

Use of hemadsorption in pediatric meningococcal sepsis, waterhouse-friderichsen-syndrome, and multiple organ failure

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Abstract

Community-acquired bacterial meningitis still represents one of the most important infectious diseases worldwide and remains a substantial cause of mortality and morbidity, particularly in both the very young and the elderly patients. The disease is characterized by a hyperinflammatory response with a rapid and excessive production of inflammatory mediators, accompanied by disseminated intravascular coagulation (DIC) and development of Waterhouse–Friderichsen syndrome. Extracorporeal blood purification therapies represent a new therapeutic approach since they seem to be able to attenuate this detrimental process by lowering systemic cytokine levels.

We herein report on an 18-year-old previously healthy male who had to be intubated and mechanically ventilated shortly after hospital admission followed by confirmation of *Neisseria meningitidis* infection. Antibiotic as well as catecholamine and volume therapy were initiated. Over time he developed excessive hyperinflammation, Waterhouse-Friderichsen-syndrome with purpura fulminans, hyperlactatemia and progressive renal failure, leading to the initiation of combined renal replacement and CytoSorb hemoadsorption therapy. This resulted in significant decrease in inflammatory parameters and a progressive reduction in catecholamine and lactate levels while peripheral perfusion was restored preventing any loss of extremities. The patient could be extubated 10 days after PICU admission. No adverse or unwanted device-related side effects were documented.

In conclusion, this case report is supporting other promising results in this highly sensitive patient cohort, by showing rapid hemodynamic stabilization and control of hyperinflammation being associated with the use of CytoSorb, however, evidence on the application of the CytoSorb adsorber in pediatrics remain rather sparse and more clinical data are needed.

Keywords

Hemadsorption; Cytokine adsorption; Meningococcal sepsis; CytoSorb; Infection.

Abbreviations

CNS: Central nervous system; PAMPs: Pathogen-associated molecular patterns; DIC: Disseminated intravascular coagulation; CRRT: Continuous renal replacement therapy.

Introduction

Community-acquired bacterial meningitis still represents one of the most important infectious diseases worldwide [1]. Despite advances in antimicrobial therapy and vaccinations, the disease remains a substantial cause of mortality and morbidity, particularly in both the very young and the elderly patients [2]. Predisposing factors for higher susceptibility and poor outcome include age, genetic predispositions, and deficiencies in innate immunity, CNS barrier defects or asplenia [3]. Meningitis is characterized by an acute inflammation of the meninges and subarachnoid space in response to bacterial infection, with the leading causative bacteria being *Streptococcus pneumoniae* and *Neisseria meningitidis*. Early administration of corticosteroids and empiric antibiotic treatment and therefore eradication of the bacterial pathogen, but also treatment of evolving neurological complications such as elevated intracranial pressure, stroke, and seizures is key for the management of patients with bacterial meningitis. However, once bacteria and pathogen-associated molecular patterns (PAMPs) enter the blood-brain barrier, effects become systemic evoking a hyperinflammatory response accompanied by a rapid and excessive production of cytokines, chemokines, and other inflammatory mediators [4], often culminating in septic shock and multiple organ failure [5]. Disseminated intravascular coagulation (DIC) and development of Waterhouse–Friderichsen syndrome (adrenal gland failure due to acute adrenal hemorrhage) also represent hyperinflammation-driven features of the disease [6]. As the excessive release of inflammatory mediators is critical in the process to go from a localized infection (CNS) to generalized hyperinflammation and septicemia, new therapeutic approaches in the form of extracorporeal blood purification therapies have come into focus. They seem to be able to attenuate this detrimental process by lowering systemic cytokine levels. In this regard, the CytoSorb hemadsorption device intended as adjunctive treatment for patients with elevated cytokine levels in the setting of SIRS, sepsis and septic shock has shown promising results in the field of critical care and cardiac surgery, not only in adults [7-9], but also in some pediatric cases [10]. Moreover, the device has been shown to also bind PAMPs and other inflammatory mediators involved in the process.

We herein report on young patient successfully treated with CytoSorb hemadsorption for meningococcal sepsis, Waterhouse-Fridrichsen-Syndrome, and multiple organ failure.

Case Presentation

An 18-year-old male without relevant medical history presented at the emergency room of a peripheral primary care hospital with nausea and headaches. During the hospital admission process, the patient increasingly developed petechiae over his entire body, resulting in the preliminary diagnosis of meningococcal sepsis. Following initiation of antibacterial therapy with cefotaxime (2 x 4g iv) and

ampicillin (3 x 5g iv) as well as administration of dexamethasone (3 x 10 mg iv), the patient had to be intubated due to respiratory insufficiency and a central venous and arterial catheter was inserted. Subsequently, catecholamine (norepinephrine 0.8 mg/h) and volume therapy (2 l isotonic saline, 2000 IE prothrombin complex, 2x fresh frozen plasma, 1x platelet concentrate) were started due to progressing hemodynamic instability. Microbiological analysis of the liquor puncture confirmed presence of *Neisseria Meningitidis type B* bacteria. The mechanically ventilated patient was then transferred under ongoing catecholamine therapy to our pediatric intensive care (PICU) unit for further diagnosis and therapy. At that time, the patient clinically exhibited a picture of full-blown Waterhouse-Fridrichsen-syndrome with purpura fulminans accompanied by ubiquitous petechial hemorrhages and hyperlactatemia (max. 10.8 mmol/l). Hydrocortisone administration was started according to the guidelines (50 mg/m² body surface) paralleled by sedation with midazolam and sufentanyl, which was later complemented by propofol and dexmedetomidin. Antibiotic therapy was supplemented by tobramycin and disseminated intravascular coagulopathy was treated by means of repeated doses of fresh frozen plasma, platelet concentrates, and vitamin K. Echocardiography revealed a restricted cardiac function with an EF of 31% and inotropic therapy was extended by epinephrine and milrinone, accordingly. Mechanical ventilation had to be intensified because of increasing bronchial secretions and left atelectasis (max positive end-expiratory pressure [PEEP] 10 mbar). Due to progressive renal failure with elevated retention parameters, continuous renal replacement therapy (CRRT) was started five hours after PICU admission and approximately twelve hours later a CytoSorb hemoadsorber was additionally added to the circuit to control excessive hyperinflammation (IL-6 >200.000 pg/ml). CytoSorb was used in combination with CRRT (CRRT 12 days in total, 2 CytoSorb cartridges for a total duration of approximately 50 hours) run in hemodiafiltration (CVVHDF) mode at a blood flow rate of average 120 ml/min using heparin anticoagulation. During combined CVVHDF and hemadsorption treatment, a significant decrease in inflammatory parameters was noticed (Figure 1A), pointing towards control of the hyperinflammatory state, while catecholamine (Figure 1B) and lactate levels could also be reduced progressively. The respiratory situation stabilized during treatment and cardiac function started to improve. Additionally, there were no further petechial hemorrhages, and no peripheral ischemia was observed. Continuous hemodiafiltration was switched to intermittent dialysis as renal function consecutively improved as evidenced by a normalization in retention parameters and return of spontaneous diuresis. The pulmonary situation slowly improved with inhalation and repeated bronchoscopy with bronchial lavage, so that the patient could be extubated 10 days after PICU admission. The further follow-up was characterized by mild delirium and development of critical illness neuropathy with pronounced tremors, which, however, resolved during his further stay. Two weeks after admission to the PICU, the patient was transferred to the general pediatric ward in stable clinical condition with a normal cardiac function (EF 70%) and was discharged from the hospital shortly afterwards.

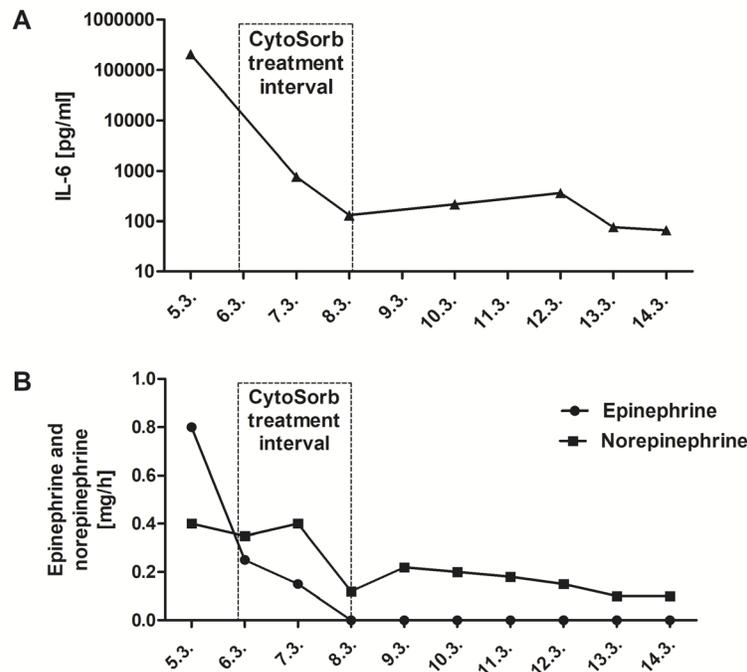


Figure 1: Course of IL-6 (A) as well as epinephrine and norepinephrine (B) throughout the CytoSorb treatment interval.

Discussion

This case shows a successful treatment of an 18-year-old patient with meningococcal sepsis, Waterhouse-Friderichsen-Syndrome, and multiple organ failure, using a combination of standard therapy, CVVHDF and CytoSorb hemadsorption. Treatment was associated with a rapid and significant reduction in plasma cytokine levels, accompanied by improved hemodynamics normalization of plasma lactate levels and restored peripheral perfusion preventing any loss of extremities. No adverse or any device-related side effects were documented during or after the treatment sessions and the combination was practical, technically feasible and appeared to be highly beneficial for the patient.

Initially deteriorating hemodynamics were most likely a result of the extreme severity of the disease with pronounced hyperinflammation and disproportionately high cytokine levels. These levels could be significantly reduced over the first 48 hours of the combined therapy (IL-6 from >200,000 to 770 pg/ml), until also a sustained hemodynamic improvement was observed. This early and rapid hemodynamic stabilization of the patient might also have contributed to avoid any amputation of extremities. Overall, these results are in line with a recent case series in five adult patients with pneumo- and meningococcal sepsis, reporting rapid and clear stabilization in hemodynamics along with a reduction in catecholamine dosages, a decrease in lactate as well as a less-than-expected loss of extremities [11]. Additionally, improvements in cardiac function were observed under hemadsorption therapy, which is in line with a recent report on the use of CytoSorb therapy in severe multisystem inflammatory syndrome (MIS-C) [12].

As with every other therapy next to proper patient selection, timing and dosing seem to be crucial aspects also for CytoSorb therapy. Early start within the first 24 hours after diagnosis of a septic/vasoplegic shock state seems to be of utmost importance [11] and therapy should be continued with new adsorbers

until sufficient stabilization of the hemodynamic condition is achieved. Evidence from a recent publication point towards beneficial effects of changing the first 1-2 adsorbers after already 12 hours to ensure maximal removal capacity [13].

Antibacterial treatment is obviously a cornerstone of causative therapy in the field of meningococcal sepsis and potential unwanted drug removal by extracorporeal therapies should always be taken into consideration. The very positive clinical course in our case, however, does not imply that relevant removal of applied antibiotic drugs was present and a recent animal study investigating the impact of CytoSorb hemadsorption on drugs was concluding that the therapy appears to have limited effect on the pharmacokinetics of the majority of drugs tested [14]. Nevertheless, therapeutic drug monitoring is recommended to increase the safety of the procedure.

Conclusion

In conclusion this case report is supporting other promising results in this highly sensitive patient cohort, by showing rapid hemodynamic stabilization and control of hyperinflammation being associated with the use of CytoSorb, however, evidence on the application of the CytoSorb adsorber in pediatrics remain rather sparse and more clinical data are needed.

Declarations

Ethics statement: Written informed consent was obtained from the child's parents for publication of the details of the medical case and any accompanying images. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Authors contributions: GM and SKD collected, retrieved, and analyzed data. RDP drafted the manuscript. All authors revised the manuscript for important intellectual content.

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