

# A New Endotoxin Adsorber in Septic Shock: Observational Case Series

T.I. Ala-Kokko J. Laurila J. Koskenkari

Division of Intensive Care Medicine, Department of Anaesthesiology, Oulu University Hospital, University of Oulu, Oulu, Finland

## Key Words

Endotoxemia · Severe sepsis · Extracorporeal therapy

## Abstract

**Aims:** Effects of a new endotoxin adsorber on the length of noradrenaline (NA) treatment, LPS (lipopolysaccharide) levels and SOFA (sequential organ failure assessment) scores in septic shock were evaluated. **Methods:** Two-hour hemoperfusion with LPS adsorber was initiated in patients with septic shock and endotoxemia. Controls were matched for age, focus and severity of illness. **Results:** Adsorption treatment (n = 9) exhibited a significant decrease in EAA (endotoxin activity assay) activity (0.55 [0.44–0.68] vs. 0.25 [0.13–0.41], p = 0.019) and NA infusion rate (0.217  $\mu\text{g}/\text{kg}/\text{min}$  [0.119–0.0508] vs. 0  $\mu\text{g}/\text{kg}/\text{min}$  [0–0.09], p = 0.026) from pretreatment to 24 h post-treatment. The median decrease in SOFA scores from pretreatment to 24 h was 3.0 points (1.5–4.5), p = 0.002. Duration of NA infusion was significantly shorter compared to controls (39 h [31–48] vs. 54 h [43–151], p = 0.03). **Conclusions:** LPS adsorber treatment was associated with a decrease in NA dose, decrease in SOFA scores and LPS concentrations.

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## Introduction

Elevated blood level of bacterial lipopolysaccharide (endotoxin) is a prominent feature of clinical sepsis, but its association with the outcome is controversial [1, 2]. It is well known that endotoxins induce a strong host immune response [3]. Endotoxin neutralization studies have, however, been disappointing, although there may be patient groups who could benefit [4]. Extracorporeal adsorption with polymyxin B – immobilized fiber column hemoperfusion (PMX) – has been routinely used in Japan since 1994 and a meta-analysis has shown benefit in shock reversal, attenuating organ dysfunction and increasing survival [5]. To date, only one large-scale multicenter study has been performed with encouraging results using PMX adsorption, with reduced mortality in severe sepsis/septic shock from intra-abdominal Gram-negative infections [6]. Polymyxin B is an antibiotic well known for its ability to bind the lipid A part of the endotoxin molecule, thereby neutralizing its activity. It is, however, also nephro- and neurotoxic – and in the hemoperfusion system it is bound to a carrier in a cartridge to overcome its toxic properties [7].

A new alternative for extracorporeal endotoxin removal has been developed consisting of a cartridge filled with porous plates of polyethylene (Alteco® LPS Adsorb-

Presented in part at the 2009 ISICEM Annual Congress in Brussels.

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0253–5068/11/0324–0303\$38.00/0

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Prof. Tero Ala-Kokko, MD, PhD, EDICM  
Division of Intensive Care Medicine, Department of Anaesthesiology  
PO Box 21  
FI-90029 OUH, Oulu (Finland)  
Tel. +358 8315 2738, E-Mail tak@cc.oulu.fi

er; Alteco Medical AB, Lund, Sweden). A tailor-made non-toxic, nondrug peptide with high affinity for endotoxin is bound to the surface of the porous plates. During hemoperfusion with this absorber, the cationic part of the peptides captures the negatively charged endotoxin molecules.

We report a case series on the use of this new device in vasopressor-dependent septic shock with endotoxemia. The length of noradrenaline (NA) infusion, endotoxin blood levels and the change in SOFA scores at 24 h post-treatment were evaluated. It was hypothesized that the adsorption treatment would be associated with a decrease in NA requirements and SOFA scores.

## Materials and Methods

The study protocol was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District (reference No. EETTMK: 11/2008). Written informed consent was obtained from each patient or next of kin. The setting was a 12-bed tertiary referral medical-surgical intensive care unit (ICU) at the Oulu University Hospital, Finland. All patients were treated according to the normal ICU protocol and current severe sepsis guidelines, including hydrocortisone supplementation in septic shock refractory to vasopressor therapy [8].

### Study Population

The study population consisted of patients with NA-dependent septic shock presumed to have endotoxemia and in whom the adsorption treatment could be started within 36 h from the beginning of shock. The study treatment was available only on weekdays during office hours. Standard definitions were used to define the criteria for SIRS (systemic inflammatory response syndrome) and septic shock [9]. At a minimum, temperature criteria and leukocyte criteria from the SIRS criteria had to be present. Endotoxemia was determined as endotoxin activity of more than 0.3 EAA units/ml (endotoxin activity assay). In accordance with Marshall et al. [3], endotoxin activity was categorized as low (0–0.39 EAA units/ml), intermediate (0.4–0.59) and high (>0.6 EAA units/ml). Exclusion criteria included age below 18 and above 85, any bleeding disorder, malignancy, unlikely survival beyond 28 days, protamine allergy and need for renal replacement therapy due to AKI (acute kidney injury). If a time window of 36 h from the beginning of the vasopressor treatment was exceeded before the hemoperfusion treatment, the patient was no longer eligible for the treatment.

NA was used to treat hypotension unresponsive to fluid therapy. The mean arterial pressure was targeted to value of 65 mm Hg or above. Adequate fluid resuscitation before the initiation of NA was defined as a CVP of at least 8 mm Hg (in mechanically ventilated patients, at least 12 mm Hg).

Control patients from a time period of January 2006–May 2010 with septic shock matched for age ( $\pm$  10 years), focus of infection and need for surgical source control were selected from our patient data management system retrospectively (Centricity Critical Care Clinisoft®; GE Healthcare, Helsinki, Finland).

### Study Procedure

After receiving consent, a 2-hour venovenous LPS (lipopolysaccharide) hemoperfusion with an Alteco LPS Adsorber was begun using a Gambro model AK10 hemodialysis machine (Gambro Lundia AB, Helsinki, Finland). All hemoperfusions were performed by the same experienced study nurse under the supervision of the investigators. Vascular access was obtained with use of double-lumen venous catheters. The cartridge was prepared according to the manufacturer's guidelines by rinsing the device with at least 500 ml of physiological saline solution (0.9%). The circuit blood flow was 150 ml/h. All cartridges were provided by Alteco Medical free of charge.

Heparin was used as an anticoagulant and the activated clotting time (ACT) was measured (0, 30, 60, 90 and 120 min). Systemic anticoagulation was achieved with heparin infusion (100 KY/ml) prefilter to gain a postfilter ACT value >200 s. The effects of heparin were antagonized by protamine infusion (1 mg/ml) in the patient to gain a patient ACT level <180 s. The infusion rates for heparin and protamine were adjusted according to the ACT values.

Endotoxin activity was measured using a commercial kit for whole blood neutrophil-dependent chemiluminescence (EAA Endotoxin Activity Assay; Spectral Diagnostics, Inc., Toronto, Ont., Canada). Arterial blood samples for EAA assay were drawn before the treatment (pretreatment), after the 2-hour hemoperfusion (LPS post-treatment) and 24 h after the first treatment (LPS24). Samples were maintained at room temperature and assayed within 15 min of collection in the ICU laboratory by a study nurse.

### Data Collection

The following information was collected from the study patients: age, sex, reason for ICU admission, focus of infection, surgical source control, severity of illness on admission as assessed by SAPSII (simplified acute physiology score) scoring [10], evolution of daily organ dysfunctions assessed by daily sequential organ failure assessment (SOFA) scores [11], length of NA infusion and maximum dose of NA required. Shock free days are calculated as the number of days a patient is alive and without NA infusion within 7 days [12]. The delta SOFA score was used to indicate the change in degree of organ dysfunction after treatment and calculated as the SOFA score at baseline minus the SOFA score at 24 h post-treatment [6]. Platelets and PCT (procalcitonin) were followed pre- and post-treatment. ICU and hospital length of stay were recorded and patients were followed until 28 days. The cardiac index was measured with a standard thermodilution technique using a pulmonary artery catheter.

### Statistical Analysis

The data were analyzed with SPSS (version 15.0; SPSS, Inc., Chicago, Ill., USA). Summary statistics are expressed as medians with 25th to 75th percentiles. Differences within the study group between pretreatment and 24 h post-treatment values were analyzed by paired samples t test. Analyses between study patients and historical controls were done with the Mann-Whitney U test. The correlations were tested with Kendall's tau correlation coefficient. Two-tailed p values are reported, and differences were considered significant at  $p < 0.05$ .

**Table 1.** Demographics and clinical outcome of the LPS adsorber-treated patients and historical controls

	Patients (n = 9)	Controls (n = 15)	p
Age, years	60 (56–80)	66 (59–79)	0.770
Male sex, %	56 (5/9)	47 (7/15)	0.673
SAPSII	41 (33–43)	46 (42–52)	0.123
SOFA on admission	9 (8–10)	8 (6–9)	0.078
Intra-abdominal focus, n (%)	7 (78)	12 (80)	
Bowel perforation	6	7	
Strangulation or volvulus	0	4	
Acute cholecystitis	1	1	
Nonoperative focus, n (%)	2	3	
Necrotising skin infection	1	2	
Pneumonia	1	1	
NA starting infusion rate, µg/min/kg	0.111 (0.069–0.217)	0.120 (0.078–0.180)	0.599
Maximum NA infusion rate, µg/min/kg	0.561 (0.146–0.930)	0.349 (0.227–0.783)	0.482
Duration of mechanical ventilation, h	35 (16–76)	110 (59–179)	0.123
Total duration of NA infusion, h	39 (31–48)	54 (43–151)	0.030
Shock free days within 7 days, days	4 (4–5)	3 (0–5)	0.293
ICU LOS, days	6 (5–8)	7 (5–9)	0.519
Hospital LOS, days	26 (10–35)	24 (16–30)	0.815
Survival at day 28, % (n/n)	89 (8/9)	87 (13/15)	0.873

Median and 25th–75th percentiles.

## Results

During the study period, April 2008–May 2010, 70 patients with septic shock were admitted to the ICU during weekdays and 26 of these patients were eligible and screened. A total of 9 patients fulfilled all the inclusion criteria and were treated with the LPS adsorber. Nineteen patients had to be excluded; the time limit for the treatment (n = 7), treatment restrictions (n = 1), malignancy (n = 3), need for RRT (n = 2), no consent (n = 3), and old age (n = 3).

The adsorption-treated patients included one with low EAA activity, 5 with intermediate activity and three with high EAA levels. The pretreatment endotoxin activity did not correlate with the NA dose, the maximum dose needed or the time of infusion. Clinical characteristics of the treated patients and the controls are presented in table 1. There were no significant differences in the demographics. The adsorption-treated patients had slightly higher SOFA scores on admission. Bowel perforation was the most common surgical diagnosis and all these cases were surgically treated. There was no difference in the NA starting infusion rate.

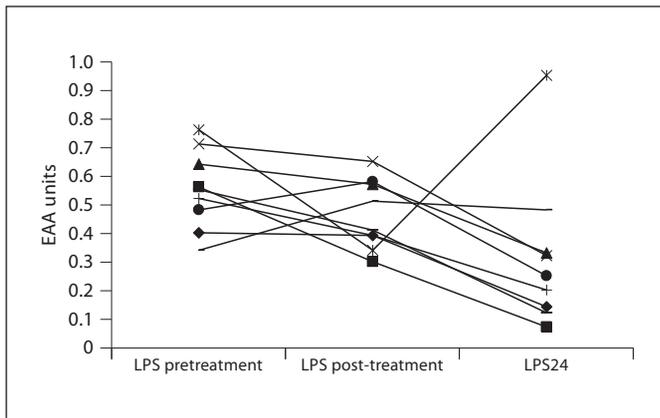
The median time to adsorption treatment was 18.5 h (13.8–22.0 h) after the onset of septic shock. Kendall's tau

correlation coefficient for the duration of NA treatment with the treatment delay was 0.722 (p = 0.007). All adsorption treatments began after adequate immediate source control. In the case of the surgically treated patients with intra-abdominal sepsis (n = 7), the median time to adsorption treatment after a laparotomy was 17.4 h (13.2–18.1)

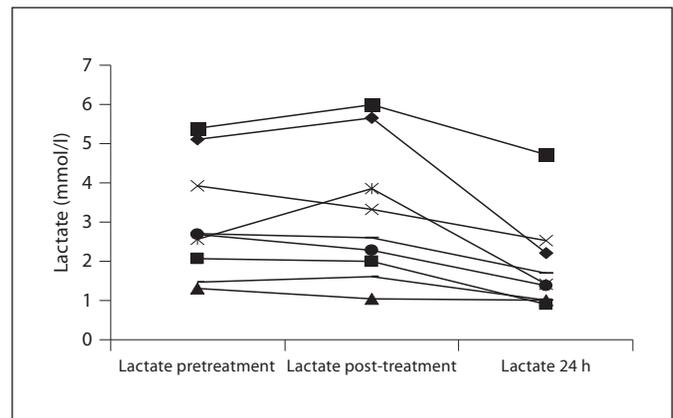
The adsorption-treated patients exhibited a significant decrease in EAA activity following treatment from pretreatment to 24 h (p = 0.019) (fig. 1). The NA infusion rate decreased significantly during the 24-hour period following the adsorption treatment (p = 0.026) (fig. 2).

The median decrease in SOFA scores from pretreatment to 24 h post-treatment was 3.0 points (1.5–4.5), p = 0.002. The decrease was due to circulatory component in all but one patient and accompanied with respiratory component in 4 and with renal component in one patient. Serum lactate levels decreased significantly from pretreatment to 24 h post-treatment (p = 0.002) (fig. 3). There was no change in procalcitonin levels from pretreatment to 24 h post-treatment (13.2 [3.5–34.9] vs. 11.1 [2.4–26.1], respectively), p = 0.148.

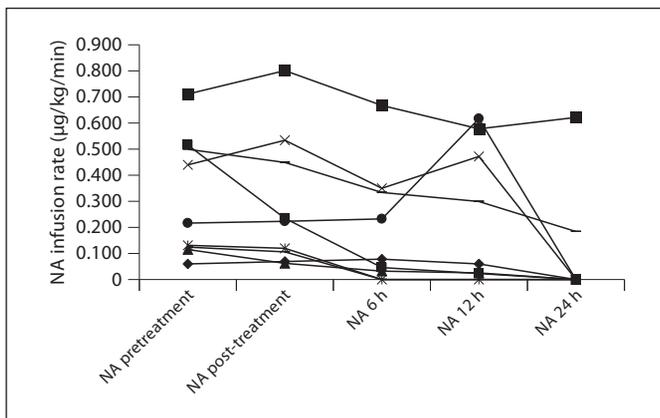
There was no statistically significant change in cardiac index from pretreatment to 24 h post-treatment; 3.3 l/min/m<sup>2</sup> (2.8–4.2) vs. 3.7 l/min/m<sup>2</sup> (3.0–4.5), respectively.



**Fig. 1.** Individual levels of endotoxin activity in LPS adsorber-treated patients (n = 9). p = 0.019 pretreatment vs. 24 h post-treatment (LPS24).



**Fig. 3.** Individual serum lactate levels in LPS adsorber-treated study patients (n = 9). p = 0.002 pretreatment vs. 24 h post-treatment (Lact24).



**Fig. 2.** Infusion rate of NA in LPS adsorber-treated patients (n = 9). Individual curves presented. p = 0.026 pretreatment vs. 24 h post-treatment (NA24).

There was no statistically significant change in mean blood pressure (MAP) from pretreatment to post-treatment at 2 h (75 mm Hg [66–81] vs. 76 mm Hg [73–84]) nor to 24 h post-treatment (75 mm Hg [73–83]). There was no statistically significant change in P/F ratio from pretreatment to 24 h post-treatment; 25.0 kPa (24.5–36.0) vs. 22.0 kPa (20.0–24.5), respectively.

The platelet values decreased significantly from pre- to post-treatment;  $137 \times 10^9/l$  (67–217) vs.  $100 \times 10^9/l$  (IQR 52–127), respectively, p = 0.028. Two surgical patients required platelet transfusions without bleeding complications. One patient needed two cartridges to

complete the 2-hour treatment due to clotting. One patient experienced a rapid atrial fibrillation 30 min after the start of the adsorption treatment and was cardioverted with 50 J to sinus rhythm without any further events. One adsorption-treated patient with cecal volvulus on admission died in the ICU due to mesenteric thrombosis and intestinal ischemia with multiorgan failure on the 10th ICU day.

The duration of NA infusion was significantly shorter in adsorber-treated patients compared to the controls, p = 0.03 (table 1). The median length of ventilator treatment was three times longer in the control patients compared to adsorption-treated patients, although this was not statistically significant. The median number of shock-free free days within 7 days was slightly higher in the adsorption-treated patients; 4 (4–5) versus 3 (0–5), respectively, p = 0.293.

The study patients presented two positive blood cultures, one for *Klebsiella* and one for *Pneumococcus*. All patients had already received antimicrobial treatment on admission to the ICU.

## Discussion

In this small observational case series with retrospective control patient data, a single 2-hour hemoperfusion procedure with the Alteco LPS Adsorber was associated with initial rapid decline in NA requirements, a decrease in EAA activity and SOFA scores, as well as a decline in platelet levels. The need for NA administration was short-

er than that of the controls and there was a moderate correlation between treatment delay and the duration of NA infusion. However, there was only statistically non significant trend to a lower number of shock-free days in the adsorption-treated patients.

Previously, polymyxin B has been used to remove endotoxin via extracorporeal therapy. The toxicity of this antimicrobial drug may be prevented by binding it to a matrix. Binding peptides to the endotoxin and immobilization in a matrix may also be used for endotoxin reduction. An earlier study has shown that the binding capacity of peptides capable of binding endotoxin differs between peptides [13]. A new Alteco LPS Adsorber contains a tailor-made peptide with a high affinity for LPS bound to the surface of the porous plates of polyethylene. During the treatment, the cationic part of the peptides captures the negatively charged endotoxin molecules with high affinity and capacity. Comparisons of the affinities and capacities of PMX and Alteco peptide do not exist. However, the Alteco product is a class IIa medical device according to the European Medical Device Directive as a nondrug and nontoxic device.

Our series showed a rapid decline in NA requirement in the adsorption-treated patients. There were, however, no significant changes in cardiac function, although 66% of the patients (6/9) increased their CI from pretreatment to 24 h post-treatment. In a pilot study using PMX hemoperfusion, cardiac function improved significantly. In contrast to our findings, in that study there was no change in the levels of endotoxin [14]. Furthermore, Vincent et al. [14] reported no significant difference in shock free days or differences between the doses of vasoactive drugs between PMX-treated study patients and controls. In contrast to our patients, in their study only 61% of the controls and 88% of the study patients received NA treatment. In our series, all treated patients and controls had NA-dependent septic shock. There was a statistically nonsignificant 1 day increase in the median number of shock-free days in the adsorption-treated patients compared to controls but the small number of patients prevents any definite conclusions on efficacy. Furthermore, there was a moderate correlation between adsorption delay and the duration of NA infusion. It could be speculated that earlier treatment could have increased the number of shock-free days.

A multicenter study on PMX hemoperfusion did, however, show a significant reduction in vasoactive drug requirements and a significant mortality benefit as compared to conventional treatment [6]. The authors did not report the duration of vasoactive treatment, but

at baseline the NA requirement was lower compared to our patients (0.27 vs. 0.31  $\mu\text{g}/\text{kg}/\text{min}$ ). Furthermore, endotoxin levels were not measured in the study by Cruz et al. [6]. The change in SOFA score was similar to ours, but gained at 72 h post-treatment in contrast to 24 h in our study.

Clinical experience with the Alteco LPS Adsorber is scarce. There is one previous case report with 1 patient [15] and a preliminary report with 6 cardiac surgical patients with nosocomial pneumonia [16]. Its safety was evaluated in a small study during heart surgery using extracorporeal circulation [17]. This latter study included only 2 patients with endotoxemia, but LPS adsorption did not have any adverse effects on coagulation or platelet levels. In our series, we saw a significant decrease in platelet levels. However, only 2 patients required platelet transfusions. None experienced bleeding complications. Furthermore, 1 patient required two cartridges due to clotting to complete the treatment. This patient with bowel perforation had a rebound increase in EAA levels but was without NA infusion at 24 h. No abdominal complications were noted. Instead, her course was complicated by postoperative pneumonia without further shock on the second day after the adsorption treatment. This could explain the rebound increase in the endotoxin level since this has been shown to be a marker of ongoing tissue injury [2]. Finally, she made a full recovery.

The significance of endotoxin levels is controversial. In an earlier study, in 51% of patients with suspected sepsis neither endotoxin nor bacteremia was detected [16]. In yet another study, a trend was seen towards an association between positive endotoxin and Gram-negative bacteremia or infection [1]. In that study, however, endotoxemia did not correlate to organ dysfunctions or mortality in patients with severe sepsis or septic shock. Interestingly, our small series included 3 patients with endotoxemia (EAA  $>0.3$ ) without NA at 24 h post-treatment. These patients only received one 2-hour treatment session with endotoxin adsorber since they were without vasopressor at 24 h. Furthermore, the baseline EAA did not correlate with the maximum NA dose or the duration of NA infusion. Higher levels of endotoxin are, however, detected in sepsis than in other conditions and show significant association with gram negative infection [19]. In a study by Guidet et al. [20], endotoxin present in the plasma of patients with severe sepsis remained detectable for a long period of time, suggesting continuous release or a defect in clearance.

One could argue after these controversial findings that endotoxin levels can not be used as a selection criterion for endotoxin removal trials. However, it is clear that endotoxin removal device to be effective there must be circulating endotoxin present. The association of endotoxin levels with Gram-negative infections, the diagnosis of sepsis and leukocytosis are affected by the method used to analyze the endotoxin (i.e. LAL assay vs. EAA activity). Generally speaking, endotoxin is present in many critically ill patients without the criteria of sepsis [3]. To date, studies neutralizing the effects of endotoxin activity have not shown any benefit, the latest being the phospholipid study [21] and the inhibitor of Toll-like receptor-4-mediated signaling study [22]. It may well be that total neutralization of endotoxin is deleterious. Adsorption therapy is an attractive alternative since it does not totally block the effects of endotoxin. However, the issue with any endotoxin removal device is that it is only a temporizing measure. It partially removes endotoxin, and may interrupt the septic cascade on the day of treatment, but does nothing to address the source of the endotoxin.

This study is limited by the small number of patients and the lack of randomized controls. Furthermore, endotoxin levels were not known in the control patients. It was evident from the beginning, considering our patient flow, that a single-center randomized study would not be feasible. At best, these results can be used for planning future studies performed in patients with detectable endo-

toxin activity. A randomized controlled study with EAA measurements to show effectiveness measured as mortality benefit in patients with septic shock is needed. In addition, further studies should determine the timing and frequency of the treatment, which patients with endotoxemia would benefit from adsorption treatments, and which levels need to be treated as well as the cost effectiveness.

## Conclusions

A new endotoxin hemoperfusion technique based on a high-affinity cartridge was associated with a decrease in endotoxin activity and a decline in NA requirements and SOFA scores. In addition, the total duration of NA infusion was significantly shorter compared to nonrandomized retrospective controls.

## Acknowledgement and Funding

The skilful performance of the hemoperfusions and the measurements of EAA activity by our study nurse Mr. Teijo Rasi, RN are greatly appreciated. Alteco Medical provided funding to the Oulu University Hospital to cover study expenses including the cartridges, the EAA analyzer and the kits for the assays. Alteco Medical had no role in study design, in the collection, analysis, and interpretation of data or in the writing of the manuscript and in the decision to submit the manuscript for publication.

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