NECA - Health Technology Reassessment

Hemoperfusion With Polymyxin B-immobilized Fiber Column

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National Evidence-based Healthcare Collaborating Agency

Summary

□ Background and Purposes

The Korea National Evidence-based Healthcare Collaborating Agency (NECA) runs a program to reassess the items that underwent Innovative Health Technology Assessment, including hemoperfusion with polymyxin B-immobilized fiber column. Hemoperfusion with polymyxin B-immobilized fiber column is a direct extracorporeal hemoperfusion technique that uses a polymyxin-B-immobilized fiber column to eliminate endotoxin from the blood of patients with sepsis or septic shock. As an adjuvant to conventional treatment for patients with sepsis or septic shock, the technology was on the no-coverage list (classification ID: Jo-801). Recently, however, its coverage status was changed to preliminary coverage. Considering that clinical evidence is insufficient and patients with severe conditions are burdened with high treatment costs, the technology's coverage status was changed to "preliminary coverage with an out-of-pocket rate of 90% (the Ministry of Health and Welfare Notification 2019-102, June 5, 2019. Date of enforcement: July 1, 2019).

Accordingly, as the need to reassess the safety and effectiveness of hemoperfusion with polymyxin B-immobilized fiber column (classification ID: Ja-709) arose, the Health Insurance Review & Assessment (HIRA) Preliminary Coverage Office requested NECA to perform a reassessment. Hence, this study was conducted to update the previous assessment by conducting an in-depth review by experts to confirm the clinical safety and effectiveness of the technology and provide evidence regarding appropriateness assessment.

□ Committee Operation

A subcommittee composed of 7 members held 3 meetings over 8 months between October 14, 2019, and June 10, 2020, to assess the safety and effectiveness of Hemoperfusion With Polymyxin B-immobilized Fiber Column.

During the 7th Health Technology Reassessment Committee meeting (July 10, 2020), a final review of the results of the safety and effectiveness assessment was performed.

□ Methods

A systematic review was performed to assess the safety and effectiveness of hemoperfusion with polymyxin-B-immobilized fiber column. The core questions were as follows. A final decision on all specific methods of assessment was made in accordance with the study purposes and based on a review by the "Hemoperfusion with Polymyxin-B-immobilized Fiber Column Subcommittee" (hereafter, the subcommittee).

Table. PICO-TS details

Categories	Details
Patients	Sepsis caused by gram-negative bacteria Septic shock
Intervention	Hemoperfusion with polymyxin-B-immobilized 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 · Inotropic score · The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PO_2/FiO_2) - Endotoxin level (EAA)
Timing	Not restricted
Study type	Randomized controlled clinical trial (RCT)
Publication year	2019 - current

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

A literature search of 5 domestic and 3 foreign databases was performed based on the core questions presented above. Two reviewers independently performed article selection according to the inclusion and exclusion criteria.

□ Results

Following the predetermined protocol, the articles published after the previous assessment but before or on February 24, 2020, were searched using the domestic and foreign databases, but no articles were extracted. Thus, the articles finally selected in the previous assessment in 2019 (4 foreign articles) were examined after a review by the subcommittee. The safety and effectiveness outcomes presented in the 4 articles are summarized as follows.

The safety of hemoperfusion with polymyxin-B-immobilized fiber column was evaluated based on procedure-related complications, serious adverse events (SAE), and severe adverse event.

The safety of PMX-DHP was reported in 2 articles. One of them (Dellinger et al., 2018) reported SAEs and the other (Payen et al., 2015) reported severe adverse event.

Dellinger et al. (2018) reported the number of all reported SAEs and the details of SAEs reported in 5 or more cases. The total number of cases with SAEs was 138 (65.1%) in the group of patients treated with hemoperfusion with polymyxin-B-immobilized fiber column (hereafter, PMX-DHP group) and 126 (57.3%) in the group of patients treated with conventional therapy (hereafter, conventional group). The following SAEs, sorted by descending order, were reported in 5 or more cases: worsening of sepsis, worsening of septic shock, worsening of multiple organ failure, cardiac arrest/cardiorespiratory failure, respiratory failure, thrombocytopenia, acute kidney injury, venous thromboembolism, and venous air embolism. Of these SAEs, venous thromboembolism and venous air embolism were directly related to hemoperfusion with polymyxin-B-immobilized fiber column.

Payen et al. (2015) reported that the number of severe adverse event was 6 (5.0%) and 3 (2.7%) in the PMX-DHP and conventional groups, respectively. Additionally, bleeding-related severe adverse event was separately reported.

The effectiveness of hemoperfusion with polymyxin-B-immobilized fiber column was evaluated based on the mortality rate (day 28, day 90, and additional points in time),

clinical symptoms (mean arterial pressure, inotropic score, and PO_2/FiO_2), and the endotoxin level (EAA).

To evaluate the effectiveness of hemoperfusion with polymyxin-B-immobilized fiber column using the day 28 mortality rate, a meta-analysis of the 4 articles was performed. The result showed that the difference between the PMX-DHP and conventional groups was not significant (RR 1.07, 95% CI 0.81 ~ 1.41, p=0.63, I^2=41%).

Day 90 mortality rate was evaluated using 2 articles. A meta-analysis of the articles showed, again, that the difference between the PMX-DHP and conventional groups was not significant (RR 1.15, 95% CI 0.89 ~ 1.49, p=0.28, I^2=30%).

The clinical symptoms used to evaluate the effectiveness of hemoperfusion with polymyxin-B-immobilized fiber column included mean arterial pressure, inotropic score, and PO_2/FiO_2.

One of 2 articles reporting on the inter-group difference in the mean arterial pressure showed that the mean arterial pressure increased in the PMX-DHP group compared with the conventional group. The other article compared the pre- and post-intervention mean arterial pressures and found that the mean arterial pressure increased after the intervention in the PMX-DHP group.

The inotropic score was examined in 2 articles. One of the articles compared the scores for the groups as well as before and after the intervention and did not find a significant reduction in either comparison. The other article did not report the inter-group difference but reported that in the PMX-DHP group, the inotropic score significantly decreased after the intervention.

PO_2/FiO_2 was reported in 2 articles. In one of them, the ratio significantly increased after the intervention in the PMX-DHP group. The other article reported that the PMX-DHP and conventional groups did not show different pre-post changes in the PO_2/FiO_2 ratio.

Two articles that examined EAA reported that the outcomes of the group comparison and the pre- and post-intervention comparison were not statistically significant.

□ Conclusion and Suggestions

In this study, the safety and effectiveness of hemoperfusion with polymyxin-B-immobilized fiber column in patients with sepsis caused by gram-negative bacteria or septic shock were assessed.

In the systematic review, the safety of the said technology was evaluated based on the SAEs reported in 2 articles. SAEs occurred in the PMX-DHP group as well as the conventional group, but only 2 cases of SAEs directly related to the device under current review (venous thromboembolism and venous air embolism) were reported. The effectiveness of the said technology was evaluated in 4 articles. It was found that the mean arterial pressure improved in the PMX-DHP group, but the day 28 and day 90 mortality rates and the EAA did not decrease. The effects on the inotropic score and PO_2/FiO_2 were reported in only 1 of the articles.

In this study, the safety and effectiveness assessment was based on RCTs. The subcommittee expressed that the overall sample size (n=804) in the study could be considered too small to uncover clinical effects; nevertheless, they considered that the results were meaningful because it is difficult to perform a large-scale RCT for sepsis given its clinical features.

Based on the results of the assessment of hemoperfusion with polymyxin-B-immobilized fiber column, the subcommittee stated the following.

Complications directly related to hemoperfusion with polymyxin-B-immobilized fiber column have rarely been reported, and the technology has few safety issues. Regarding effectiveness, it has been reported that the mean arterial pressure improved in the PMX-DHP group, but the most important outcome variable, mortality rate, did not show improvement at any of the tested time points and during the subgroup analysis. Hence, the technology is not considered effective. Accordingly, the subcommittee determined that hemoperfusion with polymyxin-B-immobilized fiber column is not appropriate as adjuvant therapy for patients with sepsis caused by gram-negative bacteria or septic shock.

Based on the subcommittee's review, the Health Technology Reassessment Committee assesses "Hemoperfusion with Polymyxin-B-immobilized Fiber Column," as follows (July 10, 2020).

Based on the review of the literature on the safety of hemoperfusion with polymyxin-B-immobilized fiber column, complications directly related to the technology have rarely

been reported. Thus, it is determined that safety may not be an issue. However, based on the review of the literature regarding effectiveness, it is determined that the technology is not effective, because mortality rate, the most important outcome variable, did not improve at any of the tested time points or during the subgroup analysis.

Accordingly, the Health Technology Reassessment Committee does not recommend hemoperfusion with polymyxin-B-immobilized fiber column in patients with sepsis or septic shock (Grade of recommendation - II).

Keywords

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