The Effect of Polymyxin B-Immobilized Fiber Column Hemoperfusion for Sepsis: A Systemic Review and Meta-Analysis

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Purpose: The objective of this study was to evaluate the effect of Polymyxin B hemoperfusion (PMX-HP) on patients with sepsis.

Methods: A systematic review and meta-analysis was performed using relevant articles retrieved from 3 databases (PubMed, Cochrane Library, EMBASE). Randomized studies from 1 January 1999 to 28 February 2022 were examined to determine the clinical results of PMX-HP. A meta-analysis was carried out using the random-effects method, meta-regression with clinical variables, and assessment of risk of bias (ROB) tool (Cochrane ROB assessment tool). Mortality was evaluated within 60 days of hospitalization (in-hospital death 28-day, 30-day, and 60-day mortality) and predictors associated with mortality were determined using meta-regression.

Results: There were 11 randomized studies with 548 patients included in the meta-analysis. The pooled mortality was 35% (95% CI, 27%-42%, 95% CI 0.53-0.96). Further subgroup analysis was performed according to the duration of PMX-HP. An extension of PMX-HP treatment beyond 2 hours (pooled mortality, 43%; 95% CI, 9%-76%) compared with a 2-hour session (pooled mortality, 33%. 95% CI, 27%-38%) showed an increase in mortality rates. However, this was not statistically significant. Univariate meta-regression showed that patient’s age, the acute physiology and chronic health evaluation score, and the sequential organ failure assessment score did not significantly impact mortality.

Conclusion: While PMX-HP is valuable in the management of septic shock, treatment duration should be based on careful assessment of the patient’s condition, the risks and benefits of prolonged therapy, and the overall treatment strategy including antimicrobial management and source control.

Keywords: hemoperfusion, meta-analysis, sepsis, Polymyxin B

Introduction

Conceptually, sepsis is an extreme systemic inflammatory response to infection which can lead to tissue damage, organ failure, or death. As a result, prognoses suggest a high mortality rate of more than 20% [1]. Because of the high mortality rate in sepsis, various treatments have been assessed, but there is no definitive treatment at present beyond the use of antibiotics and hemodynamic optimization [2]. Endotoxin is one of the major components of the outer membrane of Gram-negative bacilli, is one of the major causative agents of sepsis, and a large burden of endotoxin is associated with an increased mortality rate [3].

Polymyxin B has significant neurotoxicity and nephrotoxicity when administered intravenously, but has a marked removal effect on endotoxin by binding to the lipid A part of targeted toxins [4]. Therefore, it has been studied as a treatment method that is harmless to the human body. The use of the endotoxin adsorption removal method using Polymyxin B hemoperfusion...
(PMX-HP) with a polystyrene-based carrier fiber column has attracted attention as a therapeutic agent [5]. PMX-HP has been reported to have a beneficial effect compared with conventional treatment alone [6,7]. The PMX-HP effect increased mean arterial pressure, decreased the use of inotropic agents, improved the PaO2/FiO2 (P/F) ratio, and decreased mortality in sepsis patients [7,8]. It was also reported that serum levels of troponin T, specific to sepsis induced myocarditis, and endotoxin levels were reduced following PMX-HP [8]. In sepsis, excessive uncontrolled cytokine production leads to a cytokine storm and cytokines are a major cause of disease exacerbation by triggering a cascade response which influences the prognosis, as well as having a direct effect on endotoxin removal [9]. Despite several years of controversy, the availability of antiseptic cleansing therapy has been established for abdomen sepsis. To date, no conclusive clinical trial data has provided evidence to support its role in improving patient clinical status. We conducted this systematic review using meta-analysis to verify the therapeutic effect of PMX-HP and compared the results with conventional treatment alone to provide an assessment of whether PMX-HP improves the clinical outcomes in sepsis.

Materials and Methods

This meta-analysis was carried out and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Following a registered protocol, this meta-analysis was registered in the International Prospective Register of Systematic Reviews (Registration no.: CRD42022380568).

1. Search strategy and selection criteria

1.1. Search strategy

A search was conducted to retrieve relevant literature (in PubMed, Cochrane Library, EMBASE) between 1 January 1999 and 28 February 2022. The methodological quality of the included studies was analysis using the population, intervention, comparison, and outcomes description for this meta-analysis for reporting randomized controlled trials (RCTs; Table 1).

The following medical terms were used in the search: "Polymyxin B," "Polymyxin," "Toraymyxin," "PMX," "Polymyxin B-hemoperfusion," "Polymyxin B-immobilized fiber column," "PMX-DHP," "PMX-HP," and the meta-analysis by combining them using "AND" or "OR." No restrictions were imposed on the language of the studies and the references of the retrieved articles were checked for any additional relevant data. All studies were retrieved according to the search criteria. (Figure 1).

1.2. Inclusion criteria and ROB assessment

Observational or randomized studies examining the clinical results of PMX-HP were included in this study. The ROB assessment was performed for each included study using the Cochrane ROB 2.0 tool for RCTs [10]. Two authors (DWK, HJC) independently assessed the quality of the studies, and disagreements were resolved by a 3rd author (ISJ).

2. Studies selection and quality assessment

Three investigators (DWK, JMK, YSS) independently conducted data extraction and assessed the quality of all included studies, and discrepancies were resolved via consultation with a senior reviewer (ISJ). The extracted data included the title of the article, first author, type of study, year of publication, number of patients, patients' age and gender, and outcome measures in both surgical and nonsurgical management groups. The outcome measures included the sequential organ failure assessment (SOFA) score, duration of PMX-HP treatment, cost-effectiveness, and mortality.

Table 1. Population, Intervention, Comparison, and Outcomes Description for This Meta-Analysis

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Polymyxin B hemoperfusion</td>
</tr>
<tr>
<td>Comparison</td>
<td>None</td>
</tr>
<tr>
<td>Outcome</td>
<td>Survivals by various indications or conditions</td>
</tr>
</tbody>
</table>

Figure 1. The search strategy for the systematic review and meta-analysis.
was evaluated within 60 days of hospitalization including in-hospital death, 28-day, 30-day, and 60-day mortality, and any predictors associated with mortality with meta-regression. Titles, and abstracts were preliminary reviewed, and potentially eligible citations were searched online. At the end of the quality assessment process, 11 studies were eligible (Figure 2). The quality of the studies was evaluated for risk of bias based on the Cochrane ROB assessment tool for reporting RCTs.

3. Statistical analysis
The data was analyzed using Stata (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC). A different pooled proportional rate was observed with a 95% confidence interval (CI), using a forest plot with a random-effects model. Additionally, publication bias was checked using regression analysis through observation of symmetry in the funnel plot. Cochran Q tests and I² were used to evaluate possible heterogeneity whereby I² < 25% was considered as low heterogeneity, 25%-70% was medium heterogeneity, and > 70% was high heterogeneity. If the p value was > 0.1 and I² < 50%, the fixed effects model was selected; otherwise, the heterogeneity was assessed to determine whether the random effects model could be used. To evaluate heterogeneity across studies and investigate possible risk factors, subgroup analyses and univariate meta-regression was conducted. In the subgroup analysis, studies were grouped by duration of PMX-HP. Meta-regression at the study level was employed to assess the impact of study attributes on mortality, provided there were a minimum of 3 data points. Furthermore, a sensitivity analysis was carried out using the leave-one-out method, p < 0.05 was considered statistically significant.

Figure 2. The flow diagram for the systematic review and meta-analysis.

Figure 3. The pooled overall mortality in the 11 included studies. The pooled mortality was 72% (95% CI 0.53 - 0.96, high certainty).
Table 2. Summary of Overall Studies: Study Design, Underlying Disease, Outcome Sample Size, Mortality, and Other Clinical Characteristics

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study (y) [ref]</th>
<th>Study design</th>
<th>Underlying disease</th>
<th>Outcome</th>
<th>Sample size (n)</th>
<th>Dead (n)</th>
<th>Age (y)</th>
<th>SOFA score</th>
<th>APACHE score</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nakamura (1999) [5]</td>
<td>RCT</td>
<td>Septic shock</td>
<td>In-hospital mortality</td>
<td>30</td>
<td>12</td>
<td>54.4</td>
<td>24.8</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>3</td>
<td>Nakamura 2002 [12]</td>
<td>RCT</td>
<td>Sepsis with trauma</td>
<td>In-hospital mortality</td>
<td>9</td>
<td>2</td>
<td>41.0</td>
<td>28.5</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>4</td>
<td>Nakamura 2002 [13]</td>
<td>RCT</td>
<td>Sepsis with hemodialysis</td>
<td>In-hospital mortality</td>
<td>7</td>
<td>2</td>
<td>56.0</td>
<td>2h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Suzuki (2002) [14]</td>
<td>RCT</td>
<td>Sepsis with ARF</td>
<td>28 d mortality</td>
<td>24</td>
<td>6</td>
<td>64.0</td>
<td>25.0</td>
<td></td>
<td>&gt; 2h</td>
</tr>
<tr>
<td>6</td>
<td>Nakamura (2003) [6]</td>
<td>RCT</td>
<td>MRSA sepsis</td>
<td>60 d mortality</td>
<td>15</td>
<td>7</td>
<td>58.5</td>
<td>23.8</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>7</td>
<td>Nakamura (2004) [7]</td>
<td>RCT</td>
<td>Severe sepsis</td>
<td>In-hospital mortality</td>
<td>15</td>
<td>3</td>
<td>60.4</td>
<td>28.4</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>8</td>
<td>Vincent (2005) [15]</td>
<td>RCT</td>
<td>Sepsis with abd infection</td>
<td>28 d mortality</td>
<td>17</td>
<td>5</td>
<td>52.7</td>
<td>10.0</td>
<td>16.7</td>
<td>2h</td>
</tr>
<tr>
<td>9</td>
<td>Cruz (2009) [16]</td>
<td>RCT</td>
<td>Abd septic shock</td>
<td>28 d mortality</td>
<td>34</td>
<td>11</td>
<td>61.0</td>
<td>11.0</td>
<td>21.0</td>
<td>2h</td>
</tr>
<tr>
<td>10</td>
<td>Payen (2015) (ABDOMIX) [17]</td>
<td>RCT</td>
<td>Sepsis with peritonitis</td>
<td>28 d mortality</td>
<td>119</td>
<td>33</td>
<td>71.5</td>
<td>10.0</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>11</td>
<td>Dellinger (2018) (EUPHRATES) [9]</td>
<td>RCT</td>
<td>Septic shock</td>
<td>28 d mortality</td>
<td>224</td>
<td>84</td>
<td>60.9</td>
<td>29.4</td>
<td></td>
<td>2h</td>
</tr>
</tbody>
</table>

APACHE = acute physiology and chronic health evaluation; RCT = randomized controlled trial; SOFA = sequential organ failure assessment.
Results

A total of 11 eligible articles (randomized studies) were retrieved using the title, abstract, and full text including a total of 548 patients who were treated with PMX-HP (Figure 1). Selected studies provided information about the number of patients, underlying disease, age, publication year, study design, primary outcome, acute physiology and chronic health evaluation (APACHE), SOFA score and duration of PMX-HP of the included studies (n = 11; Table 2 [5-7,9,11-17]). The pooled overall mortality was 35% (95% CI, 27%-42% low certainty; Figure 3). Further subgroup analysis was performed across the study according to the duration of PMX-HP treatment. An extension of PMX-HP treatment beyond 2 hours (pooled mortality: 43%, 95% CI, 9%-76%), compared with a 2-hour session (pooled mortality, 33%. 95% CI, 27%-38%) resulted in an increase in mortality rates although this was not statistically significant (p = 0.57; Figure 4). Univariate meta-regression showed that patient's age [β = 0.001 (95% CI, -0.111-0.011); p = 0.981], APACHE score [β = -0.007 (95% CI, -0.31-0.156); p = 0.516], and SOFA score [β = 0.044 (95% CI, -1.302-0.219); p = 0.620] did not significantly impact mortality (Figure 5).

Discussion

Endotoxin removal therapy has been attempted from several perspectives, and systematic reviews and meta-analysis have been performed, but its effectiveness at decreasing mortality in humans remains controversial. This current systematic review and meta-analysis of 11 studies did not demonstrate reduced mortality of PMX-HP treatment for patients with sepsis using the SOFA score, duration of PMX-HP treatment, and mortality as outcome measures.

The treatment mechanism of PMX-HP for sepsis involves the direct adsorption of circulating endotoxin, additional adsorption of factors other than endotoxin, effect of PMX-HP on hemodynamics, mediators, monocyte human leukocyte antigen-DR, and pulmonary oxygenation and has been clinically applied since 1994 [4].

Monocyte Human Leukocyte Antigen-DR plays an essential role in the initiation of immune response cascades, providing antigens to T cells. This is markedly reduced in sepsis, where PMX-HP helps increase monocyte production, thereby improving the effects of the immune system [18,19]. The application of hemoperfusion with an adsorption filter potentially improves the cellular energetic function in monocytes, and this type of modality should have an anti-inflammatory effect in sepsis. Because of this anti-inflammatory effect, as well as the endotoxin removal capacity of PMX-HP treatment. This is accomplished by the reduction of vasodilating media such as anandamide and nitrogen monoxide due to PMX-HP treatment [7,20].

The systemic absorption of endotoxin leads to anti-inflammatory effects and a decrease in inflammatory responses occurs, which results in improved vital signs. Previous studies have reported the P/F ratio increased after PMX-HP treatment [14,16,22-24]. In addition, the expression of the S100A12 gene which was used as an initial marker for acute lung damage, significantly decreased after PMX-HP treatment [25].
In 2005, in Belgium, a controlled pilot study of PMX-HP treatment in 36 patients with severe sepsis secondary to intra-abdominal infection, observed significant increases in the mean arterial pressure, cardiac index, left ventricular stroke work index, and oxygen delivery [15]. The need for continuous renal replacement therapy also decreased, but there was no significant difference in changes in endotoxin and interleukin-6 levels after 24 hours of treatment. This may be the result of the insufficient removal of endotoxin by applying PMX-HP only once. Following this, a study was conducted in Italy in 2009 and Cruz et al reported improved 28-day mortality with early use of PMX-HP treatment in abdominal septic shock in the EUPHAS RCT [16]. There were 64 patients with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection and following PMX-HP treatment, a significant increase in the average arterial pressure and P/F ratio, a significant decrease in the dependency index of vasopressor and mortality were reported. However, it should be noted that the trial was stopped early due to ethical issues. Subsequently published randomized controlled clinical trials involving PMX-HP treatment have yet to report beneficial results.

The Effects of Hemoperfusion with a Polymyxin B Membrane in Peritonitis with Septic Shock (also known as the ABDO-MIX) trial in France in 2015, which enrolled 243 patients with septic shock within 12 hours of emergency surgery for peritonitis associated with organ perforation, did not report 28-day mortality [17]. Dellinger et al [9] published the trial “Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES)” in North America in 2018. In this study [9], 450 adult septic shock patients with an endotoxin activity assay (EAA) level > 0.6 and multiple organ dysfunction scores > 9 were enrolled. Patients were assigned to one of 2 groups: the PMX-HP group (n = 224) and sham group (n = 226). In the PMX-HP group, the treatment was performed twice (1.5 to 2 hours) to compare the results with a previous study. However, the EUPHRATES trial did not observe a significant improvement in mortality and EAA. The researchers commented that the relative timing, dose, and duration of PMX-HP treatment may not have been sufficient to reduce endotoxin levels and mortality. In addition, this study had the issue of infection control using only antibiotics. In a post-hoc analysis of EUPHRATES, among the participating patients, the effects of PMX-HP on multiple endpoints were evaluated in 194 septic shock patients with EAA levels between 0.60 and 0.89 in the PMX-HP group (n = 88) and the sham group (n = 106). PMX-HP had a beneficial effect on mortality, average arterial pressure, and ventilator-free days [26].

In 2003, a study reported that PMX-HP of 2-hour duration can significantly reduce the endotoxin concentration, and the standard PMX-HP duration was set to 2 hours [27], but it is unclear whether the optimal duration is 2 hours. Studies have shown that factors affecting mortality such as endotoxin removal, increased average arterial pressure, and decreased booster dependence index, have benefited patients on PMX-HP for over 2 hours [28,29]. However, no correlation between duration and prognosis was determined in these studies. It is expected that prolonging the duration of PMX-HP therapy beyond 2 hours would lead to lower mortality rates compared with a treatment lasting only 2 hours. Surprisingly, a rise in mortality rates was observed in this current systemic review meta-analysis, although this increase was not statistically significant. The higher mortality rate observed when PMX-HP was administered for 4 hours compared with 2 hours might not be directly attributable to the duration of the therapy alone, but rather to a complex interplay of factors related to the patient’s condition, the timing of intervention, and the inherent risks associated with longer treatment durations.

1. The limitations of this study

This research has some limitations. Firstly, we pooled the long study period, which may lead to considerable relatively heterogeneity. Second, in the type of underlying disease, treatment duration, sample size and APACHE score were different among included studies. Third, because the SOFA score was measured in only 3 studies, an elaborate RCT should be performed in the future.

Conclusion

PMX-HP is a valuable tool in the management of septic shock. Mortality was not significantly affected by the duration of PMX-HP when comparing 2 hours to 4 hours treatment. However, the decision regarding duration of PMX-HP treatment should be based on a careful assessment of the patient’s condition, the risks and benefits of prolonged therapy, and the overall treatment strategy, including antimicrobial management and source control. The tendency of a higher mortality rate observed with a longer PMX-HP treatment duration may reflect the complexity of septic shock management and the need for personalized treatment approaches rather than a direct consequence of the therapy’s duration. Univariate meta-regression showed that predictors associated with mortality (patient’s age, APACHE score, and the SOFA score) did not significantly impact mortality.

Author Contributions

Conceptualization: ISJ. Methodology: DWK and ISJ. Formal investigation: JMK, YSS, and RH. Data analysis: JMK, YSS, and ISJ. Writing original draft: DWK. Writing - review and editing:
DWK, HJJ, and ISJ.

Conflicts of Interest

The authors declare that they have no competing interests.

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Ethical Statement

Following a registered protocol, this meta-analysis was registered in the International Prospective Register of Systematic Reviews (Registration no.: CRD42022380568).

Data Availability

All relevant data are included in this manuscript.

References