

Impact of Extended Duration of Polymyxin B-immobilized Fiber Column Direct Hemoperfusion on Hemodynamics, Vasoactive Substance Requirement, and Pulmonary Oxygenation in Patients With Sepsis: An Observational Study

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Abstract

Background

Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) is used for patients with septic shock, and the recommended hemoperfusion period is 2 h. However, it remains unclear whether the optimal duration is 2 h or longer. The purpose of this study was to compare the effects of PMX-DHP between conventional and longer duration of PMX-DHP.

Methods

We retrospectively investigated 103 patients with sepsis who underwent PMX-DHP between April 2015 and March 2020. The demographic data, routine biochemistry, microbiological data, primary infection site were reviewed in the medical chart. The acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, heart rate, mean arterial pressure (MAP), vasoactive-inotropic score (VIS), respiratory rate, $\text{PaO}_2/\text{F}_1\text{O}_2$, at baseline and day 3 were compared between the standard group (patients received 2 h of PMX-DHP) and extended group (patients received more than 2 h of PMX-DHP). Ventilator-free days, incidence of continuous renal replacement therapy, and 28-day mortality were also compared between the groups.

Results

Median MAP was significantly lower and median VIS was significantly higher in the extended group at baseline ($p < 0.05$, 0.01 , respectively). There were no significant differences in APACHE II score, SOFA score, and $\text{PaO}_2/\text{F}_1\text{O}_2$ at baseline between the two groups. The increase of MAP and the decrease in VIS from baseline to day 3 were significantly greater in the extended group ($p < 0.01$, respectively). In the extended group, increase in $\text{PaO}_2/\text{F}_1\text{O}_2$ was significantly larger in the patients who underwent ≥ 8 h duration than that in patients who underwent < 8 h duration ($p < 0.01$). The ventilator-free days, the incidence of continuous renal replacement therapy, and the 28-day mortality were not different between the groups.

Conclusions

Longer duration of PMX-DHP effectively improved MAP and decreased the volume of vasoactive-inotropic agents compared with the conventional duration. Eight and longer hours duration of PMX-DHP improved the pulmonary oxygenation. Further studies are needed to confirm the efficacy of longer duration of PMX-DHP in patients with septic shock. (329/350 limits)

Background

Sepsis is defined as the life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock is a subset in which the risk of mortality increased [1]. Despite the progress in the understanding of pathophysiology and availability of various treatments including new antibiotics,

fluid therapy, and vasoactive-inotropic approaches, the patients' outcome has not been satisfactorily improved since the backgrounds of sepsis are highly heterogeneous [2]. Perhaps, a one-fits-all novel treatment for sepsis can not be expected.

Endotoxin, an outer membrane component of Gram-negative bacteria, plays an important role in the pathogenesis of sepsis, septic shock, and sepsis-associated organ dysfunction. Endotoxin activates macrophages and other leukocytes to induce the excess cytokines production, which in turn elicits a systemic inflammatory response and leads to the endothelial dysfunction and increased vascular permeability [3]. Endotoxin adsorption by Polymyxin B-immobilized fiber column (Toraymyxin® Cartridge, Toray Medical, Tokyo, Japan) direct hemoperfusion (PMX-DHP) has been used for the treatment of septic shock not only in Japan but also in Italy, Korea, Taiwan, and many other countries. Recently, the EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock) performed in North America has shown that PMX-DHP treatment could not reduce 28-day mortality in septic shock patients with endotoxin activity assay level ≥ 0.6 [4]. However, *a post hoc* analysis has demonstrated that PMX-DHP treatment had beneficial effects on changes in mean arterial pressure (MAP), ventilator-free days to 28 days, and 28-day mortality in septic shock patients with endotoxin activity assay (EAA) level between 0.60 and 0.89 [5]. Therefore, it is hypothesized that PMX-DHP treatment may have beneficial effects on the derangements of systemic circulation and ventilation in endotoxemic patients whose EAA level within the appropriate range for treatment. Consequently, a TIGRIS trial is planned in septic shock patients with multiple organ dysfunction score > 9 and EAA level between 0.6 and 0.89 (ClinicalTrial.gov Identifier NCT 03901807). Another possible cause of unsatisfactory result is the short duration of hemoperfusion. Although the instruction recommends 2 h of treatment [6], it remains unclear whether the optimal duration is 2 h. Some studies performed in Japan have demonstrated that longer duration of PMX-DHP had better effects on hemodynamics and pulmonary oxygenation [7, 8, 9]. Accordingly, we planned to compare the effects of PMX-DHP treatment on MAP, vasoactive-inotropic agent requirement, pulmonary oxygenation, and outcome between the conventional (2h) and the longer (> 2 h) duration of PMX-DHP.

Methods

Study design and subjects

We retrospectively reviewed septic patients who underwent PMX-DHP at the intensive care unit (ICU) of Juntendo University Hospital between April 2015 and March 2020. The inclusion criteria were age ≥ 18 years, septic patients who underwent PMX-DHP, and patients admitted to the ICU for at least 72 h of observation. Sepsis was defined as an increase in sequential organ failure assessment (SOFA) score ≥ 2 points, and septic shock was identified by a vasopressor requirement to maintain a MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L in the absence of hypovolemia according to definitions for Sepsis-3 [1,10]. The study protocol was reviewed and approved by the Ethics Committee of Juntendo University Hospital (approval number 19-291). All procedures in this study were performed in accordance with the study protocol and the 1964 Helsinki declaration as amended. The need for patient approval and informed

consent was waived due to the retrospective nature of the study. Instead, the protocol summary was publicized on the university website clearly informing of the patients' right to refuse participation.

Data collection

The following data of all patients were obtained from medical records: demographic information including age, sex, laboratory data including white blood cell count, hematocrit, platelet count, levels of total bilirubin, creatinine, C-reactive protein, procalcitonin, and lactate, primary infection site, bacterial culture results, heart rate, MAP, dose of vasoactive-inotropic agent, respiratory rate, PaO₂/F_IO₂ ratio, duration and frequency of PMX-DHP, and concomitant use of continuous renal replacement therapy (CRRT) and mechanical ventilation. In the present study, twelve patients received vasopressin in addition to norepinephrine. Therefore, the dose of vasoactive-inotropic agent was expressed as vasoactive-inotropic score (VIS) [11], and calculated as follows:

$$\text{VIS} = \text{Dopamine dose } (\mu\text{g}/\text{kg}/\text{min}) + \text{Dobutamine dose } (\mu\text{g}/\text{kg}/\text{min}) + 100 \times \text{Epinephrine dose } (\mu\text{g}/\text{kg}/\text{min}) + 10 \times \text{Milrinone dose } (\mu\text{g}/\text{kg}/\text{min}) + 10,000 \times \text{Vasopressin dose } (\text{units}/\text{kg}/\text{min}) + 100 \times \text{Norepinephrine dose } (\mu\text{g}/\text{kg}/\text{min}).$$

The severity of illness was assessed using acute physiology and chronic health evaluation (APACHE) II score [12], and the severity of organ dysfunction was assessed by SOFA score [10]. To assess the impact on the efficacy of longer duration of PMX-DHP treatment, we divided the patients into two groups: standard (2 h) group and extended (> 2 h) group and compared the above-mentioned parameters between the two groups. Changes in MAP, VIS, PaO₂/F_IO₂, SOFA score, lactate level, and platelet count from baseline to day 3 were also compared between the two groups. In addition, ventilator free days to 28 days, rate of CRRT, and the 28-day mortality were compared between the two groups.

Statistical analysis

Quantitative data are expressed as the median and interquartile range (IQR). The intergroup differences were compared using the Mann-Whitney U test. Categorical data are expressed as absolute values and percentages, and they were analyzed using the chi-square test. A *p* value of less than 0.05 was considered statistically significant for all comparisons.

Results

There were 103 septic patients who underwent PMX-DHP: the standard group (*n* = 58) and the extended group (*n* = 45). The patients' characteristics at baseline are shown in Table 1. The number of septic shock patients in the standard group and in the extended group was 41 (71%) and 45 (100%), respectively. At baseline, the median MAP in the extended group was significantly lower (*p* < 0.05), and the median VIS in the extended group was significantly higher compared with the standard group (*p* < 0.01). The number of patients with VIS ≥ 20 in the standard group and in the extended group was 13 (22 %) and 19 (42%), respectively. Thus, the number of patients with VIS ≥ 20 in the extended group was significantly larger

compared with the standard group ($p < 0.05$). At baseline, there were no significant differences in respiratory rate, lactate level, $\text{PaO}_2/\text{F}_1\text{O}_2$, APACHE II score, SOFA score, white blood cell count, hematocrit, platelet count, and levels of total bilirubin, creatinine, C-reactive protein, and procalcitonin between the two groups.

The site of infection, type of microorganisms, and rate of bacteremia are shown in Table 2. The most common site of infection in all patients was abdomen (41 %), followed by urinary tract (16 %), and blood (15 %). Of those who had positive cultures, Gram-negative organisms accounted for 59 % and Gram-positive organisms accounted for 13 %. The proportion of patients where all obtained cultures showed no growth of bacteria was 17 %. Blood cultures were positive in 56 % of the patients.

Changes in MAP, VIS, $\text{PaO}_2/\text{F}_1\text{O}_2$, SOFA score, lactate level, and platelet count from baseline to day 3 are shown in Table 3. Changes in MAP and VIS in the extended group were significantly larger compared with the standard group ($p < 0.05$, 0.01 , respectively). Changes in $\text{PaO}_2/\text{F}_1\text{O}_2$, SOFA score, lactate level, and platelet count from baseline to day 3 were not statistically different between the two groups. However, among the extended group, the patients who underwent ≥ 8 h of duration ($n = 20$) revealed median [IQR] change in $\text{PaO}_2/\text{F}_1\text{O}_2$ was 100 mmHg [74 mmHg, 168 mmHg] and the rise was significantly larger than that in the patients who underwent < 8 h duration ($n = 25$) (61 mmHg [10 mmHg, 82 mmHg], $p < 0.01$). In the extended group, 11 patients with $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 200$ mmHg at baseline had concomitant moderate or severe acute respiratory distress syndrome (ARDS) [13]. The median [IQR] $\text{PaO}_2/\text{F}_1\text{O}_2$ at baseline in the patients who underwent ≥ 8 h duration was 133 mmHg [78 mmHg, 215 mmHg] and this was significantly lower than that in the patients who underwent < 8 h duration (230 mmHg [211 mmHg, 347 mmHg], $p < 0.001$).

Implementation of PMX-DHP, CRRT, and mechanical ventilation, and 28-day mortality are shown in Table 4. A second session was not carried out when the patient's hemodynamics improved or deceased after the first session. As a result, the incidence of one session was significantly lower, and that two sessions were significantly higher in the extended group ($p < 0.05$). The median total duration of PMX-DHP was significantly ($p < 0.01$) longer in the extended group than that in the standard group. There were no significant differences in the interval between ICU admission and PMX-DHP initiation, rate of CRRT and mechanical ventilation, ventilator-free days to 28 days, and the 28-day mortality between the two groups. Mortality at 28 days based on site of infection was: abdomen [standard group 3/9 (33 %) vs. extended group 4/11 (36 %)], lung [standard group 2/9 (22 %) vs. extended group 1/11 (9 %)], urinary tract [standard group 0/9 (0 %) vs. extended group 3/11 (27 %)], blood [standard group 1/9 (11 %) vs. extended group 1/11 (9 %)], skin and soft tissue [standard group 2/9 (22 %) vs. extended group 0/11 (0 %)], and unknown [standard group 1/9 (11 %) vs. extended group 2/11 (18 %)].

Discussion

The major finding in the present study was that the longer duration of PMX-DHP treatment was associated with significant hemodynamic improvement and reduction of vasoactive-inotropic agent

requirement. At baseline, MAP was significantly lower and VIS was significantly higher in the extended group compared with the standard group. High VIS was empirically defined as ≥ 20 and maximum VIS ≥ 20 has been shown to predict poor clinical outcomes [11], and the patients with high VIS were 22 % in the standard group and 42 % in the extended group in the present study. Thus, it was estimated that a longer duration of PMX-DHP tended to be applied in patients who required more vasoactive-inotropic agents to maintain hemodynamics. Some previous studies performed in Japan have shown that longer duration of PMX-DHP had better performance on hemodynamics [7, 8, 9]. The present study also demonstrated similar results and the effects on hemodynamics were better in the extended group. These findings suggest a longer duration of more than 2 h of PMX-DHP may help the recovery of the systemic circulation and contribute to decreasing the vasoactive-inotropic agent use which may lead to the prevention of the life-threatening organ failure.

With respect to the hemoperfusion period, the previous *in vitro* study using calf serum has demonstrated that the PMX-DHP could reduce the endotoxin level considerably in 2 h of circulation [6], and this is the rationale for the 2 h standard duration of PMX-DHP treatment. However, we have previously reported that a longer duration of PMX-DHP decreased norepinephrine dose and decreased circulating adhesion molecules which resulted in the improvement of hemodynamics and pulmonary oxygenation [7]. In the present study, the sub-analysis of the extended group clarified that an increase in $\text{PaO}_2/\text{F}_i\text{O}_2$ from baseline to day 3 was significantly larger in patients who underwent ≥ 8 h duration than that in patients who underwent < 8 h duration. This finding suggests that a longer duration of PMX-DHP is necessary to improve pulmonary oxygenation than to improve hemodynamic decompensation. The reason why there was no difference in the pulmonary oxygenation between the standard group and the total extended group is probably that more than half of patients in the extended group were undergone < 8 h duration. Yamashita et al. [8] have also shown that longer duration of PMH-DHP improved hemodynamics and pulmonary oxygenation in 37 patients with septic shock. Miyamoto et al. [9] have reported in their retrospective study that 12 h duration of PMX-DHP ($n = 18$) significantly increased MAP and decreased the vasopressor dependency index compared with 2 h duration of PMX-DHP ($n = 18$). Furthermore, Kawazoe et al. [14] have demonstrated in a sub-analysis of the DESIRE trial, a Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation study, that the 28-day mortality rate was 7/22 (31.8 %) in the standard group and 0/14 (0 %) in the extended group. All studies indicated the same trends, however, the aforementioned studies including ours had a relatively small number of patients and a larger study is warranted. In other case series study, we have demonstrated that the median endotoxin removal rate was 74.4% after 24 h PMX-DHP in 19 septic shock patients, suggesting that 24 h treatment was effective in removing endotoxin [15].

Romaschin et al. [16] performed an *in vitro* experiment to examine the endotoxin adsorption capacity of PMX-DHP column (PMX-20R) using a closed-circuit system. A single introduction of endotoxin-activated bovine serum or plasma was recirculated through PMX-20R using a roller pump at 100 mL/min for 4 h. The total endotoxin amount given to the circuit was 15 μg and the initial concentration in the perfusate was 10 ng/mL. After 4 h of perfusion, the endotoxin concentration decreased to 2-3 ng/mL and the

residual endotoxin in the perfusate was approximately 3 µg. Therefore, total amount of endotoxin removal was about 12 µg. Yamashita et al. [17] also examined the adsorption equilibrium phenomenon till 24 h of PMX-01R in closed circuit system. Endotoxin was continuously injected at a fixed rate for 24 h into fetal bovine serum perfusate and the circulating endotoxin levels in PMX-01R circuit and sham-control circuit were compared. As a result, the level in the endotoxin adsorption circuit was approximately half of that in the sham-control circuit at 24 h and PMX-01R column endotoxin adsorption demonstrated a gradual decrease through 24 h suggesting the saturation point had not been reached. Eventually, endotoxin adsorption ratios were 60–80 % for first 2 h hemoperfusions and reducing to 40% thereafter. These findings indicated the possibility of continuous endotoxin removal by 24 h PMX-DHP in the future. Perhaps, continuous removal is important because endotoxin is suspected to be continuously derived from the lysed bacteria. Antibiotics induce bacteria to cell lysis and stimulate endotoxin release [18], and antibiotic-induced endotoxin release varies depending on the antibiotic class, the type of bacteria, and the site of antibiotic action [19, 20]. Moreover, endotoxin can be released into the bloodstream by translocation because of the gut barrier disruption in critically ill patients [21]. In such cases, a longer duration of PMX-DHP treatment may particularly be useful.

The initiation of PMX-DHP should be started timely. In the present study, the median interval from ICU admission to PMX-DHP initiation was 2.5 h in both groups. The most commonly observed adverse events in PMX-DHP are thrombocytopenia, transient hypotension, and allergic reactions [22]. In the present study, transient hypotension or allergic reactions was not recognized in both groups. Although platelet count tended to decrease after PMX-DHP treatment in both groups, change in platelet count from baseline to day 3 was not significantly different between the two groups.

The strengths of the present study are as follows. First, the number of patients is larger than the previous studies that examined the effects of extended PMX-DHP. Second, we compared the changes in hemodynamics, vasoactive substance requirement, and pulmonary oxygenation from baseline to 3 days after the treatment. This method allowed us to compare sustained effect of PMX-DHP on various clinically important parameters between the two groups. On the other hand, there are several limitations to this study. First, the present study is retrospective and single-center study, and the duration of PMX-DHP was not pre-fixed. Second, the level of endotoxin was not assessed beforehand. Third, 57 % of patients in the standard group and 62 % of patients in the extended group were the Gram-negative infection. Although the incidence was higher in the extended group, there was no significant difference in the rate of Gram-negative infection. Finally, there was no PMX-DHP control group.

Conclusions

Longer duration of PMX-DHP effectively improved MAP and decreased dose of vasoactive-inotropic agents compared with the conventional duration of PMX-DHP. Eight or more hours of duration of PMX-DHP effectively increased pulmonary oxygenation. There were no significant differences in the 28-day mortality between the two groups. Further prospective studies are warranted to confirm the efficacy of longer duration of PMX-DHP in patients with sepsis.

Abbreviations

PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion; EAA, endotoxin activity assay; MAP, mean arterial pressure; ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment, VIS, vasoactive-inotropic score; CRRT, continuous renal replacement therapy; IQR, interquartile range

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of Juntendo University Hospital (approval number 19-291). All procedures in this study were performed in accordance with the study protocol and the 1964 Helsinki declaration as amended. The need for patient approval and informed consent was waived due to the retrospective nature of the study. Instead, protocol summary was publicized on the university website clearly informing of the patients' right to refuse participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

In the last three years Claudio Ronco has been consulting or part of advisory boards for ASAHI, Astute, Baxter, Biomerieux, B. Braun, Cytosorbents, ESTOR, FMC, GE, Jafron, Medtronic, and Toray. The other authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to the conception and design of the study. CM, MK, IK were involved in data collection. CM and DS analyzed and interpreted the data and performed the statistical analysis. CM drafted the manuscript. TI and CR were involved in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Tables

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Supplementary Files

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- [Table1to4.docx](#)