The Use of Activated Factor VII for Ventricular Septal Defect Closure in a Pediatric Patient With Hemophilia A and a High Titer of Inhibitor

Duncan G. de Souza, MD,* Peter E. Waldron, MD,† Benjamin B. Peeler, MD,‡ and Victor C. Baum, MD*

HEMOPHILIA A IS A bleeding diathesis caused by factor VIII (FVIII) deficiency. It may be complicated by inhibitors which are auto antibodies to FVIII.[1] Recombinant activated factor VII (rFVIIa) is a potent hemostatic agent approved by the Food and Drug Administration for use in hemophiliacs with inhibitors. A case in which rFVIIa was used for the successful closure of a ventricular septal defect in a patient with hemophilia A and a high titer inhibitor is presented.

CASE REPORT

A 9-month-old, 8-kg male was scheduled for closure of a perimembranous ventricular septal defect. The patient presented in the newborn period with bleeding after circumcision. Hemophilia A was diagnosed and FVIII therapy started. At 1 month old, the patient developed inhibitors to FVIII with a titer between 10 and 20 Bethesda units (BU). Symptomatic bleeds were managed with rFVIIa. Avoidance of FVIII would hopefully decrease the inhibitor to undetectable levels and surgery could subsequently be managed with FVIII. At 6 months old, congestive heart failure developed with no decrease of inhibitor titer. The pediatric cardiology service preferred surgery rather than continued medical management. The patient had not suffered any strokes or life-threatening bleeds. He had mild asthma that was well controlled.

The perioperative plan established with the pediatric hematologist called for rFVIIa (90 μg/kg) before surgery and continued every 2 hours. After routine anesthesia induction, the trachea was intubated, and arterial and central venous catheters were placed along with a transesophageal echocardiography probe. The baseline activated coagulation time (ACT) before the administration of rFVIIa was 560 seconds. The ACT was measured every 15 minutes for the first hour after receiving rFVIIa and remained above 500 seconds. Epsilon aminocaproic acid (EACA), 100 mg/kg, was given before cardiopulmonary bypass (CPB).

Good hemostasis was present during sternotomy. The next scheduled dose of rFVIIa was due immediately before heparinization. This dose of rFVIIa was not given. The patient was given 300 U/kg of heparin before CPB. The ACT after heparin was greater than 1,000 seconds. The CPB circuit was primed in the authors' standard fashion with packed red cells, crystalloid, albumin, mannitol, heparin, sodium bicarbonate, and EACA (100 mg/kg). No rFVIIa was added to the CPB prime. The total CPB time was 65 minutes with the lowest temperature of 35°C. During CPB, the platelet count was 169,000/μL, and the fibrinogen level was 97 mg/dL.

The patient separated easily from CPB. Heparin was reversed with protamine (4 mg/kg), and 100 mg/kg of EACA was given. Fresh frozen plasma (10 mL/kg) and platelets (10 mL/kg) were infused, and then rFVIIa was administered (90 μg/kg). The ACT was 162 seconds. There was good hemostasis for sternal closure. The trachea was left intubated, and he was taken to the pediatric intensive care unit.

A low-dose narcotic anesthetic was chosen to allow for rapid neurologic assessment. The patient moved all extremities without evidence of focal neurologic deficits. The dose of rFVIIa remained 90 μg/kg every 2 hours. On the day of surgery and the first postoperative day, the mediastinal drain output noticeably increased in the last 30 minutes before the next dose of rFVIIa. Blood products were given to maintain a hemoglobin of 10 mg/dL, a platelet count of 100,000/μL, and fibrinogen of 180 mg/dL. Given his complex coagulopathy, the patient remained intubated and sedated until the 3rd postoperative day when his trachea was extubated and the mediastinal drains were removed. The dosing interval of rFVIIa was then increased to every 4 hours. On the 6th postoperative day, the dosing interval for rFVIIa was increased to every 6 hours.

Thirteen days after surgery, sternal wound breakdown, tachypnea, and fever developed. He was not receiving any drugs that might contribute to delayed wound healing or sternal dehiscence. An echocardiogram revealed a large pericardial effusion with early cardiac tamponade physiology. The rFVIIa dosing interval was reduced to every 2 hours. He returned to the operating room for mediastinal exploration and sternal wound debridement. A large amount of hematoma was removed from the anterior mediastinum, and a bloody pericardial effusion was drained. The sternum was debrided and closed. The patient tolerated the procedure well. The trachea was extubated in the operating room, and he returned to the pediatric intensive care unit for observation. The patient went on to make an uneventful recovery. Immune tolerance induction was begun before discharge.

DISCUSSION

Severe hemophilia A occurs when the FVIII is less than 1% of normal. Well-established protocols exist for the perioperative replacement of FVIII.[2] Concentrates of FVIII and the ability to measure FVIII plasma levels allow the hemophiliac to be converted into a patient with normal coagulation. All types of surgeries have been performed successfully in patients with severe hemophilia.[3] The development of inhibitors to FVIII occurs in up to 30% of patients. Inhibitors are measured in BU. A titer of 1 BU indicates that twice the FVIII dose is required to produce the expected activity. An inhibitor titer of >5 BU is considered a high titer inhibitor and would require $>2^5$ or >32 times the standard dose of FVIII.

Options for temporary treatment include immunosuppressant drugs and plasmapheresis. The only method of eradicating the inhibitor is with a form of desensitization therapy known as immune tolerance induction.[4] This requires the regular administration of FVIII over months to induce tolerance and reduce the inhibitor titer. Success rates are inversely proportional to the level of inhibitor but are quoted at 75% to 80%. Another option is to wait for the FVIII inhibitor titer to fall by avoiding FVIII concentrates. After a period without exposure to FVIII, the inhibitor may become undetectable in the plasma and the patient can be given FVIII for surgery. If tolerance has not been established, there is usually a brisk anamnestic response and inhibitor titers rise quickly. This may preclude the use of FVIII postoperatively. The last option is to overwhelm the inhibitor with supratherapeutic doses of FVIII. Overwhelming the inhibitor with large doses of FVIII is only feasible when the inhibitor titer is low (<5 BU).

In 1999, the Food and Drug Administration approved rFVIIa (Novoseven; Novo Nordisk, Bagsvaerd, Denmark) for use in patients with hemophilia A or B and inhibitors. This unique

*From the Departments of *Anesthesiology, †Pediatrics, and ‡Surgery, University of Virginia, Charlottesville, VA.*

Address reprint requests to Duncan G. de Souza, MD, Department of Anesthesiology, University of Virginia Health System, PO Box 800710, Charlottesville, VA 22908-0710. E-mail: dgd6n@virginia.edu

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agent binds with tissue factor (TF). The rFVIIa-TF complex converts factor IX and factor X to their respective activated forms, factor IXa and factor Xa. Prothrombin is converted to thrombin by factor Xa and its cofactor V. This burst of thrombin generation leads to the formation of a stable hemostatic plug, ideally confined to the site of bleeding. The rFVIIa-TF complex effectively bypasses the FVIII deficiency. Independent of tissue factor, rFVIIa can activate factor IX and factor X on the surface of activated platelets.[5]

The dose range of rFVIIa is 30 to 270 μg/kg given as an intermittent bolus. The manufacturer recommends a dose of 90 μg/kg given every 2 to 3 hours (http://factorviia.com/pi.pdf). This is supported by the hemophilia literature.[6] In cardiac surgery, rFVIIa has been used as an "off-label" drug for uncontrolled post-CPB bleeding in nonhemophiliac adult patients with marked anecdotal success.[7] The risk of thrombosis, both arterial and venous, is poorly defined.[8,9] The risk of thrombosis in the pediatric population remains unknown with little published information.[10,11] The authors' literature search did not reveal any other cases of cardiac surgery in a hemophiliac patient with inhibitors. The authors planned to use rFVIIa in a dose and interval recommended by the hemophilia literature[6] and to use a combined schedule of rFVIIa with FEIBA (activated prothrombin complex concentrate) if hemostasis was not adequate with rVIIa alone.[12] There is no accepted test to monitor rFVIIa. The prothrombin time, a test of the extrinsic pathway, is usually less than 10 seconds. The activated partial thromboplastin time, which tests the intrinsic pathway, is generally minimally elevated. Both of these results occur at rFVIIa plasma levels that are far less than those achieved with standard dosing (http://factorviia.com/pi.pdf). The effect of rFVIIa on the ACT has not been reported. The authors considered the use of thromboelastography (TEG), but the coagulation laboratory was not satisfied with the reproducibility of results.

There was considerable discussion regarding rFVIIa and CPB. Some believed that rFVIIa should be continued every 2 hours even if that meant administering a dose on CPB and the CPB circuit should be primed with rFVIIa. In this way, there would be adequate plasma levels of rFVIIa after separation from CPB. The contrary view was that rFVIIa posed a risk of catastrophic thrombosis on CPB. Furthermore, the baseline elevated ACT (>500 seconds) that did not correct with rFVIIa left the authors wary of using the ACT as an appropriate monitor of anticoagulation. Avoidance of rFVIIa on CPB, confirmed injection of heparin directly into the right atrium, and doubling of the ACT from 500 to 1,000 seconds, made the authors confident that the patient was safely anticoagulated for CPB. TEG has not been used to confirm safe anticoagulation for CPB. The authors believe that the ideal method of ensuring a safe level of heparin for CPB would be to monitor the heparin concentration, but this test is not available to the authors. The combination of rFVIIa, a large amount of circulating tissue factor, and possibly a low heparin concentration despite an elevated ACT might combine to create the "perfect storm" for thrombosis on CPB. In this regard, the authors were struck by a recent case report of massive fatal thrombosis in an adult patient who was placed on extracorporeal membrane oxygen support after failed separation from CPB.[13] Severe coagulopathy was treated with rFVIIa. The patient developed clots in the extracorporeal membrane oxygen circuit and throughout the heart and aorta within 5 minutes of receiving rFVIIa. The authors decided the safest option was to avoid rFVIIa while on CPB. The authors also decided against giving a scheduled dose of rFVIIa if the initiation of CPB was imminent.

Recombinant FVIIa can only work if there is sufficient substrate. The substrate is the platelet surface and the coagulation factors "downstream" from factor VII in the coagulation cascade. Thus, there must be sufficient levels of factor V, factor X, prothrombin, fibrinogen, and platelets. The authors used the fibrinogen level of 97 mg/dL while on CPB (normal range, 180-400 mg/dL) as a surrogate for the expected decrease in all coagulation factors. It was decided that fresh frozen plasma was a better option than cryoprecipitate, which contains large amounts of fibrinogen but little factor V, X, and prothrombin. Although the platelet count on CPB was 169,000/μL, platelets were given empirically because of concerns of further dilutional thrombocytopenia and qualitative platelet dysfunction.

The sequence of events after separation from CPB was to reverse heparin with protamine and then administer EACA, fresh frozen plasma, and platelets before beginning rFVIIa. After all the previously mentioned were given, the authors were surprised and concerned to see an ACT of 162 seconds (baseline >500 seconds). This suggested the possibility of a prothrombotic state. Fresh frozen plasma (10 mL/kg) would be expected to raise the patient's FVIII level to 20% of normal. The authors postulate that much of the inhibitor was removed on CPB. When rFVIIa was added, the ACT normalized. Despite the authors' concern, no clots were seen by echocardiography and immediate postoperative assessment showed normal gross neurologic function without evidence of stroke.

On the 13th postoperative day, the patient developed bleeding complications that required reoperation. This raises the question of whether the effect of rFVIIa should have been monitored. There are case reports of TEG-guided rFVIIa therapy, but they describe using TEG to optimize the effect of rFVIIa in situations in which a patient is actively bleeding despite standard dosing.[14,15] This does not apply to the present patient who had a slowly accumulating bloody pericardial effusion. An echocardiogram on postoperative day 9 showed no pericardial effusion. When the patient became tachypneic on postoperative day 13, the echocardiogram revealed a large pericardial effusion. Retrospectively, the authors believe daily echocardiograms during this period could have diagnosed a small effusion, allowing more frequent rFVIIa dosing.

Hemophilia patients represent a perioperative challenge to hemostasis. The presence of FVIII inhibitors further complicated the planned major cardiac surgery, requiring close collaboration among anesthesiology, surgery, and hematology. The authors were required to implement a unique hemostatic plan with rFVIIa as the cornerstone. This is a very expensive therapy with hospital acquisition costs of $309,000. A thorough understanding of the properties of rFVIIa is needed to balance the risks of bleeding versus thrombosis in this clinical scenario that has not been described before. The authors believe that rFVIIa should not be given immediately before or while on CPB, and heparin concentration testing is the ideal way to ensure safe anticoagulation for CPB. Although TEG shows some promise, the best method for assessing the efficacy of rVIIa remains to be determined.

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