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Advances in Endotoxin Adsorption Therapy Using Polymyxin B Immobilized Fiber Columns

Hisataka Shoji*

Division of Emergency and Critical Care Medicine, Toray Medical Co. Ltd., Tokyo 103-0023, Japan

***Corresponding author:** Hisataka Shoji, hisatakshoji.395@gmail.com

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Abstract

Researchers have been accumulating evidence of endotoxin removal therapy with polymyxin B immobilized column (PMXP) for the past two decades. However, the strength of the evidence remains limited. Currently, a randomized controlled trial (RCT) is underway in the US. This trial aims to identify the specific patient population with elevated blood endotoxin levels and organ dysfunction scores, within a defined range, that would likely benefit from PMX therapy. Recently, PMX has been used for different kinds of patients population such as acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) and septic shock due to viral infections such as H1N1. Improvements in hemodynamics and oxygenation have been reported in these patients' populations, especially in those with endotoxemic septic shock. It was also reported that PMX was applied for COVID-19 patients. COVID-19 patients who underwent PMX therapy showed a reduction of inflammatory state and improvement in chest radiographic findings. Interestingly, PMX therapy appears to have a similar beneficial effect across various patient populations. However, there is a pressing need to conduct comprehensive studies to understand the underlying mechanism that explains this clinical effectiveness. PMX therapy exhibits a range of actions including endotoxin removal, elimination of both pro- and anti-inflammatory mediators, enhancement of coagulation balance, elimination of proapoptotic factors, and immunomodulation via monocyte and neutrophil removal. There is a need to investigate how these actions collectively contribute to the improvement of specific organ dysfunctions.

Keywords

Septic shock
Endotoxin removal
Polymyxin B fixed column
EUPHRATES
COVID-19

1. Introduction

The adsorptive blood purifier (for endotoxin removal) polymyxin (PMX), which consists of an adsorbent on which the antibiotic polymyxin B, which has a high binding affinity for endotoxin, is immobilized, has been widely used in clinical practice for septic shock

patients with strongly suspected endotoxemia since it was included in the health insurance scheme in August 1994. It has been widely used in clinical practice in patients with septic shock in whom endotoxemia is strongly suspected. As of 2020, it is also in clinical use in other European countries (Russia, Spain, Switzerland, etc.) and Asian countries (South Korea, Taiwan, India, Thailand, etc.). As for North America, it has been approved in Canada (Health Canada).

With the development of the clinical use of PMX, numerous research papers have been published both domestically and internationally, showing improvement in clinical symptoms such as biological response to treatment and hemodynamics, and improvement in life expectancy through big data analysis and systematic reviews. On the other hand, with the recent trend to pursue evidence-based medicine (EBM), there is a greater need to prove the improvement in life expectancy through randomized controlled trials. This has led to the initiation of several controlled trials: EUPHAS (Italy, 2009), ABDOMIX (France, 2015), and EUPHRATES (North America, 2018), respectively. In the EUPHRATES trial, a post hoc analysis found a subgroup with a significantly improved prognosis among PMX-treated patients. The TIGRIS trial is currently underway in the USA in similar patients.

Improvements in hemodynamics with increased blood pressure have been reported as a significant clinical benefit of PMX in septic shock. The biological response triggered by the removal of endotoxin from the bloodstream, which results in the restoration of homeostasis, remains unclear.

Among surgical diseases, septic shock associated with perforated peritonitis is strongly suspected to be related to endotoxemia and has been considered a good candidate for PMX. On the other hand, in cases of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF), in which the involvement of endotoxemia is not always clear, the application of PMX has been reported to improve hemodynamics. Improvements in circulatory and pulmonary oxygenation capacity have also been reported in patients with AE-IPF. PMX has also been used for sepsis caused by viral infections such as H1N1, and effective cases have been reported. Recently, PMX has also been used in COVID-19 cases and has shown certain efficacy.

This article reviews the results and current status of clinical studies to establish EBM for PMX treatment. The clinical effects observed, including the recent clinical use of PMX in AE-IPF and viral infections, and possible approaches will also be discussed to infer and elucidate the mechanism of action.

2. Accumulation of evidence for PMX treatment

2.1. From the EUPHRATES trial to the TIGRIS trial

The EUPHRATES trial was a double-blind, randomized, controlled trial of PMX conducted in the USA and Canada [1]. Patients who had a septic shock that required antihypertensive drugs had developed one or more new organ failures, an infection, or a suspected infection, and an endotoxin level of ≥ 0.6 by EAA (Endotoxin Activity Assay) were included. The PMX group received two PMX cycles in addition to conventional standard treatment, while the control group received standard treatment only. An additional condition was added as a result of the interim analysis: a Multi-Organ Dysfunction Score (MODS) of ≥ 10. Among the 449 patients who completed the study, mortality rates after 28 days of treatment were not significantly different between the PMX and control groups (84/223 [37.7%] in the PMX group and 78/226 [34.5%] in the control group). There was also no difference in mortality between the two groups, even among patients with a MODS score of 10 or higher.

However, post hoc analysis detected an absolute significant difference of 10% in 28-day mortality between the two groups (23/88 [26.1%] in the PMX group and 39/106 [36.8%] in the control group), limited to patients with an EAA level between 0.6

and 0.9. Furthermore, a significant increase in mean arterial pressure and a reduction in the number of days on ventilators in the PMX group were observed [2]. An excessive endotoxin load in the body at EAA levels of 0.9 and above suggested that two treatments with PMX may be inadequate.

Based on the results of the post hoc analysis, the TIGRIS trial is ongoing in the USA, involving the same patient population as the EUPHRATES trial, with EAA levels between 0.6 and 0.9 and MODS of ≥ 10 as entry criteria. It is an open-labeled, controlled trial with a target number of 150 patients; results are awaited to determine whether the results of the post hoc analysis can be replicated.

2.2. Cohort study with propensity score matching

Nakamura *et al.* used the dataset of the JSEPTIC DIC Study involving 42 ICUs in Japan and selected 1,723 eligible patients (1,201 with PMX and 522 without) from 3,195 cases of severe sepsis and septic shock. A total of 262 cases were selected and analyzed by propensity score matching [3]. In-hospital mortality was significantly lower in the PMX-treated group (32.8% in the PMX-treated group and 41.2% in the non-treated group, $P = 0.042$). The number of days without ICU stay was significantly longer in the PMX-treated group (18 days in the PMX-treated group, 14 days in the no-treatment group, $P = 0.045$), suggesting that PMX treatment contributed to the improvement of organ failure.

Iwakami *et al.* investigated the effect of PMX treatment on life expectancy using Diagnosis Procedure Combination (DPC) data from July 2007 to March 2012 (39 months), which included patients diagnosed with sepsis in ICU that were treated with antihypertensive drugs and received Continuous Renal Replacement Therapy (CRRT). Of the 3,759 eligible cases, 1,068 were treated with PMX. Propensity score matching was used to extract and analyze 978 cases each; mortality at 28 days was significantly lower in the PMX-treated group (40.2% [393/978] in the PMX group and 46.8% [458/978] in the non-PMX group, $P = 0.003$). Regression analysis showed a significant correlation between PMX and mortality at 28 days (Odds ratio [OR] = 0.75, confidence interval (CI) = 0.62–0.91), which is significant as the effect was detected in an analysis using large-scale data from a routine DPC practice.

2.3. Systematic review.

Tzu-Chang *et al.* collected and analyzed 17 papers related to the effect of PMX treatment on life expectancy. The overall mortality risk ratio (considering various evaluation periods like 28 days, in-hospital, ICU, 90 days, and 2 weeks, depending on the study) was 0.81 (95% CI = 0.70–0.95), indicating a favorable outcome for PMX treatment compared to the group that did not receive PMX treatment. Further analysis in subgroups with different severity of disease revealed that the mortality risk ratio was 0.84 (95% CI = 0.77–0.92) for the high-risk group (with mortality rates of 60% or more) and 0.64 (95% CI = 0.52–0.78) for the moderate-risk group (with mortality rates between 30–60%). This suggests that PMX treatment demonstrated a life-saving effect, particularly for the moderate-severity patient group. On the other hand, in the low-risk group with a mortality rate of less than 30% in the comparison group, the risk ratio was 1.278 (95% CI = 0.888-1.839), which suggested that PMX did not have a life-saving effect on these patients.

The systematic review and meta-analysis paper by Terayama *et al.* also adopted seven papers and, like Tzu-Chang *et al.* found a mortality reduction effect with PMX treatment.

Fujii *et al.* conducted a meta-analysis using a total of five papers, including three papers identical to those employed by Terayama *et al.* and the recent EUPHRATES trial and one paper not previously employed, with a risk ratio of 1.03 for mortality at 28

days and no detectable risk-reducing effect on mortality with PMX treatment. However, different articles in a systematic review may lead to different results, so they should be interpreted with caution.

3. Application of PMX in various diseases

3.1. Application in septic shock with endotoxemia

A few large clinical trials have demonstrated whether lowering blood endotoxin levels is associated with improved prognosis [4]. They investigated the median reduction in blood endotoxin EAA levels from pre-treatment values to Day 3 (24 hours after the second PMX column) and whether the desired EAA level was achieved by Day 3.

The median reduction in EAA levels for all patients was 10.4%. Notably, there was a tendency towards a higher mortality rate of 26% (25/95) in both the PMX and control groups for patients who experienced a median EAA level reduction surpassing 10.4%. Similarly, the mortality rate was 38% (36/96) for those who could not attain a reduction of 10.4%, with a *P-value* of 0.1. The mortality rate at 28 days was 25% (23/91) in the group that achieved an EAA level of 0.65 or less, compared with 38% (38/96) in the group that failed to achieve an EAA level of 0.65 or less ($P = 0.1$). The PMX-treated group that achieved an EAA level of 0.65 or less on Day 3 showed a trend towards lower mortality compared to the control group (16% vs. 33%, $P = 0.06$). In addition, there was an increase in ventilator-free days (20 vs 16, $P = 0.05$) and a reduction in mortality by the Kaplan-Meier method (17%).

Based on the results of the above-mentioned studies, it is hypothesized that reducing endotoxin levels with PMX in the treatment of septic shock with endotoxemia leads to reduced mortality, which needs to be proven by a prospective, controlled trial.

3.2. Application in acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF)

The prognosis of AE-IPF has been reported to be extremely poor. Abe *et al.* retrospectively studied 160 cases of interstitial pneumonia with acute exacerbations (including 73 cases of idiopathic pulmonary fibrosis) treated with PMX in addition to standard therapy at 18 centers in Japan [5]. In AE-IPF cases, the PaO_2/FiO_2 ratio improved significantly after two PMX treatments (from 173.9 ± 105.4 to 195.2 ± 106.8 Torr, $P = 0.003$).

Oishi *et al.* retrospectively studied 50 cases of AE-IPF (PMX-treated: 27, non-PMX-treated: 23) treated at their own institution. Both groups received steroid pulse therapy. Through multivariate analysis, PMX treatment was shown to be a good prognostic predictor of 12-month survival (HR = 0.442, 95% CI = 0.223–0.873, $P = 0.019$); survival at 12 months was significantly higher in the PMX treatment group (41.7% vs. 9.8%, $P = 0.040$). The mechanism of action of PMX treatment on AE-IPF remains unclear.

3.3. Application in severe pneumonia caused by H1N1 virus and SARS-CoV-2 infection

Araki *et al.* documented a case involving severe pneumonia induced by H1N1 virus infection in 2010, which was treated with PMX. Despite fever and ventilatory support with 100% oxygen, the patient experienced persistent hypoxemia. Bilateral infiltrate shadows and frosted shadows were evident in chest radiographs. An endotracheal aspirate sample tested positive for the H1N1 virus, leading to the diagnosis of severe pneumonia attributed to the H1N1 infection. PMX treatment was administered in combination with drug therapy, and arterial partial pressure of oxygen (PaO_2) rapidly recovered from 65 mmHg to 195 mmHg as soon as the treatment started. The patient was extubated on day 16 and discharged without complications. The authors report that they considered the condition to be a cytokine storm and intended to improve hypertyrosinemia with PMX treatment.

Blood purification methods such as PMX and continuous hemodiafiltration have been used for COVID-19 in Japan and have been reported to reduce inflammation and improve chest radiographs. There is information that PMX has also been used overseas, but details have not been reported.

4. Approaches to elucidating the mechanism of action

Numerous reports have demonstrated that the administration of PMX for septic shock results in changes in the blood levels of endotoxins, mediators, and various organ dysfunction markers. Changes have been observed in cytokines such as IL-6, IL-10, and HMGB-1, as well as markers related to myocardial injury such as cardiac troponin-T. Additionally, markers linked to lung injury such as neutrophil elastase, angiopoietin-1, and angiopoietin-2, along with markers of kidney injury like urinary L-FABP (liver-type fatty acid-binding protein), have been affected. Other markers indicating endothelial cell damage, such as endothelin-1, and those associated with blood coagulation and the platelet system, including PAI-1, PF-4, thrombomodulin, and von Willebrand factor, have also been influenced. Efforts have been made to understand the mechanism of action based on the trends of these mediators and organ injury markers. However, this process is intricate and not fully elucidated.

Cell necrosis and apoptosis have been postulated as mechanisms of organ damage in sepsis, and clinical and animal studies have shown that the removal of apoptosis-promoting factors in the blood by PMX treatment is associated with the improvement of acute renal injury associated with sepsis.

Modulatory effects on immune cell function following PMX treatment have also been reported. In sepsis, inflammatory and anti-inflammatory immunosuppressive responses are thought to occur, and it has been suggested that the proportion of inflammation-inducing CD16-positive monocytes decreases after passage through PMX columns and the proportion of HLA-DR-negative monocytes, which reflect an immune non-responsive state, decreases after PMX treatment and the immune non-responsive state is improved This may be a consequence of the adsorptive removal of abnormal monocytes and neutrophils by PMX columns [6].

Regarding the mechanism of effectiveness of PMX therapy for AE-IPF, Abe *et al.* speculate that it may involve the removal of activated white blood cells. They observed that after clinical use of the PMX column, a significant amount of neutrophils expressing HLA-DR, CD14, CD62L, and CD114 was adsorbed onto the PMX column adsorbent. Additionally, they noted a significant decrease in the blood levels of MMP-9 (Matrix metalloproteinase) after PMX treatment [5].

It is presumed that PMX treatment exerts multifaceted effects, such as indirect reduction of mediator levels as a result of endotoxin adsorption and removal, direct adsorption and removal of certain mediators, removal of apoptosis promoting factors and suppression of immunomodulatory and inflammatory responses by removing activated monocytes and neutrophils. It is necessary to clarify how these effects are linked to the improvement of organ failure.

5. Conclusion

With the development of the clinical use of PMX, numerous clinical studies have been conducted and a certain amount of evidence on the improvement of organ failure has been accumulated. However, the level of evidence for improvement in life expectancy is low, as it has not been clearly demonstrated in controlled trials. PMX has been reported to exert multifaceted effects through the adsorptive removal of endotoxin from the blood. However, further studies are needed to understand how these effects are linked to the improvement of organ failure.

Disclosure statement

The author declares no conflict of interest.

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