

Successful Use of Recombinant Factor VIIa in a Patient with Intractable Bleeding During Extracorporeal Membrane Oxygenation

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Abstract

Bleeding is still the most common complication during extracorporeal membrane oxygenation (ECMO) for temporary cardio-circulatory support. We present a case of a young man suffering from intractable hemorrhage during ECMO support, who was pre-treated with glycoprotein IIb/IIIa receptor antagonist Tirofiban due to a suspicion of myocardial ischemia. After failure of conventional hemostatic means, hemostasis was achieved by the donation of recombinant Factor VIIa (rFVIIa). Aspects of bleeding control during extracorporeal circulatory support, the use of Tirofiban and rFVIIa are discussed.

Key words

Recombinant Factor VIIa · extracorporeal membrane oxygenation (ECMO) · bleeding · Tirofiban

Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a final option for the treatment of patients in cardiogenic shock. One major problem during ECMO support is massive bleeding due to platelet dysfunction and clotting system activation with the need of massive transfusion of blood and blood components [1,2].

Glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors like Tirofiban have demonstrated their benefit in patients with unstable angina and non ST-segment elevation myocardial infarction, reducing the risk of death, myocardial infarction and readmission for unstable angina. This benefit has to be weighed against the increased risk for major bleeding, which is the main cause of death with these drugs [3,4].

Recombinant Factor VIIa (rFVIIa, NovoSeven®; Novo Nordisk, Denmark), a genetically engineered concentrate of human coagulation factor VIIa, was originally designed for the treatment of life-threatening hemorrhage in patients with hemophilia A and B. In cardiac surgery the experience with rFVIIa is limited to a few case reports [5,6].

Bibliography

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We report the case of a young man who suffered from severe bleeding under Tirofiban on ECMO and was treated successfully with rFVIIa.

Case Report

A 17-year-old young man, with a history of 3 syncopes collapsed at home. Resuscitation was started with a delay of 7 min by the emergency physician. The patient presented with ventricular fibrillation, which was terminated by repeated defibrillation. After 20 min resuscitation, the circulation had slightly stabilized and the patient was transported to the next hospital. The ECG record was interpreted as anterior wall ischemia. Therefore GP IIb/IIIa-inhibitor Tirofiban was given. In the meantime high-dose inotropic support (epinephrine up to 15 µg/kg/min) was started. Because no permanent stabilization was achieved, the patient was transferred to the ICU of our Cardiology Department. An emergent coronary angiography was performed and showed a normal coronary artery system without stenoses or occlusions. Transesophageal echocardiography showed a severely impaired left ventricular function with an estimated ejection fraction of 10% and hypo- to akinesis of all wall segments. Ca-sensitizer levosimendan (6 µg/kg/min over 1 h) was added to the therapy and an intraaortic balloon pump (balloon pump: CS 100™, balloon catheter: Fidelity™, Datascope GmbH, Bensheim, Germany) was implanted percutaneously via the right femoral artery. Despite the ongoing high-dose catecholamine therapy, the patient remained in cardiogenic shock. Therefore the decision was taken to put the patient on mechanical circulatory support by implanting an ECMO. This was done via median sternotomy, cannulating the ascending aorta and right atrium with conventional cannulas. The ECMO system consisted of a centrifugal pump (Jostra Rota Flow®, Maquet Cardiopulmonary AG, Hirrlingen, Germany) and a micro porous membrane oxygenator (Hilite®, Medos Medizintechnik AG, Stolberg, Germany) with the possibility of including a heat exchanger. Additional support with very high doses of norepinephrine (up to 50 µg/kg/min) was necessary. The postoperative course was critically complicated by massive hemorrhage with blood loss of up to 1000 ml/h. Total blood loss was 8500 ml. Because of the high volume loss the circulation remained unstable with a continuous need for high dose α-adrenergic support. A massive transfusion of packed red blood cells (22 units), fresh frozen plasmas (22 units) and thrombocytes (5 aphereses) was given without improving the bleeding situation. Additional therapy with Aprotinin and Desmopressin did not minimize the bleeding. A re-thoracotomy revealed no surgical bleeding. Laboratory examination showed normal TPZ (> 100%), INR (0.83), antithrombin III (82%) and fibrinogen (2.4 g/l), a slightly elongated PTT (51 s) and highly elevated D-Dimers (6459 µg/l). Platelet counts were between 145 and 170 Gpt/l. Because bleeding still continued, we decided to administer recombinant Factor VIIa in two bolus doses (420 kIU and 360 kIU) at an interval of one hour. During the next two hours the amount of bleeding dropped dramatically to 100 ml/h. A stable circulatory equilibrium permitting a reduction of catecholamines was reached. Myocardial function, controlled by transesophageal echo, recovered and weaning from ECMO was started. After 6 days of support, it was possible to explant the ECMO and the intraaortic balloon pump. We measured a cardiac output of 4.5 l/min and mixed venous

saturation was over 70% under low inotropic support (3 µg/kg/min epinephrine). Two days after explantation of the ECMO, a re-thoracotomy because of a pericardial tamponade was necessary. Three days later the patient was extubated without neurological deficits or other permanent organ failure. He was transferred to the normal ward after 10 days. No reason for his heart failure was found. There was no evidence of an infection with cardiotropic viruses. Four weeks later he was discharged home with a recovered LV-function at a low normal level. At follow-up the young man reported that he had returned to his normal life without any limitations and was continuing his education.

Discussion

ECMO is a final option for the treatment of patients with cardiogenic shock, especially when conventional means such as catecholamines and intraaortic balloon pump fail. It is relatively simple to implant and remove compared to other assist devices. Furthermore it is less expensive. Therefore we decided to implant an ECMO in our young patient, because the neurological prognosis was completely unclear at the time of admission to our hospital. Weaning rates from ECMO vary from 30–69% [1,2], depending on the patient population, indication for implantation, time of support and site of implantation. In our patient cardiac function had recovered within 6 days and weaning was successful. Nevertheless one major complication of long-term ECMO support is major bleeding, as observed in our patient. The continuous contact of the blood with the foreign surface of the extracorporeal circulation activates platelets and the clotting system resulting in consumption of clotting factors and platelet count decrease [1]. Multiple surgical re-explorations and numerous donations of blood and blood products (FFP, platelets) are therefore characteristic for the history of ECMO patients. The incidence of re-thoracotomies as well as the amount of blood and blood component units varies very much in the literature. Re-thoracotomy rates range from 35–62%. The number of blood units transfused also varies greatly. It ranges from 7 units to 24–26 units [1,2]. Smith et al. additionally reported an excessive use of platelets (up to 100 units) and fresh frozen plasmas (70 units) [2].

The situation of our patient was aggravated by the preoperative use of the GP IIb/IIIa receptor antagonist Tirofiban, which was given because of the suspicion of myocardial ischemia. The use of GP IIb/IIIa antagonists has shown beneficial effects, especially in patients with unstable angina or non ST-elevation myocardial infarction who are scheduled for early percutaneous intervention [3]. It is important to be aware that GP IIb/IIIa antagonists can cause life-threatening hemorrhage. Brown found that major bleeding was responsible for the vast majority (≈80%) of deaths caused by therapy with Eptifibatid, Tirofiban or Abciximab [4].

In our case, bleeding could not be controlled despite massive substitution of blood, fresh frozen plasmas, thrombocytes and other hemostatic drugs (Aprotinin and Desmopressin). Having

no more options, we decided to administer rFVIIa to obtain sufficient hemostasis, which happened promptly after the second donation. rFVIIa was originally designed to treat life-threatening bleeding in patients with hemophilia A or B. It was successfully used in over 6500 of such patients with severe hemorrhage for varying reasons [5]. In cardiac surgery the experience with rFVIIa is very limited. There is one case report where excessive bleeding occurred after heart valve repair, which was successfully stopped with rFVIIa, and one small series of 5 patients with massive bleeding disorders after heart valve replacement [6].

Although the exact mechanism of rFVIIa is not clear, it seems to initiate thrombin formation in interaction with tissue factor and higher doses activate factor X binding to activated platelets, leading to thrombin formation. Therefore rFVIIa seems to be effective in generating thrombin formation where this is needed, also in patients with a deficiency of clotting factors VII, VIII or IX and thrombocytopenia and thrombocytopathia [6]. This may explain the successful outcome in our case.

Because of its high cost and the lack of controlled studies the use of rFVIIa should be limited to special clinical situations. Nevertheless its application should be considered when conventional options are exhausted and it seems to be indicated by the prognosis of the patient. In our patient rFVIIa was able to act as a life-saving agent to control excessive intractable bleeding during ECMO support after pre-treatment with Tirofiban.

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