Case Report

Perfusion

Cytosorb® hemoadsorption of apixaban during emergent cardio-pulmonary bypass: a case report

Perfusion
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DOI: 10.1177/0267659120967827
journals.sagepub.com/home/prf
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Abstract

Background: Peri-operative coagulation management of patients receiving apixaban, a new oral anticoagulant, is difficult. The CytoSorb® hemoadsorption device might represent a therapeutic option to reduce apixaban's pharmacological and inflammatory effects during high-risk surgery.

Case presentation: An 83-year-old woman treated with Apixaban underwent emergent redo mitral valve replacement for prosthetic valve endocarditis. A CytoSorb® cartridge was added to the cardio-pulmonary bypass (CPB) circuit. Apixaban-specific anti-factor Xa activity (AFXaA) were measured peri-operatively. After 100 minutes of CPB, a 50% AFXaA rate decrease was observed as compared to pre-CPB values. Furthermore, we noticed 39% and 44% reductions of AFXaA levels in comparison to the expected levels in patients with normal or altered renal function, respectively.

Conclusion: Insertion of a CytoSorb® cartridge in the CPB was safe and associated with rapid correction of Apixaban-associated anticoagulation.

Keywords

cardiopulmonary bypass; hemoadsorption; CytoSorb®; apixaban; endocarditis

Background

The new direct oral anticoagulant Apixaban is increasingly used to prevent stroke and venous thrombosis.[1] This drug is characterized by a short half-life and requires twice daily dosing. However, it can lead to bleeding complications and multiple transfusions in patients requiring emergent surgery.[1,2] Additional risk factors, such as active endocarditis, redo surgery, or age further, increase the risk of postoperative systemic inflammatory response and mortality.[3,4] The CytoSorb® hemoadsorption device (CytoSorbents Corportaion, Monmouth Junction, NJ, USA) can easily be inserted into a cardiopulmonary bypass (CPB) circuit and has been shown to efficiently retrieve pro-inflammatory mediators and drugs from the circulation.[5–8]

The aim of the present report is to describe, for the first time, the peri-operative effects of the CytoSorb® device used as an adjunct to CPB in an emergent reoperation for active endocarditis in an elderly patient anticoagulated with Apixaban.

Case presentation

A 83-year-old woman (47 kg/165 cm) was admitted to our hospital with hyperthermia and decompensated heart failure. She had a history of chronic heart failure (ejection fraction <30%), bioprosthetic mitral valve replacement 2 years prior to admission, chronic atrial

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fibrillation and a recent lower limb deep vein thrombosis treated by Apixaban (2.5 mg twice a day).

Echocardiography revealed severe mitral valve prosthesis stenosis (mean gradient = 12 mmHg) and a 20 mm vegetation on the bioprosthetic leaflets. She was admitted and scheduled for emergent mitral valve replacement (MVR). The preoperative EuroSCORE II mortality risk estimation was 54%. The last dose of apixaban was taken seven hours before surgery.

The CPB circuit included a centrifugal pump (Revolution-Centrifugal Blood Pump®, LivaNova, Sorin Group, Mirandola, Italia), a membrane oxygenator (Capiox® Fx15, Terumo Cardiovascular Systems Co, Tokyo, Japan), a hard-shell reservoir (CX-RR40®, Terumo Cardiovascular Systems Co, Tokyo, Japan) with a 70 ml minimal reservoir, a hemoconcentrator (BC 20 Plus, Maquet Cardiopulmonary AG, Hirrlingen, Germany), and a cardioplegia device (CSC 14®, LivaNova, Sorin Group, Mirandola, Italia). A NaCl 0.9% purged CytoSorb® cartridge was inserted between the oxygenator and the venous reservoir. Hemoadsorption was performed throughout the entire CPB duration.

AFXaA levels were measured by colorimetry (Biophen®, Hyphen Biomed, Neuville-sur-Oise, France) on different time points before and after the procedure. Heparin reversal with protamine was estimated based on the Hemostasis Management System Plus (HMS®, Medtronic, Minneapolis, USA).

Results

Preoperatively, the patient presented severe anemia (hemoglobin, 9.1 g/dl; hematocrit, 28%), thrombocytopenia (platelets, 146 g/l), stage II acute kidney injury (serum creatinine, 106 µmol/l) and inflammation (C-reactive protein, 126 mg/l). Activated clotting time (ACT) was 104 seconds, thromboplastin time 26 seconds and apixaban-specific anti-factor Xa activity (AFXaA) 72 ng/ml.

After administration of 27,000 IU of non-fractioned heparin, the ACT reached 409 seconds. CPB was conducted in standard fashion (ph-stat). The infected bioprosthesis was replaced with a porcine stented bioprosthesis (St Jude® Epic Mitral Valve 33 mm, Abbott, California, USA) using 1,376 ml of cold cristalloïd cardioplegia (Custodiol® HTK, Köhler Chemie GmbH, Bensheim, Germany). CPB duration was 100 minutes with 74 minutes of aortic cross-clamping.

Figure 1 illustrates peri-operative evolution of plasma AFXaA level. On anesthesia induction (T2), this level was 64 ng/ml. After heparin administration and CPB initiation (T3), it increased to 114 ng/ml and dropped to 32 ng/ml after CPB weaning and 15,000 IU of protamine administration (T5).

Finally, AFXaA levels remained stable over 7 hours but remained >20 ng/ml for the next 24 hours.

The postoperative course was uneventful. In particular, no bleeding complications were observed. The patient left ICU of post-op day 2 and hospital on post-op day 26.

Discussion

In Apixaban-treated patients requiring emergent surgery, the non-dialyzable character the drug related to its high protein-binding capacity, might lead to bleeding complications.

"Andexanet alfa" is a modified recombinant inactive form of human factor Xa that was designed specifically to bind and sequester factor Xa inhibitor molecules thereby rapidly reducing anti-factor Xa activity.[9]

In a study of 134 patients who were receiving apixaban, the median value for anti-factor Xa activity was reduced from 149.7 ng/ml at baseline to 11.1 ng/ml at the end of the 400 mg bolus Andexanet administration (95% CI: 91–93).[9]

Andexanet was approved by European Medicines Agency (EMA) in April 2019. It is, however, not yet available in most institutions (including ours) due to its high cost.

In the present case, we demonstrated, for the first time, the intraoperative clearance of Apixaban using CytoSorb®. This device can easily be inserted into the CBP circuit, and has been shown to effectively remove various inflammatory cytokines and drugs.[4,8,10]

During CPB, AFXaA levels are difficult to interpret because of the indirect inhibition of factor Xa by heparin. Nevertheless, we observed a 50% decrease of the AFXaA levels between the start (T2) and the weaning (T5) of CPB. Furthermore, we extrapolated the expected concentrations of Apixaban based on theoretical Apixaban half-lifes in normal and renal insufficient patients.[1,11] We found that the levels of AFXaA (32 ng/ml) at the end of CPB in our patient were respectively 39% and 44% lower than expected in patients with normal (52 ng/ml) or reduced renal function (57 ng/ml).

It is important to note that unfractionated heparin activity during CPB results in an increase in AFXaA activity, as measured with non-specific Biophen® test and that the results during CPB therefore cannot be interpreted. Protamine administration also influences the results, but since protamine neutralizes unfractionated heparin and not Apixaban, the residual anti-Xa activity, after heparin neutralization can be interpreted as the Apixaban activity.

We considered continuing CytoSorb® therapy in ICU, however after CPB, the patient was hemodynamically stable without bleeding. We decided to discontinue the therapy since this would require the placement of an extracorporeal circuit, which could lead to other complications.

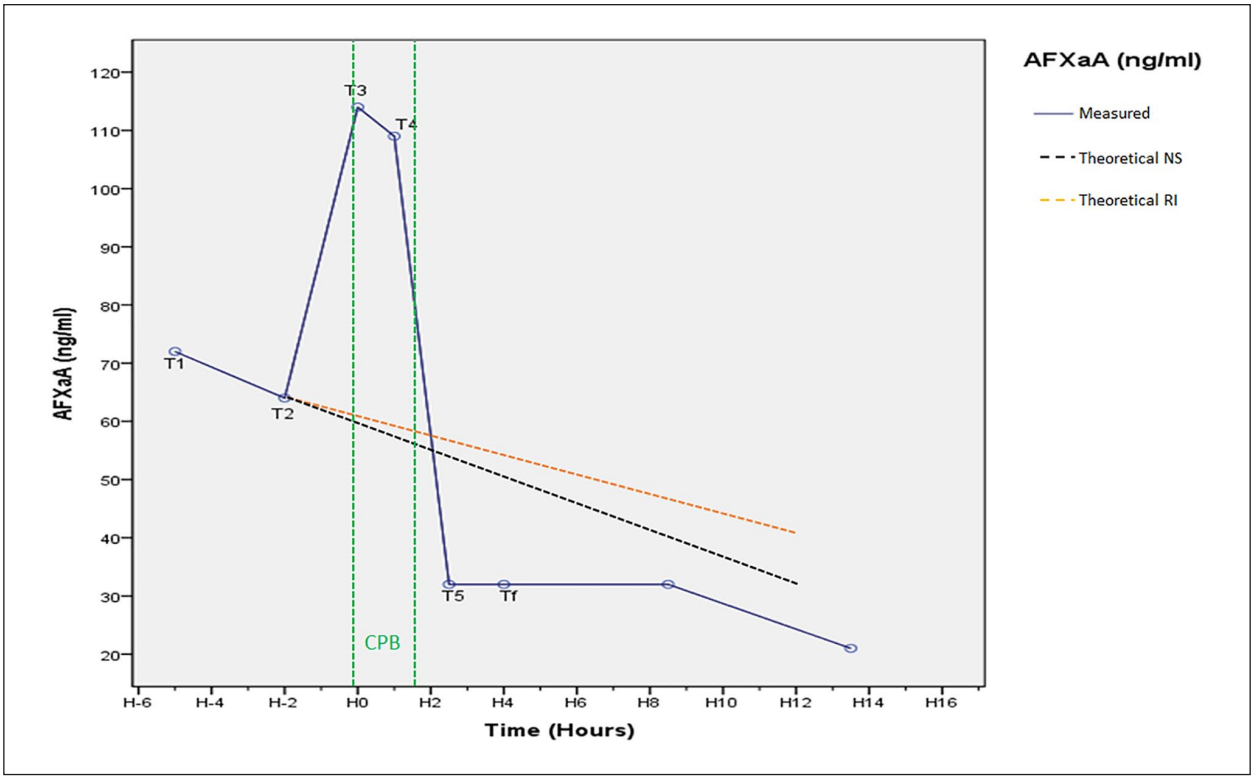

Figure 1. Evolution of AFXaA plasma levels.
CPB: cardiopulmonary bypass; NS: normal subjects; RI: estimated patient rate according to renal function; Tf: patient's admission in the intensive care unit; T1: patient's admission in operating room; T2: anesthesia induction; T3: CPB initiation; T4: CPB weaning; T5: patient's chest closure (after protamine administration). Therapeutic range: 32–67 ng/ml.

In conclusion, these observations suggest that CytoSorb® may increase Apixaban clearance and might facilitate perioperative hemostatic management.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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