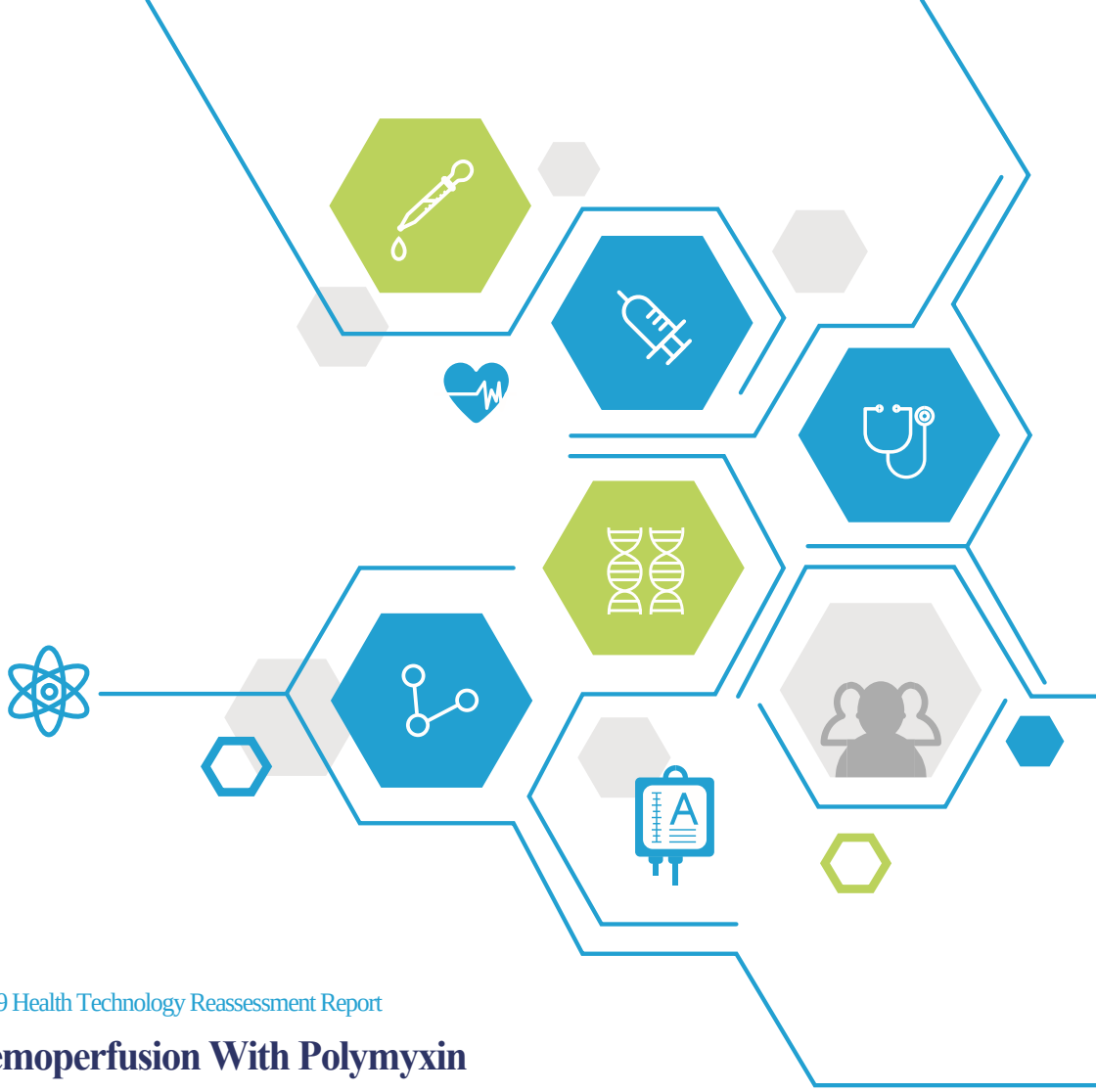

2019 Health Technology Reassessment Report

Hemoperfusion With Polymyxin B-immobilized Fiber Column

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Abstract (English)

□ Assessment background and objectives

The Korean National Evidence-based Healthcare Collaborating Agency is conducting a program to reassess existing items that have completed new health technology assessment. Among these items, hemoperfusion with an immobilized polymyxin B fiber column (PMX-DHP) is an extracorporeal direct hemoperfusion with an immobilized polymyxin B fiber column used for removing endotoxins in patients with sepsis or septic shock. PMX-DHP is a technology that was assessed as a new technology (2010-51) in the new health technology assessment in 2010. Recently, various studies have reported on the results of applying PMX-DHP in patients with sepsis or septic shock. Accordingly, the objective is to identify the clinical safety and effectiveness through profession, in-depth review and perform an updated assessment to provide evidence for suitability assessment.

□ Committee operation

A subcommittee consisting of six members held three subcommittee sessions over a 4-month period between April 30 and July 25, 2019 to assess the safety and effectiveness of this technology.

□ Assessment methods

A systematic literature review was performed to assess the safety and effectiveness of PMX-DHP. Detailed study methods were as follows and all assessment methods were established through review and approval by the “PMX-DHP Assessment Subcommittee” (*hereinafter* the Subcommittee) with

consideration for the study objectives.

Table. Details of PICO-TS

Item	Details
Patients	Sepsis caused by gram negative bacteria Septic shock
Intervention	Hemoperfusion with an immobilized polymyxin B fiber column (PMX-DHP)
Comparators	Conventional medical therapy
Outcomes	Safety - Procedure-related complications or adverse events : Serious Adverse event (SAE) Effectiveness - Mortality rate - Clinical symptoms: · Mean arterial pressure (MAP) · Inotropic score · The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PO_2/FiO_2) - Endotoxin levels (EAA)
Follow-up period (Time)	No limit
Study type	Randomized clinical trial (RCT)
Years	2009 ~ present

Item	Details

PO_2: Partial Pressure Of Oxygen, FiO_2: Fraction of inspired oxygen

For systematic literature review, five Korean and three foreign databases were searched based on the PICO-TS above. Two reviewers independently screened and selected the articles according to the selection and exclusion criteria. Risk of bias assessment was performed independently by two reviewers using RoBANS until an agreement was reached. Data were extracted independently by two reviewers using pre-determined format. If there was a disagreement between the reviewers, such cases were discussed with a third party to reach an agreement. For data analysis, since quantitative analysis was impossible, qualitative review was applied.

□ Assessment results

The safety and effectiveness of PMX-DHP were assessed based on a total of four articles (domestic articles: 0 and foreign articles: 4). After searching the domestic and foreign databases by the predetermined protocol, four articles, including one article used in previous assessment, were identified. The safety and effectiveness results were as follows:

Safety

The safety of PMX-DHP was assessed by procedure-related complications or

adverse events with serious adverse event or severe adverse event used as the indicator.

The safety of this technology was assessed by a total of two articles. One study (Dellinger et al., 2018) reported serious adverse events, while the other study (Payen et al., 2015) reported severe adverse events.

The study by Dellinger et al. (2018) reported on the total number of serious adverse events and details of serious adverse events reported five or more times. The total number of serious adverse events in the PMX-DHP and conventional treatment groups was 138 (65.1%) and 126 (57.3%), respectively. Meanwhile, the frequency of serious adverse events reported five or more times was reported in the order of exacerbation of sepsis, exacerbation of septic shock, exacerbation of multiple organ failure, cardiac/cardiorespiratory arrest, respiratory failure, thrombocytopenia, acute kidney injury, venous embolism, and venous gas embolism. Of these, venous embolism and venous gas embolism were reported to be serious adverse events directly associated with PMX-DHP.

The study by Payen et al. (2015) reported on severe adverse events; 6 (65.1%) and 3 (57.3%) cases in the PMX-DHP and conventional treatment groups, respectively. The article reported on severe adverse events in bleeding, separately from severe adverse events.

Effectiveness

The effectiveness of PMX-DHP was assessed by mortality rate (28-day, 90-day, and other time points), clinical symptoms (MAP, inotropic score, and PO_2/FiO_2), and endotoxin level as the indicators.

Among mortality rates used for assessing the effectiveness of PMX-DHP, all articles that selected overall 28-day mortality rate were assessed. Meta-analysis of four articles

showed no significant difference between the PMX-DHP and conventional treatment groups (RR 1.07, 95% CI 0.81 ~ 1.41, p=0.63, I^2=41%).

Overall 90-day mortality rate was assessed based on two articles. Meta-analysis of two articles showed no statistically significant difference between the PMX-DHP and conventional treatment groups (RR 1.15, 95% CI 0.89 ~ 1.49, p=0.28, I^2=30%).

The clinical symptoms used for assessing the effectiveness of PMX-DHP consisted of MAP, inotropic score, and PO_2/FiO_2.

Among the two studies that reported on MAP, one study compared two groups and showed higher MAP in the PMX-DHP group than in the conventional treatment group. The other study showed that MAP in the PMX-DHP group increased after the intervention, as compared to before the intervention.

Inotropic score was assessed based on two articles. One study conducted a comparison between the PMX-DHP and conventional treatment groups and a pre-post intervention comparison. The results showed significant decreases in both comparisons. The other study did not report on a comparison between the two groups, but a pre-post intervention comparison showed significant decrease after the intervention in the PMX-DHP group.

Of the two studies that assessed PO_2/FiO_2, one study reported significant increase after the intervention in the PMX-DHP group, whereas the other study reported no significant difference in the amount in pre-post change between the PMX-DHP and conventional treatment groups.

Two studies that assessed endotoxin level reported that there were no statistically significant differences in the comparison between the PMX-DHP and conventional treatment groups and the pre-post intervention comparison.

□ Conclusions and recommendations

This assessment presented the results on the safety and effectiveness of PMX-DHP in patients with septic shock or sepsis caused by gram negative bacteria.

Based on a systematic literature review, the safety of this technology was assessed by serious adverse events reported in two articles. Serious adverse events occurred in both the PMX-DHP and conventional treatment groups, but venous embolism and venous gas embolism were reported to be serious adverse events directly associated with the equipment. The effectiveness of this technology was assessed based on four articles. The results showed improved MAP in the PMX-DHP group, while 28-day mortality rate, 90-day mortality rate, and endotoxin level could not be reduced. Moreover, effectiveness on inotropic score and PO_2/FiO_2 was reported in one out of two studies. The present study used RCTs for the assessment, but the sample size included in the assessment was only 804 patients, which may be too small for identifying clinical effectiveness. However, considering that a large-scale RCT is difficult to carry out due to the clinical characteristics of sepsis, the findings in the present study have important significance. Moreover, previous systematic literature review that assess the same technology reported that PMX-DHP applied to patients with sepsis or septic shock did not have an impact on reducing the mortality rate, while the clinical guidelines published by the Japanese Society of Intensive Care in 2018 suggested against this technology as the standard treatment for patients with sepsis.

The subcommittee determined that PMX-DHP is a technology with no safety concerns since almost no severe complications directly associated with the technology were reported. As of now, only improved MAP in the PMX-DHP group has been reported from effectiveness aspect. However, because mortality is the most important variable, but there were no differences in mortality rates at all time

points and those reported in subgroup analyses, it was determined that this technology does not have effectiveness. Therefore, it is opined that use of PMX-DHP as adjuvant therapy in patients with septic shock or sepsis caused by gram negative bacteria is not suitable.

The subcommittee on PMX-DHP proposed the following based on currently available assessment results.

With respect to the safety of PMX-DHP, there were few reported complications directly associated with this technology. With respect to effectiveness, mortality is the most important variable, but there were no differences in mortality rates at all time points and those reported in subgroup analyses. Therefore, it is opined that use of PMX-DHP as adjuvant therapy in patients with septic shock or sepsis caused by gram negative bacteria is not suitable.

Accordingly, the conclusion reached by the subcommittee that PMX-DHP as adjuvant therapy in patients with septic shock or sepsis caused by gram negative bacteria does not present any safety concerns, but the technology has no clinical effectiveness was determined to be valid.

The Health Technology Reassessment Committee reviewed and determined that the findings of the subcommittee on “hemoperfusion with an immobilized polymyxin B fiber column technology” are valid (September 20, 2019).

Keywords:

Sepsis, Septic shock, Polymyxin B-immobilized fiber column, Hemoperfusion