J Anesth (2007) 21:258–260
DOI 10.1007/s00540-006-0481-y

Journal of
Anesthesia

Clinical reports

Postoperative pulmonary thromboembolism possibly associated with recombinant activated factor VII infusion for the treatment of uncontrolled hemorrhage during vertebral instrumentation

Zahid Hussain Khan[1], Alireza Ebrahim Soltani[2], and Payman Rahmani[1]

[1]Deptartment of Anesthesiology, Imam Khomeini Medical Center, Tehran University of Medical Sciences, Keshavarz Blvd., Tehran 14197, Iran
[2]Deptartment of Anesthesiology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract
We report the successful use of recombinant activated factor VII (rFVIIa) infusion in an 18-year-old man who underwent L3 laminectomy and pedicular screw fixation with severe refractory bleeding secondary to severe coagulopathy, which had remained unresponsive to conventional medical and surgical therapies. However, the patient developed a thromboembolic complication presumably associated with the use of rFVIIa. Although rFVIIa provides a dramatic response in intractable bleeding, it may cause a thromboembolic phenomenon which should be vigilantly considered and promptly treated.

Key words Recombinant activated factor VII · Thromboembolic phenomenon · Vertebral instrumentation

Introduction

Recombinant activated factor VII (rFVIIa; NOVO Seven, NOVO Nordisk, Copenhagen, Denmark) is a prohemostatic agent that can be used in patients with coagulation disorders [1].Its beneficial effect was demonstrated in hemophilia patients with inhibitors to factor VIII or IX [2] and its use has been suggested in a growing variety of hemostatic disorders, such as thrombocytopenia, thrombocytopathia [3], and disorders related to liver disease [4]. rFVIIa, a product licensed for use in patients with hemophilia and inhibitors, may be helpful in reducing bleeding in patients with refractory thrombocytopenia [5].

Indications for rFVIIa have increased as the effectiveness of rFVIIa as a hemostatic agent has been demonstrated in a number of clinical settings, including bleeding in patients following massive trauma, surgery, and warfarin overdose [6,7]. Several case reports have suggested rFVIIa to be effective in the treatment of bleeds in patients with platelet dysfunction and severe thrombocytopenia [8,9]. Adverse events, including thromboembolic phenomena, have been reported in patients receiving rFVIIa [1]. We report a case of intractable intraoperative bleeding which responded effectively to rFVIIa, but culminated in a thromboembolic phenomenon, probably associated with rFVIIa, that needed aggressive treatment.

Address correspondence to: Z. H. Khan
Received: January 19, 2006 / Accepted: November 9, 2006

Case report

An 18-year old man (American Society of Anesthesiologists [ASA] 1; height, 175 cm; weight, 70 kg) with a traumatic T10 and L3 fracture presented with lower limb weakness, partially distal and proximal paraplegia, and urinary incontinence, without any traumatic head injury, and a normal coagulation profile. Clinical examination showed a normal dorsalis pedis pulse with mild edema in both legs. Imaging studies revealed a stable T10 anterior compression fracture and L3 unstable burst fracture with compressive effect on the cauda equina. A computerized tomography (CT) scan performed within 2 h of presentation to hospital demonstrated a vertebral bone fracture. He was scheduled for L3 laminectomy and pedicular screw fixation. On the operating day, blood pressure was 125/85 mmHg. A complete blood count (CBC) was normal (hemoglobin [Hb], 13 g/dl; hematocrit [HCT], 39%; platelets [PLT], 150×10^9/l; partial prothrombin time [PTT], 39 s; PTT control, 30 s; prothrombin time [PT] control, 13 s) and PT was 15 s with an INR of 1.3 at the time of operation. He was not on anticoagulants or medications known to interfere with platelet function. The patient displayed no or hemophilia, coagulation disorder, of abnormal bleeding, and gave no history of drug usage.

Prior to induction, the patient was given diazepam 7.5 mg and sufentanil 15 μg. Anesthesia was induced

with thiopental sodium 300 mg, and endotracheal intubation was accomplished using pancuronium bromide 6 mg and lidocaine 80 mg, the latter injected 90 s prior to intubation. Anesthesia was maintained with 0.8% halothane and a fresh gas flow of 6 l·min^{-1}, comprising 31 of O2 and 31 of N2O. With the patient in the prone position, a surgical incision was initiated, extending from L1 to L5. Bleeding appeared to be abnormal just after the incision and persisted despite the attempting of surgical homeostasis. The coagulation profile obtained prior to transfusion had shown a PT of 13 s and a PTT of 38 s. As a result of ongoing refractory bleeding during surgery, 8 units of fresh frozen plasma (FFP) and 5 units of platelets were administered at room temperature. Coagulation tests obtained 1 h later showed a PT of more than 30 s and PTT more than 90 s; thus, an additional 6 units of FFP and 3 units of packed cells were administered in an attempt to normalize the coagulation profile. Surgical maneuvers for homeostasis, with FFP, platelets, and intravenous tranexamic acid (10 mg·kg^{-1}IV) administration proved to be ineffective. According to the hematologist's opinion, rFVIIa (122 µg·kg^{-1} every 2 h) was commenced and the bleeding showed a prompt reduction 5 min after its administration. The surgery lasted for 8 h and the patient was admitted to the intensive care unit for surveillance. Fortunately, with medical treatment for coagulopathy, his condition stabilized. Postoperatively, the hemostatic support continued and included rFVIIa (122 µg·kg^{-1}) every 4–8 h, and then daily for the final 5 days of admission. On the first day after surgery, a CBC showed Hb of 11 g·dl^{-1}, HCT of 33%, a white blood cell count of 8.5 $\times$ 10^{9}·/ml^{-1}, and a platelet count of 70 $\times$ 10^{9}·l^{-1}. PT returned to 16 s with an INR of 1.5, and PTT was 41 s, Fibrin degradation product was more than 160 µg·ml^{-1} and Ddimer was positive, at 1:32. On the fifth day after surgery the patient complained of chest pain but had a stable hemodynamic state revealing, a blood pressure (BP) of 110/75 mmHg, heart rate (HR) of 90·min^{-1}, arterial oxygen saturation (Sp_{O_2}) of 92% with out supplementary O_2, and an arterial blood gas (ABG) profile showing a P_{O_2} of 85 mmHg; P_{CO_2} of 34 mmHg; and HCO_3, 24 mmol·l^{-1}. Doppler sonography, using a (Color Doppler Sonoline G40 Ultrasound system (Siemens, USA) was performed, which confirmed deep venous thrombosis (DVT) located in the deep cuff and popliteal veins, possibly occurring after the use of rFVIIa. After establishing the diagnosis of DVT, treatment was initiated with 50 unit·kg^{-1}IV stat and 4 unit·kg^{-1}IV per hour of heparin. Heparin was later switched over to warfarin, and PT was maintained at 14 s and PTT at 40 s. The patient was discharged after 3 weeks with a normal coagulation profile, without residual neurological side effects, and normal Doppler sonography. His platelet count at discharge was 209 000·l^{-1}.

Discussion

rFVIIa mediates its effect via interaction with endogenous tissue factor, ultimately leading to thrombin generation [10]. High doses of rFVIIa also activate platelets and promote the conversion of prothrombin to thrombin. The use of rFVIIa is recommended in the management of bleeding occurring in hemophiliacs with inhibitors to factor VIII, and there is significant experience demonstrating its effectiveness in this setting [11]. Unfortunately, rFVIIa has a very short halflife, of 1·3 h in children and 2·7 h in adult patients [12]. The other major disadvantage of its use is its high cost.

rFVIIa can be given instantaneously without any need for confirmation of blood group or thawing of blood products, and can be given in a small volume, which is important in the setting of raised intracranial pressure where fluid restriction is desired.

Successful use of rFVIIa in controlling bleeding in patients with thrombocytopenia has been reported [8, 9, 13, 14]. High concentrations of rFVIIa activate platelets, and generate platelet surface factors IXa and Xa, ultimately leading to thrombin generation [15].

The decision to use daily doses of rFVIIa towards the end of our patient's admission, despite the short halflife of rFVIIa, was supported by a report of the successful use of daily rFVIIa in preventing ongoing bleeding in a patient with hemophilia and inhibitors to factor VIII [16]. It is possible that the clinical halflife of rFVIIa is longer than the reported half-life of 1·3–2·7 h.

rFVIIa was successfully employed by Hendricks et al. [17] as a single-dose treatment. We, on the other hand, continued it for 5 days on the explicit instructions of the hematologist. Our patient developed a thromboembolic phenomenon 5 days after the use of rFVIIa and not prior to that. If the thromboembolic phenomenon had occurred during the initial stages of the treatment, a logical option would have been discontinuation of rFVIIa. Our patient developed chest pain on the fifth day after surgery, which raised our suspicion of a possible thromboembolic phenomenon possibly related to the use of rFVIIa. Confirmation of DVT via Doppler sonography guided us to stop rFVIIa and initiate heparin therapy. Such thromboembolic events have been reported by others as well [1], and they should be kept in mind if the patient develops chest pain. Chest pain should be promptly investigated in the light of a thromboembolic episode which is stated to be a complication of rFVIIa infusion. This complication, if documented, is amenable to treatment. In our patient, chest pain and Doppler confirmation of DVT documented the diagnosis of a thromboembolic phenomenon. Pulmonary imaging studies can further help in arriving at the right and concrete diagnosis. We, however, could not obtain pulmonary imaging studies in our patient, and the diagno-

sis of a thromboembolic phenomenon was based on the Doppler sonography confirmation of DVT and the unwarranted chest pain. A possible factor that could be incriminated in this unusual cause of bleeding could be the release of necrotizing factor from damaged tissue [18].

Our case highlights the advantageous role of rFVIIa in intractable hemorrhage not responding to the conventional modes of surgical and medical treatments.

Although Deveras and Kessler [7] did not encounter any thromboembolic events while administering rFVIIa in 13 patients to reverse warfarin-induced excessive anticoagulation, we did observe DVT in our patient, which prompted aggressive and speedy management. Mayer et al. [19], in a randomized clinical trial, also noted a low frequency of thromboembolic events with rFVIIa administered after the onset of intracerebral hemorrhage, which favors the observation of DVT in our patient. The presence of DVT, coupled with the onset of unexplained chest pain, further established the occurrence of a thromboembolic phenomenon in this particular patient.

Our case highlights the fact that hypercoagulable complications, although rare, can occur with rFVIIa, and therefore patients should be carefully monitored for thromboembolic events. We, however, postulated that the chest pain in this particular patient could have been due to micro-embolic phenomena not severe enough to have caused a ventilation perfusion mismatch, as was evident in the ABG findings.

References

1. Kenneth Daivid B, Bruno R, Brian W (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double blind clinical trials. J Trauma Inj Infection & Crit Care 59:8–18
2. Lusher J, Ingerslev J, Roberts H (1998) Clinical experience with recombinant factor VIIa. Blood Coagul Fibrinolysis 9: S119–128
3. Hedner U (1998) Recombinant activated factor VII as a universal hemostatic agent. Blood Coagul Fibrinolysis 9 (Suppl II): S147–157
4. Hendriks HGD, Meijer K, de Wolf JTHM (2001) Reduced transfusion requirements by recombinant factor VII a in orthotopic liver transplantation, a pilot study. Transplantation 71: 402–405
5. Barnes C, Blanchette V, Canning P, Carcao M (2005) Recombinant FVIIa in the management of intracerebral haemorrhage in severe thrombocytopenia unresponsive to platelet-enhancing treatment. Transfus Med 15:145–150
6. O'Connell NM, Perry DJ, Hodgson AT (2003) Recombinant FVIIa in the management of uncontrolled hemorrhage. Transfusion 43:1711–1716
7. Deveras RAE, Kessler CM (2000) Reversal of warfarin induced excessive anticoagulation with recombinant factor VIIa concentrate. Ann Intern Med 137:884–888
8. Gerotziafas GT, Zervas C, Gavrielidis GM (2002) Effective hemostasis with rFVIIa treatment in two patients with severe thrombocytopenia and life-threatening hemorrhage. Am J Hematol 69:219–222
9. Billio A, Morello E, Amaddii G (2002) Treatment of refractory thrombocytopenic bleeding with rFVIIa: a case report. Blood 100:83b
10. Roberts HR, Monroe DM, Oliver JA (1998) Newer concepts of blood coagulation. Haemophilia 4:331–334
11. Lusher JM (2000) Inhibitor antibodies to factor VIII and factor IX: management. Semin Thromb Hemost 26:179–188
12. Hedner U (2000) NovoSeven as a universal haemostatic agent. Blood Coagul Fibrinolysis 11 (Suppl 1):S107–S111
13. Culic S (2003) Recombinant factor VIIa for refractive haemorrhage in autoimmune idiopathic thrombocytopenic purpura. Br J Haematol 120:909–910
14. Klamroth R, Gottstein S, Landgraf H (2002) Successful use of recombinant factor VIIa to prevent bleeding during major surgery in a patient with severe immune thrombocytopenia Blood 100:77b
15. Kjalke M, Johannessen M, Hedner U (2001) Effect of recombinant factor VIIa (Novoseven) on thrombocytopenia-like conditions in vitro. Semin Hematol 38 (4 Suppl 12):15–20
16. Saxon BR, Shanks D, Jory CB (2001) Effective prophylaxis with daily recombinant factor VIIa (rFVIIa-Novoseven) in a child with high titre inhibitors and a target joint. Thromb Haemost 86:1126–1127
17. Hendriks HGD, Van der Maaten MAA, de Wolf J (2001) An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. Anesth Analg 93:287–289
18. Haas T, Innerhofer P, Kuhbacher G (2005) Successful reversal of deleterious coagulopathy by recombinant factor VIIa. Anesth Analg 100:54–58
19. Mayer SA, Brun NC, Begtrup K (2005). Recombinant activated factor VII for acute intracerebral hemorrhage. New Engl J Med 352:777–785