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Preliminary Report regarding the Use of Selective Sorbents in Complex Cardiac Surgery Patients with Extensive Sepsis and Prolonged Intensive Care Stay

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Key Words
Sepsis · Cardiac surgery · Lipopolysaccharide adsorption

Abstract
Aims: The purpose of this publication is to evaluate the first experiences with the supplemental use of selective endotoxin adsorption cartridges in the treatment of critically ill patients complicated by severe sepsis after cardiac surgery. ***Methods:*** Thirteen patients with Gram-negative sepsis underwent the procedure of selective lipopolysaccharide (LPS) adsorption using Alteco adsorber (group I) or Toraymyxin™ columns (polymyxin-B-immobilized fiber) (group II). ***Results:*** This therapy positively influenced the course of sepsis. After the second procedure, levels of serum endotoxin and procalcitonin markedly decreased in both groups. We also discovered a positive effect on leukocytosis levels and a trend towards normalization of body temperature, improvement of hemodynamic indices and increase of the lung's oxygenating function. Blood cultures taken several days after the procedure were negative. ***Conclusion:*** Our experience with LPS adsorption shows some evidence for the potential efficacy of this method in the treatment of critically ill patients with sepsis. Further investigations are required.

Introduction

Sepsis remains one of the main problems of modern medicine, partly because of the resulting increased morbidity and mortality. Sepsis-associated mortality in intensive care units (ICUs) remains unchanged (up to 30–70%) despite the fact that extensive studies have been conducted in many countries for more than 20 years [1]. The significant increase in the number of sepsis cases observed worldwide during the last years is related to the increasing amount of invasive diagnostic and therapeutic procedures, the use of immunosuppressors, as well as the aging of the population [2]. The data presented by Martin et al. [3] reflect a significant increase in sepsis prevalence in the USA from 82.7 cases/100,000 population in 1979 to 240.4 in 2000. The real epidemiology of sepsis in Russia is not reliably known as the existing data are contradictory and depend on the inclusion criteria and analysis types of the methods used [4]. Recent epidemiological studies in several Western European countries [5, 6] revealed that the rate of sepsis in developed countries has risen to 100 cases/100,000 population. Unfortunately, up to now no such studies have been carried out in Russia even though their necessity is obvious, firstly for the organization of ICUs and secondly for the financing and planning of national healthcare.

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The pathogenesis of sepsis is an aggregate of interrelated events, and sometimes it is quite difficult to determine a treatment strategy. Sepsis can be considered as a form of systemic inflammation caused by the local and systemic action of various circulating mediators.

The most important role in the pathogenesis of sepsis is played by endotoxin, the lipopolysaccharide (LPS) of cell walls of Gram-negative bacteria. A lipid-constraining LPS formed during the lysis of bacterial cells activates macrophages, lymphocytes and platelets, and further generates pro- and anti-inflammatory mediators. Under normal conditions, the biological activity of these mediators, including a large group of peptides with medium-sized molecules (5–30 kDa), is controlled by specific inhibitors, which can act at different levels. During sepsis or systemic inflammatory response syndrome (SIRS) the homeostatic balance is changed and if the production of one mediator is disturbed another one takes over. Thus, sepsis reflects an imbalance of pro- and anti-inflammatory mediators, which causes the development of a state of immunodysregulation [7].

According to Monti [8], after extracorporeal circulation, endotoxin levels increase by the end of extracorporeal circulation and then decrease to initial values at 24 h.

Up to now, specialists from different countries have accumulated a vast amount of information and knowledge concerning different pathogenetic mechanisms and pathways participating in sepsis development. In order to support patients' lives and prevent and reverse organ dysfunction, it is necessary to conduct a target-oriented therapy, the arsenal of which should nowadays comprise a lot of methods for the complex treatment of infective complications, including those of plasma separation therapy (PST).

Amongst eventual methods of PST in patients with sepsis, one has to mention, firstly, different techniques of renal replacement therapy (RRT) such as hemofiltration, high-volume hemofiltration and hemofiltration using large bore (about 100 kDa) membranes. Besides these techniques, the therapy of sepsis and especially of severe sepsis often includes plasmapheresis or high-volume plasmapheresis as well as adsorption methods during PST.

Continuous low-flow methods of RRT actively used during the last years in ICUs made a substantial contribution to the results of the treatment of critically ill patients with multiorgan failure. These methods were thought to play an important role in the elimination of middle-molecular substances, especially inflammation mediators in SIRS. However, studies revealed significant differences between cytokine production and clearance during RRT procedures in septic patients [9, 10].

Insignificant intensity of 'plasma water' exchange, low adsorption capacity and small membrane pores were the limiting factors for the use of RRT for detoxication in the treatment of sepsis. Clinicians used RRT as a means of studying the possibility of increasing the 'dose' of hemofiltration with an increase in middle-molecule clearance [11]. The technique of high-volume hemofiltration is now widely used in clinical practice for the treatment of severe sepsis and septic shock [12, 13].

Unlike RRT, the technique of plasma exchange has some advantages for the therapy of sepsis, mainly due to the high sieving coefficient of the plasma filter's membranes. However, plasma exchange requires high volumes of plasma replacement and, hence, the use of significant volumes of donor plasma, which increases the cost of the procedure and decreases its safety.

The use of adsorption techniques of extracorporeal therapy can be an answer to the problem of the simultaneous need for prolonged RRT with high filtration capacity and for the selective removal of sepsis-associated mediators.

For decades, medicine has accumulated a lot of experience with the use of nonselective carbon sorbents for extracorporeal therapy, mainly in cases of acute intoxication. The advantage of hemoperfusion lies in its simpler circuit; however, its use requires sorbents with enhanced biocompatibility, due to their direct contact with blood cells. Charcoal has a high adsorption capacity, especially for cleavage products with low molecular weight that accumulate in renal or hepatic failure. In order to increase biocompatibility of the charcoal during hemoperfusion, its surface needs to be coated; which, in turn, leads to a significantly lower sorbent capacity due to the decrease of the cut-off level of the coating material.

Recent experimental studies demonstrated that the use of adsorption techniques allows us to achieve the effective elimination of endotoxin and a significant decrease in inflammation mediator concentrations, thus contributing to an increase in the animals' survival rate in comparison with the control group. Moreover, the authors have shown that the decrease in concentration of circulating cytokines is associated with the decrease in binding activity of nuclear factor-κB, suggesting a regression of inflammatory process activity in tissues [14].

The development and introduction of new synthetic selective sorbents into clinical practice determined the renaissance of adsorption technologies in ICUs for the

Table 1. Selection criteria for the use of LPS adsorption

Indices	Diagnostic values	Group I, % (n = 6)	Group II, % (n = 7)
Blood cultures	positive	50	100
BAL, cfu	$>10^5$	100	100
Procalcitonin, ng/ml	>0.5	100	57
LAL test, U	>0.72	83.3	71
Leukocyte count, /l	$>12 \cdot 10^6$	66.6	71
Body temperature, °C	>38	66.6	71

BAL = Bronchoalveolar lavage.

treatment of several critical states and, first of all, sepsis. Selective biocompatible cartridges for LPS adsorption, produced by Alteco (Lund, Sweden) [15, 10], and Toraymyxin™ columns (Toray Industries, Inc., Tokyo, Japan) for endotoxin adsorption during hemoperfusion, made of immobilized polymyxin B fibers [16], recently became available in the clinic in Europe. Experimental studies conducted in Sweden looking at the efficacy of the Alteco adsorber in animal models demonstrated a significant decrease in blood concentrations of LPS and inflammatory mediators and an improvement in the indices of hemodynamics, primarily of cardiac output [15]. Since 1994, adsorption techniques using Toraymyxin cartridges have been successfully used in clinical practice in Japan in more than 60,000 patients with severe sepsis.

The purpose of this publication is to evaluate the first experiences with the use of adsorption cartridges selective to endotoxin for the treatment of sepsis after cardiac surgery.

Materials and Methods

From November 2006 to July 2008, a nonrandomized clinical trial was performed at the Bakoulev Scientific Center for Cardiovascular Surgery: 13 adult patients complicated postoperatively by nosocomial pneumonia and severe sepsis caused by Gram-negative bacteria were included. All these patients received conventional therapy according to approved guidelines. In addition, selective LPS adsorption procedures were carried out. Alteco adsorber procedures were performed in 6 patients from November 2006 to December 2007 (group I). Toraymyxin columns – polymyxin B bound and immobilized to polystyrene fibers (PMX-F) – were used in 7 patients from January 2008 to July 2008 (group II). The small number of cases included in this study can be explained by the recent commercial availability in Russia and the high cost of both cartridges.

Patients' average ages were 45.5 (36–69) years in group I and 42 (33–53) years in group II.

Amongst all the patients studied, 80% were operated for valvular pathology (aortic and mitral valve replacement, tricuspid valve correction). Three patients underwent combined surgery with coronary artery bypass grafting, 1 patient was operated for hypertrophic cardiomyopathy and 1 patient had received an orthotopic heart transplantation.

The early postoperative period was complicated by low cardiac output syndrome (ejection fraction of left ventricle 15–28%) in all patients. For the maintenance of arterial pressure, it was necessary to use inotropic support by at least 2 sympathomimetic agents (epinephrine and/or norepinephrine, dopamine and dobutamine). An intra-aortic balloon pump was also needed in 1 patient of each group.

Respiratory failure, accompanied by deterioration of blood gas indices (oxygenation index within 140–250), necessitated prolonged mechanical ventilation. Its duration in group I was 19 (17–21) days, while it was markedly longer, 29 (7–88) days, in group II.

Four patients in group I had acute kidney injury (AKI) (RIFLE [11, 17] stage: injury), while in the remaining patients the level of renal function disturbance was assessed as 'failure', which was one of the indications for RRT, either prolonged daily bicarbonate online hemodialysis or online hemodiafiltration (HDF). In group II there were 3 patients with AKI, all of them in failure stage. These patients needed long RRT. In 2 cases, we used prolonged intermittent online HDF, 1 patient needed continuous veno-venous HDF for the first 184 h, with subsequent prolonged intermittent online HDF.

Hyperthermia of >38°C was observed in 67% of cases in group I and in 75% of patients in group II.

Leukocytosis with left shift in the leukocyte formula attained the values of 16.9 (13.6 to 19.6)$\cdot 10^6$/l in group I and 15.6 (10.8 to 28.5)$\cdot 10^6$/l in group II.

Coagulopathy presenting with thrombocytopenia, hypocoagulation and disseminated intravascular coagulopathy (DIC syndrome) with markers in blood (SFMC, D-dimers) were seen in both groups of patients. In both groups, the source of infection was hospital-acquired ventilator-associated pneumonia confirmed by X-ray examination.

Positive blood cultures *(Klebsiella pneumoniae)* were found in half of the patients of group I, and bronchoalveolar lavage in all these patients revealed the following bacteria: *K. pneumoniae* in 4, *Pseudomonas aeruginosa* in 1 and *Acinetobacter lwoffii* in 1 patient. Bacteriological analyses of blood cultures and bronchoalveolar lavage in group II revealed *K. pneumoniae* in 4 patients and *P. aeruginosa* in 3 patients (table 1). Bacterial load was reflected by high blood titers of endotoxin revealed by the limulus amebocyte lysate (LAL) test (Cambrex, Charles City, Iowa, USA).

An important role in the early diagnostics and dynamic follow-up of the course of infection is played by monitoring of blood plasma procalcitonin (BRAHMS AG, Hennigsdorf, Germany), a biochemical marker of inflammation (values before LPS adsorption: 12.53 (0.81–36.42) ng/ml in group I and 25.98 (0.5–93.46) ng/ml in group II).

The severity of state of the patients studied was assessed by integral APACHE II score (group I: 25 (22–28) points; group II: 28 (31–38) points). The degree of sepsis-related organ failure was assessed using the SOFA scale (group I: 14.5 (13–15) points; group II: 10 (6–17) points). Data are shown as median with interquartile range (25th–75th percentiles).

Therapy of sepsis in all patients from both groups included hemodynamic and respiratory support, antibacterial, hormonal and immunocorrective therapy, prevention of thromboembolism, protection of the gastrointestinal tract and adequate nutritive support. Immunocorrective therapy consisted of the prescription of immunoglobulins, particularly of Pentaglobin in 6 of the patients studied (3 in group I and 3 in group II). In order to protect against perfusion disturbances and organ dysfunction based on coagulation cascade activation, 2 patients with sepsis (1 in each group) were treated with activated protein C (Xigris®). One patient in group II who had received an orthotopic heart transplantation needed 3-component immunosuppressive therapy.

As all patients were in a hypercatabolic state, adequate nutritive support was necessary. All patients in both groups received mixed enteral and parenteral nutrition with a minimum energetic value of 25–35 kcal/kg/day.

The selection criteria for LPS adsorption procedures in both groups are presented in table 1.

Technique of Lipopolysaccharide Adsorption

The main indication for starting Alteco LPS adsorption as well as hemoperfusion with immobilized polymyxin B primarily consisted in the development of Gram-negative infection on the basis of multiorgan failure, confirmed by clinical and laboratory data.

Vascular approach was achieved by means of the Seldinger method; a 2-lm catheter (12–14 F) was inserted in one of the central veins. The procedure was carried out using a perfusion module BSM-22 (Hospal S.A., Lyon, France). According to the protocol, extracorporeal tubing was primed with 1,000 ml of NaCl 0.9% solution with the addition of heparin (10,000 U) and subsequent replacement of this solution by the patient's own blood.

The blood flow rate was maintained within 100–150 ml/min. Anticoagulation with unfractionated heparin was matched on an individual basis, depending on the initial state of the blood clotting system and activated clotting time indices before and during the procedure. On average, the heparin dose was 4–10 U/kg/h. Activated clotting time was maintained within 180–200 s.

The Alteco LPS adsorber is an adsorption column consisting of 20 porous polyethylene slabs with a summary surface area of 3.3 m^2 and with a filling volume of 20 ml. These slabs are immobilized by a special peptide HAE 27, which can bind and adsorb LPS.

During the treatment process we performed 12 Alteco procedures in 6 patients of group I (2 sessions with maximum duration of 120 min/patient).

One patient with AKI underwent a combined procedure of high-volume online HDF and LPS adsorption. In this case, the adsorption column was inserted in the extracorporeal system before the filter. Replacement solutions were supplied in a predilution mode, with the purpose of reducing the heparin dose needed and preventing circuit thrombosis. The blood flow rate was maintained at about 150 ml/min and the replacement solution supply at 200 ml/min. The replacement volume during the procedure was 52 liters, dialyzate flow was 500 ml/min, and the procedure lasted 4.5 h.

Toraymyxin PMX-F adsorption columns are made of a thread adsorbent, where polymyxin B is covalently bound to α-chloracetamide methyl polystyrene and immobilized to polypropylene fibers. It is known that polymyxin B can counteract the biological activity of endotoxin by binding lipid A. The products of polystyrene strengthened by polypropylene applied to the fibers are used in PMX-F columns to avoid polymyxin B desorption into blood during the procedure (marked neuro- and nephrotoxic effects).

The high adsorptive capacity of Toraymyxin columns can be explained by their large surface area as a result of the small diameter (30–40 μm) and high porosity of the fiber. Their priming volume is 135 ml.

We carried out 14 procedures of hemoperfusion with immobilized polymyxin B in 7 patients of group II. Each of them underwent 2 procedures, which lasted about 120 min, as in group I patients.

While performing this study, we gave priority to the evaluation of the safety of the procedures, i.e. influence on hemodynamic indices, respiratory lung function, and development of immediate hypersensitivity responses (pyrogenic, allergic).

During treatment we used routine clinical and laboratory procedures, including monitoring of hemodynamic and respiratory parameters, control of blood gases and acid-base balance, standard biochemical indices, clinical blood count and evaluation of hemostasis. Besides the above parameters, we studied the dynamics of inflammation mediator levels – TNF-α, IL-1β and IL-6 – before and after the procedures. The effectiveness of the therapy was assessed on the basis of monitored endotoxin and procalcitonin levels, microbiological investigation of blood and sputum and observation of the general clinical status of our patients.

Results

The procedures of Alteco LPS adsorption were started on average at day 8 (3–11) after surgical intervention if the patients developed signs of systemic inflammatory response and had laboratory confirmation of Gram-negative infection.

In all cases, the source of infection was nosocomial pneumonia with deterioration of blood gas composition, necessitating mechanical ventilation with oxygen fraction >0.6 and PEEP >5 cm H_2O. During the procedures of LPS adsorption we noted an improvement of the lung's oxygenating function. The increase in oxygenation index, probably related to the increase of recruiting pulmonary tissue with the regression seen on X-ray resulted in the diagnosis of pneumonia.

While carrying out the procedures of selective adsorption, we did not see any deterioration of hemodynamic indices in any patient, except for 2 cases of short-lasting decrease in mean arterial pressure (MAP) (by 15%) and peripheral resistance (by 17%) with preserved cardiac output in group I. Basic hemodynamic indices improved as a result of adsorption procedures in both groups. The mean duration of hemodynamic support was 20.5 (13–24) days in group I and 59 (12–88) days in group II.

Table 2. Dynamics of clinical and laboratory indices during Alteco LPS adsorption

Indices	Before the first procedure	At 24 h after the second procedure
MAP, mm Hg	76 (68–82)	98 (92–100)
Heart rate, beats/min	105 (83–108)	98 (78–102)
Epinephrine, μg/kg/min	0.17 (0.1–0.2)	0.1 (0.08–0.18)
Body temperature, °C	38.2 (37.1–38.6)	37.7 (37.4–37.9)
Leukocytes, 10^6/l	16.9 (13.6–19.3)	11.3 (10–12.7)
Platelets, 10^9/l	93 (69–104)	86 (67–110)
Procalcitonin, ng/ml	12.53 (0.81–36.42)	3.05 (1.18–7.13)
Endotoxin, U	1.44 (0.72–1.44)	0.03 (0–0.03)
PaO_2/FiO_2	159 (129–268)	238 (210–308)
SOFA	14.5 (13–15)	12 (10–13)
IL-1, pg/ml	27.28 (12.87–31.03)	30.57 (15.11–40.48)
IL-6, pg/ml	24.19 (17.81–46.72)	20.14 (18.7–70.26)
TNF-α, pg/ml	5.14 (5.14–7.24)	4.76 (4–7.28)

Table 3. Dynamics of clinical and laboratory indices during hemoperfusion using immobilized polymyxin B

Indices	Before the first procedure	At 24 h after the second procedure
MAP, mm Hg	61 (56–88)	86 (79–92)
Heart rate, beats/min	89 (85–97)	89 (75–110)
Epinephrine, μg/kg/min	0.04 (0.03–0.07)	0.03 (0.02–0.06)
Body temperature, °C	38 (37.3–38.5)	36.7 (36.3–37.4)
Leukocytes, 10^6/l	15.6 (10.5–28.5)	14.5 (11.2–22.4)
Platelets,10^9/l	127 (62–198)	90 (38–236)
Procalcitonin, ng/ml	25.98 (0.5–93.46)	18.85 (0.81–73.78)
Endotoxin, U	1.44 (1.44–1.44)	0.27 (0–1.44)
PaO_2/FiO_2	207.5 (160–258)	212 (136–327)
SOFA	10 (6–17)	10 (5–15)
IL-1, pg/ml	37.42 (13.47–75.48)	14.62 (6.96–18.34)
IL-6, pg/ml	42.66 (19.18–57.46)	18.16 (4.41–44.35)
TNF-α, pg/ml	2.19 (1.81–3.72)	3.24 (2.38–4.38)

The inclusion of LPS adsorption in intensive therapy was accompanied by positive dynamics of endotoxin and procalcitonin serum concentrations in both studied groups. After the second procedure the level of endotoxin decreased by 76% in group I and 88% in group II. A similar tendency was observed in the dynamics of blood procalcitonin levels: in group I they decreased by 86% and in group II by 76%.

In both groups, the favorable influence of LPS adsorption on the course of infection was also confirmed by the dynamics of leukocytosis levels and the trend towards normalization of body temperature. The results of blood cultures performed several days after the second procedures were negative in both groups, which generally points to considering the effectiveness of intensive therapy for severe sepsis by LPS adsorption techniques. The data are shown in tables 2 and 3.

The mean duration of mechanical ventilation was 19 (17–21) and 29 (7–88) days in groups I and II, respectively. Until the 28th day of observation, 2 patients in group I and 2 in group II had survived. The relatively high mortality is explained by the severe condition of the patients enrolled in the study.

No cases of thrombus formation in the extracorporeal circuits were noted. The above allows considering both procedures of LPS adsorption as safe.

Discussion

The improvement of clinical and laboratory parameters with selective LPS adsorption is, first of all, related to the effective elimination of endotoxin as the main etiological factor of the Gram-negative infective process.

The increase in MAP and ejection fraction due to the trend towards decreasing inotropic support, as observed in our patients, was noted in previous publications [18–20]. A 26% average increase in MAP with adsorption therapy was noted. In patients with initially low MAP (<70 mm Hg), the increase in MAP was lower than in patients with baseline MAP >70 mm Hg (16 vs. 26 mm Hg).

One of the most important findings was the improvement of oxygenating function of the lung after adsorption therapy, also noted by several authors [21–28].

The dynamics of procalcitonin levels, with a trend towards decrease after hemoperfusion procedures, are suggestive of an optimization of the course of bacterial infection by LPS adsorption [28].

Sepsis is accompanied by a deep dysregulation of circulating immune modulators, which is finally responsible for cell and tissue damage. This can explain the favorable effect of extracorporeal selective adsorption techniques in sepsis as they not only allow the elimination of circulating SIRS mediators, but also the restoration of immune homeostasis.

It is known that the disturbed balance of pro- and anti-inflammatory mediators is of great pathophysiological significance [10, 29]. The evaluation of the dynamics of circulating inflammatory mediators during adsorption therapy allowed us to draw a conclusion regarding the tendency towards immune balance recovery. Kojika et al. [22] and Tani et al. [30] report an obvious decrease in TNF-α, IL-6, IL-10 and neutrophilic elastase, and a release of metalloprotease-9 and plasminogen 1 activators after adsorption therapy. The above-mentioned parallel decrease in blood LPS levels together with the decrease of mediators release explains the reduced evidence of SIRS in these patients [31].

The elimination of endotoxin from circulating blood in the presence of an ongoing inflammatory reaction cascade cannot lead to total regression of the pathological process, because biologically active substances present in blood continue to sustain SIRS. However, the use of LPS adsorption in sepsis therapy allows prevention of the progression of immune system activation at the earlier stages of its development.

Thus, our preliminary experience with the clinical use of LPS adsorption suggests an undoubted rationale for the inclusion of selective hemoperfusion in treatment of sepsis in the critically ill.

Some authors described a reliable decrease in endotoxin levels (from 0.69 to 0.43) after 2 procedures of LPS adsorption using Toraymyxin cartridges [8]. One can notice that the decrease in endotoxin levels is accompanied by a significant decrease in ICU as well as in hospital mortality.

Worldwide experience with the use of Alteco technologies is rather poor, but the experimental results published show a favorable influence of LPS adsorption on the course of infective processes [32].

The experience with the use of cartridges containing immobilized polymyxin B in sepsis was analyzed and summarized in a meta-analysis performed by a group of Italian authors in 2007 [33]. The authors generalized the results of 28 published trials, including the results of treatment of over 1,400 patients from 7 countries. However, as the groups were heterogeneous and not all the reports contained data on the procedure's influence on mortality, the results of these trials must be interpreted with caution.

It is difficult to separate the influence of adsorption techniques on the course of sepsis, as the complex of intensive therapy comprised other methods. Thus, despite 10 years of experience with the use of this selective technique, only 1 randomized trial has been performed so far [27]. This trial included a small group of patients with low APACHE II score and the long-term results of treatment were not studied.

It is obvious that, due to the insufficient number of cases, the results of our study do not allow us to make a clear judgment on the safety and efficacy of LPS adsorption procedures in critically ill patients. However, this publication of the first results from Russia will hopefully encourage other researchers to continue their studies on the use of selective sorbents in the therapy of sepsis in patients after cardiovascular surgery.

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