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ORIGINAL ARTICLE

Apheresis

Early induction of direct hemoperfusion with a polymyxin-B immobilized column is associated with amelioration of hemodynamic derangement and mortality in patients with septic shock

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Abstract This study was conducted to clarify the effectiveness of induction timing of direct hemoperfusion with a polymyxin-B immobilized column (PMX-DHP) for amelioration of hemodynamic derangement and outcome in patients with septic shock. Suspected Gram-negative septic shock patients who received PMX-DHP therapy from January 2010 to December 2014 in our ICU were enrolled in this study. The patients were divided into two groups that received PMX-DHP therapy within 8 h (early group) and more than 8 h (late group) from catecholamine administration. Changes in catecholamine dose [catecholamine index (CAI)], catecholamine dose/mean arterial pressure [catecholamine index pressure (CAIP)], PaO_2/FiO_2 and PEEP level were determined at the start of and 24 h after the start of PMX-DHP therapy. Ventilator-free days (VFD), ICU-free days (IFD), 28-day and hospital mortality were also determined. There were no significant differences in patients' characteristics between the two groups. CAI and CAIP were significantly decreased in the early group. PaO_2/FiO_2 was not changed whereas PEEP level in the early group was significantly decreased during PMX-DHP therapy. IFD and VFD were not different in the two groups. Mortality at 28 days was significantly improved in the early group. Endotoxin acts as an early mediator in sepsis patients with suspected Gram-negative infection. Earlier induction of PMX-DHP therapy as in our study is closely associated with earlier weaning from hemodynamic derangement and with improvement of mortality. Therefore, early induction of PMX-DHP therapy is recommended for the treatment of septic shock in patients with presumed Gram-negative infection.

Keywords Septic shock · Direct hemoperfusion with polymyxin-B immobilized column · Catecholamine · Prognosis

Introduction

Despite advances in modern medicine, morbidity and mortality of severe sepsis and septic shock are still high [1]. The precise mechanisms underlying the development of sepsis have not been clarified, but some pathogen-originating substances called pathogen-associated molecular patterns (PAMPs) have recently been shown to play a pivotal role in the pathogenesis of sepsis [2]. Lipopolysaccharides (LPS) are constituents of endotoxin that act as PAMPs. LPS have various bioactivities and are associated with the development of sepsis. LPS activate monocytes/macrophages via Toll-like receptor (TLR) 4, resulting in the production of various mediators such as TNF-α, IL-1β and nitrous oxide [3]. Therefore, production and release of LPS from Gram-negative microorganisms is thought to be one of the key steps in the clinical course of septic shock and severe sepsis.

In a clinical setting, regulation of LPS can potentially result in a favorable outcome in patients with sepsis. It is known that polymyxin B, an antibiotic, has a strong affinity to endotoxin but has strong adverse effects when administered into the blood stream. To avoid these adverse effects of polymyxin-B, direct hemoperfusion with a

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polymyxin-B immobilized column (PMX-DHP) system has been used for adsorption of endotoxin in patients with sepsis.

In the management of severe sepsis and septic shock, PMX-DHP is not mentioned in the Surviving Sepsis Campaign Guidelines (SSCG) 2008 [4], but some clinical trials using PMX-DHP in patients with endotoxin related septic shock have shown favorable effects and outcome [5]. The optimal timing to perform PMX-DHP therapy in patients with septic shock is unclear. Therefore, this study was conducted to clarify whether the induction period of PMX-DHP therapy affects the clinical outcome in patients with septic shock.

Patients and methods

This study was approved by the Ethical Review Board of Sapporo Medical University.

Patients

Septic shock patients who were suffering from presumed Gram-negative infection and who were treated with PMX-DHP in our intensive care unit from January 2010 to December 2014 were enrolled in this study. Patients less than 15 years of age, having hematological malignancy and receiving immunosuppressive therapy were excluded. Eligible patients were divided into early and late groups that were defined by the time from vasopressor administration to initiation of PMX-DHP (within 8 h and more than 8 h, respectively). The reason for group division by 8 h is that 8 h was median time from vasopressor administration to initiation of PMX-DHP in all patients. PMX-DHP therapy was performed when the catecholamine dose represented by catecholamine index (CAI) was more than 5. CAI was calculated as follows: (dose of dopamine and dobutamine) + (dose of noradrenaline and adrenaline) × 100. All doses were expressed as μg/kg/min.

Treatment of sepsis

Septic shock was defined according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [6]. Septic shock was treated according to the initial resuscitation bundle of Surviving Sepsis Campaign Guidelines 2008. Briefly, monitoring of lactate level, appropriate volume replacement, blood culture prior to antibiotic administration and noradrenaline administration were performed within 6 h. Cultures of blood, sputum, urine, feces, pleural effusion, ascites and drainage fluid were performed several times during ICU admission.

Data collection

Age, gender, SOFA score on admission, APACHE II score, time from catecholamine administration to PMX-DHP induction, time from ICU admission to induction of PMX-DHP, duration and frequency of PMX-DHP therapy, concomitant use of CRRT, 28-days mortality, hospital mortality, ICU free days (IFD) and ventilator-free days (VFD) were compared between the two groups.

Catecholamine index pressure (CAIP) was used to evaluate the hemodynamic condition. CAIP was calculated as follows: CAI/mean blood pressure. Changes in oxygenation (PaO_2/FiO_2) and PEEP level were compared.

Procedures for PMX-DHP and apparatus used in this study

The devices used in this study were TR-55X (Toray Medical Co. Ltd, Tokyo, Japan) as a machine, JCH-SMU (JUNKEN, Tokyo, Japan) as an extracorporeal circuit and PMX-20R (Toray Medical, Tokyo, Japan) as an endotoxin removal column. Nafamostat mesilate was administered as an anticoagulant at a rate of 30 mg/h. Blood flow was set at a rate of 80–100 ml/min. The planned duration of PMX-DHP therapy was 24 h.

Statistical analysis

Data are expressed as mean±standard deviation (SD) unless otherwise stated. Comparison of the two groups was performed using the Mann–Whitney U test. A p value <0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics of patients. There were no significant differences in age, gender, APACHE II score and SOFA score between the two groups. The time from catecholamine administration to induction of PMX-DHP therapy in the early group was significantly longer than that in the late group. There was a significant difference between the time from catecholamine administration to ICU admission in the early group and that in the late group. There were no significant differences in the time from ICU admission to induction of PMX-DHP therapy, duration and frequency of PMX-DHP therapy, and concomitant use of CRRT between the two groups.

More than half of the infectious foci were in the lungs and abdomen, and *E. coli* and *Pseudomonas aeruginosa* were positive by culture of sputum, ascites or drainage fluid. Mortality rate after 28 days from admission to the ICU was significantly lower in the early group than in the

Table 1 Demographics of patients prior to PMX-DHP therapy

	Early group	Late group	*p*
Number	23	24	–
Age (years)	66.3 ± 12.7	69.2 ± 13.8	0.3378
Gender (male/female)	16/7	20/4	0.2651
APACHE II score	28.7 ± 7.1	28.7 ± 6.2	0.9830
SOFA score	12.0 ± 3.4	12.2 ± 2.5	0.9400
Time from cathecholamine administration to induction of PMX-DHP (h)	4.0 ± 2.0	13.1 ± 12.4	0.0001
Time from ICU admission to induction of PMX-DHP (h)	4.5 ± 3.2	8.1 ± 9.2	0.8389
Time from cathecholamine administration to ICU admission (h)	1.8 ± 2.4	9.9 ± 10.3	0.0003
Duration of PMX-DHP (h)	18.1 ± 4.4	17.1 ± 6.0	0.7815
Concomitant use of CRRT	20	19	0.4775
Infectious foci			
Lung	9	11	0.6422
Abdominal	8	8	1.0000
Urinary tract	2	2	0.9645
Mediastinum	2	1	0.5255
CRBSI	2	2	1.0000
Detected microorganisms			
E. coli	10	9	0.6763
Pseudomonas aeruginosa	7	5	0.4505
Klebsiella pneumoniae	2	2	0.9645
Enterobacter cloacae/aerogenes	2	2	0.9645
Unknown	2	6	0.2448

CRBSI catheter related blood stream infection

Table 2 Mortality, ICU free days and ventilator-free days

	Early group	Late group	*p*
28 days mortality (%)	15.4	42.8	**0.0310**
Hospital mortality (%)	19.2	42.8	0.0567
ICU free days (day)	14.9 ± 9.9	11.8 ± 10.6	0.2687
Ventilator free days (day)	20.3 ± 9.2	13.8 ± 12.2	0.0605

Bold indicates $p < 0.05$

late group. Hospital mortality was not significantly different in the two groups. IFD and VFD were not significantly different in the two groups (Table 2).

Table 3 shows hemodynamic and pulmonary variables prior to PMX-DHP therapy and 24 h after PMX-DHP therapy. There was no significant difference in CAI between the two groups prior to PMX-DHP therapy. Constituents of given doses of noradrenaline and dopamine in two groups were the same prior to PMX-DHP therapy. However, CAI in the early group was significantly decreased at 24 h after PMX-DHP therapy, whereas CAI in the late group was not changed at 24 h after PMX-DHP therapy. CAIP in the early group was significantly decreased during the first 24 h of PMX-DHP therapy. On the other hand, CAIP in the late group did not change during the first 24 h of PMX-DHP therapy. There was a significant difference in CAIP at 24 h after initiation of PMX-DHP therapy between the early group and the late group.

PaO_2/FiO_2 ratio was increased in both groups during the first 24 h. However, the changes in PaO_2/FiO_2 ratio were not significantly different in the two groups. There was no significant difference in PEEP level between the early group and the late group prior to PMX-DHP therapy or 24 h after PMX-DHP therapy. PEEP level in the early group was significantly decreased during the first 24 h of PMX-DHP therapy (Table 3).

Discussion

Many studies have shown the clinical effectiveness of PMX-DHP therapy in septic patients with suspected Gram-negative bacterial infection [7]. A meta-analysis of PMX-DHP efficiency in the early period from 1998 to 2006 showed improvement of hypotension with the reduction in catecholamine requirement and impaired oxygenation, increase in urine volume, and decrease in mortality [8, 9]. However, the number of patients in these studies were

Table 3 Hemodynamic and pulmonary variables prior to PMX-DHP therapy and 24 h after PMX-DHP therapy

	Prior to PMX therapy			24 h after PMX therapy		
	Early group	Late group	*p* value	Early group	Late group	*p value*
CAI (μg/kg/min)	16.3 ± 8.2	16.7 ± 13.2	0.5231	4.2 ± 6.9$^{\#\#}$	10.5 ± 10.3	**0.0170**
Dopamine dose (μg/kg/min)	4.0 ± 4.3	3.7 ± 4.0	0.1135	0.7 ± 1.5$^{\#\#}$	2.1 ± 2.6	0.0578
Noradrenaline dose (μg/kg/min)	0.12 ± 0.08	0.11 ± 0.11	0.2582	0.03 ± 0.07$^{\#\#}$	0.08 ± 0.08	**0.0361**
CAIP (μg/kg/min/mmHg)	0.20 ± 0.13	0.20 ± 0.18	0.7252	0.04 ± 0.07$^{\#\#}$	0.12 ± 0.13	**0.0134**
PaO_2/FiO_2	240 ± 100	239 ± 91	1.0000	246 ± 112	208 ± 105	0.1835
PEEP level (cmH_2O)	7.8 ± 2.5	7.0 ± 2.5	0.3041	5.9 ± 1.5$^{\#}$	7.3 ± 2.8	0.0855

Bold indicates $p < 0.05$

PMX direct hemoperfusion with polymyxin-B immobilized column, *CAI* catecholamine index, *CAIP* catecholamine index pressure, *PEEP* positive end-expiratory pressure (cmH_2O)

$^{\#}$ $p < 0.05$ vs prior to PMX therapy, $^{\#\#}$ $p < 0.01$ vs prior to PMX therapy

small, and they were observational and non-blinded studies. Randomized controlled study (EUPHAS study) has demonstrated beneficial effects of PMX-DHP therapy on hypotension, inotropic requirement, organ failure and 28-day mortality [10]. In that study, initiation of PMX-DHP therapy was set within 6 h after abdominal surgery, and this early application of PMX-DHP therapy may have resulted in the beneficial outcome. Our results showed that early induction of PMX-DHP therapy within 8 h after catecholamine administration resulted in a favorable outcome compared to late induction of PMX-DHP therapy more than 24 h after catecholamine administration. These results are consistent with results of recent studies [11, 12]. These studies showed that delay in PMX-DHP therapy is associated with increase in mortality. Therefore, it is recommended that PMX-DHP therapy be performed as early as possible when catecholamines are being administered for treatment of septic shock.

Endotoxin is known to act as PAMPs and this initial mediator of sepsis plays an important role in the development to septic shock. A new possible candidate for induction of septic shock has been shown in recent years. Several studies have demonstrated that sepsis induces production of endocannabinoide, which includes anandamide (ANA) and 2-arachidonylglycerol (2-AG), from activated monocytes/macrophages and activated platelets, resulting in severe hypotension in the early period of septic shock [13, 14]. Additionally, it has been demonstrated that polymyxin-B has a strong affinity to these septic shock-induced initial mediators, ANA and 2-AG. Indeed, Wang et al. [15] demonstrated that a polymyxin-B immobilized column adsorbs ANA and 2-AG in vitro. These findings can explain why PMX-DHP therapy sometimes improves hypotension within only 15–30 min after initiation of treatment. Since endotoxin adsorption requires about 2 h to exert its efficacy via immune system regulation, this extremely early effectiveness is attributable to a factor other than endotoxin removal. Therefore, PMX-DHP therapy adsorbs not only endotoxin but also ANA and 2-AG and exerts its therapeutic efficacy when applied in the early period of septic shock.

In this study, long-term PMX-DHP therapy (mean duration of 18 h) was performed. Possible mechanisms for improvement of hypotension after PMX-DHP therapy include adsorption of activated neutrophils [16] and monocytes [17] and matrix metallopeptidase-9 (MMP-9) [18] in addition to the above-mentioned anandamides. Activated neutrophils play a pivotal role in the pathogenesis of acute lung injury in the early stage [19]. Therefore, regulation of activated neutrophils may result in improvement of lung injury in sepsis. Our results showed that PaO_2/FiO_2 was not improved significantly at 24 h after PMX-DHP therapy in either group. However, PEEP level in the early group was significantly decreased. This result shows the possible favorable effect of PMX-DHP therapy on impaired oxygenation and may be associated with regulation of activated neutrophils by long-term PMX-DHP therapy, especially in the early period of septic shock [20].

Limitations

Our study was carried out by a retrospective observational method. Moreover, the sample size in each group was very small. The inclusion criterion in this study was initiation of catecholamine administration. This criterion means that some patients in the late group received initial resuscitation in the general ward prior to ICU admission. Insufficient initial resuscitation against septic shock might have affected prognosis in our study. Therefore, a large-scale and prospective study is required to clarify whether early initiation of PMX-DHP therapy results in a favorable outcome in septic shock patients. However, the results of our study provide a rationale for investigation of the

potential improvement of hemodynamic derangement with early induction of PMX-DHP.

Conclusion

Early induction of PMX therapy is recommended for treatment of septic shock in patients with presumed Gram-negative infection.

Compliance with ethical standards

Conflict of interest The authors declare that we have no conflict of interests regarding this manuscript.

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