의학석사 학위논문

Efficacy of use of Polymyxin B Hemoperfusion in patients with sepsis: A Korean multicenter cohort study

한국의 다기관 코호트 연구에서 polymyxin B hemoperfusion 의 패혈증 환자에서의 효과

울 산 대 학 교 대 학 원

의 학 과

이 아 영

Efficacy of use of Polymyxin B Hemoperfusion in patients with sepsis: A Korean multicenter cohort study

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

울 산 대 학 교　대 학 원

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Abstract

PURPOSE

Although Polymyxin B hemoperfusion improved the survival of patients with sepsis in a meta-analysis, its effectiveness remains controversial due to the high risk of bias. We aimed to determine whether PMX-HP is effective in sepsis patients.

MATERIALS AND METHODS

This retrospective study evaluated the efficacy of PMX-HP compared with continuous renal replacement therapy (CRRT), in delaying progression to multiple organ failure (MOF) determined using the delta Sequential Organ Failure Assessment (SOFA) scores of 194 critically ill sepsis patients from 15 different hospitals in South Korea. The secondary outcomes included in-hospital mortality rate, length of ICU stay, change in clinical frailty scale, ventilator-free days within 28 days, and length of hospital stay.

RESULTS

Among 194 eligible patients (mean age, 68.9 years; 90[46.9%] women, mean SOFA score 8.61), 41 received Polymyxin B hemoperfusion treatment (PMX-HP), while 153

patients received CRRT. Polymyxin B hemoperfusion did not show advantage of slowing progression in multiple organ failure progression over CRRT (change in SOFA between day0 and day7, 1.83 vs 1.32; p=0.012; change in SOFA between day0 and day14, 1.83 vs 2.17; p=0.368). The 7-day (hazard ratio [HR], 0.182; 95% confidence interval [CI], 0.057 to 0.581; p=0.004), 14-day ([HR], 0.39; 95% [CI], 0.129 to 0.690; p=0.005), 28-day mortality rate ([HR], 0.39; 95% [CI], 0.19 to 0.78; p=0.008) were not significantly different between the two groups. The number of ventilator-free day within 28 days (absolute difference [AD], 0.8 days; standard deviation (SD), 1.36; 95% CI, −3.49 to 1.88; p=0.557), length of ICU stay (AD, 2.15 days; SD, 1.98; 95% CI, −1.75 to 6.06; p=0.278), clinical frailty scale change (p=0.051), and change in the use of vasopressor (p=0.158) were not significantly different between the two groups. Meanwhile, a significant difference was observed in platelet count change (p=0.019) and length of hospital stay (p=0.003) between the two groups.

CONCLUSIONS

In sepsis patients, PMX-HP treatment did not significantly lead to delayed progression to MOF compared with CRRT

차례

표 차례

그림 차례

Introduction

Sepsis and septic shock remain fatal, resulting in high mortality (20-50%) in patients, especially with advanced organ failure worldwide.[1-5] Therefore, most the patients admitted to intensive care units(ICUs) to ensure the intensive monitoring of patients' hemodynamic status.[6] Early aggressive fluid resuscitation; the use of appropriate antibiotics; and control of the source of infection are required to rescue these patients.[7,8] The surviving sepsis campaign(SSC) has provided guidelines for managing patients with sepsis since 2002 and has highlighted sepsis bundle[9,10]. Since then, the survival of sepsis has improved.[3,4] However, sepsis still shows a high mortality rate, and frequently progresses to multiple organ failure[1](MOF). Hence, efforts have been made to find other effective methods, such as CRRT, PMXB, and Cytosorb, to manage sepsis.

Endotoxin plays a significant role in the development of sepsis and triggers inflammatory responses; the disequilibrium of inflammatory mediators results in MOF[11-13]. The immune response to the pathogen itself can be exaggerated and cause MOF syndrome and death[14]. In addition, prolonged release of inflammatory mediators can cause severely impaired immunity and immunoparalysis leading to severe secondary

nosocomial infections[15,16]. Hemodialysis may help remove endotoxins and pro-inflammatory and inflammatory markers, suggesting that it can reduce the inflammatory responses mediated by cytokines[16-18]. The hemoperfusion method involves the direct contact of the sorbent material with blood or plasma via the extracorporeal circuit. It has different removal characteristics according to the type of sorbent used.[17,19-22] Polymyxin B (PMX) has a high affinity of irreversibly binding to endotoxins, especially Lipopolysaccharide(LPS), the concentration of which is associated with the severity of sepsis[23,24]. More specifically, polystyrene fiber bound with PMX antibiotics absorbs endotoxin[23]. PMX hemoperfusion (PMX-HP) was first introduced in Japan and has been widely studied worldwide since then[24].

Although PMX-HP's efficacy of reducing the severity of sepsis or improving mortality has remained controversial, a randomized controlled trial and a post-hoc analysis showed positive results[25-28]. We, therefore, conducted a retrospective review of data in 15 ICUs and hypothesized that the use of PMX-HP delays progression to MOF in patients with sepsis.

Methods

PARTICIPANTS AND DATA COLLECTION

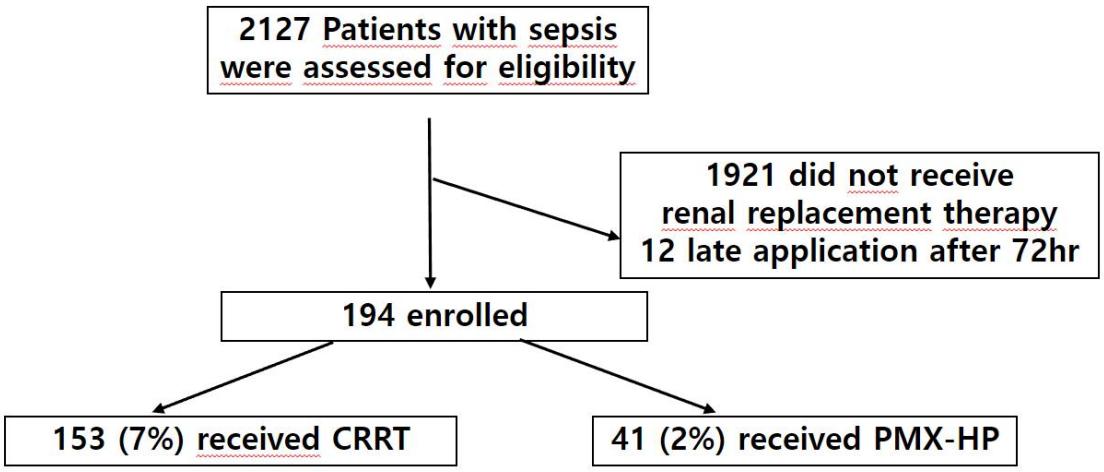
Data on the study conducted by Korean Sepsis Alliance (KSA) (September 2019-February 2020; ICU units at tertiary hospitals in South Korea) were searched and extracted from 15 tertiary hospitals in South Korea. This retrospective observational study was approved by the Institutional Review Board (IRB Number, 2018-0675).

Patients aged > 19years, who had been admitted in the non-ICU hospital wards or emergency room were enrolled in this study. Patients from the emergency room who met the following criteria: those (1) who had a quick Sepsis-related Organ Failure Assessment(qSOFA) ≥ 1; (2) who had a known or suspected infection; and (3) who underwent blood culture. Moreover, patients from general wards who met the following criteria were also eligible to participate.[29,30]: Those (1) with known or suspected infection and (2) a SOFA score of 2 or higher than that at baseline. The SOFA score (scores range, 0-24; higher scores mean worse organ function)[31] was used to determine the progression of organ dysfunction. Changes in SOFA score were indicated by using a delta SOFA.[28,32] Patients who did not receive renal replacement therapy (RRT) or received RRT only after

3days were excluded.

Figure1 Screening and analysis.

The number of patients excluded for not receiving renal replacement therapy, but some were excluded because of late application after ICU Day 3.



DESIGN AND SETTING

We retrospectively screened data for the 6-months from 15 different ICUs in South Korea. The patients were divided into two groups: those who received continuous renal replacement therapy (CRRT) and those who underwent PMX-HP. The application of PMX-HP was not explicitly indicated in current guidelines, but the treatment was recommended among patients with sepsis.[30] In all patients, Toraymyxin® cartridge (Toray

Medical Company, Tokyo, Japan) was used to perform PMX-HP. The delta SOFA score was used to indicate the change in the degree of organ dysfunction and was calculated as the SOFA score at day7 or day14 minus the SOFA score at baseline.

ENDPOINTS AND ASSESSMENT

The primary outcome was the difference in delta SOFA score between the two groups.[33] The secondary outcome included the length of ICU stay and 7-day, 14-day, and 28-day mortality rates. Other secondary outcomes were ventilator-free days by 28 days, change in clinical frailty scale from ICU admission to hospital discharge, the time to hospital discharge, changes in vasopressor use, platelet count, and its change from time zero to day7 as well as day14. Moreover, the clinical factors independently associated with the 28-day mortality and change in SOFA score were identified.

STATISTICAL ANALYSIS

Kolmogorov-Smirnov test was performed to determine the distribution of variables. Continuous variables with normal distribution were presented as mean (standard deviation (SD)), while those with non-normal distribution were presented as median (interquartile range [IQR]). Other descriptive variables were described as actual numbers and percentages, as appropriate.

The primary efficacy analysis for assessing change in SOFA score in the PMX-HP group compared with that in the CRRT was performed using paired t-test and two-sample t-test. Multivariate and univariate Cox regression models were performed to determine the clinical factors independently associated with 28-day mortality. The findings were interpreted based on the 95% confidence intervals (CI) for the estimated measures of association. The results were based on the 95% Cis for the estimated measurements of association. Survival analyses, with censoring patients' data at 7 days, 14 days, and 28 days, were performed using a Kaplan-Meier curve, Cox proportional hazards analysis, and logistic regression analysis with propensity score matching. The p-value for the difference between the two groups was calculated by log-rank analysis. A logistic regression model was used to generate a propensity score for PMX-HP or CRRT use based on the

systematically collected data on different baseline variables between the two groups. The differences in the number of ventilator-free days, length of ICU and hospital stays, and change in clinical frailty scale from ICU admission to hospital discharge were analyzed using Student's t-test. A chi-square test was also conducted to compare the differences in the frequency of vasopressor use at day 0, day 7, day 14; between-group comparisons of the change in vasopressor use were also performed between day 0 and day 7 as well as day 14. Patients with missing data were considered to require vasopressor treatment if they died upon discharge from the ICU and did not require this treatment if they survived upon release from this unit.

The results were considered significant if the two-sided p-value was less than 0.05. All statistical analyses were performed using SPSS ver. 25. Software.

Table 1. Clinical characteristics in the study population.

	CRRT	PMX	P†
	n=153	n=41	
Age (median [IQR])	69.43[61,80]	66.83[60,77]	0.385
Sex (male (%))	82(53.6)	22(53.7)	0.994
Severity scale			
SAPS (mean (SD))	83.08(15.34)	75.76(18.02)	0.021
Initial SOFA (mean (SD))	8.98(3.22)	7(3.47)	0.001
Clinical Frailty scale (median [IQR])	4.46[3,6]	5.24[3,7]	0.041
Charlson (median [IQR])	5.47[4,7]	5.76[5,7]	0.314
Comorbidity			
Hematologic disease (%)	19(12.4)	2(4.9)	0.135
Chronic liver disease (%)	131(85.62)	35(85.37)	0.967
Chronic kidney disease (%)	117(76.47)	26(63.41)	0.100
Chronic kidney disease (%)	36(23.53)	15(36.59)	0.100
DM (%)	46(30.07)	16(39.02)	0.280
Solid cancer (%)	45(29.41)	9(21.95)	0.335
Cardiovascular Disease (%)	23(15.03)	12(29.27)	0.044
Respiratory Disease (%)	15(9.80)	4(9.76)	0.993
Chronic neurologic disease (%)	25(16.34)	4(9.76)	0.293
Laboratory data			
Procalcitonin (median [IQR])	42.76[0.49,14.41]	21.75[1.61,61.84]	0.008
Bicarbonate (mean (SD))	15.32(5.94)	18.3(5.75)	0.005
Lactate (median [IQR])	5.98[1.4,4.7]	4.25[2.55,7.7]	0.006
PLT, $10^3/\mu$ (median [IQR])	144[52.5,224.0]	185[90.0,252.0]	0.002
Vital sign & Initial treatment			
Mean Arterial pressure (median [IQR])	64.98[53.3,71]	79.63[63.3,100]	0.001
Steroid (%)	52(34.0)	7(17.1)	0.233
MV (%)	72(47.1)	22(53.7)	0.453
ECMO (%)	6(3.92)	0(0.0)	0.089

Abbreviation: SOFA=Sequential Organ Failure Assessment, MV=Mechanical ventilation, SAPS=Simplified Acute Physiology score, PLT=platelet count IQR=Interquartile range, SD=standard deviation, ECMO=Extracorporeal Membrane Oxygenation D1=day1, DM=diabetes mellitus, CNS= central nervous system, Charlson=Charlson comorbidity score

†For categorical variables, the Chi-square test or Fisher's exact test was used, and n (%) was reported. For continuous variables, normally distributed data are described as mean ± SD and non-normally distributed data as median (interquartile range). t-test (normally distributed data) or Mann-Whitney test (non-normally distributed data) was used.

Table2. Isolated Microorganisms by Treatment Group

Organisms and Sites	CRRT	PMX	P†
	n=153	n=41	
Microorganism. Identified (%)	90(58.8)	21(51.2)	0.384
Organisms			
Gram-positive infection (%)	27(17.7)	10(24.40)	0.359
Gram-negative infection (%)	69(45.10)	15(36.59)	0.370
Fungus imp (%)	3(1.9)	1(2.4)	0.693
Virus infection (%)	3(1.96)	0	0.487
Multipathogenes (%)	25(16.34)	8(19.51)	0.631
Sites			
Pulmonary infection (%)	36(23.52)	8(19.51)	0.585
Intra-abdominal infection (%)	51(33.33)	2(4.88)	0.000
Urinary infection (%)	23(15.03)	2(4.88)	0.084
Others (%)	32(20.91)	12(29.27)	0.256
Multiple site infection (%)	14(9.15)	2(4.88)	0.377

†Chi-square test or Fisher's exact test was used.

Results

PATIENTS AND TREATMENT

The retrospective cohort consisted of 2,127 patients, and the data were collected between September 2019 and February 2020 from 15 ICUs in South Korea. Among 2,127 patients with sepsis, 206 were considered eligible to receive RRT, while 12 who underwent RRT after day 4 were excluded. Of the 194 participants, 41 underwent hemoperfusion covalently bound with PMX-HP (Figure 1). Tables 1 and 2 show the key characteristics of the patients. The initial total SOFA score, cardiovascular SOFA score, coagulation SOFA score, SAPS score, and initial lactate level were higher in the CRRT group. The mean arterial pressure was lower, and the number of participants who required vasopressors was relatively high in the CRRT group. In addition, the proportion of patients with intra-abdominal infection was higher in the CRRT group.

PRIMARY OUTCOMES

One hundred fifty-three patients who received CRRT were analyzed to determine the primary efficacy of this treatment, whereas all 41 patients who underwent PMX-HP were

included in the primary analysis. The CRRT group had an initial sofa score of 8.95 ± 3.27 (mean ± SD), but it changed to 10.17 ± 3.85 on day 7 (mean difference [MD]), 1.32; 95% CI, 0.23–2.42; p=0.019) and to 10.80 ± 4.75 on day 14 (MD, 2.17; 95% CI, 0.43–3.91; p=0.074) after CRRT. Meanwhile, the SOFA scores in the PMX-HP group were 7.00 ± 3.47 to 8.91 ± 3.40 (MD, 1.83; 95% CI, 0.94–3.76; p=0.053) between day 0 and day 7, and 7.94 ± 3.52 (MD, 1.83; 95% CI, −1.70 to 3.35; p=0.289) between day 0 and day 14. A significant difference was observed in the change in SOFA scores from day 0 to day 7 between the two groups (p for change=0.012); meanwhile, no significant difference was observed in the change in SOFA scores from day 0 to day 14 between the two groups (p for change=0.368). The results of primary efficacy endpoint analysis are shown in Table 3. However, no significant difference was observed in the change in SOFA scores from day 0 to day 7 (p for baseline=0.473, p for day 7=0.663, p for change=0.145) and from day 0 to day 14 (p for baseline=0.473, p for day 14=0.685, p for change=0.910) between the two groups after adjusting for several baseline characteristics (Table 4).

Table3. Change in SOFA score from baseline

			Change from baseline		Group difference		
Group	**SOFA_DAY0**	**SOFA_DAY7**	**Mean difference (95% CI)**	**P†**	**P for baseline‡**	**P for DAY7**	**P for change‡**
CRRT	8.95 ± 3.27 (n=153)	10.17 ± 3.85 (n=76)	1.32 (0.23, 2.42)	0.019	0.012	0.157	0.012
PMXB	7.00 ± 3.47 (n=41)	8.91 ± 3.40 (n=24)	1.83 (0.94, 3.76)	0.053			
Group	**SOFA_DAY0**	**SOFA_DAY14**	**Mean difference (95% CI)**	**P†**	**P for baseline‡**	**P for DAY14**	**P for change‡**
CRRT	8.95 ± 3.27 (n=153)	10.80 ± 4.75 (n=37)	2.17 (0.43, 3.91)	0.074	0.033	0.032	0.368
PMXB	7.00 ± 3.47 (n=41)	7.94 ± 3.52 (n=16)	1.83 (-1.70, 3.35)	0.289			

Data are shown as mean ± SD.

†Paired T-test was used.

‡Two-sample T-test was used.

Table4. Change in SOFA score from baseline after propensity matching

			Change from baseline		Group difference		
Group	**SOFA_DAY0**	**SOFA_DAY7**	**Mean difference (95% CI)**	**P†**	**P for baseline‡**	**P for DAY7**	**P for change‡**
CRRT	6.84 ±2.52 (n=26)	8.64 ±3.17 (n=14)	2.42(0.20,4.65)	0.035	0.473	0.663	0.145
PMXB	7.46 ±3.53 (n=26)	8.07 ±3.81 (n=15)	0.2(-2.08,2.48)	0.854			
Group	**SOFA_DAY0**	**SOFA_DAY14**	**Mean**	**P†**	**P for**	**P for**	**P for**

			difference (95% CI)		baseline ‡	DAY14	change ‡
CRRT	6.84 ±2.52 (n=26)	7.43±2.94 (n=7)	3.75 (3.12, 4.38)	0.308	0.473	0.685	0.910
PMXB	7.46 ±3.53 (n=26)	8.00±2.71 (n=10)	2.04 (0.70, 3.37)	0.502			

Data are shown as mean ± SD.

†Paired T-test was used.

‡Two-sample T-test was used.

SECONDARY OUTCOME

The Kaplan–Meier estimates of mortality at 28 days was significantly lower in the PMX-HP group, with deaths reported in 82 of 153 patients (53.6%) in the CRRT group and 10 of 41 patients (24.4%) in the PMX-HP group (hazard ratio [HR], 0.39; 95% CI, 0.19 to 0.78; p=0.008) (Figure 2). The result was also the same at 7 days (HR, 0.182; 95% CI, 0.057 to 0.581; p=0.004) and at 14 days (HR, 0.39; 95% CI, 0.129 to 0.690; p=0.005) in the crude analysis (Table 5). Likewise, after adjusting for initial SOFA score only or lactate levels and initial SOFA score, the association between PMX-HP use and reduced mortality was evident. However, after adjusting for multiple factors, such as procalcitonin, lactate level, initial SOFA score, arterial pressure, clinical frailty scale, the incidence of abdominal infection, initial use of vasopressors, bicarbonate concentration, SAPS, and underlying cardiovascular disease, the PMX-HP group did not show changes in the mortality rate compared with the CRRT group (Table 6).

Figure 2. Kaplan-Meier Estimates of Survival:

Estimation of Survival Rate According to Treatment Group (p=0.001)

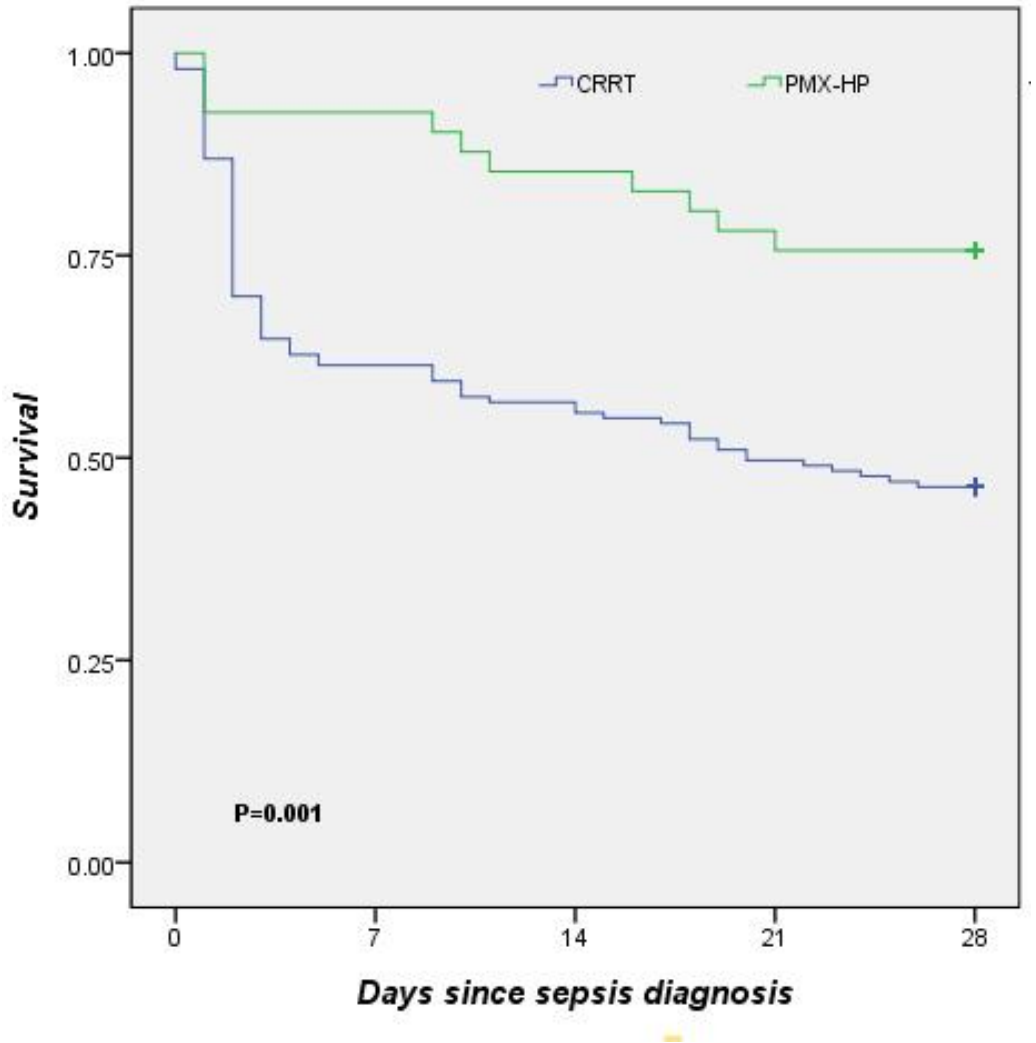


Table 5. Secondary outcomes

	CRRT only(N=153)	PMX-HP(N=41)	P-value†
No. of deaths at 7days (%)	56(36.6)	3(7.32)	0.001
No. of deaths at 14days (%)	65(42.5)	6(14.6)	0.001
No. of deaths at 28days (%)	82(53.6)	10(24.4)	0.001
MV free day (median [IQR])	23.1[0,27]	22.3[22.5,28]	0.557
ICU stay days (mean (SD))	8.869(11.4878)	11.0244(10.344)	0.278
Hospital stays days	17.34(17.93)	27.85(25.18)	0.003
Change in CFscale	1[-2,2.25]	0.26[-1,3]	0.051
Change in PLT, $10^3/\mu$ (Median [IQR]) ¶	53.7[-22,171]	141.04[17,206]	0.019
Vasopressor use			
day0	102(66.7%)	18(43.9%)	0.011
day7	93(60.8%)	13(31.7%)	0.001
day14	84(54.9%)	9(22.5%)	0
Change (day0, day7) ‖	-0.43(0.59)	-0.25(0.570)	0.158
Change (day0, day14) ‖	-0.25(0.55)	-0.38(0.59)	0.470

Abbreviation: PLT= platelet count, Cath.infection=catheter-related infection, CFscale=Clinical frailty scale, IQR=Interquartile range, SD=standard deviation

†For categorical variables, the Chi-square test or Fisher's exact test was used, and n (%) was reported. A t-test or Mann-Whitney test was used for continuous variables, and mean (SD) or median [IQR] was reported. Kaplan Meier analysis and Log-rank analysis were used to compare mortality between two groups.

¶Difference in platelet count between day0 and day 7

‖Fisher's exact test was performed, and the average value of the difference was obtained.

Table6. Cox Proportional Hazards Analysis of PMX-HP Use and Mortality Among Propensity-Matched Patients. (Number of patients=52)

Model	Hazard Ratio (95% CI)	p
7 days mortality after multivariable adjustment	0.257[0.32,2.09]	0.137
14 days mortality after multivariable adjustment	0.261[0.054,1.257]	0.065
28 days mortality after multivariable adjustment	0.329[0.087,1.242]	0.081

†Adjusted for initial SOFA score, initial mean arterial pressure, clinical frailty scale, bicarbonate, abdominal infection, lactate, initially use in vasopressor, simplified acute physiology score(SAPS), underlying cardiovascular disease, platelet count

The number of ventilator-free days at 28days was not significantly different between the PMX-HP group (median, 22.3days; SD, 9.12; 95%CI, 19.7 to 25.3) and CRRT group (median, 23.1days; SD, 7.35; 95% CI, 21.9 to 24.3) (absolute difference [AD], -0.8days; SD, 1.36; 95% CI, -3.49 to 1.88; p=0.557). Similarly, no significant difference was found between the PMX-HP group and CRRT group in terms of the length of ICU stay days (median, 11.02 vs. 8.87; AD, 2.15days; SD, 1.98; 95% CI, -1.75 to 6.06; p=0.278), change in clinical frailty scale (p for change=0.051), and change in use of vasopressor from time zero to day 7(p for change=0.158) as well as day14 (p for change=0.470). However, a significant difference was observed in the length of hospital stay (median, 25.18 vs. 17.34; AD 10.51; SD, 3.46; 95% CI, 3.69 to 17.33) and change in platelet count from time zero to day7(p for change=0.019) (Table 5).

UNIVARIABLE AND MULTIVARIABLE ANALYSIS FOR PREDICTORS FOR MORTALITY

Table 7 shows the key characteristics of patients who died or survived. The clinical factors independently associated with sepsis were PMX-HP or CRRT use, presence or absence of hematological disease, and SAPS score (Table 8).

Table 7. Baseline characteristics in patients alive or dead
(Total number=194; Number of dead patients =91)

	Alive n=103	**Dead** n=91	**P**†
Age (mean (SD))	69.78(14.18)	68.10(13.61)	0.404
Gender (male, %)	49(47.57%)	55(60.44%)	0.950
Mean arterial pressure (mean (SD))	65.49(16.34)	70.36(22.49)	0.085
SAPS (Mean (SD))	88.27(15.55)	75.58(14.37)	0.000
Initial SOFA (mean (SD))	9.10(3.34)	8.09(3.33)	0.037
Respiratory SOFA.D1(mean (SD))	1.49(0.998)	1.35(1.07)	0.334
Cardiovascular SOFA.D1(mean (SD))	1.85(1.44)	1.50(1.50)	0.101
Liver SOFA.D1 (mean (SD))	0.96(1.17)	0.64(1.00)	0.048
Coagulation SOFA.D1 (mean (SD))	1.65(1.447)	1(1.25)	0.001
Kidney SOFA.D1 (mean (SD))	1.70(1.18)	2.17(1.48)	0.017
CNS SOFA.D1 (mean (SD))	1.45(1.31)	1.44(1.28)	0.942
Charlson comorbidity score (mean (SD))	5.65(2.93)	5.43(2.33)	0.567
Hematologic disease (%)	14(13.59)	7(7.69)	0.054
Chronic liver disease (%)	16(15.53)	12(13.19)	0.240
Chronic kidney disease (%)	17(16.50)	34(37.36)	0.023
DM (%)	25(24.27)	37(40.66)	0.207
Solid cancer (%)	27(29.67)	27(26.21)	0.591
Cardiovascular Disease (%)	16(15.53)	19(20.88)	0.875
Respiratory disease (%)	10(9.71)	9(9.89)	0.598
Chronic neurologic disease (%)	14(13.59)	15(16.48)	0.872
Procalcitonin (median [IQR])	52.07[0.81,31.10]	27.40[2.15,90.52]	0.031
Lactate (median [IQR])	6.55[1.8,6.2]	4.79[3.1,8.4]	0.008
Bicarbonate (mean (SD))	15.96(5.80)	15.96(6.27)	0.997
PLT, 10^3/μ (median [IQR])	178.3[85.0,256]	125[35.0,186.0]	0.058
Recent Use in antibiotics or chemotherapy	26(25.24)	18(19.78)	0.065
Steroid (%)	34(33.01)	28(30.77)	0.129
Initial use in vasopressor %)	81(78.64)	73(80.22)	0.001
MV (%)	54(52.43)	40(43.96)	0.004
ECMO (%)	3(2.91)	1(1.10)	0.255

Abbreviation: SOFA=Sequential Organ Failure Assessment, MV=Mechanical ventilation, SAPS=Simplified Acute Physiology score, PLT=platelet count, IQR=Interquartile range, SD=standard deviation, ECMO=Extracorporeal Membrane Oxygenation D1=day1, DM=diabetes mellitus, CNS= central nervous system

†For categorical variables, the Chi-square test or Fisher's exact test was used, and n (%) was reported.
A t-test or Mann-Whitney test was used for continuous variables, and mean (SD) or median [IQR] was reported.

Table 8. Univariate and multivariate Cox regression analysis of 28-day mortality (Total N=194; Number of dead patients = 91).

		Univariate		Multivariate	
		HR (95% CI)	**P**	**HR (95% CI)**	**P**
Group	CRRT	Ref		Ref	
	PMXB	0.37(0.19,0.71)	0.001	0.39(0.19,0.78)	0.008
Age		0.99(0.98,1.01)	0.669	0.99(0.97,1.01)	0.467
Lactate		1.05(1.02,1.10)	0.008	1.04(0.99,1.08)	0.054
Initial SOFA		1.05(1.00,1.12)	0.072	0.94(0.87,1.01)	0.114
MV	0	Ref		Ref	
	1	2.07(1.35,3.15)	<.001	1.05(0.59,1.86)	0.85
Steroid	0	Ref		Ref	
	1	1.22(0.80,1.87)	0.158	0.84(0.52,1.35)	0.473
SAPS		1.03(1.02,1.05)	<.001	1.04(1.02,1.06)	<.001
Hema.	0	Ref		Ref	
	1	2.41(1.38,4.21)	0.020	1.91(1.01,3.62)	0.045
Charlson		0.97(0.90,1.06)	0.963	0.96(0.87,1.05)	0.391

Abbreviation: SOFA=Sequential Organ Failure Assessment, MV=Mechanical ventilation, SAPS=Simplified Acute Physiology score, Charlson=Charlson comorbidity score

DISCUSSION

Our registry was created to describe the actual clinical use of the PMX-HP investigating data from unselected populations with sepsis. In this retrospective, multicenter cohort study involving adult patients with sepsis admitted in the ICUs, we found that no significant difference was observed in the delta SOFA score between the PMX-HP and CRRT groups, which implies that the use of PMX-HP did not reduce the progression to multiorgan failure compared with the use of CRRT. The results of our study suggest that the use of PMX-HP has an advantage in terms of survival at day 28 compared with the use of CRRT, as shown in the crude analysis. However, the mortality rate of the PMX-HP group did not improve compared to that of the CRRT group after adjusting for multiple baseline variables. Moreover, significant differences were observed in the number of ventilator-free days at 28 days, the length of ICU stay, change in clinical frailty scale, and change in the use of vasopressors from day 0 to day 7 as well as day 14 between the two groups; significant difference was also observed in the length of hospital stay and change in platelet count from day 0 to day 7 between two groups.

Inflammatory response to sepsis, including increased cytokine levels and endotoxin levels, has been correlated with MOF, and extracorporeal therapies have been considered supplementary procedures by removing such mediators or lowering the levels of endotoxins[16,34-39]. Moreover, the

technological progressions in blood purification for patients with sepsis have a broadened spectrum, such as high-volume hemofiltration, coupled plasma filtration adsorption, and hemadsorption with PMX or CytoSorb. However, their validity in modulating systemic inflammation and improving the different physiologic parameters and mortality rates remained controversial[17,18,24,25,40].

The mortality rate of the PMX-HP group in this study proved to be lower than that of CRRT only group using multivariate cox regression analysis and Kaplan Meier analysis. Brouwer WP et al. reported that the mortality rate of the CRRT only group was lower than the estimated mortality rate in patients with sepsis.[41,42] In real-world studies, the mortality rate of CRRT was shown to be 51% according to Brouwer WP et al. and 47.6% according to Christopher Rugg et al.[41,43] The mortality rate of the CRRT group in this study was similar compared to that reported in other studies. The mortality rate of the PMX-HP group was 32% according to Dinna N. et al. and 25% according to Cantaluppi et al.; the mortality rate of the PMX-HP group in this study was similar to that reported in previous studies. Taken together, our study suggests that PMX-HP improved the survival of patients with sepsis[28,44], as shown in the results of the crude analysis. However, mortality benefit has disappeared after propensity matching was conducted, which implies that the multivariable factors in baseline characteristics affect the results of the crude analysis. This result matches with those of

some previous studies, which showed that PMX-HP had no benefits in mortality.[26,40,45,46]

Trends in progression to organ failure, expressed as delta SOFA score in our study, were not significantly delayed in the PMX-HP group as compared with the CRRT group, and this was unexpected in this study. In this study, the difference in the SOFA score between the two groups obtained through crude analysis on day 7 was not seen after propensity score matching. The difference in crude analysis appears to be due to the difference in severity between the two groups. We also assume that it is because, in this study, many patients died in the CRRT only group (37.9%) compared with the PMX-HP group (0%) within 6days from time zero. This means that the delta SOFA score was compared to only survivors in both groups, which might have affected the results.

The change in the use of vasopressors between day0 and day7 as well as day 14 was presented as cardiovascular delta SOFA and showed no difference between the two groups. This result conflicts with those of previous studies by Cutuli SL et al., and Ruberto F et al., which reported an improvement in hemodynamics status after undergoing PMX-HP.[47-49] Additional studies are warranted to compare the PMX-HP group with the CRRP only group.

Platelet count was regarded as an index representing DIC shown in the sepsis course. In other studies, significant platelet count reduction in the PMX-HP group was reported; this result corresponds to that of our research but was regardless of the worsening clinical condition of the

patients. The phenomenon can also be explained as septic cascade evolution.[47,50]

Our study has strengths. This was a multicenter trial using the data of sepsis patients who were recruited within a certain period. In addition, previous studies focused on identifying the effect of PMX-HP on mortality, while the present study focused on monitoring the change in SOFA score; hence, the result of this study is significant practically because organ dysfunction is the common concern among patients in the ICU.

We also have several limitations. A retrospective trial has limitations. First, we could not determine the proper techniques for performing CRRT or PMX-HP and are unsure whether the standardized RRT methods should be applied. However, this study provides more practical data because PMX-HP has been applied in different ways in various centers worldwide. Second, follow-up data on procalcitonin level, lactate level, whether the patients were still alive or died on day 28, the status of vasopressor use on a particular date, and sofa score on day 7 were missing. In this study, a group of patients treated with CRRT or polymyxin B within 72 hours was enrolled. Therefore, one of the reasons why there is so much missing data is that we did not look at day 2 or day 3 set the criteria as day 7 or day 14. Third, a difference was observed in the baseline severity of patients probably due to the different criteria applied in performing PMX-HP or CRRT by various centers, and the PMX-HP and CRRT use were not randomly assigned in the patient population. The initial multiorgan

failure and hypoperfusion parameters in global tissues including lactate levels, initial SOFA scores, and SAPS scores were higher, while the mean arterial pressure was lower in patients treated with CRRT, which indicates hemodynamic stability, than in patients treated with PMX-HD[31,51]. However, potential confounding and selection biases were accounted for by developing a propensity score for PMX-HP and CRRT use. We were able to observe the intervention effects on the process of organ dysfunction and mortality rates, after adjusting for multiple factors. Fourth, the effect of antibiotic elimination through adsorption therapy was not considered, which was reported previously[52-55]. However, the efficacy of some antibiotics, such as meropenem, which is used in patients with sepsis, is not influenced by PMX-HP.[56] Fifth, the calculation of SOFA score is based on the laboratory data and may not reflect the actual condition of the affected organs; renal SOFA scores can be influenced by dialysis itself[31]. Moreover, the different strategies for managing sepsis especially CRRT or PMX-HP vary between countries. In a Japanese study, CRRT was applied in 87% of patients, while PMX-HP was performed in 13% of patients[1]. However, in this study, only 7% and 2% of the patients with sepsis used CRRT and PMX-HP, respectively; therefore, more international registries or randomized controlled trials should be evaluated in order to confirm the applicability of this treatment worldwide.

CONCLUSION

In conclusion, the use of polymyxin B hemoperfusion has no significant role in delaying the progression of organ failure compared to the CRRT-only group i this multicenter, retrospective observational study involving patients with sepsis in South Korea.

REFERENCE

1. Fujimori K, Tarasawa K, Fushimi K. Effects of polymyxin B hemoperfusion in patients with sepsis requiring continuous hemodiafiltration: Analysis of a nationwide administrative database in Japan. *Therapeutic Apheresis and Dialysis*. 2021;25(4):384-389. doi:https://doi.org/10.1111/1744-9987.13655
2. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention, and treatment. *Kidney International*. 2019;96(5):1083-1099. doi:https://doi.org/10.1016/j.kint.2019.05.026
3. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311(13):1308-1316. doi:10.1001/jama.2014.2637
4. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA*. 2017;318(13):1241-1249. doi:10.1001/jama.2017.13836
5. Quenot J-P, Binquet C, Kara F, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. *Critical Care*. 2013;17(2):R65. doi:10.1186/cc12598
6. Rhee C, Jones TM, Hamad Y, et al. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. *JAMA Network Open*. 2019; e187571-e187571. doi:10.1001/jamanetworkopen.2018.7571
7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. Nov 8 2001;345(19):1368-77. doi:10.1056/NEJMoa010307
8. Seymour CW, Gesten F, Prescott HC, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *N Engl J Med*. Jun 8 2017;376(23):2235-2244. doi:10.1056/NEJMoa1703058
9. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. Mar 2017;45(3):486-552. doi:10.1097/ccm.0000000000002255
10. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med*. Jun 2018;44(6):925-928. doi:10.1007/s00134-018-5085-0
11. Klein DJ, Derzko A, Foster D, et al. DAILY VARIATION IN ENDOTOXIN LEVELS IS ASSOCIATED WITH INCREASED ORGAN FAILURE IN CRITICALLY ILL PATIENTS. *Shock*. 2007;28(5):524-529. doi:10.1097/shk.0b013e31805363c6
12. Marshall JC, Foster D, Vincent J-L, et al. Diagnostic and Prognostic Implications of Endotoxemia in Critical Illness: Results of the MEDIC Study. *The Journal of Infectious Diseases*. 2004;190(3):527-534. doi:10.1086/422254
13. Peters K, Unger RE, Brunner J, Kirkpatrick CJ. Molecular basis of endothelial dysfunction in sepsis. *Cardiovascular Research*. 2003;60(1):49-57. doi:10.1016/s0008-6363(03)00397-3
14. Fajgenbaum DC, June CH. Cytokine Storm. *New England Journal of Medicine*. 2020;383(23):2255-2273. doi:10.1056/NEJMra2026131

15. Hotchkiss RS, Coopersmith CM, McDunn JE, Ferguson TA. The sepsis seesaw: tilting toward immunosuppression. *Nature Medicine*. 2009;15(5):496-497. doi:10.1038/nm0509-496

16. Ronco C BR, McCullough PA Blood Purification in Sepsis: A New Paradigm. *Cardiorenal Syndromes in Critical Care Contrib Nephrol Basel, Karger*. 2010;165:pp 322–328.

17. Rimmelé T, Kellum John A, Warner David S. High-volume Hemofiltration in the Intensive Care Unit: A Blood Purification Therapy. *Anesthesiology*. 2012;116(6):1377-1387. doi:10.1097/ALN.0b013e318256f0c0

18. Rimmelé T, Kellum JA. Clinical review: Blood purification for sepsis. *Critical Care*. 2011;15(1):205. doi:10.1186/cc9411

19. Yekebas EF, Eisenberger CF, Ohnesorge H, et al. Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. *Critical Care Medicine*. 2001;29(7):1423-1430.

20. Cornejo R, Downey P, Castro R, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. *Intensive Care Med*. May 2006;32(5):713-22. doi:10.1007/s00134-006-0118-5

21. Putzu A, Fang M-X, Boscolo Berto M, et al. Blood purification with continuous veno-venous hemofiltration in patients with sepsis or ARDS: a systematic review and meta-analysis. *Minerva Anestesiol*. 2017;83(8):867-877. doi:10.23736/s0375-9393.17.11946-2

22. Payen D, Mateo J, Cavaillon JM, et al. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial*. *Critical Care Medicine*. 2009;37(3):803-810. doi:10.1097/CCM.0b013e3181962316

23. Shoji H. Extracorporeal Endotoxin Removal For The Treatment of Sepsis:Endotoxin Adsorption Cartridge (Toraymyxin). *Therapeutic Apheresis and Dialysis*. 2003;7(1):108-114. doi:https://doi.org/10.1046/j.1526-0968.2003.00005.x

24. Shoji H, Tani T, Hanasawa K, Kodama M. Extracorporeal Endotoxin Removal by Polymyxin B Immobilized Fiber Cartridge: Designing and Antiendotoxin Efficacy in the Clinical Application. *Therapeutic Apheresis*. 1998;2(1):3-12. doi:https://doi.org/10.1111/j.1744-9987.1998.tb00066.x

25. 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(14):1455-1463. doi:10.1001/jama.2018.14618

26. 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 Medicine*. 2015;41(6):975-984. doi:10.1007/s00134-015-3751-z

27. Fujii T, Ganeko R, Kataoka Y, et al. Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. Feb 2018;44(2):167-178. doi:10.1007/s00134-017-5004-9

28. 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(23):2445-2452. doi:10.1001/jama.2009.856

29. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for

Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

30. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine*. 2021;49(11):e1063-e1143. doi:10.1097/ccm.0000000000005337

31. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine*. 1996;22(7):707-710. doi:10.1007/BF01709751

32. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation*. *Critical Care Medicine*. 2009;37(5):1649-1654. doi:10.1097/CCM.0b013e31819def97

33. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent J-L. Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients. *JAMA*. 2001;286(14):1754-1758. doi:10.1001/jama.286.14.1754

34. Oda S, Hirasawa H, Shiga H, Nakanishi K, Matsuda K-i, Nakamua M. Sequential measurement of IL-6 blood levels in patients with systemic inflammatory response syndrome (SIRS)/sepsis. *Cytokine*. 2005;29(4):169-175. doi:https://doi.org/10.1016/j.cyto.2004.10.010

35. Kellum JA, Kong L, Fink MP, et al. Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Archives of Internal Medicine*. 2007;167(15):1655-1663. doi:10.1001/archinte.167.15.1655

36. Turnbull IR, Javadi P, Buchman TG, Hotchkiss RS, Karl IE, Coopersmith CM. Antibiotics Improve Survival in Sepsis Independent of Injury Severity but do not Change Mortality in Mice with Markedly Elevated Interleukin 6 Levels. *Shock*. 2004;21(2):121-125. doi:10.1097/01.shk.0000108399.56565.e7

37. Levy B, Collin S, Sennoun N, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. *Intensive Care Medicine*. 2010;36(12):2019-2029. doi:10.1007/s00134-010-2045-8

38. Goal-Directed Resuscitation for Patients with Early Septic Shock. *New England Journal of Medicine*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380

39. Bello G, Di Muzio F, Maviglia R, Antonelli M. New membranes for extracorporeal blood purification in septic conditions. *Minerva Anestesiol*. 2012;78(11):1265-1281.

40. Coudroy R, Payen D, Launey Y, et al. Modulation by Polymyxin-B Hemoperfusion of Inflammatory Response Related to Severe Peritonitis. *Shock*. Jan 2017;47(1):93-99. doi:10.1097/SHK.0000000000000725

41. Brouwer WP, Duran S, Kuijper M, Ince C. Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. *Critical Care*. 2019;23(1):317. doi:10.1186/s13054-019-2588-1

42. Shiga H, Hirasawa H, Nishida O, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary report. *Blood Purif*. 2014;38(3-4):211-8. doi:10.1159/000369377

43. Rugg C, Klose R, Hornung R, et al. Hemoadsorption with CytoSorb in Septic Shock Reduces Catecholamine Requirements and In-Hospital Mortality: A Single-Center Retrospective 'Genetic' Matched Analysis. *Biomedicines*. 2020;8(12):539.

44. Li X, Liu C, Mao Z, Qi S, Song R, Zhou F. Effectiveness of polymyxin B-immobilized hemoperfusion

against sepsis and septic shock: A systematic review and meta-analysis. *Journal of Critical Care*. 2021;63:187-195. doi:https://doi.org/10.1016/j.jcrc.2020.09.007

45. 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*. Oct 9 2018;320(14):1455-1463. doi:10.1001/jama.2018.14618

46. Vincent J-L, Laterre P-F, Cohen J, et al. A PILOT-CONTROLLED STUDY OF A POLYMYXIN B-IMMOBILIZED HEMOPERFUSION CARTRIDGE IN PATIENTS WITH SEVERE SEPSIS SECONDARY TO INTRA-ABDOMINAL INFECTION. *Shock*. 2005;23(5):400-405. doi:10.1097/01.shk.0000159930.87737.8a

47. Cutuli SL, Artigas A, Fumagalli R, et al. Polymyxin-B hemoperfusion in septic patients: analysis of a multicenter registry. *Annals of Intensive Care*. 2016;6(1):77. doi:10.1186/s13613-016-0178-9

48. Ruberto F, Pugliese F, D'Alio A, et al. Clinical effects of direct hemoperfusion using a polymyxin-B immobilized column in solid organ transplanted patients with signs of severe sepsis and septic shock. A pilot study. *Int J Artif Organs*. Oct 2007;30(10):915-22. doi:10.1177/039139880703001009

49. 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 Medicine*. 2018;44(12):2205-2212. doi:10.1007/s00134-018-5463-7

50. Iba T, Nagaoka I, Yamada A, Nagayama M, Miki T. Effect of hemoperfusion using polymyxin B-immobilized fibers on acute lung injury in a rat sepsis model. *Int J Med Sci*. 2014;11(3):255-261. doi:10.7150/ijms.6276

51. Nguyen HB, Loomba M, Yang JJ, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *Journal of Inflammation*. 2010;7(1):6. doi:10.1186/1476-9255-7-6

52. Shimokawa K-i, Takakuwa R, Taya K, et al. Adsorption of various antimicrobial agents to endotoxin removal polymyxin-B immobilized fiber (Toraymyxin®). *Colloids and Surfaces B: Biointerfaces*. 2012;90:58-61. doi:https://doi.org/10.1016/j.colsurfb.2011.09.046

53. Shimokawa K-i, Takakuwa R, Wada Y, Yamazaki N, Ishii F. Adsorption of various antimicrobial agents to endotoxin removal polymyxin-B immobilized fiber (Toraymyxin®). Part 2: Adsorption of two drugs to Toraymyxin PMX-20R cartridges. *Colloids and Surfaces B: Biointerfaces*. 2013;101:350-352. doi:https://doi.org/10.1016/j.colsurfb.2012.06.032

54. Reiter K, Bordoni V, Dall'Olio G, et al. In vitro Removal of Therapeutic Drugs with a Novel Adsorbent System. *Blood Purification*. 2002;20(4):380-388. doi:10.1159/000063108

55. Schneider AG, André P, Scheier J, et al. Pharmacokinetics of anti-infective agents during CytoSorb hemoadsorption. *Scientific Reports*. 2021;11(1):10493. doi:10.1038/s41598-021-89965-z

56. Singhan W, Vadcharavivad S, Areepium N, Wittayalertpanya S, Chaijamorn W, Srisawat N. The effect of direct hemoperfusion with polymyxin B immobilized cartridge on meropenem in critically ill patients requiring renal support. *Journal of Critical Care*. 2019;51:71-76. doi:https://doi.org/10.1016/j.jcrc.2019.02.007

국문 요약

연구배경

폴리믹신B를 이용한 혈액관류은 이전 메타분석에서 패혈증 환자의 생존율을 향상시킨 바 있으나 편견의 위험이 높았고 따라서 이의 효과에 대해 논란이 있다. 본 연구는 패혈증 환자에서 폴리믹신B를 이용한 혈액관류의 임상적 효과를 확인하기 위해 시행되었다.

연구 방법

대한민국 패혈증 연대(KSA)에서 다기관 연구를 진행하고 있고, 이 연구는 15개 병원에서 194명의 패혈증 환자를 대상으로 후향적으로 진행되었다. 환자는 입원 3일 이내에 지속성 혈액 여과 투석 혹은 폴리믹신B를 사용한 경우를 대상으로 하였고 일차적인 효과는 다발성 장기 부전의 지표인 SOFA 점수를 이용하여 두 군의 점수를 7일째, 14일째 비교하였다.

차적인 효과는 중환자실 재원기간, 병원 재원기간 7일,14일,28일 사망률, 임상적으로 취약정도의 변화정도, ICU 입실 일자부터 28일동안 인공호흡기를 사용하지 않은 날 수, 투석과 연관된 부작용을 분석하였다.

연구 결과

194명의 연구에 적합한 환자들(평균 연령: 68.9세, 여성 46.9%, 평균 SOFA 점수: 8.61) 중 41명에게 폴리믹신B를 이용한 혈액관류가 적용되었고 153명의 환자들은 지속성 혈액 여과 투석이 적용되었다. 일차결과로 폴리믹신B를 이용한 혈액관류가 지속성 혈액 여과 투석 단독 사용에 비하여 다발성 장기 부전 진행을 늦추지 못하였다. (두 군의 day0 과 day 7의 SOFA 점수 차이, 1.83 vs 1.32; p=0.012; 두 군의 day0 과 day 14의 SOFA 점수 차이, 1.83 vs 2.17; p=0.368). 이차결과로 폴리믹신B를 이용한 혈액관류를 적용한 경우 7일째(위험비율[HR], 0.182; 95% 신뢰구간[CI], 0.057 to 0.581; p=0.004), 14일째([위험비율], 0.39; 95% [신뢰구간], 0.129 to 0.690; p=0.005), 28일째([위험비율], 0.39; 95% [신뢰구간], 0.19 to 0.78; p=0.008) 사망률이 낮은 것으로 나타났지만(여러 인자에 대해 성향매칭을 시행한 후 7일째([위험비율], 0.231; 95% [신뢰구간], 0.32 to 2.09; p=0.137), 14일째([위험비율], 0.261; 95% [신뢰구간], 0.054 to 1.257; p=0.005), 28일째 ([위험비율], 0.329; 95% [신뢰구간], 0.087 to 1.242; p=0.081) 사망률에 있어 유의한 이점을 보이지 않았다.

중환자실 재원기간(절대차[AD], 2.15days; 표준편차SD, 1.98; 95% 신뢰구간, -1.75 to 6.06; p=0.278), 중환자실 입실 일자부터 입실 7일 사이 임상적으로 취약정도의 변화정도(p for change=0.051), ICU 입실 일자부터 28일동안 인공호흡기를 사용하지 않은 날 수([절대차]-0.8days; 표준편차, 1.36; 95% 신뢰구간, -3.49 to 1.88; p=0.557), 투석과 연관된 부작용 중 부정맥([교차비], 0.81; 95% 신뢰구간, 0.33 to 2.00; p=0.648), 카테터와 연관된 감염([교차비], 0.61; 95%CI, -0.07 to 5.24; p=0.651), 중환자실 입실 일자부터 입실 7일 사이 승압제 사용유무의 변화(p for change=0.158)는 두 군 간의 유의한 차이를 보이지 않았다. 중환자실 입실 일자부터 입실 7일 사이 혈소판수치의 변화(p for change=0.019), 병원재원

기간(p=0.003)은 두 군 간의 유의한 차이가 있었다.

결론

본 연구에서는 패혈증 환자에서 폴리믹신B를 이용한 혈액관류의 사용은 지속성 혈액 여과 투석 단독 사용군에 비해 다발성 장기부전의 진행을 늦추는데 있어 효과를 보여주지 못하였다.