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Case report

Fatal thrombosis with activated factor VII in a paediatric patient on extracorporeal membrane oxygenation

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Abstract

Bleeding remains a potential complication for patients requiring extracorporeal life support systems. Recombinant activated factor VII (rFVIIa) is one of the drugs used in controlling bleeding. Its use is generally found to be safe. We report a paediatric patient who developed fatal thrombosis with the use of rFVIIa whilst on extracorporeal membrane oxygenation and discuss the possible factors that lead to fatal thrombosis.

Keywords: Extracorporeal membrane oxygenation; Thrombosis; Bleeding

1. Introduction

Extracorporeal membrane oxygenation (ECMO) requires systemic anticoagulation to prevent in-circuit thrombosis. Patients who undergo surgical interventions whilst on ECMO, or require ECMO after surgical intervention are at risk of major bleeding despite refinements in the technique of anticoagulation. The usual approach for such patients is to exclude a surgical cause, correct coagulopathy and use antifibrinolytic drugs. Some patients continue to bleed despite this approach. In such patients the use of recombinant activated factor VII (rFVIIa) was described [1,2] to be safe and effective. We have used rFVIIa on several patients (both adult and paediatric) in similar situations with no untoward effects and have achieved good control of bleeding. However one of our paediatric patients developed fatal thrombosis with the use of recombinant activated factor VII whilst on ECMO due to a combination of factors that we discuss in this case report.

2. Case report

An 18-month-old female (weighing 7.3 kg) was admitted to our unit for mitral valve replacement. On admission she had a recent history of vomiting with marked decrease in oral intake. Intravenous fluids and enteral feeds were commenced to improve hydration. Four days later she became febrile with leucocytosis due to gram-negative sepsis and hence surgery was postponed. She deteriorated further later the same day with profound bradycardia and hypotension requiring cardiac massage and inotropes. As there was no improvement in cardiac function in spite of resuscitation for about 30 min she was cannulated for veno-arterial (VA) ECMO. The ECMO circuit had a servo controlled roller pump (Stockert; Sorin Biomedical, Saluggia, Italy) with a collapsible assist reservoir (Avecor, Medtronic), a 3/8″ raceway made of Tygon S-65-HL tubing (Norton Performance Plastics, Akron, Ohio, USA), and a Medos Hi-Lite 2400 LT Poly-Methyl Pentene oxygenator, with integral counter current heat exchanger. The anticoagulation targets were used according to our standard protocol, aiming for an activated clotting time (ACT) of 160–200 s. She also required haemofiltration to support her renal function. After 5 days her myocardial function improved but her lungs remained significantly consolidated. She was taken for surgery whilst on ECMO at this stage as the white cell count and other inflammatory markers were improving. Mitral valve replacement was performed with a mechanical valve. During the operation her lungs were found to be consolidated, with no expansion at a peak inspiratory pressure of 60 cmsH_2O. Following surgery the skin was closed and she was explored again on the next day and a formal closure of sternotomy was performed.

She remained on ECMO over the week and serial echocardiograms confirmed improving cardiac function. However the lungs did not improve despite use of high frequency ventilation, surfactant and nitric oxide. On the 8th postoperative day she developed ST segment changes on electrocardiogram in lead II, aVL and V4-6 with worsening

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cardiac output. Echocardiogram at this stage was suggestive of a large thrombus adherent to the right atrial wall with a poor right ventricular function. There however was no elevation in troponin levels. The next day she was re-explored. Intraoperatively we found no intra-luminal clot in the right or left atria. However there was an intramural haematoma, related to the atrial septum being repeatedly sucked into the tip of the ECMO drainage cannula. The cannula was advanced past the mural haematoma deeper into the right atrium. As there was significant coagulopathy at this stage the chest was packed with swabs and a formal closure was planned after correcting coagulopathy. The patient was commenced on an infusion of aprotinin (Trasylol®, Bayer) (7 ml/h). Postoperatively there was persistent blood loss from the pericardial drains despite further surgical re-exploration and correction of coagulopathy. The total blood loss through the drains was 1645 ml over the immediate six hours postoperatively and during this time she received a total of 1502 ml of blood and blood products (245 ml of human albumin solution, 340 ml of cryoprecipitate, 282 ml of platelets and 632 ml of packed red cells). An echocardiogram showed poor ventricular function with spontaneous left ventricular contrast. At this point, according to our protocol we administered 90 mcg/kg of rFVIIa to control blood loss.

Shortly after commencing the infusion the patient became profoundly hypotensive, with cyanosis and mottling associated with an inability to maintain ECMO flow. There was clot formation in the oxygenator. Echocardiogram showed extensive thrombus in the left ventricle and aortic arch with reduced flow through the arterial cannula. As there was evidence of multiple thromboemboli in the aortic arch and peripheries, we felt there would be inevitable severe brain damage and little chance of a successful outcome. Following a discussion with her parents, and at their request, treatment was withdrawn.

3. Discussion

The published experience of rFVIIa seems to be mostly positive and there is a prevailing impression that it has a good safety record. Retrospective analysis of case series and trial data has suggested approximately 1% risk of thrombosis [3,4].

Steiner et al. summarised five case series of patients requiring cardiac surgery and endorsed the benefits of rFVIIa in reducing overall volume loss and blood product requirements with no adverse outcomes [5]. A further series including patients undergoing heart valve replacement surgery showed no significant adverse events [6]. The use of rFVIIa in non-haemophiliac and non-cardiac surgical patients estimated the risk of thromboembolism to be 1.4% [3]. In the cardiothoracic literature its use for intractable bleeding and the serious complication rate is also between 1% and 2% [7]. Previous experimental data have suggested that disseminated intravascular coagulation (DIC) may be responsible for thromboembolic complications due to increased circulating level of tissue factor [3]. Despite this rFVIIa has been successfully administered in a number of patients with DIC [4,8].

Amongst ECMO patients there is limited safety data available due to the small numbers involved. Two recent case series comprising five paediatric patients on ECMO after cardiac surgery reported rapid control of bleeding with no adverse reactions [1,2]. Our audit figures for the past 2 years show no adverse reactions in 10 paediatric patients who received rFVIIa whilst on ECMO.

Our case report differs from previous studies in which rFVIIa was used. The patient had a combination of multiple surgical interventions and a low flow rate across the mechanical mitral valve (with diminished leaflet movement) whilst on VA ECMO which probably predisposed to thrombus formation. We recommend that rFVIIa should probably be avoided in patients with disseminated intravascular coagulation on ECMO who have spontaneous ventricular contrast on echocardiogram (indicating stagnation of blood in the ventricle) and a mechanical valve prosthesis.

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