Polymyxin B-immobilized Hemoperfusion and Mortality in Critically Ill Patients with Sepsis/Septic Shock: Systematic Review and Meta-Analysis

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BACKGROUND

Sepsis remains desperately fatal and septic shock carries hospital mortality as high as around 20% worldwide. Many efforts have been made to improve the prognosis of sepsis, but large multi-centered trials of various therapies have failed to demonstrate consistent benefit.

Polymyxin (PMX) is a cyclic cationic polypeptide antibiotic with high affinity for endotoxin. A novel strategy whereby PMX is bound and immobilized to polystyrene fibers in a hemoperfusion device was developed in Japan. The suggested mechanism of action of PMX hemoperfusion (PMX-HP) is to remove circulating endotoxin by adsorption, which modulates and limits the host response to infection and the progression of the biological cascade of sepsis.

Selected randomized trials have largely focused on surrogate endpoints or have been small and underpowered to detect effects on clinically important outcomes. Additional studies have recently been completed evaluating PMX-HP, including two larger multi-centre RCTs. Accordingly, we have performed an up to date systematic review and evidence synthesis evaluating the impact of PMX-HP as an adjuvant therapy for critically ill patients with sepsis or septic shock on clinical outcomes and health services utilization.

METHOD

Data Sources: MEDLINE, EMBASE, Cochrane Library, Health Technology Assessment Database, Cumulative Index to Nursing and Allied Health Literature, Pubmed, and "Igaku Chuo Zasshi", National Institute of Health Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform, University Hospital Medical Information Network Clinical Trials Registry, reference lists, and experts in the critical care nephrology and manufacturer of a PMX-HP column.

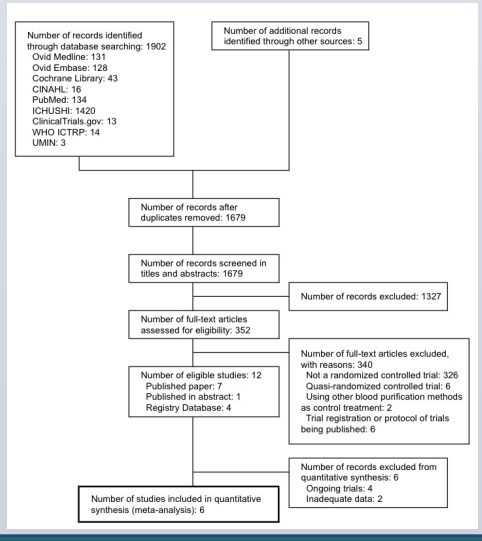
Study Selection: Randomized controlled trials comparing PMX-HP with standard therapy in critically ill patients with sepsis or septic shock.

Data Extraction and Synthesis: Two reviewers independently extracted trial-level aggregated data including population characteristics, interventions, outcomes, and funding sources. The risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias, and the strength of evidence was adjudicated using the GRADE methodology.

Main Outcomes and Measures: 28-day all-cause mortality, changes in organ dysfunction scores, and any adverse events.

RESULT

1. Study flow chart



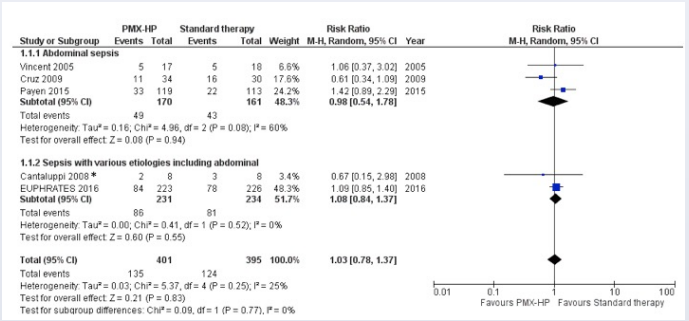
RESULTS (cont.)

2. Characteristics of the 6 trials included in the meta-analysis

Source	Country	Study cites	Funding	No. of patients	Exclusion[‡]	Age, Mean (SD), y	Male, Female, n	Patient status	Duration, No. of session
Nakamura, 2003	Japan	NA	Investigator initiated	60	0	56 (NA)	40, 20	Culture positive sepsis	2hr, twice
Vincent, 2005	6 countries in Europe	Multicenter	Industry sponsored	35	0	57.7 (15.6)*	22, 13	Abdominal sepsis, Surgical	2hr, once
Cantaluppi, 2008	Italy	Two center	Investigator initiated	16	0	60 (11.3)	12, 4	Confirmed Gram-negative sepsis	2hr, twice
Cruz, 2009	Italy	Multicenter	Industry sponsored	64	0	63.8 (14.2)*	42, 22	Abdominal sepsis, Surgical	2hr, twice
Payen, 2015	France	Multicenter	Industry sponsored	243	11	69.7 (11.6)	134, 98	Abdominal sepsis, Surgical, Septic shock	2hr, twice
EUPHRATES, 2016 ref. Klein 2014	US, Canada	Multicenter	Industry sponsored	450	1	60.0[§] (14.7)[§]	262[§], 170[§]	Septic shock, High endotoxin activity assay	2hr, twice

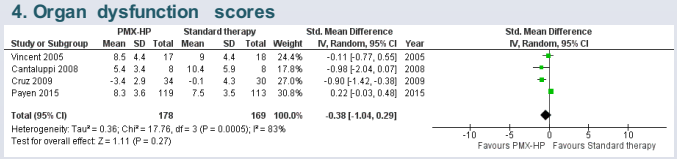
[‡]Exclusion from ITT analysis
*Data provided by the each study author
[§]Data of 432 safety monitoring population

3. 28-day mortality

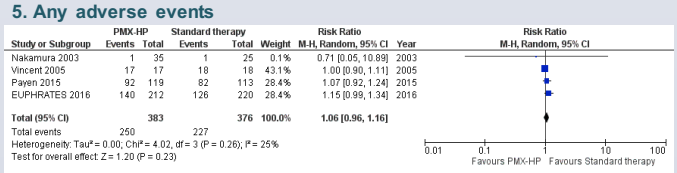


Strength of evidence (GRADE): moderate

4. Organ dysfunction scores



5. Any adverse events



CONCLUSION

- PMX-HP was not proven to reduce 28-day mortality.
- PMX-HP did not significantly improve organ dysfunction scores or increase the risk of adverse events.
- Available evidence does not support the routine use of PMX-HP as an adjuvant therapy for patients with sepsis or septic shock.
- Future work, ideally incorporating individual patient data, should further explore whether selected subgroups may derive benefit.

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