Alteco endotoxin hemoadsorption in Gram-negative septic shock patients

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Abstract

Background and Aims: Severe sepsis and septic shock are common causes of mortality and morbidity in an intensive care unit setting. Endotoxin, derived from the outer membranes of Gram-negative bacteria, is considered a major factor in the pathogenesis of sepsis. This study investigated the effect of Alteco endotoxin hemoadsorption device on Gram-negative septic shock patients. **Materials and Methods:** An open, controlled, prospective, randomized, single-center trial was conducted between February 2010 and June 2012. Patients with septic shock due to intra-abdominal sepsis were randomized to either conventional therapy ($n = 8$) or conventional therapy plus two 2-hourly sessions of Alteco endotoxin hemoadsorption ($n = 7$). Primary endpoint was the Sequential Organ Failure Assessment (SOFA) score changes from 0 to 72 h. Secondary end points included vasopressor requirement, PaO_2/FiO_2 ratio (PFR), length of stay (LOS), and 28-day mortality. **Results:** This study was terminated early as interim analysis showed a low probability of significant findings. No significant difference was noted between the two groups with respect to change in SOFA score, vasopressor score, PFR, LOS, and 28-day mortality. Side-effect was minimal. **Conclusions:** We could not identify any clinical benefit on the addition of Alteco endotoxin hemoadsorption to conventional therapy in patients who suffered from intra-abdominal sepsis with shock. The side effect profile of this novel device was acceptable.

Keywords: Endotoxins, hemoadsorption, septic shock, outcome

Introduction

Severe sepsis and septic shock are common causes of mortality and morbidity in an intensive care unit (ICU) setting. The endotoxin (lipopolysaccharide [LPS]) derived from the outer membranes of Gram-negative bacteria is considered a major factor in the pathogenesis of sepsis.[1,2] The toll-like receptor (TLR) family can be found in mammalian cells. Endotoxins transduce their signal through the TLR4 transmembrane receptor, and innate immune cascades are initiated,[3] which promote excessive cytokine release and tissue damage. The endotoxin level is associated with clinical outcome and higher activity correlates with greater ICU mortality.[4] Therapeutic strategies aimed at minimizing or preventing the action of endotoxins are, therefore, attractive. However, the blockage of an endotoxin via binding with monoclonal antibodies has failed to improve outcome in clinical studies.[5,6] Extracorporeal removal is another measure that can reduce endotoxin level. Sorbents can effectively bind endotoxins via electrostatic and hydrophobic interactions. The reduction of endotoxin levels or blockage of endotoxins can potentially interrupt the biological cascade of sepsis. Polymyxin B (PMX) is an antibiotic agent that has strong Gram-negative bactericidal activity and carries very high affinity for endotoxins. Intravenous (IV) administration of PMX has significant nephrotoxicity and neurotoxicity, which has limited its clinical use. PMX can be immobilized covalently on polystyrene-based carrier fibers which preserve its endotoxin binding capacity without producing toxicity.[7] A PMX immobilized fiber column was shown to improve blood pressure, oxygenation and mortality in patients with severe sepsis.[8,9] The Alteco endotoxin

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hemoadsorber (Alteco Medical AB, Lund, Sweden) is a similar device with strong endotoxin-binding capacity. During the treatment, the endotoxin-binding peptides capture endotoxins from the patient's bloodstream. The device is aimed at venovenous hemoperfusion.

We performed this randomized controlled trial (RCT) in patients who suffered from septic shock due to intra-abdominal sepsis. We hypothesized that Alteco endotoxin hemoadsorption may provide extraclinical benefit in terms of faster organ function improvement and hemodynamic stabilization when compared with conventional treatment.

Materials and Methods

Patients

This prospective RCT was approved by the institution's Ethics Committee and registered with Australian New Zealand Clinical Trials Registry (ANZCTR, ACTRN12610000892011). The study was conducted in the adult ICU of Pamela Youde Nethersole Eastern Hospital, which is a 2300-bed acute care tertiary hospital that provides comprehensive care, except for cardiothoracic surgery, transplant surgery, and burns. The ICU is a 22-bed closed mixed medical-surgical unit with an average admission of 1400 patients/year. We enrolled patients who fulfilled the following inclusion criteria: (1) Age ≥18 and ≤85 years old; (2) presence of severe sepsis due to intra-abdominal infection where severe sepsis was defined using the American College of Chest Physicians/Society of Critical Care Medicine/European Society of Intensive Care Medicine criteria;[10] (3) presence of shock with mean arterial pressure (MAP) ≤65 mmHg; (4) requirement of vasopressor support (noradrenaline 0.2 µg/kg/min or equivalent); and (5) on hydrocortisone 200-300 mg IV/day or equivalent to cover potential relative adrenal insufficiency. Exclusion criteria of the study were: Pregnancy, terminally ill patients with life expectancy ≤3 months, hypersensitivity to heparin or low molecular heparin or any component of the formulation, known history of heparin-induced thrombocytopenia; severe thrombocytopenia (<50,000/mm^3), uncontrolled active bleeding except when due to disseminated intravascular coagulation, and inclusion in other ICU studies. Informed consent was obtained from patients directly. For those with impaired consciousness due to underlying illness or the use of sedatives, consent was obtained from their close relatives/surrogate.

Randomization and interventions

Block randomization was performed using a computer generated scheme, and the allocation sequence was concealed in sealed envelopes which were available 24 h a day in the ICU. The control group (CG) received conventional therapy for septic shock, namely: Infective sources control, early appropriate antibiotics, fluid challenge and vasopressor infusion, and lung protected ventilatory strategy based on Surviving Sepsis Campaign guidelines.[11] Continuous renal replacement therapy (CRRT) in the form of citrate-based postdilution continuous venovenous hemofiltration using polysulfone high flux hemofilter (F × 80, Fresenius Medical Care, Germany) was provided in the presence of acute kidney injury categorized as "injury" or more based on Risk, Injury, Failure, Loss, and End-stage (RIFLE) criteria.[12] Treatment group (TG) (endotoxin hemoadsorption group) received endotoxin hemoadsorption in addition to conventional therapy. A double lumen 12-F hemodialysis catheter (ARROWguard blue plus antimicrobial catheter, Arrow International Inc., USA) was inserted into either the internal jugular or femoral vein for vascular access by the attending intensivists/physicians immediately after randomization. Endotoxin hemoadsorption was performed with Alteco endotoxin hemoadsorber using AK10 machine (Gambro-Hospal, Stockholm, Sweden) at a blood flow rate of 120-150 ml/h. Each patient received two 2-hourly sessions of hemoadsorption 24 h apart. The treatment duration was based on manufacturer's recommendation and previous case series.[13] Low molecular weight heparin (LMWH) was used for anticoagulation at the discretion of the treating physician, with tinzaparin 1000 IU IV as the default dosage. CRRT was started in-between two sessions of hemoadsorption and afterwards based on the same starting criteria for CG if necessary.

Follow-up and data collection

Demographic data were collected on ICU admission. Disease severity and prognosis were assessed with Acute Physiology and Chronic Health Evaluation (APACHE) IV score.[14] Clinical parameters and laboratory data were recorded at 0, 24, 48, and 72 h of randomization. Organ dysfunction was assessed using Sequential Organ Failure Assessment (SOFA) score.[15] Dosage of vasopressor was expressed as vasopressor score (VS) using the formula: (Dopamine dose × 1) + (dobutamine dose × 1) + (adrenaline dose × 100) + (noradrenaline dose × 100) + (phenylephrine dose × 100), wherein all doses are expressed as µg/kg/min.[16] Dose-response relationship between vasopressor and blood pressure was expressed as vasopressor dependency index (VDI) and was calculated using the formula: VS/MAP.[9] Primary end point was the change of the SOFA score from 0 to 72 h of randomization.

Secondary end points included changes of VS, VDI, PaO_2/FiO_2 ratio, ICU length of stay (LOS), hospital LOS, and 28-day mortality.

Statistical analysis

Sample size was estimated based on previous study findings.[9] With the power of 80%, type I error probability of 0.05, mean SOFA score difference of 2, standard deviation of 1.5, the estimated sample size was 20. Univariate analysis was performed using Fisher's exact test for categorical data or Mann–Whitney U-test for continuous data where appropriate. The analysis was performed by the Statistical Package for Social Sciences for Windows, version 16.0 (SPSS, Chicago, IL, United States).

Results

This study was terminated early by the monitoring committee as an interim analysis could not identify any significant clinical benefit. From February 2010 to June 2012, 15 patients were recruited (seven in the LPS hemoadsorption group and eight in the CG). Figure 1 shows the randomization process. Table 1 shows the baseline characteristics of all recruited patients. There were no significant differences between the two groups. Disease severity as assessed by APACHE IV score and SOFA score were similar. All patients except one from CG yielded Gram-negative bacteria from saved microbiological culture specimens. Among them, *Klebsiella* species were the most commonly isolated organisms (total 40%, TG vs. CG = 29% vs. 50%), followed by *Escherichia coli* (total 33%,

TG vs. CG = 29% vs. 38%). Multiple bacteria were isolated from 27% of cases (TG vs. CG = 29% vs. 25%). Surgical interventions or an interventional radiological drainage were performed for all patients. Adequate, appropriate initial antibiotic coverage (based on subsequent microbial sensitivity pattern) were given to 93% of patients within 24 h of recruitment (TG vs. CG = 86% vs. 100%). SOFA score showed more obvious improvement among CG group at 48 h and 72 h, but this was not statistically significant [Table 2]. Both groups showed decreased use of vasopressor over time, but the improvement did not differ between groups. Improvement of oxygenation was more obvious among the TG group but did not reach statistical significance. Urine output changes did not show any significant difference between groups. Continuous veno-venous hemofiltration was given in all

Table 1: Baseline characteristics at the time of randomization

	Treatment group (n=7)	Control group (n=8)	P
Age (years)	75 (60, 80)	73.5 (58.8, 76.8)	0.642
Body weight (kg)	68 (68, 72)	66.5 (57.5, 71.0)	0.194
APACHE IV score	135 (88, 156)	112.5 (91.5, 131.5)	0.418
APACHE IV risk of death	0.65 (0.26, 0.9)	0.49 (0.29, 0.77)	0.415
Initial total SOFA score	13 (10, 15)	14.5 (14, 17.3)	0.143
Initial MAP (mmHg)	68 (64, 84)	71.5 (67.3, 75.8)	0.907
Initial VS	50.5 (36.0, 99.6)	46.6 (37.7, 62.0)	0.487
Initial VDI	0.96 (0.48, 1.46)	0.67 (0.54, 0.83)	0.817
pH	7.38 (7.28, 7.40)	7.36 (7.22, 7.40)	0.685
Base excess	−5.1 (−4.4, −7.3)	−4.6 (−2.7, −10.8)	0.602
Creatinine (μmol/L)	193 (141, 297)	228 (173, 279)	0.487

All data displayed as median (IQR) unless otherwise specified. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IQR: Interquartile range; VDI: Vasopressor dependency index; VS: Vasopressor score; MAP: Mean arterial pressure
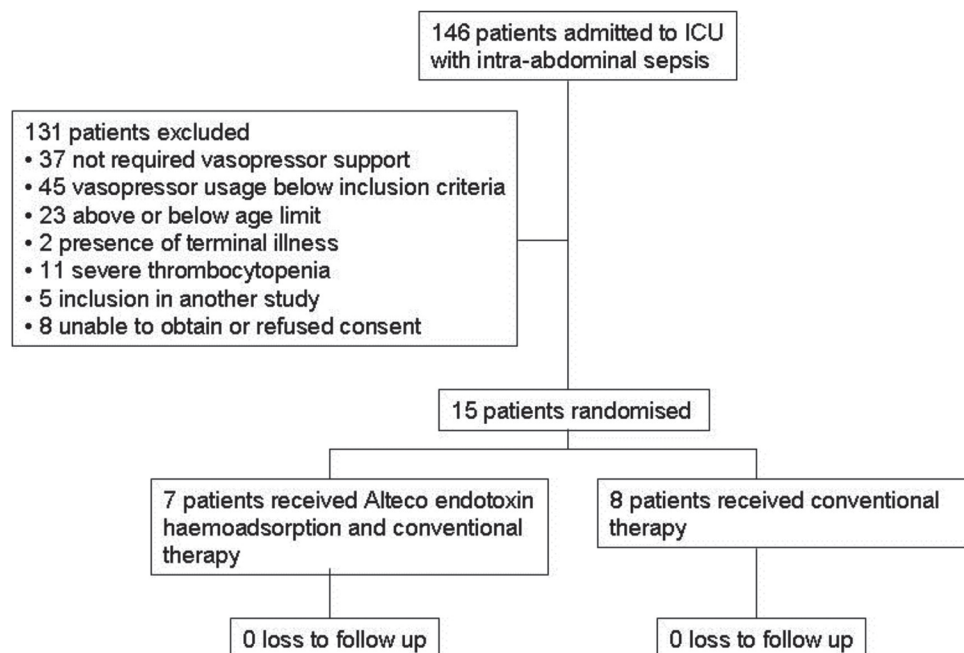

Figure 1: Randomization and follow-up of study patients

Table 2: Outcome parameters

	Treatment group (n=7)	Control group (n=8)	P
SOFA score changes (0-48 h)*	1 (−3, 2)	−2 (−6.7, 7)	0.559
SOFA score changes (0-72 h)*	1 (−3, 3)	−5.5 (−9.8, 7.5)	0.382
VS changes (0-48 h)*	−27.8 (−88.7, −13.3)	−37.6 (−48.4, −16.1)	0.886
VS changes (0-72 h)*	−29.0 (−93.1, −5.7)	−46.6 (−61.3, −25.7)	0.775
VDI changes (0-48 h)*	−0.49 (−1.32, −0.17)	−0.54 (−0.68, −0.27)	0.775
VDI changes (0-72 h)*	−0.49 (−1.36, −0.11)	−0.65 (−0.79, −0.35)	0.568
PFR changes (0-48 h)#	39.3 (−41.4, 66.1)	125.5 (−1.1, 225.4)	0.568
PFR changes (0-72 h)#	−26.3 (−56.5, 100)	162.6 (−54.7, 258.2)	0.199
Percentage urine output change (day 1 to day 3)	−32.4 (−90.9, 350)	−6.8 (−94.3, 57.5)	0.643
Total urine output 0-72 h	385 (91, 2490)	4570 (106, 7137)	0.355
ICU LOS (days)	12.5 (7.1, 15.7)	5.3 (2.9, 13.2)	0.203
Hospital LOS (days)	54.8 (33.1, 66.4)	17.8 (5.3, 60.5)	0.203
ICU mortality (n, %)	1 (14.3)	2 (25)	1.0
28-day mortality (n, %)	1 (14.3)	3 (37.5)	0.569

All data displayed as median (IQR) unless otherwise specified. *For SOFA score, VS and VDI, negative means improvement; #For P/F ratio, positive means improvement.
SOFA: Sequential Organ Failure Assessment; PFR: PaO_2/FiO_2 ratio; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; VDI: Vasopressor dependency index; VS: Vasopressor score

TG patients and 63% of CG patients. ICU and hospital LOS, ICU, and 28-day mortality were similar. For those ICU survivors (six from treatment and control arm respectively), no patient required dialysis support within 1 and 3 months after recruitment. Concerning the adverse events during Alteco endotoxin hemoadsorption, severe thrombocytopenia (platelet count $<20 \times 10^3/mm^3$) occurred in one patient but no bleeding event was reported. Platelet transfusion was not given for that index case. Transient hypotension (MAP ≤60 mmHg) occurred in one patient during the initiation of the first endotoxin hemoadsorption, who required increased vasopressor support. Cartridge clotting did not occur in any treatment sessions (total 14 sessions).

Discussion

To our best knowledge, the current study is the first RCT to investigate the therapeutic effect of this new endotoxin hemoadsorption device (Alteco endotoxin hemoadsorber, Alteco Medical AB, Lund, Sweden) in Gram-negative septic shock patients. It also represented the first application of endotoxin hemoadsorption technique in Hong Kong. Unfortunately, the study was terminated early by the monitoring committee as an interim analysis showed a low probability of significant findings.

Extracorporeal blood purification as a treatment for sepsis consists of multiple treatment modalities; these either targeted inflammatory mediators or bacterial toxins like endotoxins or both. CRRT is commonly performed in ICU settings for patient with septic acute kidney injury. However, the use of low or normal volume continuous venovenous hemodialysis or hemofiltration failed to demonstrate an improvement of patient outcomes in severe sepsis.[17,18] High volume hemofiltration (HVHF) or pulse HVHF removed cytokines effectively, and initial study showed promising results.[19] However, recently published IVOIRE study could not identify any significant mortality nor organ function benefit when compared with standard volume hemofiltration.[20] Moreover, HVHF incurred an increase of nursing workload (especially without the use of online treatment modality), higher treatment cost due to the use of large volumes of replacement fluid and potential electrolytes/drug concentration disturbances. Hemodialysis or hemodiafiltration using high cutoff membrane offers a good cytokine clearance,[21] but significant albumin loss, together with albumin-bound drugs are the key problem which require particular attention. Coupled plasma filtration adsorption is a relatively investigational tool, although initial experiences were impressive.[22,23]

Hemoperfusion with cytokines and/or endotoxin hemoadsorption columns require simple set up and equipment, which is more feasible in an ICU setting. Nowadays, there are three different methods for endotoxin hemoadsorption in septic shock which have more clinical experience. PMX immobilized fiber column hemoperfusion (Toraymyxin, Toray Industries, Tokyo, Japan) is the most commonly used device. This device has been used for the treatment of septic shock since 1994 in Japan and since 2002 in Europe. It has gained popularity worldwide in recent years, especially after the EUPHAS (Early Use of PMX B Hemoperfusion in Abdominal Sepsis) study.[9] The clinical experience is huge. A recent meta-analysis by Mitaka clearly showed that PMX hemoperfusion treatment had significant beneficial effects on patient hemodynamics, pulmonary oxygenation, and mortality.[24] Endotoxins may also be bound to an adsorber contained albumin (Matisse, Fresenius Medical Care, Bad Homburg, Germany).

Trends in the improvement of morbidity and organ dysfunction were found in initial nonrandomized studies.[25,26] However, a subsequent multicenter RCT could not identify any significant clinical benefit,[27] which then limited its clinical use.

Endotoxin capture by specially designed synthetic peptides is another method (Alteco endotoxin hemoadsorber, Alteco Medical AB, Lund, Sweden). This device was launched in 2006. It is a class IIa medical extracorporeal device consisting of a rigid porous matrix which can significantly increase its blood contact area. The housing of the device is filled with plates of polyethylene. Tailor-made synthetic peptides with a high affinity for endotoxins are connected to the surface of the polyethylene plates with a covalent bonding technique. The clinical experience for this device is scarce and is limited to case reports and case series.[13,28,29] The largest one by Ala-Kokko *et al*. showed that the duration of noradrenaline infusion was significantly shorter in adsorber-treated patients compared to controls (P = 0.03).[13] In our study, vasopressor use decreased nicely in adsorber-treated patients but this also occurred in control patients. Compared with the study by Ala-Kokko *et al*.,[13] our study cases were older (75 vs. 60 years old), had more significant organ failure as expressed by SOFA score (13 vs. 9), were on huge doses of vasopressor (VS 50.5 vs. 11.1) and had much higher predicted mortality (65% vs. 27%). These findings also apply when compared with PMX hemoperfusion-treated patients in the EUPHAS study.[9] which indicated that our adsorber-treated cases were much sicker. By closely examining the difference between the adsorber-treated patients and the controls, we noted that the control cases had faster organ recovery as expressed by a more rapid drop in SOFA score, less vasopressor use, better oxygenation improvement, and lower ICU length of stay. Although there was no statistically significant difference due to the small sample size, the APACHE IV score predicted mortality rate was much higher in adsorber-treated patients compared with controls, which may provide a good explanation on the discrepancy in clinical outcome parameters. It is possible that with such severe cases, the addition of endotoxin hemoadsorption offered no further clinical benefit when compared with standard intensive care, although suboptimal organ support or ineffective endotoxin removal could be other reasons for this. Concerning the first alternative (suboptimal organ support), the standardized mortality ratio by APACHE IV risk of death for the adsorber-treated patients was 0.7 which was fair; this indicated that suboptimal care was less likely. For the second reason, due to great difficulty in sourcing a quantitative endotoxin assay and limited funding, no endotoxin assay was performed. Therefore, we could not be sure that the patients had adequate endotoxin removal during hemoadsorption.

Concerning the side effects of Alteco endotoxin hemoadsorption, Ala-Kokko *et al*. found that platelet values decreased significantly from pretreatment to posttreatment.[13] In fact, thrombocytopenia (platelet count <150 × 10^3/mm^3) occurred in all adsorber-treated patients but only one case suffered from severe thrombocytopenia (platelet count <20 × 10^3/mm^3). No bleeding event was noted, and no platelet transfusion was given. In the case series by Ala-Kokko *et al*.,[13] clotting of the device occurred once among the nine treatment sessions. However, we did not experience any clotting events during all 14 hemoadsorption sessions. This may be related to the fact that we used LMWH for anticoagulation instead of unfractionated heparin (UFH) used in Ala-Kokko *et al*.'s cases.[13] The pharmacokinetics of LMWH are more predictable than UFH, which may be more obvious in septic patients. Transient hypotension occurred once and required an increase in vasopressor support, but no arrhythmia was documented, as in the cases reported by Ala-Kokko *et al*.[13]

This study is limited by the small sample size. The sample size was estimated based on previous studies, but early termination of this study further limited its power. Given that there are early reports on the effectiveness of hemoadsorption technique on treatment of septic shock, this negative study could offer readers information on patient's clinical response and side effect profile of this novel device. For this single-center study, case recruitment proved to be quite difficult as the endotoxin hemoadsorption technique was a new treatment option in our locality. Failure or refusal to consent was quite common. Recruitment rate was slow and multiple center collaboration could be the only means to resolve this issue. An endotoxin activity assay (EAA) was not performed in our study, similar to the landmark EUPHAS study,[9] due to the unavailability of the point-of-care testing device in our locality. Although endotoxin activity reflects the severity of illness in critically ill septic shock patients, its prognostic value is poor.[30-32] We believed that the availability of EAA result should be a bonus but not a must for this study. However, in order to minimize potential error on cases recruitment, we targeted only those suffering from intra-abdominal sepsis with shock. So far, the microbiological findings have yielded Gram-negative bacteria in almost all of the recruited cases. Finally, blinding was not possible for this study and may have contributed to further bias.

Conclusion

We could not identify any clinical benefit on the addition of Alteco endotoxin hemoadsorption to conventional therapy in patients who suffered from intra-abdominal sepsis with shock. The side effect profile of this device was acceptable. Given that there are early reports on the effectiveness of hemoadsorption technique on treatment of septic shock, larger multicenter study is indicated to further investigate the potential benefit or drawback of this novel device.

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