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Effects of Polymyxin B Hemoperfusion on Septic Shock Patients Requiring Noradrenaline: Analysis of a Nationwide Administrative Database in Japan

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Keywords
Septic shock · Polymyxin B hemoperfusion · Propensity-matched analysis

Abstract
Introduction: Polymyxin B hemoperfusion (PMX) reduces endotoxin in septic shock patients' blood and can improve hemodynamics and organ functions. However, its effects on the reduction of septic shock mortality are controversial. ***Methods:*** Using the Japanese diagnosis procedure combination database from April 2016 to March 2019, we identified adult septic shock patients treated with noradrenaline. This study used propensity score matching to compare the outcome between PMX-treated and non-treated patients. The primary endpoint was 28-day mortality, counting from the day of noradrenaline initiation. The secondary endpoints were noradrenaline-, ventilator-, and continuous hemodiafiltration (CHDF)-free days at day 28. ***Results:*** Of 30,731 eligible patients, 4,766 received PMX. Propensity score matching produced a matched cohort of 4,141 pairs with well-balanced patient backgrounds. The 28-day survival rate was 77.9% in the PMX group and 71.1% in the control group ($p < 0.0001$). Median days of noradrenalin-, CHDF-, and ventilator-free days were 2 days ($p < 0.0001$), 2 days ($p < 0.0001$), and 6 days ($p < 0.0001$) longer in the PMX group than in the control group, respectively. When stratified with the maximum daily dose of noradrenaline, the PMX group showed a statistically significant survival benefit in the groups with noradrenaline dose <20 mg/day but not in the noradrenaline group dose ≥20 mg/day. ***Conclusion:*** Analysis of large Japanese databases showed that septic shock patients who received noradrenaline might benefit from PMX treatment.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infections [1]. It is a leading cause of mortality in the intensive care unit (ICU), especially when a patient's condition progresses to septic shock, with a high mortality rate as high as 42% [2]. Various inflammatory mediators are involved in the pathophysiology of septic shock. In recent years, extracorporeal blood purification has been widely used to control mediators in the blood as adjunctive therapy for improving the pathological condition of septic shock. Direct hemoperfusion using polymyxin B-immobilized fibers (PMX) is a treatment targeting endotoxin, an essential pathogenic trigger of the whole-body inflammatory cascade [3, 4].

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Numerous studies have reported the effectiveness of PMX, which includes the improvement of hemodynamics and the reduction of organ damage in septic shock patients. However, the results of multicenter randomized controlled trials showed inconsistent findings regarding the effects on mortality. The EUPHAS study conducted in Italy recruited abdominal septic shock patients. In this study, the 28-day mortality rate in the PMX-treated group was 31%, significantly lower than 54% in the control group [5]. On the other hand, in the French study, ABDO-MIX, there was no significant difference in the mortality rate between the PMX group and the control group [6]. In the latest EUPHRATES trial conducted in North America, PMX showed improvements in mean arterial pressure and ventilator-free days. However, the mortality rate was not significantly different between groups [7].

In addition to randomized controlled trials, several observational studies analyzed the effectiveness of PMX, which analyzed data from large-scale sepsis registries. One study from Japan analyzed data of septic shock collected in 42 Japanese ICU. After propensity score matching, hospital mortality of PMX-treated patients was 32.8%, significantly lower than that of non-treated patients (41.2%) [8]. There are 2 studies on PMX, which analyzed the Japanese nationwide inpatient database, Diagnosis Procedure Combination (DPC). One study that examined the cohort of septic shock with gastrointestinal perforation found no difference in the 28-day mortality of PMX-treated and non-treated groups [9]. On the other hand, a study focused on septic shock patients receiving continuous renal replacement therapy (CRRT) due to acute kidney injury showed a significantly lower mortality rate from PMX [10].

All of these registry studies on PMX used relatively old data collected before 2013. Since the standard of sepsis management has been changing over the years, the effectiveness of PMX as adjunctive therapy of sepsis may have changed. The results obtained from the new data may be different from the previous studies. In this study, we used DPC data collected from 2016 to 2018 to reexamine the efficacy of PMX when applied in combination with current standard management on septic shock patients.

Materials and Methods

Study Design and Data Source

This retrospective observational study used inpatient data included in the Japanese DPC database. The DPC database includes discharge and administrative claims data for all inpatients discharged from more than 1,000 participating hospitals, covering 92% of all tertiary-care emergency hospitals in Japan [11, 12]. The database includes patient baseline information such as sex, age, primary diagnosis, admission-precipitating diagnosis, comorbidities on admission, and post-admission complications coded with International Classification of Diseases 10th Revision (ICD-10) codes. The DPC database also includes the dosages and dates of all drugs and blood products administered each day during hospitalization.

Patient Selection and Definitions

We extracted patient data recorded from April 2016 to March 2019. Selected patients aged 20 years or older met the following criteria: (1) whose primary diagnosis was sepsis based on the ICD-10 codes and (2) administered noradrenaline during the hospitalization. We excluded patients recruited in clinical trials who died within 3 days after the start of noradrenaline or transferred to other hospitals within 28 days after beginning noradrenalin treatment. We defined the day of first noradrenaline administration as the "shock onset day."

Covariates and Endpoints

We collected baseline information of the patients, such as age at admission, gender, emergency versus elective hospital admission, and Charlson Comorbidity Index (CCI) [13, 14], from the database. This study identified the following procedures and treatments performed from the day before to the day after the shock onset day from the database: continuous hemodiafiltration (CHDF), hemodialysis, mechanical ventilation, administration of γ-globulin, antithrombotic drugs (antithrombin III or recombinant soluble thrombomodulin), red blood cell transfusion, platelet transfusion, and PMX. We also recorded admissions to emergency rooms or ICU. This study defined a surgical operation performed between 7 days before the shock onset day and the day of shock onset as surgery. It does not include the following emergency treatment procedures: cardiopulmonary bypass, balloon pumping, tracheotomy, and transfusion. The study classified hospitals as either university or non-university. It defined the highest noradrenaline dose per day from the shock onset day to day 28 as the maximum noradrenaline dose.

The primary endpoint was 28-day mortality, counting from the day of shock onset. The secondary endpoints were noradrenaline-, CHDF-, and ventilator-free days at day 28. We defined free days as days alive and free from noradrenaline, CHDF, and ventilator between day 0 and day 28. Free days were counted as 0 when a patient died before day 28.

Propensity Score Matching Analysis

We performed a propensity score matching analysis between PMX-treated and control groups. The study estimated the propensity score using a logistic regression model for the use of PMX as a function of following confounders. These included patient characteristics and treatments: age, sex, CCI, emergency admission, type of hospital (university or non-university hospital), surgery, ER/ICU admission, maximum noradrenaline dose per day, CHDF, hemodialysis, mechanical ventilation, γ-globulin, antithrombotic drugs, red blood cell transfusion, and platelet transfusion. We calculated the C-statistic to evaluate the best match. A one-to-one matched analysis using the nearest-neighbor matching was performed based on the estimated propensity score of each patient.

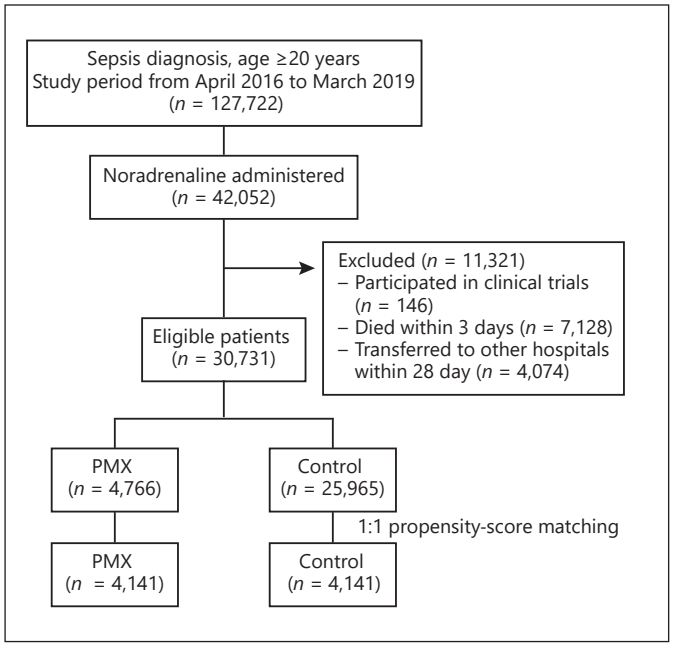

Fig. 1. Flowchart of patient selection.

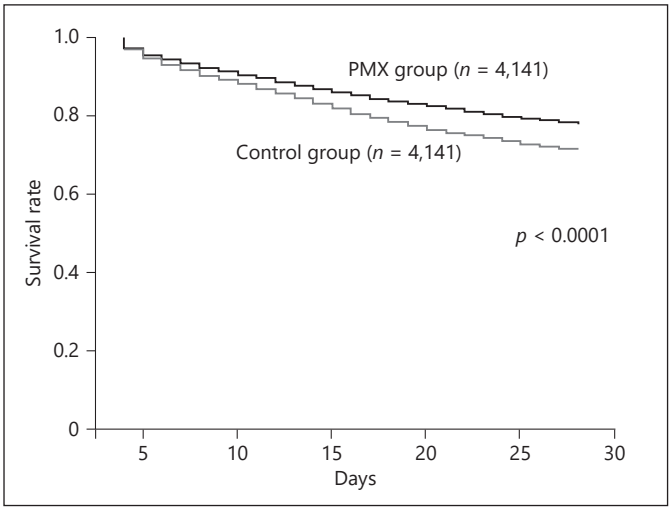

Fig. 2. Kaplan-Meier survival curves of propensity-matched patients.

We used a caliper width of 0.2 of the standard deviation of the propensity score. We evaluated the balance among covariates using absolute standardized difference (ASD), which considers a difference below 10% to be well balanced.

Subgroup Analysis

The patients were separated into 4 groups by the median and interquartile of the maximum daily noradrenalin dose. Specifically, group 1 (<6 mg/day), group 2 (6–9.9 mg/day), group 3 (10–19.9 mg/day), and group 4 (≥20 mg/day). We performed multivariate logistic regression analysis in each group using the same covariates used in the above propensity score estimation. We calculated the odds of survival by using PMX.

Statistical Analysis

Using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables, we performed the Kaplan-Meier analysis for survival until day 28. This study considered a two-sided p value of 0.05 to be statistically significant and used JMP Pro 15.1.0 (SAS Institute) for all statistical analyses.

Results

Patients

During the study period, 42,052 patients fulfilled the inclusion criteria. Of these, we excluded 11,321 and included 30,731 patients in the study. Among them, 4,766 patients received PMX treatment (PMX group), and 25,965 patients did not (control group). After the propensity score matching, we created a pair of 4,141 patients (Fig. 1). The C-statistic of the propensity score was 0.867.

Table 1 shows the baseline characteristics of patients before and after propensity score matching. Before the matching, the PMX group showed higher maximum noradrenaline dose. It also indicated a higher percentage of patients who received CHDF, mechanical ventilation, red blood cell, platelet transfusion, γ-globulin, and antithrombotic drug and ICU admission. These results indicated that PMX group patients were more severely ill patients. Surgery was more common, and emergency admission was less common in the PMX group. After propensity-score matching, all confounders were well balanced between the groups, with less than 10% of ASD for all covariates.

Endpoints

Figure 2 shows the survival curve from the day of first noradrenaline administration (shock onset day) to day 28. The survival rate at day 28 was 77.9% in the PMX group and 71.1% in the control group ($p < 0.0001$), and the odds ratio was 1.433 (95% CI, 1.298–1.584, $p < 0.0001$).

In this propensity-matched cohorts, the number of noradrenalin-free days, CHDF-free days, and ventilator-free days were significantly longer in the PMX group compared to the control group, with a median difference of 2 days ($p < 0.0001$), 2 days ($p < 0.0001$), and 6 days ($p < 0.0001$), respectively (Table 2).

Table 1. Baseline patient characteristics before and after propensity score matching

Variable	Unmatched groups			Matched groups		
	PMX (n = 4,766)	control (n = 25,965)	ASD, %	PMX (n = 4,141)	control (n = 4,141)	ASD, %
Age						
≤50 years	318 (6.7)	1,502 (5.8)	3.0	286 (6.7)	291 (7.0)	1.0
51–70 years	1,499 (31.7)	7,253 (28.0)	6.6	1,334 (31.7)	1,377 (33.3)	2.7
>70 years	2,916 (61.6)	17,096 (66.2)	7.8	2,521 (61.6)	2,473 (59.7)	3.2
Sex (male)	2,742 (57.5)	14,810 (57.0)	0.8	2,424 (58.5)	2,485 (60.0)	2.4
Emergency admission	4,266 (89.5)	24,165 (93.1)	10.8	3,723 (89.9)	3,709 (89.6)	0.9
CCI						
0	1,009 (23.1)	5,085 (21.5)	3.1	927 (22.4)	940 (22.7)	0.6
1	990 (20.8)	5,920 (22.8)	4.0	877 (21.2)	854 (20.6)	1.1
2	1,095 (23.0)	5,723 (22.0)	1.8	949 (22.9)	921 (22.2)	1.3
≥3	1,582 (33.2)	8,737 (33.8)	1.0	1,388 (33.5)	1,426 (34.4)	1.6
University hospital	956 (20.1)	4,225 (16.3)	8.1	858 (20.7)	893 (21.6)	1.7
Maximum noradrenaline dose						
<6 mg/day	721 (15.5)	6,651 (25.6)	20.8	657 (15.9)	643 (15.5)	0.8
6–9.9 mg/day	686 (14.4)	4,434 (17.1)	6.0	590 (14.3)	560 (13.5)	1.7
10–19.9 mg/day	1,645 (34.5)	8,112 (31.2)	5.7	1,421 (34.3)	1,407 (34.0)	0.6
≥20 mg/day	1,714 (36.0)	6,768 (26.1)	17.8	1,473 (35.6)	1,531 (37.0)	2.4
CHDF	3,036 (63.7)	5,041 (19.4)	84.9	2,460 (59.4)	2,549 (61.6)	3.6
HD	348 (7.3)	1,529 (5.9)	4.7	307 (7.4)	364 (8.8)	4.1
Mechanical ventilation	3,353 (74.1)	9,824 (37.8)	63.1	2,961 (71.5)	3,073 (74.2)	5.0
Surgery	2,883 (60.5)	6,150 (23.7)	42.3	2,311 (55.8)	2,237 (54.0)	2.9
ICU admission	3,433 (72.0)	14,881 (57.3)	25.0	2,990 (72.2)	3,140 (75.8)	6.8
γ-Globulin	1,890 (39.7)	3,336 (12.9)	55.7	1,468 (35.5)	1,393 (33.6)	3.1
Antithrombotic drugs	2,963 (62.2)	4,989 (18.9	83.5	2,373 (57.3)	2,337 (56.4)	1.4
RBC transfusion	2,163 (45.4)	5,798 (22.3)	42.3	1,779 (43.0)	1,835 (44.3)	2.2
Platelet transfusion	983 (30.6)	2,387 (9.2)	49.2	845 (20.4)	851 (20.6)	0.3

Data are presented as numbers (%). CCI, Charlson Comorbidity Index; CHDF, continuous hemodiafiltration; HD, hemodialysis; ICU, intensive care unit; RBC, red blood cell.

Table 2. Noradrenalin-, ventilator-, and CHDF-free days at day 28

	PMX (n = 4,141)	Control (n = 4,141)	p value
Noradrenaline-free days	24 (11–26)	22 (0–25)	<0.0001
CHDF-free days	24 (9–28)	22 (0–28)	<0.0001
Ventilator-free days	20 (1–28)	14 (0–28)	<0.0001

Data are presented as median (IQR). CHDF, continuous hemodiafiltration; IQR, interquartile range.

Subgroup Analysis

Figure 3 shows the odds ratio of survival at day 28, stratified with the maximum noradrenaline dose. We performed the propensity score matching analysis in each of 4 groups, and the ASD of all covariates was <10% after matching (data not shown). In groups 1, 2, and 3, which correspond to the patients with <6, 6–9.9, and 10–19.9 mg/day dose of maximum noradrenaline, the PMX group showed statistically significant survival benefit. In contrast, in group 4, with the highest maximum noradrenaline dose (≥20 mg/day), the survival rate was not statistically different between PMX and control groups.

Discussion

This study analyzed the nationwide inpatient database of Japan using propensity score matching methods. We found that the survival rate of PMX-treated patients was significantly higher than that of non-treated patients. Also, noradrenaline-free days, CHDF-free days, and ventilator-free days were substantially longer in PMX-treated patients.

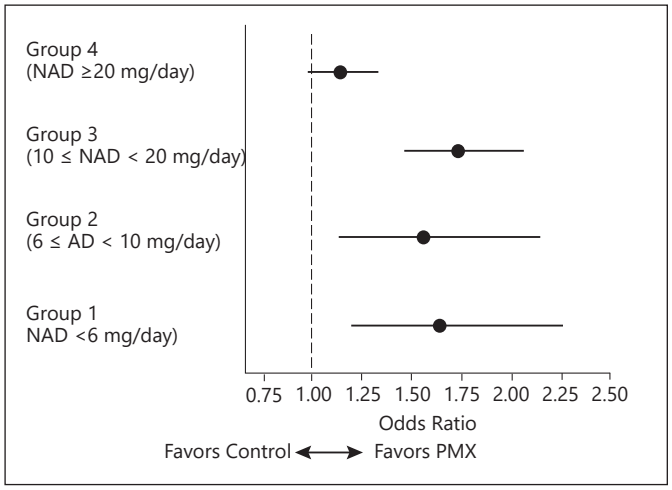

Fig. 3. Subgroup analysis of the effect of PMX stratified according to the maximum noradrenaline dose, the highest dose of noradrenaline per day from the shock onset day to day 28.

Over 25 plus years, about 200,000 patients received PMX treatment, mainly in Japan. Several RCTs conducted on PMX evaluated the efficacy of PMX. Although most of the studies showed clinical effects of PMX on the conditions of a patient, the impact of PMX on mortality reduction is controversial. Among the 3 significant RCTs conducted outside Japan, the survival benefit was obtained in the EUPHAS study but not verified in the ABDO-MIX and EUPHRATES studies. One problem of those RCTs is that the number of patients recruited is not large enough to evaluate the mortality difference. Even in the largest EUPHRATES trial, the total number of patients included was 449. Assuming that showing significant survival benefit would be difficult unless there is a vast difference in the mortality between groups.

Besides RCTs, the other approach to evaluate the efficacy of various treatments for diseases is to analyze large-scale databases collected in real-world clinical settings. One data source available in Japan is the DPC. Two studies analyzed the DPC database to evaluate the efficacy of PMX. In one study examining the data of septic shock due to lower intestinal perforation, the mortality of the PMX group ($n = 590$) and control group ($n = 590$) was 17.1 and 16.3%, respectively, without significant difference ($p = 0.696$) [9]. In the other study, which analyzed a cohort of septic shock data requiring CRRT, the mortality of PMX-treated ($n = 978$) and non-treated groups ($n = 978$) was 40.2 and 46.7%, respectively. This result showed a significant difference between the groups ($p = 0.003$) [10]. The data collected in the above 2 studies are from 2007 to 2011 and from 2007 to 2012. The standard management in sepsis has been changing over the years based on the international guideline of sepsis management, Surviving Sepsis Campaign guideline (SSCG) [15–17]. In Japan, the Japanese sepsis guideline (J-SSCG) is also referenced. Both guidelines are revised every 4 years [18]. PMX is one of the adjunctive therapies for septic shock, used in combination with standard management of sepsis. The changes in this baseline management may affect the effectiveness of PMX therapy. Our study used the data from 2016 to 2019, reflecting the latest sepsis management based on the SSCG 2016 and J-SSCG 2016.

Our study analyzed the cohort of septic shock patients requiring noradrenaline. Interestingly, when the amount of noradrenaline dose stratified the patients, the survival benefit was less prominent in the highest noradrenaline group (≥20 mg/day), compared to the other 3 groups (<6 mg, 6–9.9 mg, and 10–19.9 mg/day). This finding may indicate that PMX used in the late stage of septic shock (after the shock has become too severe) is less effective than in the early stage of septic shock. Previous observational studies also indicated that the early use of PMX is more effective than the late use [19, 20], which is consistent with our results.

In addition to the mortality difference, we found a significant difference in the days requiring noradrenaline, ventilator, or CHDF. For example, the median ventilator-free days at day 28 were 6 days longer in the PMX group ($p < 0.001$). This result is consistent with the result obtained in the EUPHRATES trial, which showed a mean difference of 2.9 days and a median difference of 11 days in favor of the PMX group. Early weaning from a ventilator is essential for the patients and for reducing ICU stay and reducing medical expenses.

Our study has several limitations. First, the study is a retrospective, observational study. Although we adjusted for several potential confounding factors by propensity score matching, we cannot eliminate residual confounding factors. These include vital signs or laboratory data, which are not available from the DPC database. Second, the disease code of sepsis used for patient selection is administrative claims, and they may not be precise. Third, only daily data are available from the DPC database. We based the amount of noradrenaline used for the classification of patients on the daily dose. It may not reflect the hourly change of drug dose. Finally, we could not follow-up on the data after discharge, including survival status, since the DPC database contains only inpatient data. For this reason, we excluded the data of patients transferred to other hospitals.

Conclusion

Analysis of a sizable nationwide database revealed that PMX treatment might be useful in reducing the mortality of septic shock patients requiring noradrenaline. PMX also reduced the days on noradrenaline, CHDF, and ventilator. A prospective randomized controlled trial needs to validate these results.

Statement of Ethics

The study was approved by the Institutional Review Board of the Tokyo Medical and Dental University, which waived the requirement for informed patient consent because of the anonymous nature of the data.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

K.F.: responsible for study concept, design, data extraction, data analysis, and manuscript preparation. K.T.: accountable for statistics and manuscript preparation. K. Fushimi: responsible for database organization and review.

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