Original Article

"Impact of timing of polymyxin B-immobilized fiber column direct hemoperfusion on outcome in patients with septic shock: a single-center observational study"

Tomoki Tanaka,[1] [iD] Takahisa Tabata,[2] Kazunori Fujino,[2] Yasuyuki Tsujita,[1] and Yutaka Eguchi[2]

[1]Shiga University of Medical Science Emergency and Intensive Care Unit, Otsu, Japan, and [2]Department of Critical and Intensive Care Medicine, Shiga University of Medical Science, Otsu, Japan

Aim: The effect of polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) is controversial. The present study investigates whether outcome in septic shock patients is affected by the time until PMX-DHP initiation and the location of the infection site (intra- or extra-abdominal infection (IAI/EAI)].

Methods: This retrospective observational study included patients receiving PMX-DHP for septic shock but excluded those treated after cardiac surgery or cardiac arrest. Based on the median and/or quartile time from catecholamine treatment to PMX-DHP initiation, the patient cohort was divided into four groups and the IAI and EAI groups into two subgroups.

Results: Among the 49 eligible patients, overall 90-day mortality in group 1 (PMX-DHP within 6 h) at 8.3% was significantly lower than in groups 2 (6–9 h; 46.1%), 3 (9–29 h; 58.3%) and 4 (>29 h; 75.0%) ($P = 0.021$). Multivariate logistic regression analysis showed that the duration from catecholamine treatment to PMX-DHP initiation correlated with 90-day mortality (odds ratio 1.060; 95% confidence interval, 1.004–1.117; $P = 0.028$). Among the 29 IAI patients, 90-day mortality was significantly lower in the early (within 9 h) than the late group (>9 h) (13.3% versus 64.2%; $P = 0.003$), but no significant intergroup difference was noted among the 20 EAI patients.

Conclusion: Our results suggest that early PMX-DHP initiation (within 9 h after catecholamine treatment) reduces mortality from septic shock, especially in IAI patients.

Key words: Endotoxin tolerance, extra-abdominal infection, intra-abdominal infection, PMX-DHP, SOFA score

INTRODUCTION

SEPSIS IS DE fined as severe infection with organ dysfunction resulting from dysregulated host response; mortality from sepsis and septic shock remains high.[1] Inflammatory responses to infection are enhanced by pathogen-associated molecular pattern molecules, such as endotoxin, a lipopolysaccharide component of the outer membrane of Gram-negative bacteria.[2] Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) can selectively adsorb endotoxin and theoretically prevent the progression or halt the sepsis cascade and decrease inflammatory humoral mediators.[3]

The efficacy of PMX-DHP has been evaluated in many studies, including three major randomized controlled trials, EUPHAS[4] (early use of polymyxin B hemoperfusion in abdominal sepsis), ABDOMIX,[5] and EUPHRATES[6] (evaluation of polymyxin B hemoperfusion in a randomized controlled trial of adults with endotoxemia and septic shock), which nevertheless reported varying levels of efficacy in septic shock:[7,8] Polymyxin B-immobilized fiber column direct hemoperfusion was associated with significant difference in 28-day mortality in the EUPHAS trial and post hoc analysis of the EUPHRATES trial,[9] but not in the ABDO-MIX or EUPHRATES trials. The efficacy of PMX-DHP in septic shock therefore remains controversial.

We propose that these variations could be explained by the timing of PMX-DHP initiation and/or infection site. The first PMX-DHP session was carried out within 24 h after

abdominal surgery in the EUPHAS trial and within 12 h in the ABDOMIX trial. In the EUPHRATES trial, the mean time between randomization and intervention was 3.5 h, but no detailed PMX-DHP initiation time is given. Regarding infection site, in the EUPHAS and ABDOMIX trials, patients with intra-abdominal infection (IAI) were included, whereas, in the EUPHRATES trial, patients with high endotoxin activity assay (EAA) levels were included regardless of infection site: 35.2% with IAI and 35.9% with lung infection. The other studies also showed variations in patient groups and timing of PMX-DHP initiation.[7]

Our present study investigated the effects of PMX-DHP on outcome in septic shock depending on initiation time and infection site (intra- versus extra-abdominal).

METHODS

Study cohort

THE STUDY WAS undertaken at the intensive care unit (ICU) of Shiga University of Medical Science Hospital (Otsu, Japan) from May 2010 to March 2015. Septic shock patients in the ICU receiving PMX-DHP were eligible. Septic shock was defined according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.[10] We excluded patients younger than 18 years or who had undergone cardiac surgery or suffered cardiac arrest and also those not undergoing catecholamine treatment or i.v. fluid resuscitation with a bolus of 30 mL/kg within 3 h before PMX-DHP initiation. Patients were divided into four groups according to the interval between catecholamine treatment and PMX-DHP initiation, and further subdivided into two groups according to infection site, intra- or extra-abdominal (IAI/EAI). The study was approved by the Shiga University of Medical Science institutional review board (approval no. 29-167) and carried out in accordance with the principles of the Declaration of Helsinki (amended 2013). It was publicized by a protocol summary on the university website clearly informing of the patient's right to refuse participation.

Data collection

The following data were retrieved: demographic information including: age, sex, and ICU admission route; pre-existing conditions including hypertension, diabetes, chronic heart failure, chronic kidney disease, and hepatic cirrhosis; primary infection site and bacterial culture results; laboratory data including white blood cell count, C-reactive protein, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, and lactate; vasopressor dose on PMX-DHP initiation; and details of PMX-DHP and continuous renal replacement therapy (CRRT), including time from catecholamine treatment to PMX-DHP initiation, PMX-DHP duration and frequency, and concomitant use of CRRT. Illness severity was assessed using Acute Physiology and Chronic Health Evaluation (APACHE) II, and the severity of organ dysfunction or failure was expressed by the Sequential Organ Failure Assessment (SOFA) score on ICU admission. The vasopressor agent dose was expressed as vasoactive–inotropic score (VIS),[11] calculated as follows:

$$\begin{aligned} VIS = {} & \text{dopamine dose}\,(\mu g/kg/min) \\ & + \text{dobutamine dose}\,(\mu g/kg/min) + 100 \\ & \times \text{epinephrine dose}\,(\mu g/kg/min) + 10 \\ & \times \text{milrinone dose}\,(\mu g/kg/min) + 10,000 \\ & \times \text{vasopressin dose}\,(units/kg/min) + 100 \\ & \times \text{norepinephrine dose}\,(\mu g/kg/min) \end{aligned}$$

Procedures

Polymyxin B-immobilized fiber column direct hemoperfusion was carried out with an adsorbent column containing 5 mg polymyxin B per gram of polystyrene fiber (Toraymyxin; Toray Medical Co., Tokyo, Japan). The decision to initiate PMX-DHP and CRRT was made by the responsible physicians after adequate fluid resuscitation and catecholamine support. A second PMX-DHP was carried out only when the patient hemodynamics did not improve after the first PMX-DHP and/or CRRT. Nafamostat mesilate was used as an anticoagulant at a dose adjusted to maintain an activated coagulation time of 180–200 s. Blood flow was set at 80–100 mL/min. The planned duration of PMX-DHP was 24 h. We used a polymethyl methacrylate membrane hemofilter (CH-1.8W or BG-2.1PQ; Toray Medical Co.) or a polysulfone membrane hemofilter (AEF-10; Asahi Kasei, Tokyo, Japan) for patients diagnosed with acute kidney injury based on the KDIGO classification,[12] and an acrylonitrile-co-methallyl sulfonate surface-treated membrane hemofilter (AN69ST; sepXiris150, Baxter Co., Tokyo, Japan) for non-acute kidney injury patients.

Statistical analysis

Data are expressed as median with interquartile range for continuous variables or as number (%) for categorical variables. Continuous variables were compared between groups using the Mann–Whitney *U*-test or Kruskal–Wallis test, and categorical variables using Pearson's χ^2-test or the Kruskal–Wallis test, as appropriate. The survival estimate was based on the Kaplan–Meier method and compared between groups

using the log–rank test. We undertook univariate and multivariate logistic regression analyses (Enter method) to evaluate the association of 90-day mortality with the interval from catecholamine treatment to PMX-DHP initiation. Variables considered were age, APACHE II score, and whether the patient underwent emergency surgery or drainage. A *P*-value of <0.05 was considered statistically significant for all comparisons. Statistical analyses were undertaken using SPSS 22 (SPSS, Chicago, IL, USA).

RESULTS

THE STUDY ENROLLED 62 patients during the observation period. The final 49 eligible patients were categorized into four groups of 12 or 13 each by quartile of interval (Fig. 1). The median interval from catecholamine treatment to PMX-DHP initiation was 9 h (interquartile range, 6–29 h).

Table 1 presents baseline clinical characteristics. The four groups showed no significant difference in age, SOFA score, APACHE II score, or pre-existing conditions, but did differ in the interval between catecholamine treatment and PMX-DHP initiation ($P < 0.001$). In the 90-day survival curves in Figure 2, significant differences were noted between groups 1, 2, 3, and 4 in 90-day mortality (8.3%, 46.1%, 58.3%, and 75.0%, respectively; $P = 0.021$). The results of univariate and multivariate analyses are shown in Table 2. The interval

from catecholamine treatment to PMX-DHP initiation and APACHE II score were correlated with 90-day mortality (odds ratio 1.060, 1.117; 95% confidence interval [CI], 1.004–1.117, 1.021–1.221; $P = 0.028$, 0.015; Table 2). Table 1 shows differences in infection site and organism between the four groups. Specifically, the number of patients with lung infection was lower in group 1 (groups 1, 2, 3 and 4: 8.3%, 30.6%, 33.3%, and 25.0%, respectively). To assess the resulting impact on the efficacy of early PMX-DHP initiation, we divided the patients into two groups according to infection site, intra- or extra-abdominal, and evaluated the efficacy of early PMX-DHP initiation in each group.

Given the median interval of 9 h from catecholamine treatment to PMX-DHP initiation, we divided the 29 IAI patients into an early group (within 9 h, $n = 15$) and a late group (>9 h, $n = 14$) (Fig. 3). No significant intergroup differences in age, SOFA score, APACHE II score, or pre-existing conditions were noted (Table 3), but the total number of patients undergoing emergency operation or drainage did differ significantly ($P = 0.034$). In the 90-day survival curves in Figure 4A, the early group had significantly lower 90-day mortality (13.3% versus 64.2%; $P = 0.003$).The results of univariate and multivariate analyses are shown in Table 4. The interval from catecholamine treatment to PMX-DHP initiation was associated with 90-day mortality (odds ratio 1.058; 95% CI, 1.000–1.119; $P = 0.049$) (Table 4).
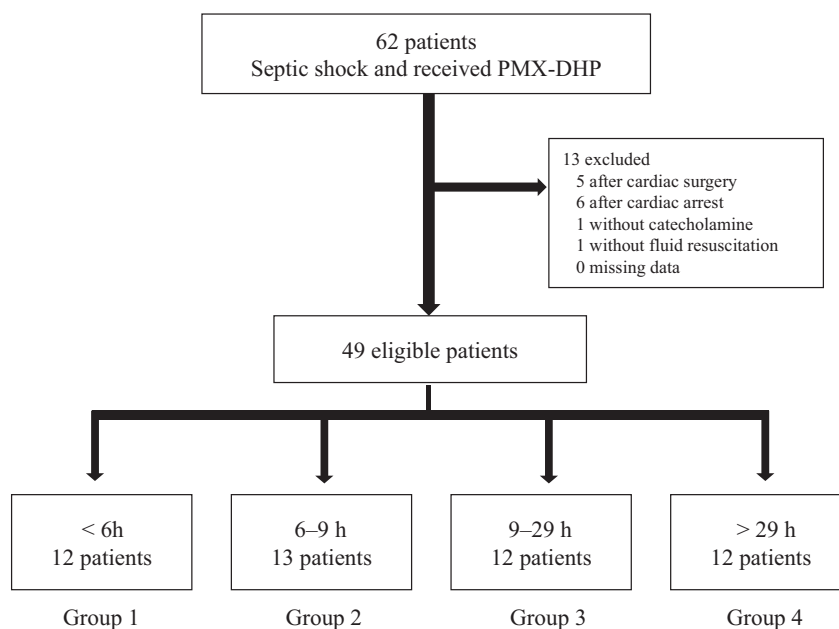

Fig. 1. Outline of all study participants. Study flowchart of patients with septic shock based on the interval between catecholamine treatment and initiation of direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP).

Table 1. Characteristics of four groups of patients with septic shock

	Group 1	Group 2	Group 3	Group 4	P-value
Number of patients	12	13	12	12	
Age, years	73.5 (65.2–78.7)	74.0 (64.5–78.0)	67.5 (41.0–78.0)	74.0 (68.0–80.5)	0.534
Sex, male; n (%)	8 (66.6)	8 (61.5)	7 (58.3)	7 (58.3)	0.973
Height, cm	164.5 (159.7–171.8)	161.9 (160.6–170.0)	164.0 (157.2–171.3)	159.5 (155.0–166.5)	0.346
Weight, kg	63.6 (53.0–68.8)	56.2 (45.3–61.4)	48.5 (42.7–61.4)	53.7 (46.7–66.9)	0.490
Time from catecholamine initiation to PMX-DHP initiation, h	3.5 (2.0–5.3)	8.0 (6.1–8.7)	18.0 (14.0–21.0)	46 (31.1–82.0)	<0.001*
APACHE II score	22 (16.0–33.0)	27.0 (18.0–34.5)	24.0 (20.7–30.7)	29.0 (19.2–39.2)	0.301
SOFA score	12.5 (11.2–16.0)	14.0 (11.5–15.5)	9.5 (7.5–14.0)	14.5 (11.2–17.0)	0.181
PaO_2/FiO_2	121.0 (118.2–261.6)	125.0 (84.1–210.5)	114.5 (70.0–279.5)	114.0 (91.0–192.9)	0.349
WBC, $\times 10^3/\mu L$	9.8 (4.4–29.8)	6.7 (1.1–11.4)	8.0 (1.3–15.2)	6.9 (2.5–18.2)	0.422
CRP, mg/dL	12.2 (3.9–16.6)	16.7 (4.5–23.0)	15.3 (9.9–19.9)	13.6 (4.3–18.5)	0.578
HR, b.p.m.	121.0 (97.2–142)	106.0 (93.5–121.5)	110 (101.7–130.7)	114.5 (88.2–135)	0.784
MAP, mmHg	67.0 (57.5–82.0)	70.6 (54.5–85.5)	69.1 (62.5–81.1)	74.0 (50.6–84.4)	0.978
Lactate on PMX-DHP initiation, mg/dL	26.0 (20–83.0)	27.0 (18.0–40.0)	34.0 (20.0–72.0)	45.0 (16.0–73.0)	0.616
VIS on PMX-DHP initiation	15.4 (7.0–28.8)	23.0 (13.5–47.7)	21.0 (10.1–25.8)	28.0 (14.2–36.8)	0.385
Concomitant use of CRRT, n (%)	12 (100.0)	13 (100.0)	11 (91.6)	11 (91.6)	0.546
Duration of PMX-DHP, h	17.0 (9.2–23.0)	11.0 (7.4–19.5)	13.5 (9.1–20.2)	18.5 (9.5–24.0)	0.684
Two sessions of PMX-DHP, n (%)	2 (16.6)	0 (0.0)	2 (16.6)	0 (0.0)	0.217
Initiation of PMX-DHP before CRRT, n (%)	7 (58.3)	5 (38.4)	6 (50.0)	1 (8.3)	0.069
Underwent emergency surgery or drainage, n (%)	5 (41.6)	6 (46.1)	3 (25)	3 (25)	0.373
Admission route to ICU, n (%)					
Emergency department	4 (33.0)	5 (38.4)	2 (16.6)	2 (16.6)	0.942
Other hospital	1 (8.3)	1 (7.6)	3 (25.0)	4 (33.3)	
Hospital ward	7 (58.3)	7 (53.8)	7 (58.3)	6 (50.0)	
Organism					
Escherichia coli	3	3	3	1	
Enterococcus spp.	2	2	0	4	
Klebsiella spp.	1	3	3	1	
Streptococcus spp.	3	2	1	0	
MRSA	0	1	1	1	
Pseudomonas spp.	1	1	0	0	
Aeromonas spp.	0	0	1	0	
Proteus spp.	1	0	0	0	
Prevotella spp.	1	0	0	0	
Haemophilus influenzae	0	1	0	0	
Enterobacter spp.	0	1	0	0	
Stenotrophomonas maltophilia	0	0	1	1	
Unknown	0	2	2	4	
Site					
Abdomen	7	8	6	8	
Lung	1	4	4	3	
Urinary tract	2	0	0	1	
Mediastinum	1	0	0	0	

Table 1. (Continued)

	Group 1	Group 2	Group 3	Group 4	*P*-value
Central nervous system	1	0	1	0	
Blood	0	1	0	0	
Soft tissue	0	0	1	0	

Data are presented as the median (first quartile to third quartile) or number (%). **P < 0.05.*
APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; MRSA, Methicillin-resistant *Staphylococcus aureus*; PMX-DHP, direct hemoperfusion with polymyxin B-immobilized fiber column; SOFA, Sequential Organ Failure Assessment; VIS, vasoactive–inotropic score; WBC, white blood cell.
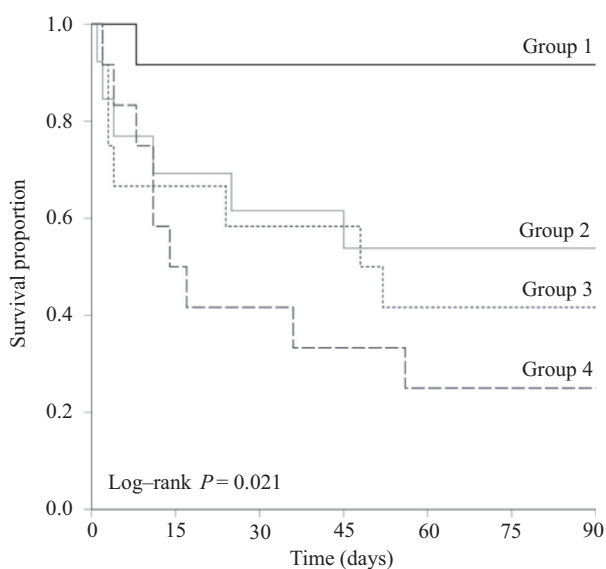

Fig. 2. Survival of all study participants with septic shock. Kaplan–Meier survival curves according to the interval between catecholamine treatment and initiation of direct hemoperfusion with polymyxin B-immobilized fiber column. Group 1, <6 h; group 2, 6–9 h; group 3, 9–29 h; and group 4, >29 h.

Given the median interval of 9 h from catecholamine treatment to PMX-DHP initiation, we divided the 20 EAI patients (Figure 3) into an early (within 9 h, *n* = 10) and a late group (>9 h, *n* = 10). No significant intergroup differences in age, SOFA score, APACHE II score, or pre-existing conditions were noted (Table 2). In the 90-day survival curves in Figure 4B, the two groups had similar 90-day mortality (50.0% versus 70.0%; *P* = 0.564), and the interval from catecholamine treatment to PMX-DHP initiation was not associated with 90-day mortality (odds ratio 1.119; 95% CI, 0.936–1.338; *P* = 0.217) (Table 4).

DISCUSSION

PREVIOUS STUDIES OF the timing of PMX-DHP initiation have reported that early initiation could reduce mortality in septic shock patients or reduce catecholamine requirement.[13,14] However, there have been no reports that differentiated according to infection site (IAI/EAI) and evaluated the effectiveness of early PMX-DHP initiation. Our results suggested that initiation of PMX-DHP therapy within 9 h after catecholamine treatment produces a survival benefit in septic shock with IAI.

First, we divided all study patients into four groups according to the interval between catecholamine treatment and PMX-DHP initiation and we noted the efficacy of early initiation (Fig. 2). However, although the proportion of abdominal infection patients was similar in all four groups, the number of patients with lung infection was lower in group 1 than other groups, and the number who had undergone emergency surgery or drainage was lower in groups 1 and 2 than groups 3 and 4. We therefore assumed that infection site correlated with different group characteristics, such as SOFA score, catecholamine requirement (VIS), and organisms, and proposed that these differences influenced the efficacy of early PMX-DHP initiation. We therefore divided the patients into two groups according to infection site, intra- or extra-abdominal, and evaluated the efficacy of early initiation in each group. This subanalysis showed that early PMX-DHP initiation produces a survival benefit in septic shock with IAI, suggesting that a differentiation by infection site, especially IAI and EAI, is necessary when considering the effect of PMX-DHP.

One possible explanation for the effect of early PMX-DHP initiation in septic shock could be catecholamine reduction due to PMX-DHP. Table 1 shows that VIS on PMX-DHP initiation in group 1 was lower than in other groups. We therefore compared the reduction in
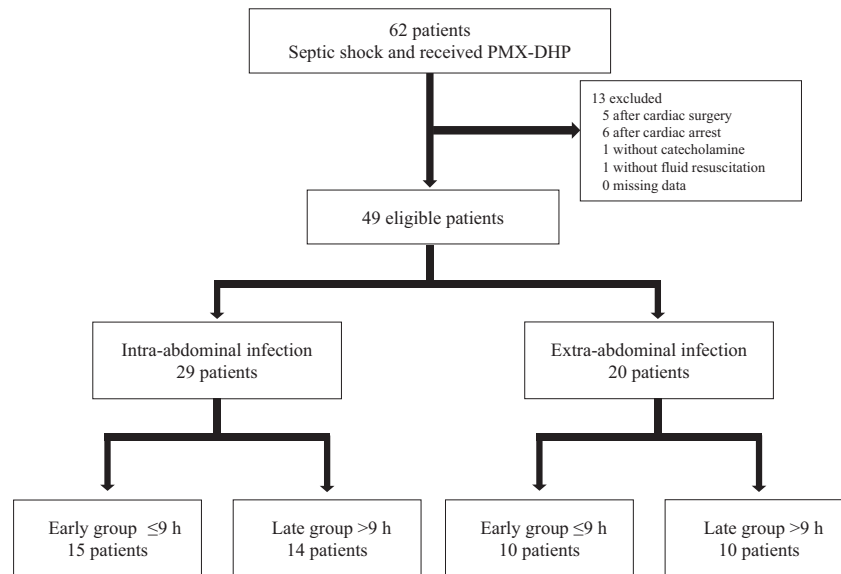
Fig. 3. Enrollment of patients with intra-abdominal infection and extra-abdominal infection. Study flowchart of patients with septic shock based on the infection site and the interval between catecholamine treatment and initiation of direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP).

Table 2. Risk factors related to 90-day mortality in 49 patients with septic shock

Item	Univariate analysis		P-value	Multivariate analysis		P-value
	Odds ratio	95% CI		Odds ratio	95% CI	
Age (years)	1.034	0.986–1.085	0.169	1.033	0.978–1.090	0.251
APACHE II score	1.113	1.034–1.197	0.004	1.117	1.021–1.221	0.015
Underwent emergency surgery or drainage (yes/no)	2.424	0.725–8.133	0.150	0.709	0.282–6.434	0.709
Time from catecholamine treatment to PMX-DHP initiation (h)	1.061	1.012-1.112	0.014	1.060	1.004-1.117	0.028

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; PMX-DHP, direct hemoperfusion with polymyxin B-immobilized fiber column.

catecholamine between groups and found that the amount of decrease was greater in the early than in the late group, but not to a statistically significant extent (mean ΔVIS = VIS on PMX-DHP initiation − VIS after 24 h). All patients: group 1, 4.0; group 2, −2.2; group 3, 2.0; group 4, 1.0; P = 0.618. In IAI patients: early group, 3.3; late group, 1.0; P = 0.085. In EAI patients: early group, 2.6; late group, −2.3; P = 0.436. Similarly, APACHE II score in the early group was lower, but not significantly so (Table 1). We therefore carried out univariate and multivariate logistic regression analyses and found that early PMX-DHP initiation was significantly associated with 90-day mortality (Tables 3 and 4).

These results suggest that reduction of catecholamine might help to prevent organ failure, resulting in reduced mortality.

Another possible explanation is endotoxin tolerance of monocytes. Previous research has established that the function of a monocyte shifts from a pro-inflammatory to an immunosuppressive phenotype within a few hours after exposure to lipopolysaccharide.[15,16] Based on these data, we propose that initiation of PMX-DHP before development of endotoxin tolerance could be the most effective strategy to control endotoxin and inflammatory mediators.

The survival rate in the present study was somewhat higher than in other studies. A possible explanation is PMX-

Table 3. Characteristics of two groups of patients with intra-abdominal infection and extra-abdominal infection

	Intra-abdominal infection			Extra-abdominal infection		
	Early group	Late group	*P*-value	Early group	Late group	*P*-value
Number of patients	15	14		10	10	
Age, years	74.0 (65.0–78.0)	75.5 (66.7–81.2)	0.505	73.5 (63.7–78.7)	67.0 (53.0–75.2)	0.19
Sex, male; *n* (%)	10 (66.6)	7 (50.0)	0.362	6 (60.0)	7 (70.0)	0.639
Height, cm	165.0 (159.6–172.3)	161.2 (153.7–169.6)	0.4	162.7 (156.2–166.2)	160.0 (156.7–168.1)	1
Weight, kg	56.7 (51.8–64.7)	53.7 (44.8–63.8)	0.451	61.6 (41.9–66.2)	47.9 (45.3–63.6)	0.631
Time from catecholamine initiation to PMX-DHP initiation, h	6.0 (4.0–8.0)	29.0 (18.5–60.7)	<0.001*	5.8 (3.0–8.6)	21.0 (14.6–44.0)	<0.001*
APACHE II score	19.0 (16.0–24.0)	23.5 (18.5–31.0)	0.201	29.5 (19.2–38.0)	31.0 (23.0–40.2)	0.739
SOFA score	12.0 (12.0–16.0)	13 (9.7–16.2)	0.914	14.0 (11.0–16.2)	12.6 (9.0–15.5)	0.353
PaO_2/FiO_2	170.4 (125.0–267.8)	120.5 (98.0–295.5)	0.715	106.5 (91.5–178.0)	108.5 (86.5–133.0)	0.481
WBC, $\times 10^3/\mu L$	7.3 (3.9–17.1)	9.0 (3.1–17.0)	0.914	7.4 (1.0–17.9)	6.8 (0.3–14.2)	0.579
CRP, mg/dL	14.1 (7.0–17.5)	13.3 (5.3–17.0)	0.780	11.4 (2.8–22.1)	15.9 (10.3–21.9)	0.529
HR, b.p.m.	106.0 (96.0–137.0)	110.5 (100.2–133.2)	0.533	115.0 (97.0–133.7)	115.0 (86.5–95.7)	0.971
MAP, mmHg	70.3 (57.3–85.6)	79.0 (61.9–87.5)	0.813	68.8 (51.5–72.9)	68.8 (51.5–73.1)	0.912
Lactate on PMX-DHP initiation, mg/dL	27.5 (16.7–47.2)	66.5 (29.7–102.0)	0.074	23.5 (20.0–72.2)	27.0 (12.5–50.0)	0.673
VIS on PMX-DHP initiation	15.7 (6.0–28.9)	22.5 (10.5–30.2)	0.425	24.4 (16.3–37.0)	23.0 (11.8–32.1)	0.529
Concomitant use of CRRT, *n* (%)	15 (100.0)	13 (92.8)	0.292	10 (100.0)	9 (90.0)	0.305
Duration of PMX-DHP, h	15.0 (9.0–22.0)	18 (10.3–24.0)	0.652	14.0 (7.4–18.5)	13.5 (9.0–23.1)	0.684
Two sessions of PMX-DHP, *n* (%)	2 (13.3)	2 (14.2)	0.941	0 (0.0)	0 (0.0)	
Initiation of PMX-DHP before CRRT, *n* (%)	11 (73.3)	5 (35.7)	0.042*	1 (10.0)	2 (20.0)	0.531
Underwent emergency surgery or drainage, *n* (%)	12 (80.0)	6 (42.5)	0.034*	0 (0.0)	0 (0.0)	
Admission route to ICU, *n* (%)						
Emergency department	4 (26.6)	4 (28.5)	0.156	5 (50.0)	0 (0.0)	0.014*
Other hospital	1 (6.6)	6 (42.8)		1 (10.0)	1 (10.0)	
Hospital ward	10 (66.6)	4 (28.5)		4 (40.0)	9 (90.0)	
Organism						
Escherichia coli	4	4		2	0	
Enterococcus spp.	4	4		0	0	
Klebsiella spp.	2	1		2	3	
Streptococcus spp.	1	0		4	1	
MRSA	0	0		1	3	
Pseudomonas spp.	2	0		0	0	
Aeromonas spp.	0	1		0	0	
Proteus spp.	0	0		1	0	
Prevotella spp.	1	0		0	0	
	0	0		1	0	

Table 3. (Continued)

	Intra-abdominal infection			Extra-abdominal infection		
	Early group	Late group	*P*-value	Early group	Late group	*P*-value
Haemophilus influenzae						
Enterobacter spp.	1	0		0	0	
Stenotrophomonas maltophilia	0	1		0	1	
Unknown	1	4		1	2	
Site						
Abdomen	15	14		0	0	
Lung	0	0		5	7	
Urinary tract	0	0		2	1	
Mediastinum	0	0		1	0	
Central nervous system	0	0		1	1	
Blood	0	0		1	0	
Soft tissue	0	0		0	1	

Data are presented as the median (first quartile to third quartile) or number (percentage). *$*P < 0.05$.
APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; MRSA, Methicillin-resistant *Staphylococcus aureus*; PMX-DHP, direct hemoperfusion with polymyxin B-immobilized fiber column; SOFA, Sequential Organ Failure Assessment; VIS, vasoactive–inotropic score; WBC, white blood cell.

Table 4. Risk factors related to 90-day mortality in patients with intra-abdominal infection (IAI) or extra-abdominal infection (EAI)

Item	Univariate analysis		*P*-value	Multivariate analysis		*P*-value
	Odds ratio	95% CI		Odds ratio	95% CI	
Patients with IAI						
Age (years)	1.064	0.978–1.158	0.148	1.057	0.961–1.164	0.254
APACHE II score	1.054	0.959–1.159	0.274	1.042	0.927–1.172	0.489
Underwent emergency surgery or drainage (yes/no)	0.600	0.129–2.796	0.515	0.772	0.069–5.707	0.772
Time from catecholamine treatment to PMX-DHP initiation (h)	1.062	1.004–1.124	0.036	1.058	1.000–1.119	0.049
Patients with EAI						
Age (years)	1.027	0.958–1.100	0.456	1.044	0.949–1.148	0.376
APACHE II score	1.213	1.025–1.436	0.025	1.230	1.005–1.505	0.045
Time from catecholamine treatment to PMX-DHP initiation (h)	1.073	0.972–1.186	0.163	1.119	0.936–1.338	0.217

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; PMX-DHP, direct hemoperfusion with polymyxin B-immobilized fiber column.

DHP duration. In previous randomized controlled trials, the target duration for each PMX-DHP was 2 h. In our ICU, PMX-DHP was typically given in one session for 24 h.

Recent research suggests that PMX-DHP is able to adsorb endotoxin for longer than 2 h[17] and that prolonged PMX-DHP treatment is effective in improving hemodynamics in
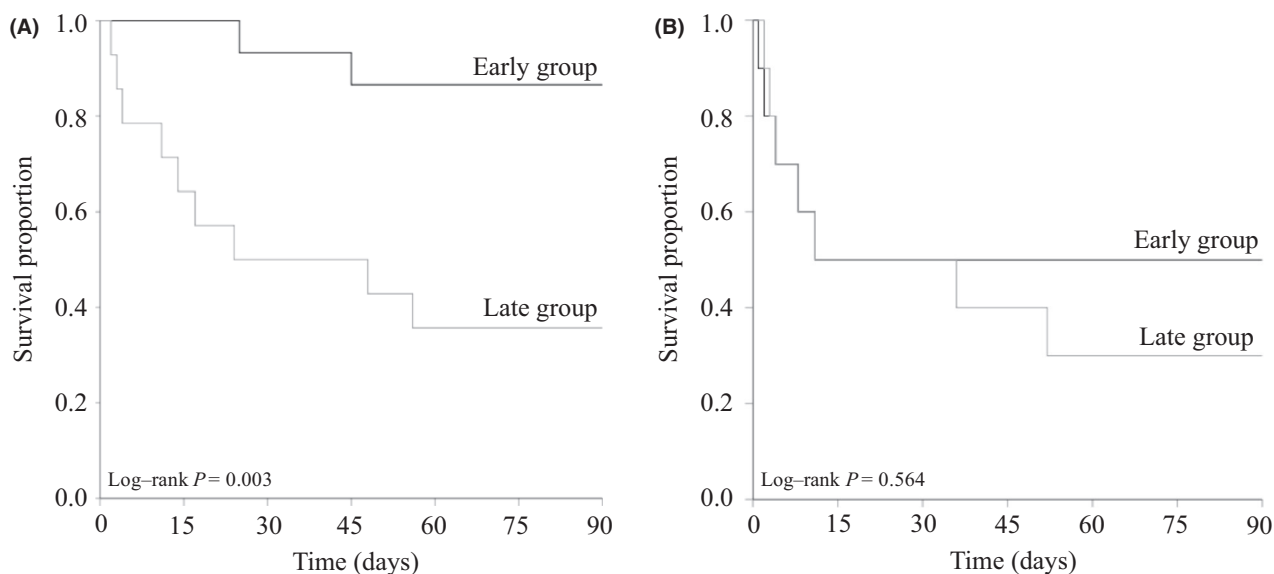
Fig. 4. Survival study of patients with intra-abdominal infection (IAI) and extra-abdominal infection (EAI). Kaplan–Meier survival curves according to the infection site and the interval between catecholamine treatment and initiation of direct hemoperfusion with polymyxin B-immobilized fiber column. A, IAI group (*n* = 29): early group (within 9 h) and late group (>9 h). B, EAI group (*n* = 20): early group (within 9 h) and late group (>9 h).

severe sepsis or septic shock.[18,19] Taken together with our data, this indicates that early initiation and prolonged treatment could influence PMX-DHP efficacy in septic shock.

A possible reason for the absence of a survival benefit from early PMX-DHP initiation in septic shock with EAI could be patient selection and/or use of a single session of PMX-DHP. There could have been fewer patients with endotoxemia who benefited from PMX-DHP among the EAI patients than among the IAI patients. Indeed, in the present study, the number of cases with Gram-positive bacteria was higher among the former (40.9% versus 29.0%). Marshall *et al*. showed that endotoxin levels were also increased in cases involving Gram-positive infections.[20] It was difficult to distinguish the EAI patients with endotoxemia in the present study as EAA was not measured. Another possible reason for the lack of improved outcome is that EAI patients might need two PMX-DHP sessions. The catecholamine requirement (median VIS) at 24 h after PMX-DHP initiation was 10.0 in IAI patients and 21.0 in EAI patients, suggesting that a single PMX-DHP session is insufficient to improve hemodynamics in EAI patients. Two PMX-DHP sessions might offer a survival benefit in EAI patients and this possibility needs further investigation.

Several limitations of the present study need to be considered. First, the retrospective design and small number of patients limited its power. Given the retrospective design, it is possible that the early PMX-DHP initiation group

included patients who would have improved without PMX-DHP and that the late initiation group included patients who had failed to respond to any prior treatment. These factors could cause a large survival bias. Our results therefore indicate only a possible association between early PMX-DHP initiation and mortality in septic shock. A larger-scale study on adaptive patients over an appropriate period is therefore needed to clarify whether early PMX-DHP initiation of PMX-DHP has a measurable survival benefit in septic shock. Second, the study groups differed in terms of certain baseline characteristics, such as lactate level on PMX-DHP initiation and admission route. These differences are likely to be associated with the interval between catecholamine treatment and PMX-DHP initiation. Patients from hospital wards received operation or PMX-DHP promptly, but patients from other hospitals experienced a delay and therefore had a higher lactate level at PMX-DHP initiation. Moreover, within the IAI group, there were significant differences in the number of patients undergoing emergency operation or drainage, but no significant difference in illness severity as measured by APACHE II and SOFA scores. Finally, we were unable to determine the exact time of sepsis onset retrospectively. For study purposes, we took the time of catecholamine treatment as the basis. The study nevertheless showed that, when using PMX-DHP, the timing of initiation is important. Specifically, PMX-DHP should be initiated as soon as possible after sepsis is diagnosed.

CONCLUSIONS

EARLY INITIATION OF PMX-DHP (within 9 h after catecholamine treatment) was effective in improving clinical outcome in septic shock due to IAI.

ACKNOWLEDGMENTS

DISCLOSURE

Approval of the research protocol: The present study was approved by the institutional review board of Shiga University of Medical Science.

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal study: N/A.

Conflict of interest: Tabata received grants from KONICA MINOLTA, outside the submitted work. Tsujita received personal fees from Ono Pharmaceutical Co., outside the submitted work. The other authors have nothing to disclose.

REFERENCES

1 Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat. Rev. Dis. Primers 2016; 2: 16045.

2 Janeway CA, Medzhitov R. Introduction: the role of innate immunity in the adaptive immune response. Semin. Immunol. 1998; 10: 349–50.

3 Aoki H, Kodama M, Tani T, Hanasawa K. Treatment of sepsis by extracorporeal elimination of endotoxin using polymyxin B-immobilized fiber. Am. J. Surg. 1994; 167: 412–7.

4 Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 2009; 301: 2445–52.

5 Payen DM, Guilhot J, Launey Y, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med. 2015; 41: 975–84.

6 Dellinger RP, Bagshaw SM, Antonelli M, et al. Effect of targeted polymyxin B hemoperfusion on 28-Day mortality in patients With septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. JAMA 2018; 320: 1455–63.

7 Chang T, Tu YK, Lee CT, et al. Effects of polymyxin B hemoperfusion on mortality in patients with severe sepsis and septic shock: a systemic review, meta-analysis update, and disease severity subgroup meta-analysis. Crit. Care Med. 2017; 45: e858–64.

8 Nakamura Y, Kitamura T, Kiyomi F, et al. Potential survival benefit of polymyxin B hemoperfusion in patients with septic shock: a propensity-matched cohort study. Crit. Care 2017; 21: 134.

9 Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018; 44: 2205–12.

10 Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit. Care Med. 2003; 31: 1250–6.

11 Gaies MG, Jeffries HE, Niebler RA, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. Pediatr. Crit. Care. Med. 2014; 15: 529–37.

12 Kdigo, AKI WorkGroup. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. Suppl. 2012; 2: 1–138.

13 Takeyama N, Noguchi H, Hirakawa A, et al. Time to initiation of treatment with polymyxin B cartridge hemoperfusion in septic shock patients. Blood Purif. 2012; 33: 252–6.

14 Chihara S, Masuda Y, Tatsumi H, et al. 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. J. Artif. Organs. 2017; 20: 71–5.

15 Venet F, Monneret G. Advances in the understanding and treatment of sepsis-induced immunosuppression. Nat. Rev. Nephrol. 2018; 14: 121–37.

16 Shalova IN, Lim JY, Chittezhath M, et al. Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1alpha. Immunity 2015; 42: 484–98.

17 Mitaka C, Fujiwara N, Yamamoto M, Toyofuku T, Haraguchi G, Tomita M. Polymyxin B-immobilized fiber column hemoperfusion removes endotoxin throughout a 24-hour treatment period. J. Crit. Care 2014; 29: 728–32.

18 Mitaka C, Tsuchida N, Kawada K, Nakajima Y, Imai T, Sasaki S. A longer duration of polymyxin B-immobilized fiber column hemoperfusion improves pulmonary oxygenation in patients with septic shock. Shock 2009; 32: 478–83.

19 Yamashita C, Hara Y, Kuriyama N, Nakamura T, Nishida O. Clinical effects of a longer duration of polymyxin B-immobilized fiber column direct hemoperfusion therapy for severe sepsis and septic shock. Ther. Apher. Dial. 2015; 19: 316–23.

20 Marshall JC, Foster D, Vincent JL, et al. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J. Infect. Dis. 2004; 190: 527–34.