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EDITORIAL

Hemoadsorption in septic shock – PRO

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Introduction

Hemoadsorption (formerly hemoperfusion) is an extracorporeal blood and plasma purification therapy for selective or broad-spectrum removal of solutes, cells and pathogens that are not amenable to diffusive or convective clearance [1, 2] (Table 1). The technique has markedly evolved in the last two decades and been investigated in various clinical conditions but particularly in sepsis.

Pathophysiological rationale

Sepsis is the result of a dysregulated immune response to infection and is associated with endothelial dysfunction, leukocyte adhesion and release of inflammatory mediators, leading to microcirculatory dysfunction and acute organ dysfunction. Numerous studies have found that survivors of sepsis have lower inflammatory mediator burden and resolve their inflammation more rapidly compared to non-survivors [3]. Similarly, endotoxin activity in the blood, measured using endotoxin activity assay (EAA), is associated with intensive care unit (ICU) mortality [4]. Gruda et al. showed that hemadsorption through porous polymer bead devices reduced the concentrations of cytokines, damage-associated and pathogen-associated molecular patterns [5]. The degree of cytokine and endotoxin removal depends on the type of cartridge and timing and intensity of the therapy [6]. Special affinity binder cartridges are also available to remove pathogens and pathogen components, aiming to reduce the microbial burden.

Clinical data

Polymyxin B (PMX) hemoadsorption has been studied the most. The two largest multi-center randomized clinical trials (RCTs) comparing PMX hemoadsorption with conventional treatment in septic shock, i.e., ABDOMIX [7] and EUPHRATES [8], showed no survival benefit or improvement in organ failure. However, in vitro studies have demonstrated that EAA results of 0.9 and greater equate to endotoxin levels beyond the capability of the device to remove [9]. In a post hoc analysis of the EUPHRATES trial, PMX hemoadsorption appeared to be beneficial in patients with EAA levels between 0.60 and 0.89 [10]. In addition, analysis of a Japanese database including 4766 patients treated with PMX hemoadsorption between 2016 and 2019 demonstrated a 3–7% absolute risk reduction of hospital mortality with PMX therapy [11].

A meta-analysis of RCTs published up to 2019 found that hemoadsorption was associated with lower mortality compared to conventional therapy (relative risk 0.88 [95% CI, 0.78 to 0.98], $p=0.02$, very low certainty evidence) [12] and a recent systematic review of 30 studies published up to June 2022 concluded that PMX hemoadsorption therapy could reduce 28-day mortality in patients with sepsis [13].

Heterogenous results have been reported with some hemoadsorption devices. For instance, cytokine removal with Cytosorb® can attenuate hyperinflammation and vasoplegia in patients with septic shock, leading to quicker hemodynamic stabilization and shock reversal [14]. A literature review highlighted the important contribution of early hemoadsorption with Cytosorb® in achieving rapid hemodynamic stabilization of patients with refractory vasoplegic shock [15]. However, a recent meta-analysis including 2611 patients with sepsis did not show any difference in norepinephrine requirement, length of stay or survival between patients treated with Cytosorb® versus standard of care [16].

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Table 1 Description of selected hemoadsorption technologies and suggested indications

	Technology	Structure	Surface area (m^2)	Target of removal	Duration of treatment session	Specific sepsis sub-phenotypes
Non-selective removal	Porous polymer beads of polystyrene divinylbenzene (CytoSorb®)	Beads with average diameter of 0.3–0.8 mm	> 40,000	Hydrophobic molecules with MW up to 60 kDa, including cytokines	4–12 h	Hyperinflammation (i.e., hypercytokinemia)
	Adsorbing beads made of styrene–divinyl–benzene copolymers (Jafron®)	Beads with a mean diameter of 0.8 mm	54,000	Molecules with MW up to 60 kDa	2–4 h	Hyperinflammation (i.e., hypercytokinemia)
Selective removal	Polymyxin B bound to polypropylene-polystyrene fiber (TORAYMYXIN™)	Polymyxin B covalently bonded to polystyrene-derivative fibers	> 500	Endotoxin	2 h	Endotoxic septic shock (EAA > 0.6 with multiple organ failure)
	Polyethylene beads (Seraph® 100)	Beads coated with negatively charged heparan sulphate; medium diameter 0.3 mm	40	Bacteria, fungi, viruses	6 h	Viremia, bacteremia, fungemia

AKI acute kidney injury, *EAA* endotoxin activity assay, *HD* hemodialysis, *HDF* hemodiafiltration, *HF* hemofiltration, *MW* molecular weight

Hemoadsorption devices capable of directly removing pathogens or inflammatory cells exist, too, thus targeting the cellular level of the immune response. For example, the Seraph-100 hemoadsorption cartridge contains polyethylene beads coated with negatively charged heparan sulfate, which can bind Gram-positive and Gram-negative bacteria, viruses and cytokines. Its use during surgery for aortic vascular or endovascular graft infections was associated with excellent outcomes [17].

The technology to remove inflammatory mediators and pathogens clearly exists. However, results of clinical trials are limited by heterogeneous patient populations, diverse sepsis sub-phenotypes, the dynamic nature of sepsis, and the application of different hemoadsorption prescriptions. Severity of sepsis also varied between studies. Only the EUPHRATES trial measured EAA and restricted enrollment to patients with septic shock and EAA levels ≥ 0.60 [8]. However, 17% patients had EAA levels ≥ 0.90 which may not represent treatable levels [10]. After excluding these patients, the 28-day mortality was 26.1% in patients randomized to PMX hemoadsorption versus 36.8% in the sham group (odds ratio 0.52 (95% CI 0.27–0.99), $p = 0.047$).

Opportunities

Existing data suggest that hemoadsorption has potential effectiveness in managing sepsis, particularly in reducing inflammatory mediators, improving hemodynamic instability and potentially improving outcomes. Current evidence is insufficient to recommend routine use for all patients with sepsis but specific patients appear to benefit. The chances of improvement depend on the characteristics of the patient, the severity and phase of sepsis, the type of adsorber and the timing, intensity and duration of the treatment. The need for targeted patient selection is becoming increasingly clear (i.e., concept of precision medicine). In the US, a trial is ongoing exploring the role of standard medical care combined with the PMX cartridge versus standard medical care alone, in subjects with septic shock and endotoxemia (EAA ≥ 0.60 and < 0.90). (ClinicalTrials.gov, NCT03901807).

Future studies

Tools are urgently needed to identify patients who may benefit most from hemoadsorption therapy and those who are unlikely to respond or potentially be harmed. EAA levels, cytokine concentrations and novel biomarkers may have a role in selecting appropriate individuals and guiding the initiation, titration and discontinuation of the treatment.

It will be necessary to include appropriate non-mortality endpoints in future trials. In our view, an important objective of a hemoadsorption trial should be to achieve

the desired action by the intervention used at a specific time-point, including prevention and management of organ dysfunction.

Conclusion

Hemoadsorption has been shown to be effective in specific patients with high but treatable concentrations of target solutes (e.g., endotoxin) and serves as a tool toward precision medicine. It is the lack of diagnostic tools to identify these patients easily and the application of heterogenous protocols that may have led to conflicting trial results rather than the treatments per se.

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Declarations

Conflicts of interest

MO has received research funding from Baxter which was paid to the institution. TR has received honorarium for lectures at scientific conferences from Baxter, Fresenius Medical Care, Jafron, Estor and Exthera.

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