

Intraoperative Recombinant Activated Factor VII for Emergent Epidural Hematoma Evacuation

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We report a case of a chronically anticoagulated 59-year-old woman who underwent an L4 to L5 epidural block to relieve her low back pain and subsequently developed a T7 to L5 epidural hematoma with cauda equina and conus compression. Fresh frozen plasma and vitamin K were given before surgery, whereas recombinant activated factor VII was administered during surgery to

reverse the coagulopathy and to enable the emergent laminectomy and hematoma evacuation. Recombinant activated factor VII administration proved to be a useful adjunct in the emergent surgical management of a thoracolumbar epidural hematoma.

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The most common complication of coumadin use is adverse bleeding, with an estimated 3% chance for major hemorrhage every year. The intensity and duration of anticoagulation directly correlates with the incidence of hemorrhagic events (1,2). Epidural hematomas are dangerous complications of anticoagulant therapy and should be suspected in any anticoagulated patient presenting with spinal pain associated with motor and sensory deficits or urinary retention. Such patients often present as surgical emergencies because of impending neurological deficits.

Emergent reversal of coumadin-induced anticoagulation is not always easy: activated prothrombin complex concentrates may be thrombogenic, and fresh frozen plasma (FFP) may transmit bloodborne viruses and prions. Moreover, not every patient can tolerate the intravascular volume load associated with FFP administration.

Recombinant activated factor VII (rFVIIa) was originally developed to control bleeding episodes in hemophilia A and B patients with inhibitors to FVIII or FIX (3). In this report, we describe the intraoperative application of rFVIIa that enabled the successful evacuation of a thoracolumbar epidural hematoma in an anticoagulated patient.

Case Report

The patient was a 59-year-old woman with chronic low back pain, dilated cardiomyopathy, and paroxysmal atrial fibrillation on coumadin. She was treated with periodic epidural pain blocks for back pain by a physical medicine/rehabilitation physician. Eight hours after an L4-5 epidural injection, she developed increasing right lower extremity pain. She was taken to the emergency room, and her international normalized ratio (INR) was found to be 8.41; partial thromboplastin time (PTT) was 84.5 s.

Neurologic examination showed (right and left lower extremities, respectively) 4/5 4/5 iliopsoas, quadriceps, hamstrings, 5/5 4/5 gastrocnemius, and 4/5 4/5 anterior tibial and extensor hallucis longus muscle strengths. Sensation to pinprick and light touch was decreased equally on both lower extremities, but joint position sensation was intact on the left lower extremity. Perianal sensation and rectal tone were also decreased. Subsequently, the patient was given 5 mg of vitamin K IV.

An emergent magnetic resonance image revealed an extensive epidural hematoma involving the lower thoracic and lumbar spinal canal and extending from T7 to L5. The hematoma caused severe cauda equina and conus compression. At that time, 4 h after admission, 3 U of FFP was given, and she was transferred to SUNY Upstate University Hospital, where 2 U of FFP and 10 mg of vitamin K were given. Repeated coagulation studies, 9 h after the first emergency room visit, indicated prothrombin time (PT)/PTT/INR values of 24.4 s/45.6 s/2.14.

The patient was taken to the operating room. After the induction of anesthesia, but before surgical incision, 3.6 mg of rFVIIa (NovoSeven; Novo Nordisk, Princeton, NJ) was given IV. The dose was repeated 2 h later. A T9 to L5 decompressive laminectomy and epidural hematoma evacuation were performed. Estimated blood loss was 800 mL. On the first postoperative day, her PT/PTT/INR values were 13.6 s/21.1 s/1.06. Motor examination showed 5/5 strength in bilateral lower extremity muscles. Sensory examination

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was intact to light touch and pinprick on the right and slightly decreased on the left. A day later, the patient was able to stand and walk with a walker and was discharged home on the fifth postoperative day. Her coumadin was withheld for 2 wk.

Discussion

Emergent operations on coagulopathic patients are always challenging for the surgeon and the anesthesiologist. Prompt surgical management is often delayed in hemophiliacs, patients with hepatic dysfunction, and therapeutically anticoagulated patients because of the inability to correct the coagulopathy with FFP, vitamin K, or activated prothrombin complex concentrate. rFVIIa was developed in the late 1980s to achieve hemostasis in hemophilia A and B patients.

Several possible mechanisms of action of rFVIIa have been described. Upon endothelial injury, a tissue factor/FVIIa complex is formed. This complex activates FX and FIX, leading to the formation of small amounts of thrombin, which, in turn, activates platelets and other coagulation factors, leading to further thrombin generation. FIXa binds to FVIIIa. The platelet-bound FIXa/FVIIIa complex further facilitates the FIX to FIXa conversion. Eventually, a full thrombin burst occurs that is mediated by FXa and FVa (3).

A tissue factor/FIX/FVIII-independent mechanism of action has also been postulated, because rFVIIa is also effective in hemophilia B patients and in individuals with acquired inhibitors to FVIII or FIX (4). Although rFVIIa probably exerts its hemostatic effect at the site of vascular injury, rare thromboembolic complications have also been reported (5,6). The procoagulant effects of rFVIIa can be monitored by PT, FVII clotting activity, plasma concentrations of FVIIa, and clinical assessment (cessation of bleeding and stability of hematocrit).

The rFVIIa does not transmit bloodborne pathogens. It is fast and easy to administer, and, because of its small volume (2.2 mL/1.2-mg vial), it can safely be given to patients with borderline cardiac function or congestive heart failure. Adequate hemostasis can be achieved with small doses (20–40 $\mu\text{g}/\text{kg}$), and its short elimination half-life (approximately two hours) renders rFVIIa an ideal drug to reverse anticoagulation before invasive diagnostic or therapeutic interventions (7); however, rFVIIa is expensive. One 1.2-mg vial costs \$2138 in our institution, which is comparable to 8 U of packed red blood cells (\$265 each) or four packs of platelet concentrates (\$554 each).

An IV bolus of rFVIIa resulted in reduced blood loss in retropubic prostatectomy patients (8), reversed dilutional coagulopathy in children undergoing posterior spinal fusion (9), and also proved beneficial during total hip arthroplasty (10). It has been successfully applied in cardiac surgery for redo coronary artery

bypass grafting, valve replacement and repair, left ventricular assist device implantation, and heart transplantation in a hemophiliac patient (11–15). After partial correction of the INR with FFP, a single dose of rFVIIa (40–90 $\mu\text{g}/\text{kg}$) successfully corrected the coagulopathy (secondary to coumadin administration, trauma, or end-stage liver disease) in nonhemophilic neurosurgical patients. Epidural or subdural hematomas and intraparenchymal or intraventricular hemorrhages could be successfully treated with craniotomies and ventriculostomies. Intracranial pressure monitor insertions could also be performed in patients with cerebral edema. Postprocedure imaging did not reveal any hemorrhagic complications (16,17). A rapidly deteriorating patient with an acute subdural hematoma and a preoperative INR of 6.39 received a single large-dose (120 $\mu\text{g}/\text{kg}$) rFVIIa injection, because time did not permit initiation of the standard treatment with vitamin K and FFP (18).

Since our patient presented with moderate congestive heart failure, she might not have been able to tolerate the intravascular volume load of further FFP transfusions. Moreover, her impending neurological deficits prompted emergent surgical intervention. Her coumadin-induced coagulopathy was successfully reversed with the combination of vitamin K, FFP, and two doses of intraoperatively administered rFVIIa. No complications were encountered.

In conclusion, rFVIIa administration, together with vitamin K and FFP, proved to be a useful adjunct in the emergent surgical management of a thoracolumbar epidural hematoma.

References

1. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)—Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996;348:423–8.
2. Ansell J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. *Chest* 2001;119:S22–38.
3. Hedner U. NovoSeven as a universal haemostatic agent. *Blood Coagul Fibrinolysis* 2000;11:S107–11.
4. Hoffman M, Monroe DM, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis* 1998;9:S61–5.
5. Peerlinck K, Vermeylen J. Acute myocardial infarction following administration of recombinant activated factor VII (NovoSeven) in a patient with haemophilia A and inhibitor. *Thromb Haemost* 1999;82:1775–6.
6. Rosenfeld SB, Watkinson KK, Thompson BH, et al. Pulmonary embolism after sequential use of recombinant factor VIIa and activated prothrombin complex concentrate in a factor VIII inhibitor patient. *Thromb Haemost* 2002;87:925–6.
7. Deveras RA, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002;137:884–8.
8. Friederich PW, Henry CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomized trial. *Lancet* 2003;361:201–5.

9. Tobias JD. Synthetic factor VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. *Anesthesiology* 2002;96:1522-5.
10. Slappendel R, Huvers FC, Benraad B, et al. Use of recombinant factor VIIa (NovoSeven) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. *Anesthesiology* 2002;96:1525-7.
11. von Heymann C, Hotz H, Konertz W, et al. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2002;16:615-6.
12. Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa (rFVIIa) after aortic valve replacement in a patient with osteogenesis imperfecta. *Ann Thorac Surg* 2002;74:910-2.
13. Hendriks HG, van der Maaten JM, de Wolf J, et al. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesth Analg* 2001;93:287-9.
14. Zietkiewicz M, Garlicki M, Domagala J, et al. Successful use of activated recombinant factor VII to control bleeding abnormalities in a patient with a left ventricular assist device. *J Thorac Cardiovasc Surg* 2002;123:384-5.
15. Sheth S, Dimichele D, Lee M, et al. Heart transplant in a factor VIII-deficient patient with a high-titre inhibitor: perioperative management using high-dose continuous infusion factor VIII and recombinant factor VIIa. *Haemophilia* 2001;7:227-32.
16. Lin J, Hanigan WC, Tarantino M, et al. The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. *J Neurosurg* 2003;98:737-40.
17. Park P, Fewel ME, Garton HJ, et al. Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. *Neurosurgery* 2003;53:34-8.
18. Veschev I, Elran H, Salame K. Recombinant coagulation factor VIIa for rapid preoperative correction of warfarin-related coagulopathy in patients with acute subdural hematoma. *Med Sci Monit* 2002;8:CS98-100.