DE GRUYTER OPEN

The Journal of Critical Care Medicine 2017;3(2):73-78

CASE REPORT

DOI: 10.1515/jccm-2017-0010

The Use of Endotoxin Adsorption in Extracorporeal Blood Purification Techniques. A Case Report

Adina N. Hadade[1], Caius M. Breazu[1,2*], Iulian V. Ilie[3], Calin I. Mitre[1]

[1] University of Medicine and Pharmacy " Iuliu Hatieganu", Cluj-Napoca, 1st Department of Anesthesia and Intensive Care, Cluj-Napoca, Romania

[2] Regional Institute of Gastroenterology and Hepathology " Octavian Fodor", Cluj-Napoca, Romania

[3] University of Veterinary Medicine, Cluj-Napoca, Romania

Abstract

Sepsis and septic shock are major healthcare problems, resulting in high morbidity and mortality. The Surviving Sepsis Campaign (SSC), which standardised the approach to sepsis, was recently updated. Strategies to decrease the systemic inflammatory response have been proposed to modulate organ dysfunctions. Endotoxin, derived from the membrane of Gram-negative bacteria, is considered a major factor in the pathogenesis of sepsis. Endotoxin adsorption, if effective, has the potential to reduce the biological cascade of Gram-negative sepsis.

We present a case of a 64-year-old man with severe Gram-negative sepsis, following purulent peritonitis secondary to rectosigmoid adenocarcinoma. To reduce the amplitude of the general effects of endotoxins we used a novel device, the Alteco® LPS Adsorber (Alteco Medical AB, Lund, Sweden), for lipopolysaccharide (LPS) adsorption.

The efficacy markers were: the overall haemodynamic profile, translated into decreased vasopressor requirements, the normalisation of the cardiac index, the systemic vascular resistance index combined with the lactate level and the reduction in procalcitonin (PCT) levels. A decrease in the sequential organ failure assessment (SOFA) score at twenty-four hours was demonstrated.

The clinical course following treatment was favourable for the days immediately following the treatment.This was attributed to the removal of endotoxin from the systemic circulation. The patient died one week after the endotoxin removal session, developing an ischemic bowel perforation with subsequent multiple organ failures.

Keywords: endotoxin, Alteco® LPS Adsorber, Gram-negative abdominal sepsis, Haemadsorption, haemodynamics

Received: 19 January 2017 / Accepted: 25 March 2017

Introduction

Sepsis is associated with life-threatening organ dysfunction caused by a dysregulated host response to infection [1,2]. Sepsis and septic shock are major healthcare problems which result in high morbidity and mortality. New guidelines have been provided to improve clinical outcomes and the cellular /metabolic dysfunction associated with septic shock [3].

Endotoxin (lipopolysaccharide), derived from the membrane of Gram-negative bacteria, is considered a major factor in the pathogenesis of sepsis [4]. Removal of endotoxin could be an effective adjunctive therapy in sepsis management. Therapeutic removal of lipopolysaccharide (LPS) by medication or by extracorporeal methods of adsorption is controversial. Devices that adsorb endotoxin or inflammatory cytokines have been designed as a strategy to treat sepsis and septic shock LPS-driven inflammatory processes [5]. Human trials have confirmed the positive effect on the parameters of the patients' haemodynamics and reduction of inflammatory cytokines, but not on the morbidity or survival which were attributed to the heterogeneity of patients suffering from the consequences of severe infectious diseases and sepsis [6]. Several studies have demonstrated efficient endotoxin removal with the Polymyxin B – immobilised fibre column, as well as the suppression of *Staphylococcus aureus* lipoteichoic acid, induced TNF-α production [7-12].

* Correspondence to: Caius M. Breazu, University of Medicine and Pharmacy " Iuliu Hatieganu", Cluj-Napoca, 1st Department of Anesthesia and Intensive Care; Regional Institute of Gastroenterology and Hepathology " Octavian Fodor", Cluj-Napoca. Email: csbreazu@yahoo.com

New adsorbers have been proposed for bacterial endotoxins removal [7].

The *Alteco*® LPS *Adsorber* (Alteco Medical AB, Lund, Sweden) is a new device with a strong endotoxin-binding capacity. During the treatment, the endotoxin-binding peptides pick up endotoxins from the patient's bloodstream. Adamik et al. (2015) showed a significant improvement in haemodynamic parameters and organ function, within the first twenty-four hours of treatment, when the *Alteco*® LPS *Adsorber* in addition to conventional medical therapy was used in patients with septic shock and suspected Gram-negative infection [8].

Case presentation

This case report describes that of a 64-year-old man with *Escherichia coli* Gram-negative septic shock, due to purulent peritonitis secondary to rectosigmoid junction adenocarcinoma. On admission to the Intensive Care Unit (ICU) the patient was slightly disoriented, hypotensive (blood pressure of 110/55 mmHg), with lactic acidosis. Laboratory tests showed an elevated white blood cell count (WBC) of 22680/μL, PCT, 10 ng/mL, renal insufficiency with elevated creatinine, 1.88 mg/dL, hyperglycemia, 263 mg/dL and lactic acidosis (base excess -8.1 mmol/L, lactate 2 mmol/L). Treatment was initiated promptly with fluids resuscitation (crystalloids and albumin), broad-spectrum antibiotics, meropenem 3g/24h and metronidazole 1.5g/24h and insulin, invasive monitoring using a Vigileo monitor (Flo Trac/Vigileo™, Edwards Lifesciences, Irvine, CA, USA). Emergency surgical intervention was necessary due to the persistence of intestinal subocclusions, and sepsis. Intraoperatively, the diagnosis was established as a generalised purulent peritonitis with septic shock, following perforation of the rectosigmoid junction adenocarcinoma. A rectosigmoid palliative resection with abundant peritoneal lavage and drainage was performed. Bacteriological samples from the peritoneal fluid were taken.

Postoperatively, the patient was readmitted to the ICU, intubated and mechanically ventilated.

On the first postoperative day, the patient became febrile, with persistent leukocytosis (WBC of 20090 /μL), elevated PCT levels (10 ng/mL) with signs of septic encephalopathy (GCS 10 points). Vasoactive support with noradrenaline (0.11 μg/kg/min) was required despite adequate fluid transfusion. Minimally invasive haemodynamic monitoring revealed a hyperdynamic state in the context of a septic shock. The following parameters were recorded: cardiac output (CO) 7.3 L/min, cardiac index (CI) 3.1 L/min/m^2, systemic vascular resistance index (SVRI) 1897 dyn*s/cm^{5}*m^2.

The SOFA score was 10 points, and the APACHE II score was 23 points. Blood and urine cultures were taken and empirically vancomycin (2g/24h), and fluconazole (200mg/24h) were added to the antibiotic regimen.

For reduction of the endotoxin systemic effect and faster organ function improvement, adjunctive extracorporeal endotoxin adsorption treatment with an *Alteco*® LPS *Adsorber* (Alteco Medical AB, Lund, Sweden) was used during the first twenty-four hours postoperatively.

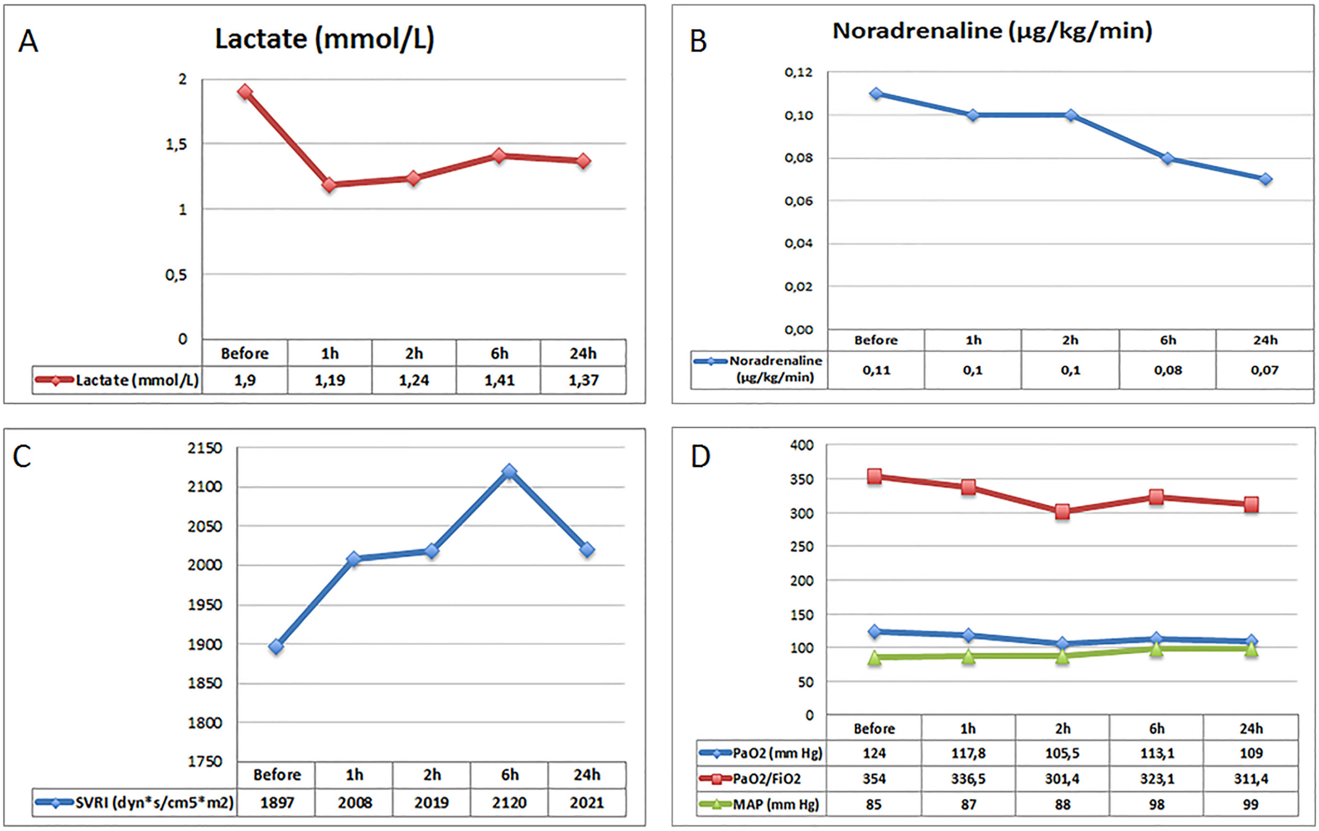
For vascular access, a double lumen 12Fr catheter was introduced into the right femoral vein. The adsorber was connected to an extracorporeal circuit including an HF 440 blood pump (Infomed, Geneva, Switzerland) (Figure 4). Haemofiltration was not performed, either before, during or after LPS adsorption. Unfractionated heparin was used to maintain APTT between 50 and 70 s, at a rate of 1000 U/h. The blood flow rate was set at 150 ml/min, and the duration of the treatment was 120 minutes.

PCT, haemodynamic parameters, vasopressor requirements and SOFA score were evaluated before treatment, and at specific intervals during the first twenty-four hours of treatment.

The adsorption treatment produced a significant improvement in the hemodynamic status with a 36% reduction in the noradrenaline infusion rate from pretreatment levels of 0.11 μg/kg/min, to 24 hours post treatment levels of 0.07 μg/kg/minutes, an increase in MAP from 85 mmHg before endotoxin elimination therapy to 99 mmHg at 24 h post treatment and CI pretreatment levels of 3,1 L/min/m^2 to 3,7 L/min/m^2, twenty-four hours after the end of the session. (Figure 1).

Endotoxin elimination did not have a significant bearing on the changes in the oxygenation parameters with PaO_2 reducing from 124 mmHg pretreatment to 109 mmHg and PaO_2/FiO_2 from 354 to 311.4.

There was a reduction in PCT levels from 10 ng/mL to 4 ng/mL after endotoxin removal (Figure 2). Likewise, a decrease was also observed in lactate levels from 1.9 mmol/L to 1.37 mmol/L at twenty-four hours post-treatment (Figure 1).



PaO2= arterial partial pressure of oxygen; PaO2/FiO2 = arterial partial pressure of oxygen/fraction of inspired oxygen ratio: SVRI = systemic vascular resistance index, MAP= mean arterial pressure

Fig. 1. Changes in the measured haemodynamic and biochemical data before and after treatment with the LPS Adsorber

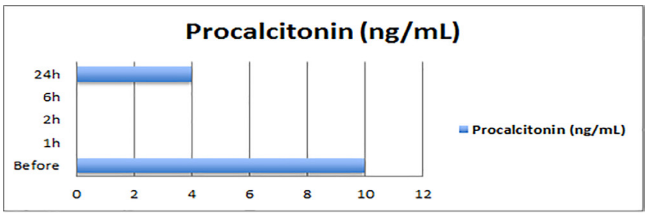


Fig. 2. Changes in the PCT values before and after treatment with the LPS Adsorber

The improvements in the cardiovascular system parameters were responsible for a significant decrease in the SOFA score from 10 points baseline to 7 points at twenty-four hours post adsorption therapy, with a median decrease of 3 points (Figure 3).

The clinical progress following treatment was favourable for the next few days, but one week after the endotoxin removal session, the patient developed a postoperative complication with a localised peritonitis due to an ischemic bowel perforation. The patient died two days later due to multiple organ failures.

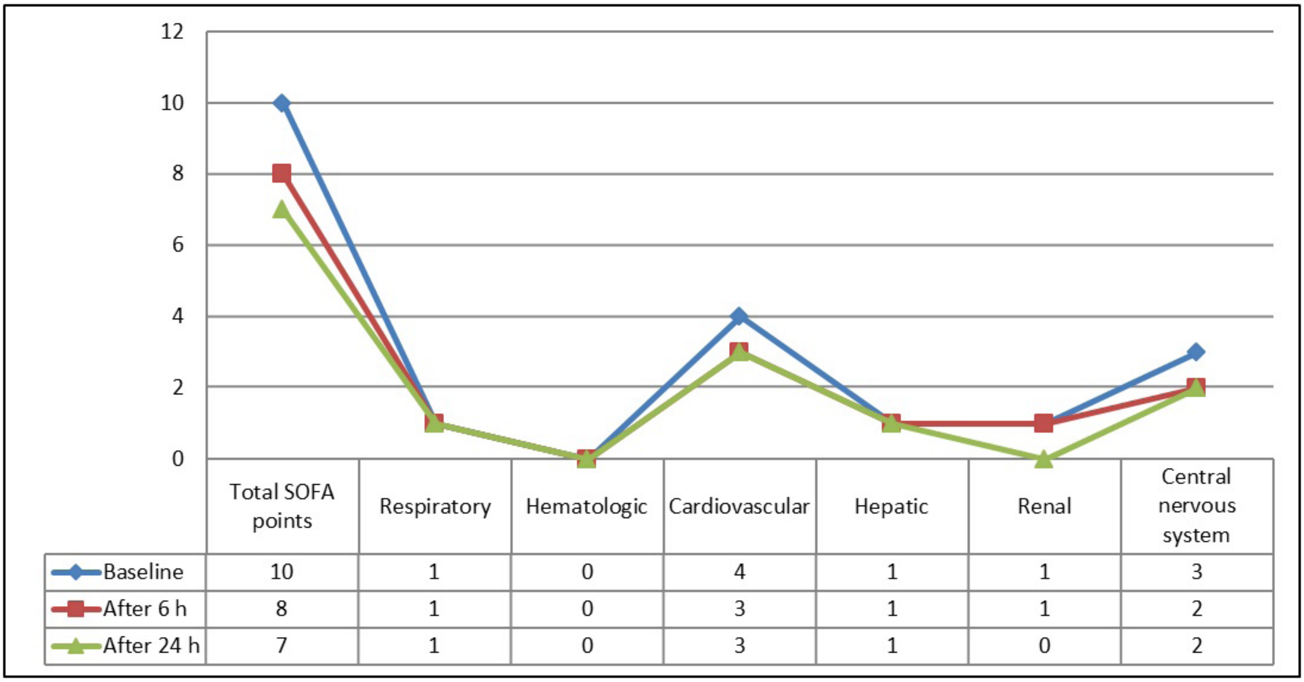
Discussion

Extracorporeal blood purification can be used as an adjunct in the treatment of the sepsis. It targets either inflammatory mediators or bacterial endotoxins or both [4].

Newer haemofiltration techniques have been proposed to moderate the inflammatory cascade as well as providing endotoxin adsorption, as a rationale for modifying the biological cascade in Gram-negative sepsis cases [9].

Direct hemoperfusion using a PMB-immobilized fibre column has been used for the treatment of septic shock for more than fifteen years and is approved as a therapeutic device in Japan [13-15].

The *Alteco®* LPS *Adsorber* (Alteco Medical, AB, Lund, Sweden) is a class IIa medical extracorporeal device consisting of a rigid porous matrix, which significantly increases its blood contact area. Tailor-made synthetic peptides with a high affinity for endotoxins are connected to the surface of the polyethylene plates with a covalent bonding technique [4]. However, the



	Total SOFA points	Respiratory	Hematologic	Cardiovascular	Hepatic	Renal	Central nervous system
Baseline	10	1	0	4	1	1	3
After 6 h	8	1	0	3	1	1	2
After 24 h	7	1	0	3	1	0	2

SOFA= sequential organ failure assessment score

Fig. 3. Organ dysfunction indicated by the SOFA score before and after endotoxin elimination therapy

Fig. 4. LPS Adsorber was connected to an extracorporeal circuit including an HF 440 blood pump. (Infomed, Geneva, Switzerland)

clinical experience for this device is scarce and is limited to case reports and case series [11,12].

The study by Ala-Kokko et al. (2011) showed that the duration of noradrenaline infusion was significantly lower twenty-four hours postoperatively in adsorber-treated patients, compared to controls. Yaroustovsky, et al. (2013) showed a decrease of 76% in the LPS level in patients with gram-negative nosocomial pneumonia, forty-eight hours after haemoperfusion [16]. The effective elimination of endotoxin was associated with a significant increase in the mean arterial pressure noted at 24 hours after endotoxin elimination, and the consecutive reduction in the noradrenaline dose [8].

In patients with septic complications after cardiac surgery, a significant correlation was noted between endotoxin activity (EA) and PCT levels [17]. Our results corroborate these studies.

It is uncertain if the noted haemodynamic improvement is for a limited period or how often the endotoxin removal session should be repeated or if endotoxin elimination has a significant impact on the ICU length of stay or ICU mortality. Further studies are necessary to solve these problems. Two studies reported the use of either an Alteco® LPS Adsorber or polymyxin B cartridge for a two-hour session [11, 10]. Adamik et al. (2015) reported using the procedure for a maximum of two times, the time being dependent on the patient's clinical response and EA level. Their results showed a significant improvement in organ function demonstrated by a decrease in the SOFA score.

As mentioned above, timing and intervals for the treatment as well as firm control over the source of infection may improve mortality.

Confirmation is still required to prove if endotoxin adsorbents in extracorporeal blood purification therapies is an effective method. There are conflicting results regarding best adsorber material, and further projects are needed to define newer endotoxin-binding substances [18]. Favourable results on overall mortality with haemadsorption techniques [19] encourage further research to clarify the clinical benefit of blood purification in septic patients.

Conclusion

This case report highlights the efficacy of a new adsorptive therapy for the clearance of endotoxins in septic shock of abdominal origin. Early application of an endotoxin adsorber showed a reduction of vasopressor requirements, elevation of blood pressure and a decrease in inflammatory markers. Endotoxin elimination did not have a significant effect on the ICU length of stay or ICU mortality.

Conflicts of interest

Nothing to declare.

Acknowledgements

The authors would like to thank Kapamed International for the donation of the LPS Adsorber column as well as Infomed Fluids for assistance in the hemoperfusion therapy.

Abbreviations: LPS lipopolysaccharide; EA endotoxin activity; PCT procalcitonin; APACHE Acute Physiology and Chronic Health Evaluation; MAP mean arterial pressure; PR pulse rate; ICU intensive care unit; PaO_2/FiO_2 arterial partial pressure of oxygen/fraction of inspired oxygen; PMX-F polymixin-B immobilized fiber column; CO cardiac output; CI cardiac index; SVR systemic vascular resistance; SVRI systemic vascular resistance index

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801-810.
2. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):762-774.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304-377.
4. Shum HP, Leung YW, Lam SM, Chan KC, Yan WW. Alteco endotoxin hem adsorption in gram-negative septic shock patients. Indian J Crit Care Med. 2014;18(12):783-788.
5. Esteban E, Ferrer R, Alsina L, Artigas A. Immunomodulation in sepsis: The role of endotoxin removal by polymyxin B-immobilized cartridge. Mediators Inflamm. 2013;2013:507539.
6. Buttenschoen K, Radermacher P, Bracht H. Endotoxin elimination in sepsis: Physiology and therapeutic application. Langenbeck's Archives of Surgery. 2010;395(6):597-605.
7. Arias-Verdu D, Herrera Gutierrez M, Seller-Perez G, Benitez-Moreno P, Aguiar-Flores E, Quesada-Garcia G. Comparison of two different adsorptive therapies for the treatment of endotoxemia. . 2012;38:S286-S286.
8. Adamik B, Zielinski S, Smiechowicz J, Kübler A. Endotoxin elimination in patients with septic shock: An observation study. Arch Immunol Ther Exp (Warsz). 2015;63(6):475-483.
9. Andersen TH, Jensen TH, Andersen LW. Adjunctive therapy of severe sepsis and septic shock in adults. Current Anaesthesia & Critical Care. 2009;20(5–6):254-258.
10. Cruz DN, Perazella MA, Bellomo R, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: A systematic review. Critical Care. 2007;11(2):1.
11. Ala-Kokko TI, Laurila J, Koskenkari J. A new endotoxin adsorber in septic shock: Observational case series. Blood Purif. 2011;32(4):303-309.
12. Kulabukhov V. Use of an endotoxin adsorber in the treatment of severe abdominal sepsis. Acta Anaesthesiol Scand. 2008;52(7):1024-1025.
13. Aoki H, Kodama M, Tani T, Hanasawa K. Treatment of sepsis by extracorporeal elimination of endotoxin using polymyxin B-inimobilized fiber. The American Journal of Surgery. 1994;167(4):412-417.
14. Garidel P, Brandenburg K. Current understanding of polymyxin B applications in bacteraemia/sepsis therapy prevention: Clinical, pharmaceutical, structural and mechanistic aspects. Anti-Infective Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Infective Agents). 2009;8(4):367-385.
15. Payen DM, Guilhot J, Launey Y, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: A multicenter randomized control trial. Intensive Care Med.

2015;41(6):975-984.

16. Yaroustovsky M, Plyushch M, Popov D, et al. Prognostic value of endotoxin activity assay in patients with severe sepsis after cardiac surgery. J Inflamm. 2013;10(1):1.
17. Yaroustovsky M, Abramyan M, Popok Z, et al. Preliminary report regarding the use of selective sorbents in complex cardiac surgery patients with extensive sepsis and prolonged intensive care stay. Blood Purif. 2009;28(3):227-233.
18. Harm S, Falkenhagen D, Hartmann J. Endotoxin adsorbents in extracorporeal blood purification: Do they fulfill expectations? Int J Artif Organs. 2014;37(3):222-232.
19. Zhou F, Peng Z, Murugan R, Kellum JA. Blood purification and mortality in sepsis: A meta-analysis of randomized trials. Crit Care Med. 2013;41(9):2209-2220.