EDITORIAL

Polymyxin B Hemoperfusion in Sepsis: A Possible Silver Lining to the Dark Clouds?

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Sepsis the most important cause of mortality in ICU patients. This is especially higher in patients with septic shock, amounting to around 9–31%.[1] Sepsis has been defined as "life-threatening organ dysfunction due to dysregulated host response to infection" and bacterial endotoxins have been identified as powerful modulators of this response to infection, responsible for perpetrating the organ dysfunction caused by sepsis.[2,3] The levels of these endotoxins have also been directly related to the degree of organ dysfunction, thereby affecting the overall mortality.[4] The dysregulated production of pro and anti-inflammatory mediators like IL-1, IL-6, TNF-α, etc., leads to "cytokine storms" and organ dysfunction in sepsis.

The standard management of sepsis includes early administration of antibiotics, vasopressors and intravenous fluids, along with source control. Based on the pathophysiology of sepsis, the removal of inflammatory mediators from the blood by extracorporeal purification techniques, to restore a balanced immune response, has emerged as another adjunctive modality.[5] Many hypotheses have been given regarding the mechanism of action of these blood purification modalities. The "Cytokine Peak Hypothesis" states that the removal of pro-and anti-inflammatory cytokines in early sepsis decreases the concentration of these mediators, thereby avoiding their deleterious effects.[6] The "Threshold immunomodulation" hypothesis states that the removal of cytokines from the blood would remove them from the tissues due to the concentration gradient and avoid the local deleterious effects. The "Cytokinetic model" states that a restored gradient in cytokine concentration leads to effective leucocyte chemotaxis to the tissues.[5] Certain extracorporeal therapies may also function via immune modulation, like antigen presentation, expression of surface molecules etc.[7]

Various modalities have been studied for extracorporeal blood purification. High-volume hemofiltration (HVHF) removes middle-molecular-weight molecules, but studies have shown inconsistent results in terms of patient improvement or mortality.[8] High cut-off (HCO) membranes maximize the removal of inflammatory mediators but cause massive albumin leakage and have also not shown any improvement in morbidity or mortality.[9] Coupled plasma filtration and adsorption (CPFA) combines both plasma filtration via a high cut-off filter and adsorption by a sorbent cartridge. COMPACT-1 and COMPACT-2 trials on CPFA demonstrated many adverse effects and no significant mortality benefit. COMPACT-2 trial was terminated prematurely due to the adverse effects.[10] Therefore, the use of CPFA also remains controversial.

Novel membranes with high adsorptive capacity have been developed, that provide kidney support and manage septic shock. "Cytosorb" is one such modality, that uses a hemoperfusion cartridge to remove 90–95% cytokines, growth factors, complement factors, bile acids, myoglobin, bilirubin, etc., at the end of 120 minutes. The evidence in support of Cytosorb in septic shock remains inconsequential, as none of the studies have shown a clear mortality benefit, but only a reduction in cytokine levels.[11] "Oxiris" is a membrane that is pretreated with polyethyleneimine (PEI) and pregrafted with heparin. It is designed for removal of cytokines and endotoxins with continuous renal replacement therapy (CRRT). It has shown to significantly reduce the endotoxin levels, improve hemodynamics, improve organ dysfunction in some cases, but has not been shown to have any mortality benefit till date.[12]

Polymyxin B immobilized to a polystyrene fiber column (Toraymyxin, Japan) is another adsorption technique, commonly used to remove endotoxins from gram negative bacteria (GNB) from the blood. Polymyxin B is a polypeptide cationic antibiotic that binds to lipopolysaccharides (LPS) of GNB and inactivates the toxins. The mechanism of polymyxin B hemoperfusion relies mainly on the affinity of LPS towards polymyxin B. The affinity is due to hydrophobic interactions at shorter distances and ionic interactions between the lipid A of LPS and cationic charges on polymyxin B at larger distances. The covalent bond between polymyxin B and polystyrene fiber protects the patient from the neurotoxicity and nephrotoxicity of the antibiotic.[13] The polymyxin B fiber column has also been associated with a reduction in WBC count, mainly due to a removal of inflammatory cells like monocytes and neutrophils. They are probably removed due to binding with LPS, which in turn binds to polymyxin B or due to physical removal by the fiber column.[14]

Polymyxin B hemoperfusion has been investigated in many randomized control trials. Early use of polymyxin hemoperfusion in abdominal septic shock (EUPHAS) trial demonstrated an improvement in hemodynamic parameters and organ function

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scores, along with improved 28-day mortality.[15] These results should be carefully accepted, as this study was not adequately powered to study the mortality benefit, and the primary outcome was an improvement in mean arterial pressure (MAP) and vasopressor requirements. ABDOMIX study was conducted in a similar set of patients, which was powered to study 28-day mortality showed no significant mortality benefit, or improvement in hemodynamic parameters and organ function. This study also had its limitations, as the therapy was not completed in almost 38% of the patients.[16]

The Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Sepstic Shock (EUPHRATES) trial studied 450 patients with septic shock and those with an endotoxin assay of more than 0.60, including those with an extra abdominal source of sepsis and gram-positive sepsis. Although this trial was designed to study patients with high endotoxin assays, it showed no improvement in 28-day mortality with the use of Polymyxin hemoperfusion therapy, neither in patients with a multiple organ dysfunction syndrome (MODS) score of more than 9 nor in the other patients.[17] A *post hoc* analysis of the same trial, done on patients without extreme endotoxemia, i.e., an endotoxin assay of 0.6–0.9, showed an improvement in 28 day mortality, ventilator-free days and hemodynamic parameters.[18] The possible causes of failure to show benefit in these trials are underestimation of the level of endotoxemia with blood assays, inadequate dosing and duration of the therapy, and extremely high endotoxin levels at baseline.

A propensity score analysis of the Japan septic disseminated intravascular coagulation (JSEPTIC DIC) study, studied data on 1,723 septic shock patients and stated that the all-cause mortality and length of ICU stay were significantly lower in patients with Polymyxin B hemoperfusion therapy.[19] A recent randomized control trial conducted in Lucknow, Uttar Pradesh, India studied the effect of Polymyxin B hemoperfusion in 50 septic shock patients who had at least one new-onset organ dysfunction. They studied the effect of polymyxin B hemoperfusion on the course of sepsis and found that the use of this therapy led to faster and greater improvement in SOFA scores, translating to a faster reduction in vasopressor requirement, an improvement in organ function, and a trend towards reduction in mortality at 7 days, which was statistically non-significant.[20]

Despite the advances in the management of sepsis, the mortality rate still remains very high. Emerging resistance to antibiotics is a very important factor in treatment failure and high mortality. These warrants the search for other techniques for blood purification and reducing organ dysfunction, in the hope of subsequent reduction in mortality. Polymyxin B hemoperfusion along with other extracorporeal techniques, are of special interest in this concern. None of the available evidences are sufficient to recommend routine use of polymyxin B hemoperfusion therapy, but it should be individualized according to the patient's condition and the available resources. Although, the current surviving sepsis guidelines recommend against the routine use of polymyxin B hemoperfusion or extracorporeal therapies, but these are based upon the randomized control trials (RCTs) available at that time and do not take into account observational studies and other scientific evidences. Further research in this area is expected to open new horizons in the management of sepsis patients and hopefully reduce mortality and morbidity in these patients.

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