Blood Purification

Case Report

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The Seraph®-100 Microbind Affinity Blood Filter Does Not Affect Vancomycin, Tacrolimus, and Mycophenolic Acid Plasma Concentrations

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Seraph®-100 · Drug elimination · Pathogen bioburden · Blood stream infection · Vancomycin · Tacrolimus

Abstract
Extracorporeal blood purification is considered an adjunct therapy in critically ill patients with life-threatening conditions such as sepsis and septic shock. It consists of cytokine removal, removal of endotoxins, a combination of both, or the removal of pathogens themselves. The latter technique was introduced for clinical application very recently. This case study describes a case of a 69-year-old female lung transplant recipient patient with a persistent VV-ECMO-related septic deep vein thrombosis with continuous renal replacement therapy-dependent acute kidney injury initiated on the Seraph®-100 Microbind Affinity Filter in order to control the persistent bacteraemia with coagulase-negative staphylococci. Drug plasma concentrations (vancomycin, tacrolimus, and mycophenolic acid) were measured before and after the device to calculate absorber-related drug clearance.

Introduction

Sepsis and blood stream infections are a leading and increasing cause of mortality in critically ill patients [1]. Antibiotics should be instituted as soon as sepsis is suspected, with a clear evidence of increased mortality with every hour of delay in first antibiotic administration [2]. Blood stream infections with non-resistant bacteria are typically well treated when the appropriate antibiotics are instituted. This results, most of the time, in negative blood cultures within hours or days. However, when the blood stream bioburden is multi-resistant to standard antibiotics or when a persistent intravascular focus (e.g., deep vein thrombosis) maintains the existence of the microbes, quick pathogen elimination from the blood stream is much more difficult to achieve.

Cannula-associated deep vein thrombosis is reported to be prevalent in 85% of patients treated with veno-venous extracorporeal membrane oxygenation (VV-ECMO) [3]. The main treatment is therapeutic anticoagulation for at least 3 months after decannulation. There are no available data on the incidence of persistent septic deep vein thrombosis in these patients, although it seems

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plausible that an immunocompromised state as such in (lung) transplant recipients adds to its occurrence.

Extracorporeal removal of pathogens or pathogen-related molecules (lipopolysaccharides) is an upcoming scientifically investigated adjunct to the current palette of sepsis-related treatment options [4]. Several membranes and filters with a specific binding profile are currently available for clinical use. The Seraph-100® Microbind Affinity Filter (Exthera Medical, Martinez, CA, USA) contains ultrahigh-molecular weight polyethylene beads with end point-attached heparin and is approved for the reduction of pathogens from the bloodstream. Bacteria, fungi, and viruses have been shown to bind to the immobilized heparin in a similar way to the interaction with heparin sulphate on the cell surface. This removes the pathogens irreversibly from the bloodstream [5].

The Seraph®-100 Microbind Affinity Filter can be set up in either an intermittent haemodialysis circuit applying higher blood flow rates and shorter treatment times (3.5–4 h) or in a continuous renal replacement therapy (CRRT) circuit allowing longer filter run times (24 h) with lower blood flow rates [6, 7]. The modality of choice may influence drug removal either through dialysis-related clearance or through adsorption on the extracorporeal surface membranes. To achieve desired therapeutic goals of water-soluble antibiotics such as vancomycin during CRRT, the most effective dosing optimization strategy is to use therapeutic drug monitoring (TDM) [8]. Tacrolimus and mycophenolic acid plasma concentrations are unaffected by CRRT, and thus additional TDM is in essence unnecessary. However, adsorption of these drugs to an adsorption column such as the Seraph®-100 Microbind Affinity Filter is possible and needs to be tested when the column is applied in a clinical setting. Here, we present a case study of a patient with a persistent severe septic deep vein thrombosis after VV-ECMO initiation in the context of lung transplantation in which the Seraph®-100 Microbind Affinity Filter was applied. The filter was initiated in the idea to reduce the bioburden of the blood stream bacteria during the renewal of the central venous catheters (CVCs). For safety reasons, data of pre- and post-filter plasma drug concentrations were collected to calculate the filter extraction ratio and filter-related plasma drug clearance.

Case Report

This case report describes a 69-year-old female patient, with a history of anti-CCP-positive erosive rheumatoid arthritis for which she was described methotrexate for several years. During the course of time, she developed rheumatoid-associated interstitial lung disease with a non-specific interstitial pneumonia (mixed fibrotic and cellular) pattern. The deterioration of her pulmonary condition necessitated a bilateral lung transplantation which was complicated during surgery by a haemorrhagic shock due to tear of the arteria pulmonalis sinistra. In order to control the situation in the theatre, VV-ECMO was initiated, and the patient was transferred to the ICU. Despite an adequate activated partial thromboplastin time and anti-Xa levels during the entire VV-ECMO run, severe thrombosis developed in the right brachial and axillar vein and the right common iliac vein until the bifurcation in both VV-ECMO canule trajectories. After a few days, the patient was weaned from the VV-ECMO, and the canules were removed. Furthermore, severe AKI KDIGO stage III developed for which citrate-based continuous veno-venous-haemodialysis (CVVHD-CiCa) was initiated (prescribed renal dose 30 mL/kg/h). A few days later, an obstructive shock due to a haematothorax needed to be surgically relieved in the operating room. During the following postoperative days, our patient suffered several episodes of high fever, and her blood cultures repeatedly turned positive for the same strain of coagulase-negative staphylococci (CNS) (Fig. 1). The CVCs were replaced several times supported by a continuous IV vancomycin infusion combined with frequent TDM (target plasma levels 20–25 mg/L). Still, the blood cultures stayed positive for CNS. Computer-assisted tomography 2 weeks after the ultrasonography showed thrombosis in the left jugular vein reaching down to the superior caval vein, in the right jugular vein, in the left subclavian vein, in the left iliac vein, and in the right iliac vein reaching down to the right femoral vein. Without any other evident infection source, despite a pulmonary colonization with *Chryseobacterium indologenes* and *Aspergillus* antigen 0.9, the patient was diagnosed with "septic deep vein thrombosis," and in an attempt to reduce the amount of CVCs, she was switched from CVVHD to continuous ambulant peritoneal dialysis after placement of the acquired peritoneal access. Unfortunately, after 2 weeks of continuous ambulant peritoneal dialysis treatment, our patient developed an acute abdomen due to transmural colon ischaemia (submucosal thrombus formation and normal patent mesenterial vessels) for which a left hemicolectomy and colostomy were performed. Supported by the continuous infusion of IV vancomycin, the blood cultures remained negative up until 5 weeks after the initial transplantation. Despite adequate vancomycin plasma levels (Fig. 1, another 2 cultures showed the evident strain of CNS together with the clinical context of fever and rising C-reactive protein, and it was concluded that the intravascular infection source was yet still not under control. With only 2 sites available for re-insertion of new CVCs being the right subclavian vein and the left femoral vein, we anticipated that the initiation of the Seraph-100® Microbind Affinity Blood Filter might be of help to reduce the alleged bioburden in the patient's bloodstream. The idea was that this could be of help to reduce the chance of renewed adherence of microbes to the newly inserted catheters. The Seraph®-100 Filter was set up in series in the existing extracorporeal CiCa-CVVHD circuit (Fresenius Medical Care), and two 24-h runs were performed using 2 Seraph®-100 membranes (Fig. 2). The CRRT treatment prescription was blood flow rate 100 mL/min, dialysate flow rate 2,000 mL/h, citrate concentration 4 mmol/L, and calcium 1.7 mmol/L in a prescribed renal dose of 30 mL/kg/h (patient weight = 65 kg). The UF rate was 50 mL/h, and the applied dialysis membrane was the Ultra flux AV1000 (Fresenius). Blood samples were drawn before and after

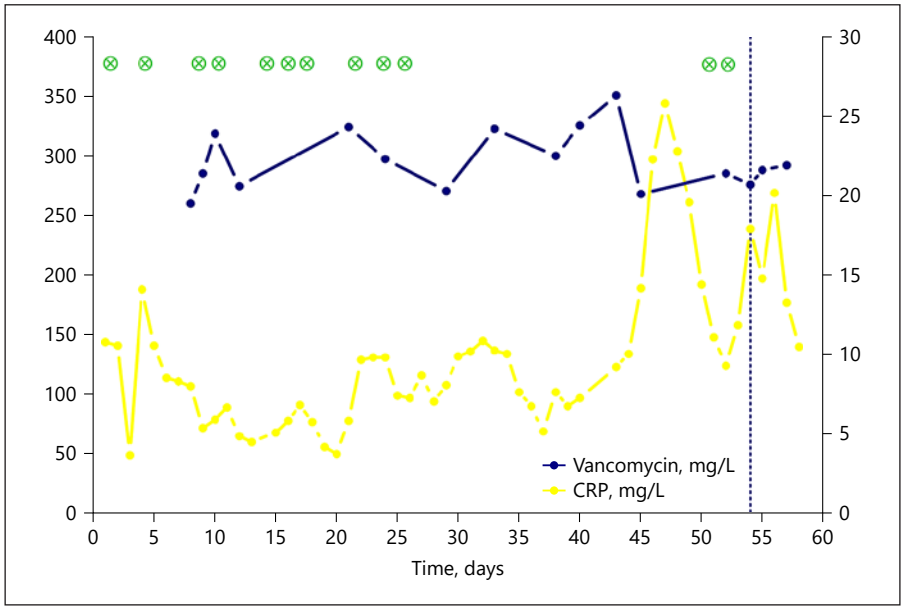

Fig. 1. Evolution over time of CRP (left *y* axis) and vancomycin plasma levels (right *y* axis) in relation to blood culture positivity with CNS (⊗) over time. Dotted line represents the day Seraph®-100 was initiated. CRP, C-reactive protein; CNS, coagulase-negative staphylococci.

Table 1. Pre- and post-Exthera® membrane plasma drug concentrations of vancomycin, tacrolimus, and mycophenolic acid

	Pre-Seraph®-100 (C_{pre})	Post-Seraph®-100 (C_{post})	ER, %	Filter CL, mL/min
Day 1				
Vancomycin	23.1 mg/L	22.7 mg/L	1.7	1.3
Tacrolimus	7.9 µg/L	7.7 µg/L	2.5	1.8
Mycophenolic acid	5.7 mg/L	5.5 mg/L	3.7	2.7
Day 2				
Vancomycin	21.6 mg/L	21.5 mg/L	0.5	0.3
Tacrolimus	8.9 µg/L	8.0 µg/L	10	7.3
Mycophenolic acid	0.1 mg/L	0.1 mg/L	0	0

A new Seraph®-100 filter was used for both day 1 and day 2. CL = drug plasma clearance of the Seraph-100 Microbind Filter in mL/min calculated using the equation (CL drug = $Q_e \times (C_{pre} - C_{post})/C_{pre}$), where Q_e = plasma flow (73 mL/min) (calculated using circuit blood flow = 100 mL/min and haematocrit = 0.27); ER = filter extraction ratio of the investigated drug. Mycophenolic acid plasma concentration on day 1 was measured directly after intake and on day 2 before intake.

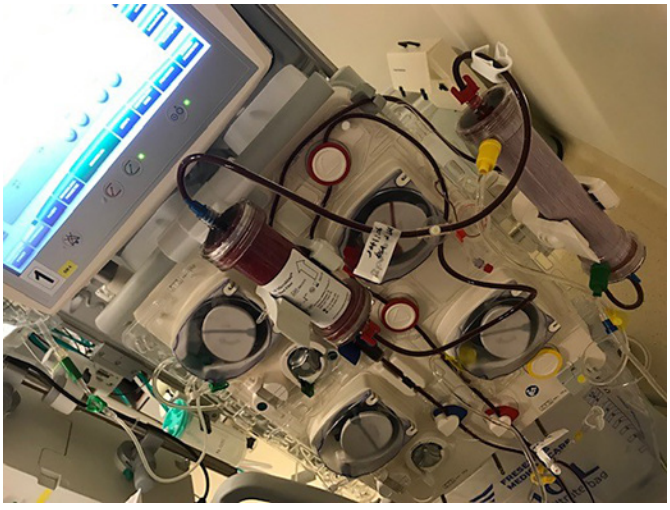

Fig. 2. Seraph®-100 Microbind Affinity Blood Filter installed in series in a CiCa-CVVHD (Fresenius Medical Care) extracorporeal circuit.

Seraph-100® Filter for blood cultures (aerobic and anaerobic and yeast and fungi). For TDM and safety reasons, several plasma drug concentrations were measured as well (vancomycin, tacrolimus, and mycophenolic acid). Pre- and post-Seraph®-100 Filter blood samples for TDM were obtained 30 min after start of each circuit on day 1 and day 2. Additional blood cultures were drawn 8 h after initiation. The addition of Seraph®-100 to the CRRT circuit was well tolerated, and no adverse events were observed during the 48-h treatment period. The norepinephrine dose was practically unchanged during treatment (0.32 µg/kg/min), and there were no relevant effects on patient core temperature measurements (36–37°C) or oxygen saturation (FiO_2 requirement during PS ventila-

tion remained 40%). The blood cultures drawn pre- and post-Seraph-100® filter did not show any growth of bacteria, fungi, and yeast. The catheter tip cultures remained negative as well. The pre- and post-filter plasma drug concentrations were practically unaffected (Table 1: filter extraction ratio and filter-related plasma drug clearance). In the following 4 weeks, another 5 sets of blood cultures showed the same CNS strain, despite adequate vancomycin plasma concentrations and the addition of daptomycin. The clinical course was further complicated by a progressive pulmonary superinfection with *Aspergillus fumigatus* treated with voriconazole, severe non-resolving ICU-acquired weakness with severe joint contractures in lower extremities with the inability to be revalidated or trained, non-resolving AKI with permanent dialysis dependency, a persistent need for vasoactive drugs to maintain adequate blood pressures, failure to wean off the ventilator, and severe oedema due to persistent venous thrombosis in various limbs. After 41 days of intensive care treatment, it was concluded that no objectifiable reversible treatment goals could be identified, and further treatment was deemed futile

Discussion

This case study describes the first in vivo application of the Seraph®-100 Microbind Affinity Filter connected in series with a CRRT device in a lung transplant recipient. Although the anticipated primary treatment purpose (blood clearance of CNS) was not met (because the bacteraemia had stopped before the time Seraph®-100 was applied, as it became clear after the blood cultures were analysed), the secondary measures of absorber-related drug plasma clearance rates are of interest for the future clinical application of the membrane. Vancomycin, tacrolimus, and mycophenolic acid plasma concentrations were unaffected by the interaction with the membrane in this specific patient.

Extracorporeal blood purification therapies are proposed as possible adjunctive treatment options to modulate the life-threatening dysregulated inflammatory host response in sepsis and to reduce the pathogen-related bioburden in critically ill patients. Most of these clinically available techniques target the non-specific reduction of inflammatory response mediators such as cytokines (Cytosorb®), the reduction of pathogen-associated molecular patterns (lipopolysaccharide and endotoxins) (Toraymyxin®), or a combination of both (oXiris®) [9]. Pathogen removal with an extracorporeal cartridge is yet somewhat less common. Several techniques have been developed to reduce blood pathogen load such as filtration, magnetic nanoparticle separation, bendable polycrystalline nanowires/carbon foam, and polyethylene beads with end point-attached heparin (Seraph®-100) [10].

The Seraph®-100 Microbind Affinity Filter is the first CE-approved extracorporeal device to adsorb pathogens from the blood. The successful reduction of blood-borne pathogens depends on the microbe's affinity to the heparin sulphate-coated microbeads. This in itself depends on the specific adhesion expression on the pathogen's cell or core surface which enables the electrostatic interaction with the heparin sulphate. Differences in adherence and reduction rates between pathogen species have been reported [5, 11]. Secondly, in vitro studies report a significant reduction in TNF-α levels as well (59%). Although theoretically the technique is very promising, the challenge for the clinical implementation of the absorber lies in the correct timing of the institution and definition of the best window of opportunity for its superimposed effect on clinical outcome, of which this case report is a perfect clinical example. Current clinical practice focusses on an as short as possible (or even no) delay in antibiotic administration, and therefore logically associated with a significant reduction in the chance of persistence of blood stream-circulating pathogens. However, these chances change in case of multi-drug-resistant bacteria, in case of persistent viraemia without antiviral therapy options in severely immunocompromised patients, or in case of ongoing sepsis due to a persistent intravascular infection focus.

Extracorporeal membrane-related plasma drug clearance is a worrisome potential hazard for suboptimal therapeutic drug concentrations with a risk of (unnoticed) adverse outcomes in the critically ill. The plasma drug interaction with extracorporeal devices such as ECMO membranes, dialysis filters, and cytokine absorbers is unpredictable especially when frequent TDM is not readily available for every drug in every clinical setting. In this case study, vancomycin, tacrolimus, and mycophenolic acid absorber clearance was calculated and found to be neglectable. The reported in vitro vancomycin absorber clearance (with a plasma flow Q_e = 250 mL/min) was similar to our in vivo (whole blood) measured filter-related clearance (with a plasma flow Q_e = 78 mL/min) [11]. Of notice is that in this in vitro study, higher reduction rates for aminoglycosides, which might be due to adsorption during the first pass of the plasma through the filter, were reported. This urges the importance of frequent TDM during any extracorporeal membrane-based clinical therapeutical intervention until enough scientific data are collected to ensure solid pharmacokinetic prediction modelling.

In summary, this case study shows that vancomycin, tacrolimus, and mycophenolic acid plasma drug concen-

trations were unaffected by the Seraph®-100 Microbind Affinity Blood Filter. However, the difficulty will be to find an adequate window for its clinical application which results in a clear clinical benefit when a bacteraemia is suspected yet not proven. Therefore, the Seraph®-100 membrane can be safely instituted in transplant recipients using these drugs, although frequent determination of plasma drug concentrations in these patients remains advisable, and haemoperfusion remains an experimental therapy that should be further investigated in well-designed randomized clinical trials [12].

Statement of Ethics

Written informed consent for publication was obtained from the patient's next of kin (husband) for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare no funding source relevant to this case report.

Author Contributions

H.R.H.G. designed the report and acquired data. T.S., N.H., and R.E. performed, analysed, and interpreted drug concentrations. H.R.H.G. drafted the manuscript. All authors commented and revised the manuscript before final agreement.

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