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Effects of prolonged direct hemoperfusion using a polymyxin B immobilized fiber cartridge on interleukin-6 concentration in patients with septic shock: a prospective exploratory trial

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Abstract

Background: The aim of this study was to evaluate the effect of prolonged direct hemoperfusion using polymyxin B immobilized fiber cartridges (PMX-DHP) on interleukin-6 (IL-6) concentration in patients with septic shock.

Methods: A total of 16 patients received a total of 26 sessions of 12-h PMX-DHP (PMX-DHP-12h group) and 7 patients received a total of 11 sessions of 2-h PMX-DHP (PMX-DHP-2h group). We compared serum IL-6 concentrations and other secondary outcomes between the two treatment groups. IL-6 concentrations were measured at 0, 2, 5, 8, and 12 h.

Results: The median age was 78 years (interquartile range [IQR] 60–84) in PMX-DHP-12h group and 75 years (IQR 66–81) in PMX-DHP-2h group ($P = 0.92$). The median acute physiology and chronic health evaluation II score was 23 (IQR 18–31) in the PMX-DHP-12h group and 21 (IQR 17–28) in the PMX-DHP-2h group ($P = 0.64$). A major source of infection in both groups was the abdomen. The serum IL-6 concentrations in both groups significantly decreased at each time point after 0 h ($P < 0.05$). However, the decrease in IL-6 concentration did not differ between the groups ($P = 0.92$). In-hospital mortality was not significantly different in the PMX-DHP-12h group vs. PMX-DHP-2h group (7 patients [44%] vs. 1 patient [14%]; $P = 0.35$).

Conclusions: We could not confirm the additional effect that 12 h of PMX-DHP had on the reduction in serum IL-6 concentrations over that exerted by 2 h of this regimen.

Trial registration: UMIN-CTR, UMIN000016654. Registered 3 March 2015

Keywords: Interleukin-6, PMX-DHP, Septic shock

Introduction

Treatment of septic shock remains a major challenge because of the associated high mortality (nearly 40%) and morbidity [1]. In patients with septic shock, endotoxins, which are pathogen-associated molecular patterns, induce inflammatory cytokines such as interleukin-6 (IL-6) in a dose-dependent fashion [2]. An excessive inflammatory response can cause hypotension, shock, organ failure, and death [3]. Moreover, previous studies have shown that the inflammatory response may be a therapeutic target of septic shock [4].

In Japan, direct hemoperfusion using polymyxin B immobilized fiber cartridges (PMX-DHP) is usually performed to remove endotoxins and to restore blood pressure in patients with septic shock. Conventionally, PMX-DHP is performed for 2 h in one or two treatment sessions. A retrospective study showed that prolonged PMX-DHP could remove endotoxin throughout a 24-h

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treatment period [5]. Additionally, we recently reported that prolonged PMX-DHP provides sustained circulatory stabilization [6]. Thus, prolonged PMX-DHP might be more effective than conventional PMX-DHP. However, prospective, controlled studies examining prolonged PMX-DHP are scarce, and conclusive data regarding the anti-inflammatory effects of prolonged PMX-DHP are lacking. Therefore, we conducted a pilot study to compare IL-6 concentrations between patients who underwent conventional PMX-DHP and those who underwent prolonged PMX-DHP.

Materials and methods

We designed a prospective, single-center, open-label, sequential-period, interventional study (UMIN000016654 [University hospital Medical Information Network Clinical Trials Registry]) that compared the effects of 2 h and 12 h of PMX-DHP among patients with septic shock. We conducted this study between April 2015 and August 2016. This study was approved by the institutional review board of Wakayama Medical University. We obtained written informed consent from patients or patients' families.

We included septic shock patients who were admitted to the intensive care unit (ICU). In this study, we defined septic shock as systemic inflammatory response syndrome due to infection and needing high doses of vasopressor (inotropic score ≥ 10). We excluded patients with allergies to polymyxin B, patients who were lactating or pregnant, and patients with do-not-attempt-resuscitation orders. Among those from the PMX-DHP-12h group, 16 were included in one previous study [6], and 7 were included in the other studies [7, 8].

Included patients immediately received a round of PMX-DHP through a Toraymyxin (PMX-20R; Toray Industries, Tokyo, Japan) adsorption column. We used nafamostat mesilate anticoagulant to prevent circuit coagulation. The blood flow rate of PMX-DHP was 100 ml/min. If the patients still needed a high dose of vasopressors 24 h after this initial round, then a second round of PMX-DHP was performed. Between April 2015 and May 15, 2016, PMX-DHP was conducted with the duration of 12 h (PMX-DHP-12 h group). Between May 16, 2016, and August 2016, PMX-DHP was conducted with the duration of 2 h (PMX-DHP-2h group). After starting patient enrollment for the PMX-DHP-12h group, we decided to extend the study and add a PMX-DHP-2h group as a control. Due to the exploratory nature of this study, no a priori sample size calculation was performed. This study was terminated prematurely (before a sufficient number of patients could be included in the PMX-DHP-2h group) because of a lack of funding. Except for the application of the PMX-DHP regimen, all treatments made were decided by the attending physician based on the published guideline of Guidelines for the Management of Sepsis by the Japanese Society of Intensive Care Medicine [9].

The primary outcome was serum IL-6 concentration noted at varying time points during the first session of PMX-DHP administration. We performed point-of-care serum IL-6 quantification using a fluorescence enzyme immunoassay (Ray-FAST, Toray Industries, Tokyo, Japan). Measurements were taken before starting PMX-DHP (0 h) and at 2, 5, 8 and 12 h after starting PMX-DHP. The upper limit of the measurement was 10,000 pg/ml. The secondary outcomes included mean blood pressure, inotropic score and vasopressor dependency index, serum lactate concentration, PaO_2/FiO_2 ratio, ICU-free days, vasopressor-free days, renal replacement therapy (RRT)-free days, ventilator-free days, ICU mortality, and hospital mortality. Inotropic score was calculated as follows: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + adrenaline dose (μg/kg/min) × 100 + noradrenaline dose (μg/kg/min) × 100 + phenylephrine dose (μg/kg/min) × 100 [10]. The vaso pressor dependency index was calculated as previously described: (inotropic score)/(mean blood pressure) [10]. As possible adverse events, we also evaluated thrombocytopenia and leukopenia during the first 5 days after inclusion. Thrombocytopenia was defined as a platelet count of 5.0×10^4/mcl or lower and leukopenia as a leukocyte count of 4000/mcl or lower. Acute kidney injury (AKI) and its stage were diagnosed from the serum creatinine at inclusion in concordance with the Kidney Disease Improving Global Outcomes criteria [11, 12].

Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD) or as the median with interquartile range (IQR). Categorical variables were presented as numbers and percentages (%). For comparisons between the two treatment groups, we used Fisher's exact test for categorical variables and the *t* test, paired *t* test, or Wilcoxon rank sum test for continuous variables. The serum IL-6 concentrations were transformed to a natural logarithm for analysis. Serum IL-6 concentrations, mean blood pressure, inotropic score, vasopressor dependency index, serum lactate concentration, and PaO_2/FiO_2 ratio during the first session of PMX-DHP administration were compared between the groups using a two-way repeated measurements analysis of variance. A two-sided *P* value of < 0.05 was considered statistically significant, and all analyses were performed using JMP Pro software (version 12.2; SAS Institute Inc., Cary, NC, USA).

Results

A total of 25 patients were eligible for this study, and 2 patients declined to participate. Twenty-three patients were included in this study. A total of 16 patients received a total of 26 sessions of 12-h PMX-DHP (PMX-DHP-12h

group) and 7 patients received a total of 11 sessions of 2-h PMX-DHP (PMX-DHP-2h group) (Fig. 1). The duration from the diagnosis of septic shock to the first session of PMX-DHP administration was 4 h (IQR 3–5) in the PMX-DHP-12h group and 3 h (IQR 2–6) in the PMX-DHP-2h group ($P = 0.59$). The patients' characteristics in both groups appeared to be similar (Table 1). A major source of infection in both groups was the abdomen. The serum lactate concentration was higher than 2 mmol/l in 16 patients. There were 10 (63%) and 3 (43%) post-operative patients in the PMX-DHP-12h and PMX-DHP-2h groups, respectively ($P = 0.65$). In the PMX-DHP-12h and PMX-DHP-2h groups, there were 5 (31%) and 2 (29%) patients with stage 1 AKI, 4 (25%) and 0 (0%) with stage 2 AKI, and 1 (6%) and 1 (14%) with stage 3 AKI, respectively ($P = 0.30$). Eight patients in the PMX-DHP-12h group and 1 patient in the PMX-DHP-2h group were treated with continuous renal replacement therapy (CRRT). The mode of CRRT was continuous hemodiafiltration in all patients. The hemofilter used in CRRT was an acrylonitrile-co-methallyl sulfonate surface-treated membrane in 1 patient in the PMX-DHP-12h group and a polysulfone membrane in all the other 8 patients.

The primary outcome is shown in Fig. 2. For both groups, the serum IL-6 concentration significantly decreased at each time point after 0 h ($P < 0.05$). However, serum IL-6 concentration did not significantly differ between the groups during 12 h ($P = 0.92$).

The mean blood pressure, the inotropic scores, and the vasopressor dependency index were taken at varying time points and are shown in Figs. 3, 4, and 5, respectively. The dose of each vasopressor is shown in Additional file 1: Table S1. In both groups, all three circulatory indices appeared to improve over time; however, more time points had significant changes in PMX-DHP-12h group from baseline. In addition, the mean blood pressure, the inotropic scores, and the vasopressor dependency index did not significantly differ between the groups.

Serum lactate concentrations and the PaO_2/FiO_2 ratio are shown in Table 2. Serum lactate concentrations and the PaO_2/FiO_2 ratio did not significantly change in either group during the 12 h after starting PMX-DHP.

Other secondary outcomes are shown in Table 3. ICU-free days, vasopressor-free days, RRT-free days, ventilator-free days, ICU mortality, and hospital mortality were similar between both groups. Thrombocytopenia occurred in 9 patients (56%) in the PMX-DHP-12h group and in 5 (71%) in the PMX-DHP-2h group ($P = 0.66$). Leukopenia occurred in 4 patients (25%) in the PMX-DHP-12h group and 2 (29%) in the PMX-DHP-2h group ($P = 1.0$).

Discussion

In this study, we found that the serum IL-6 concentrations significantly decreased over time in both groups. However, the serum IL-6 concentration did not differ between the groups. We also did not find a difference in any secondary outcomes such as mean blood pressure or mortality.

Several studies have reported that PMX-DHP significantly reduces the plasma level of IL-6 24 h after PMX-DHP treatment in patients with sepsis or septic shock [13, 14]. In accordance with these results, serum IL-6 concentrations decreased over time in both groups in our study.

A small, retrospective, observational study showed that the median endotoxin removal rate was well maintained at 74.4% after 24 h during prolonged PMX-DHP [5]. Recently, an in vitro study also showed that PMX-DHP column adsorbed endotoxin for at least 24 h [15]. In sepsis, endotoxins stimulate immune cells to secrete proinflammatory cytokines such as IL-6 [16]. Thus, prolonged PMX-DHP administration is expected to reduce IL-6

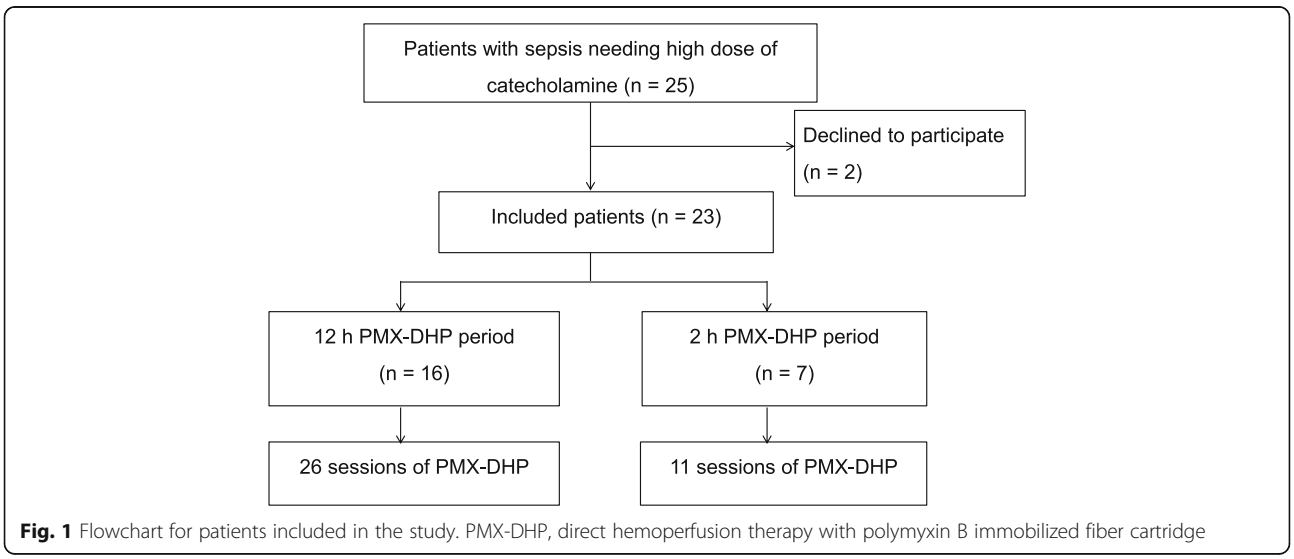

Fig. 1 Flowchart for patients included in the study. PMX-DHP, direct hemoperfusion therapy with polymyxin B immobilized fiber cartridge

Table 1 Patients characteristics

	PMX-DHP-2h ($n = 7$)	PMX-DHP-12h ($n = 16$)	P value
Age, year, median (IQR)	75 (66–81)	78 (60–84)	0.92
Male, number (%)	4 (57%)	6 (38%)	0.65
Body mass index, median (IQR)	20.2 (18.8–22.2)	22.3 (21.6–25.7)	0.04
APACHE II score at ICU admission, median (IQR)	21 (17–28)	23 (18–31)	0.64
SOFA score at the day of the first PMX-DHP session, median (IQR)	11 (7–11)	10 (8–14)	0.84
Comorbidity			
Immunosuppression, number (%)	2 (29%)	4 (25%)	1.00
Chronic dialysis, number (%)	1 (14%)	2 (13%)	1.00
Home oxygenation therapy, number (%)	0 (0%)	1 (7%)	1.00
Decompensate heart failure, number (%)	1 (14%)	1 (7%)	0.53
Diabetes mellitus, number (%)	0 (0%)	3 (19%)	0.53
Site of infection			0.11
Abdomen, number (%)	3 (43%)	13 (81%)	
Urinary tract, number (%)	2 (29%)	1 (6%)	
Others, number (%)*	2 (29%)	2 (13%)	
Causative organisms			0.10
Gram-negative rod, number (%)	2 (29%)	1 (6%)	
Mixed, number (%)	1 (14%)	7 (44%)	
Gram-positive bacteria, number (%)	2 (29%)	3 (19%)	
Fungi, number (%)	0 (0%)	1 (6%)	
Unknown, number (%)	2 (29%)	4 (25%)	
Number of PMX-DHP session			1.00
1 session, number (%)	3 (43%)	6 (38%)	
2 sessions, number (%)	4 (57%)	10 (62%)	
Treatment in ICU			
Continuous renal replacement therapy, number (%)	1 (15%)	8 (50%)	0.18
Mechanical ventilation, number (%)	7 (100%)	16 (100%)	1.00
Low dose steroid, number (%)	5 (71%)	14 (87%)	0.56
Laboratory test†			
White blood cell, 10^2/mcl, median (IQR)	89 (14–121)	88 (34–144)	0.53
C reactive protein, mg/dl, median (IQR)	9.1 (6.1–18.9)	15.9 (8.0–24.4)	0.15
Total bilirubin, mg/dl, median (IQR)	0.9 (0.7–1.5)	0.8 (0.5–2.0)	0.81
Creatinine, mg/dl, median (IQR)	1.8 (0.9–2.6)	1.6 (1.2–2.5)	0.76
PT-INR, median (IQR)	1.3 (1.1–1.4)	1.3 (1.2–1.7)	0.71
Lactate, mmol/l, median (IQR)	5.1 (1.4–8.5)	3.8 (2.0–7.5)	0.84

PMX-DHP-2h polymyxin direct hemoperfusion for 2 h, *PMX-DHP-12h* polymyxin direct hemoperfusion for 12 h, *IQR* interquartile range, *APACHE II* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment, *ICU* intensive care unit, *PT-INR* prothrombin time-international normalized ratio
*Other site of infection includes infectious endocarditis, necrotizing fasciitis, neutropenic fever, and septic shock of unknown origin (each site is 1 case)
†Laboratory tests were performed on the day of the first PMX-DHP session. The serum lactate concentration noted here was the maximum value observed from the diagnosis of septic shock to the initiation of PMX-DHP administration

more effectively than conventional PMX-DHP. However, IL-6 concentrations did not differ between patients with prolonged and those with conventional PMX-DHP in this study. Conventional PMX-DHP might be enough to reduce the serum IL-6 concentration effectively.

Several studies have reported a beneficial effect of prolonged PMX-DHP for hemodynamic or respiratory improvement [6, 17]. In a small prospective study of 16 patients with septic shock, Mitaka et al. reported that prolonged PMX-DHP (16.9 ± 7.0 h) reduced noradrenaline

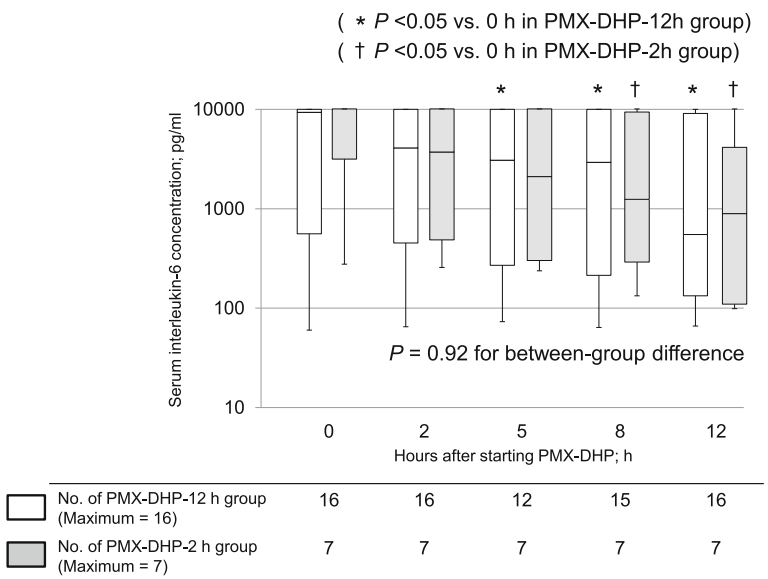

Fig. 2 Time points of serum interleukin-6 concentrations over 12 h. The two groups were compared using a two-way repeated measurements analysis of variance. Interleukin-6 concentration was transformed into the natural logarithm before it was included in the analysis. For both groups, a paired *t* test was performed between 0 h and each additional time point. *$P < 0.05$. PMX-DHP, direct hemoperfusion therapy with polymyxin B immobilized fiber cartridge

dosage and improved PaO_2/FiO_2 ratio compared with conventional PMX-DHP (2 h) [17]. A recent retrospective study of 32 patients with septic shock showed that the vasopressor dependency index significantly decreased at 12 h of PMX-DHP but not at 2 h of PMX-DHP [6]. In this context, 12-h PMX-DHP administration was also marginally associated with improved circulatory indexes in the present study. Because the sample size in this study is smaller than the sample size of our previous study, detecting a statistically significant difference in outcomes will be more difficult. However, these studies only evaluated the short-term circulatory index, including the time

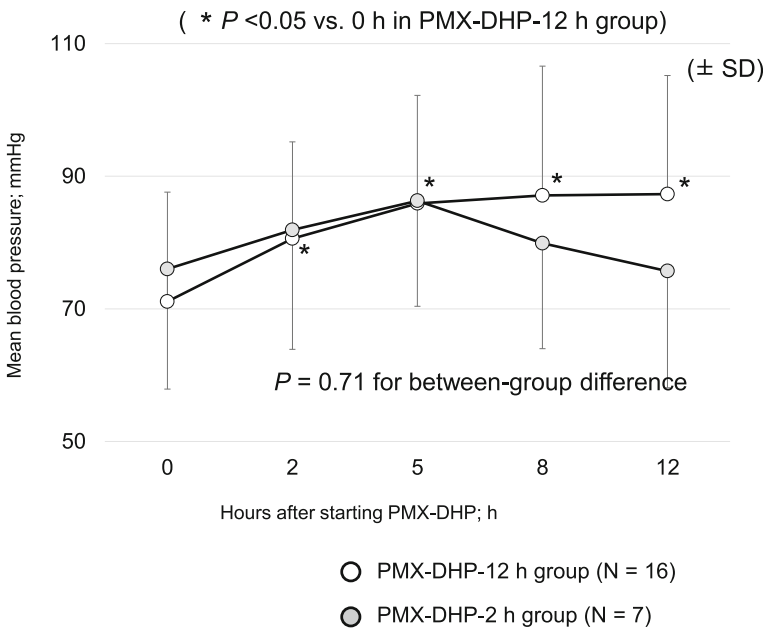

Fig. 3 Time points of mean blood pressure over 12 h. The two groups were compared using two-way repeated measurements analysis of variance. For both groups, a paired *t* test was performed between 0 h and each additional time point. *$P < 0.05$. PMX-DHP, direct hemoperfusion therapy with polymyxin B immobilized fiber cartridge; SD, standard deviation

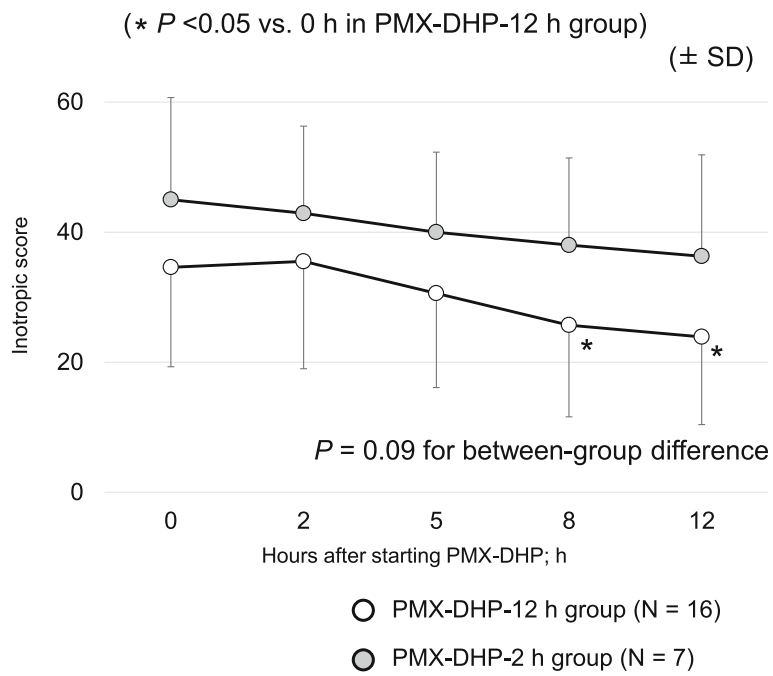

Fig. 4 Time points of inotropic score over 12 h. The two groups were compared using two-way repeated measurements analysis of variance. Inotropic score was calculated as follows: (dopamine dose [μg/kg/min]) + (dobutamine dose [μg/kg/min]) + (adrenaline dose [μg/kg/min]) × 100 + (noradrenaline dose [μg/kg/min]) × 100 + phenylephrine dose [μg/kg/min]) × 100. For both groups, a paired *t* test was performed between 0 h and each additional time point. *$P < 0.05$. PMX-DHP, direct hemoperfusion therapy with polymyxin B immobilized fiber cartridge; SD, standard deviation

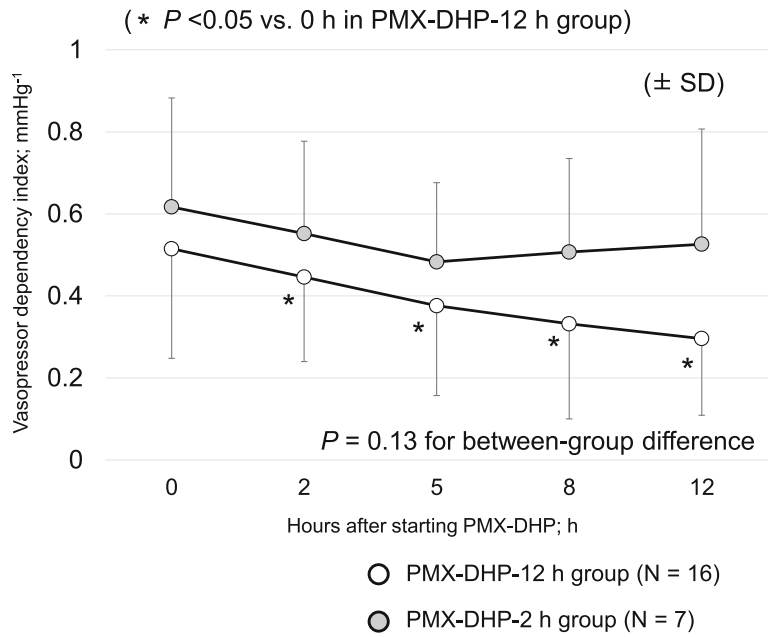

Fig. 5 Time points of vasopressor dependency index over 12 h. The two groups were compared using two-way repeated measurements analysis of variance. Vasopressor dependency index was calculated as follows: (inotropic score)/(mean blood pressure). For both groups, a paired *t* test was performed between 0 h and each additional time point. *$P < 0.05$. PMX-DHP: direct hemoperfusion therapy with polymyxin B immobilized fiber cartridge, SD: standard deviation

Table 2 Serum lactate concentration and PaO_2/FiO_2 ratio

	PMX-DHP-2 h ($n = 7$)	PMX-DHP-12 h ($n = 16$)	*P* value
Serum lactate concentration, mmol/l			0.53
0 h (baseline), *N*	7	16	
median (IQR)	4.3 (1.3–6.0)	2.9 (1.3–6.7)	
2 h, *N*	7	16	
median (IQR)	2.9 (1.4–6.1)	3.2 (1.7–6.0)	
5 h, *N*	6	14	
median (IQR)	2.0 (1.5–6.2)	2.6 (1.6–4.0)	
8 h, *N*	7	15	
median (IQR)	1.8 (1.6–4.0)	2.9 (1.9–3.6)	
12 h, *N*	7	14	
median (IQR)	1.5 (1.2–2.7)	2.6 (1.7–3.7)	
PaO_2/FiO_2 ratio			0.53
0 h (baseline), *N*	7	15	
mean ± SD	278 ± 138	260 ± 128	
2 h, *N*	7	15	
mean ± SD	287 ± 108	279 ± 124	
5 h, *N*	6	13	
mean ± SD	329 ± 109	283 ± 120	
8 h, *N*	7	14	
mean ± SD	310 ± 124	289 ± 108	
12 h, *N*	7	14	
mean ± SD	318 ± 94	281 ± 109	

The two groups were compared using a two-way repeated measurements analysis of variance. Serum lactate and PaO_2/FiO_2 were measured just before starting PMX-DHP administration (0 h). Serum lactate concentration was transformed into the natural logarithm before it was included in the analysis
PMX-DHP-2h polymyxin direct hemoperfusion for 2 h, *PMX-DHP-12h* polymyxin direct hemoperfusion for 12 h, *IQR* interquartile range, *SD* standard deviation

during longer-duration PMX-DHP. It remains unclear whether short-term circulatory improvement affects long-term outcomes, such as mortality.

The strength of our study was its prospective design. While past studies implied hemodynamic or even survival benefit of prolonged PMX-DHP, many of these studies were retrospective in nature [6, 8]. Our study adds significant information to the existing literature. Considering the discrepancy between the results of our study and existing literature, we need high-quality and large prospective trials to evaluate the true efficacy of prolonged PMX-DHP.

This study has several limitations. First, this study is a nonrandomized, nonblinded study. So, the characteristics of patients and treatments other than PMX-DHP might be biased. However, we applied objective inclusion criteria and treated septic shock according to the Japanese sepsis guideline [9]. Hence, patients' characteristics and treatment in the ICU should be similar in both groups. Furthermore, we evaluated IL-6 as a primary

Table 3 Secondary outcomes

	PMX-DHP-2 h ($n = 7$)	PMX-DHP-12 h ($n = 16$)	*P* value
ICU-free days at day 28, median (IQR)	22 (18–23)	18 (2–24)	0.36
Vasopressor-free days at day 28, median (IQR)	18 (16–25)	21 (5–24)	0.97
RRT-free days at day 28, median (IQR)*	28 (8–28)	20 (26–28)	0.19
Ventilator-free days at day 28, median (IQR)	23 (13–24)	18 (0–25)	0.57
ICU mortality, number (%)	1 (14%)	3 (19%)	1.00
Hospital mortality, number (%)	1 (14%)	7 (44%)	0.35

PMX-DHP-2h polymyxin direct hemoperfusion for 2 h, *PMX-DHP-12h* polymyxin direct hemoperfusion for 12 h, *ICU* intensive care unit, *RRT* renal replacement therapy, *IQR* interquartile range
*RRT-free days were compared between groups after excluding patients undergoing chronic dialysis

outcome, and this seemed to have avoided interobserver bias. A second limitation is that due to the small sample size, the study is underpowered and thus less likely to detect any difference in important clinical outcomes such as mortality. Furthermore, because of the exploratory nature of our study, we did not perform any a priori sample size calculation and stopped before completion, which reduced the credibility of our results. Hence, our study should be regarded as a hypothesis-generating one. Future larger studies are needed to evaluate these outcomes for prolonged PMX-DHP. Third, the upper limit of measurement of IL-6 was 10,000 pg/mL; however, about 40% of IL-6 measurements were more than 10,000 pg/mL at baseline (0 h). Fourth, we did not evaluate endotoxin activity in this study and removal of endotoxin is the main role of PMX-DHP [18]. Furthermore, our cohort included 5 patients with gram-positive bacterial infection. However, PMX-DHP has other roles such as removing activated monocytes and neutrophils [19]. Except for the removal of endotoxins, these mechanisms including the removal of activated monocytes and neutrophils finally reduced the serum concentrations of inflammatory cytokines such as IL-6 [18]. Therefore, serum IL-6 concentration was the primary outcome in this study. In this study, we measured endotoxin level in a few patients but no valuable results were provided (data not shown). Furthermore, in the subgroup analysis that excluded patients with gram-positive bacterial infection, no significant difference in IL-6 concentration was observed between the groups (data not shown). Fifth, we did not include patients according to the Sepsis-3 definition of septic shock, because the Sepsis-3 had not been published at the time of planning our study. About 30% of our cohort had serum lactate concentrations of 2.0 mmol/l or less and thus did not meet the Sepsis-3 definition of septic shock. Future studies should include patients according to the Sepsis-3 definition.

This study failed to show that prolonged PMX-DHP influenced serum IL-6 concentrations. These results do not support the routine use of prolonged PMX-DHP to control hypercytokinemia in patients with septic shock. To the best of our knowledge, this study is the first to use multiple time points to compare IL-6 and hemodynamic index between prolonged and conventional PMX-DHP.

Conclusions

Among patients with septic shock, prolonged PMX-DHP did not significantly reduce serum IL-6 concentrations compared to conventional PMX-DHP. We could not confirm the additional effect that 12 h of PMX-DHP had on the reduction in serum IL-6 concentrations over that exerted by 2 h of this regimen.

Additional file

Additional file 1: Table S1. Catecholamine usage within 12 h of starting PMX-DHP and the doses administered (DOCX 28 kb)

Abbreviations

AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; IL-6: Interleukin-6; IQR: Interquartile range; PMX-DHP: Direct hemoperfusion using a polymyxin B immobilized fiber cartridges; RRT: Renal replacement therapy; SD: Standard deviation; UMIN: University Hospital Medical Information Network Clinical Trials Registry

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to privacy concerns and institutional policy.

Authors' contributions

KM and YK conceived the study idea and designed the study. YK provided methodological advice on study design and data analysis and obtained funding. SN, MO, and TS managed patients in ICU especially for performing PMX-DHP. KM, YK, NS, AO, NS, KK, YS, NY, MK, MK, and MT managed patients, obtained informed consent from patients, and measured IL-6. SN, NS, AO, NS, KK, YS, NY, MK, MK, MT, MO, TS, and SK helped to draft this manuscript and revised it. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in Wakayama Medical University and was approved by the Institutional Review Board. The written informed consent was obtained.

Consent for publication

The written informed consent was obtained for publication.

Competing interests

KM reports receipt of lecture fees from Becton Dickinson and Maruishi Pharmaceutical. TS is the editor in chief of this "Renal Replacement Therapy" journal. MO is also an editorial board member of "Renal Replacement Therapy" journal.

Publisher's Note

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