Thus, we concluded that the superior efficacy of long-duration over short-duration PMX-DHP is related mainly to the extended perfusion time in AE-IP.

Adverse effects with PMX-DHP include thrombocytopenia and hypotension during perfusion. Our previous study showed that platelet levels decreased in 4 of 5 patients with AE-IP, but they recovered spontaneously. In the present study, although the levels of platelets, hemoglobin, and leukocytes significantly declined after long-duration, but not short-duration PMX-DHP, there were no serious adverse events. In addition, no patients needed blood transfusion. These observations suggest that long-duration PMX-DHP can be well tolerated, and safely applied to patients with AE-IP.

The mechanism by which PMX-DHP improves pulmonary oxygenation in AE-IP has not been elucidated. The removal of plasma endotoxin does not have a major role, because serum levels of endotoxin were within the normal range in our cases as well as previously reported cases of AE-IP [17–20]. Recent studies have reported that PMX-DHP reduces metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 [15], neutrophil reactive oxygen species [28], neutrophil elastase and interleukin-8 [16], which cause lung injury, and increase vascular permeability as well as the intrapulmonary shunt ratio. These mediators are known to be released from neutrophils and monocytes, and it has been shown that the polymyxin B-immobilized fiber column itself traps activated blood neutrophils and monocytes, which may be involved in the reduction of releasing mediators [29–31]. The extended use of PMX-DHP may increase the absorption of inflammatory mediators and their producers.

Further studies will be required to clarify the precise mechanism of PMX-DHP in AE-IP.

There are several limitations to the present study. First, this was a retrospective and non-randomized study, so there were selection and recall biases. Second, although this study included a relatively large proportion of patients with AE-IP, the sample size was still too small to determine the appropriate duration of perfusion. Third, this was evaluated in the heterogenous population of AE-IP. For all of these reasons, there was the possibility that confounding factors other than the duration of treatment were associated, in part, with the results observed in the present study.

In conclusion, the present data suggest that the extended perfusion duration of PMX-DHP is more efficacious without serious adverse events for the treatment of AE-IP. This warrants future prospective studies in a larger series of patients with AE-IP to confirm our observations.

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