CASE REPORT

Successful Treatment of Intractable Hemothorax with Recombinant Factor VIIa in a Nonhemophilic Patient

Yu-Feng Wei,[1,3] Chao-Chi Ho,[1,2] Ming-Tzer Lin,[1] Ang Yuan,[2] Chong-Jen Yu[1]*

Recombinant factor VIIa (rFVIIa) was developed for the treatment of bleeding in hemophilic patients with inhibitors. It has also been used to stop bleeding in nonhemophilic patients who fail to respond to conventional treatment. We report a case of catastrophic hemothorax in which bleeding was stopped by administration of rFVIIa. A 68-year-old woman with chronic hepatitis C-related liver cirrhosis was admitted due to pneumonia and parapneumonic effusion. The patient developed hemothorax and hypovolemic shock after thoracentesis. Conventional therapies including tube thoracostomy and transarterial embolization failed to stop the life-threatening bleeding. The bleeding stopped after administration of rFVIIa 100 μg/kg/BW at 2-hour intervals for a total of two doses on the 3rd day of hospitalization. Despite intensive care, however, the patient died due to nosocomial infection and multiple organ failure on the 12th day of hospitalization. Hemothorax in a nonhemophilic patient can be successfully treated with rFVIIa. [*J Formos Med Assoc* 2006;105(9):765–769]

Key Words: hemothorax, nonhemophilia, recombinant factor VIIa

Recombinant factor VIIa (rFVIIa) has been widely used in the treatment of bleeding episodes in hemophilic patients with inhibitors. Its mechanism in hemostatic efficiency, however, is not fully understood.[1] Factor VIIa plays a central role in initiating the process of blood coagulation by forming a complex with tissue factor (TF), when TF is exposed to circulation due to the damage of blood vessels.[2] In such systems, therapeutic doses of rFVIIa have been shown to induce normal thrombin generation and platelet activation in the absence of factors VIII and IX.[3] Although rFVIIa was designed for the treatment of hemophilic patients with inhibitors to factors VIII and IX, it has also been used "off-label" to enhance hemostasis in nonhemophilic patients who experience bleeding episodes unresponsive to conventional therapy.[4] There have been anecdotal reports of the successful use of rFVIIa in the control of life-threatening bleeding in patients with liver disease, but failures such as recurrent bleeding have also been reported.[5]

Case Report

A 68-year-old woman presented at our emergency department complaining of dyspnea and fever for 1 week. Her medical history revealed chronic hepatitis C virus (HCV) related liver cirrhosis, diabetes, hypertension and congestive heart failure. Pneumonia over the right lower lung field was

Departments of [1]Internal Medicine and [2]Emergency Medicine, National Taiwan University Hospital, Taipei, and [3]Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan.

Received: June 13, 2005
Revised: September 15, 2005
Accepted: November 1, 2005

***Correspondence to**: Dr Chao-Chi Ho, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shang South Road, Taipei 100, Taiwan.
E-mail: cch6677@ha.mc.ntu.edu.tw

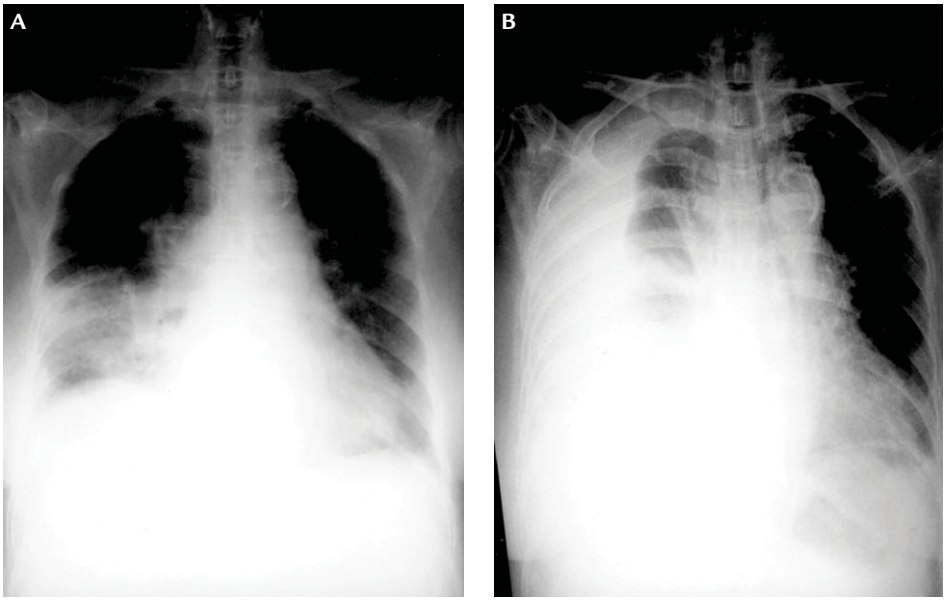

Figure 1. Initial chest roentgenography shows: (A) a pneumonic patch over the right lower lung field with parapneumonic effusion; (B) 5 hours after the procedure, a rapid accumulation of right pleural effusion is apparent.

initially diagnosed. Diagnostic thoracentesis from right pleural cavity disclosed parapneumonic effusion. Sudden onset of dyspnea and hypotension developed 5 hours after the procedure. Hemothorax was suspected because chest radiographs showed rapid accumulation of right side pleural effusion (Figure 1), and hemoglobin decreased from 9.1 to 6.9 g/dL. A chest tube was inserted into the right chest, and 1.6 L of uncoagulable blood was drained out immediately. Surgical intervention was not suggested by the chest surgeon due to the tendency of bleeding (international normalized ratio (INR) 1.7 and thrombocytopenia). The patient received blood transfusion and was admitted to the intensive care unit (ICU) in a stable condition on the same day.

In the ICU, physical examination showed a pulse rate of 82/min, respiration rate of 24/min, body temperature of 36.5°C and blood pressure of 120/70 mmHg under 6 μg/kg/min dopamine infusion. Pale conjunctivae and icteric sclerae were noted. Chest wall expansion and breathing sounds decreased over the right side. A chest tube was inserted into the right hemithorax with poor function. The abdomen was soft without tenderness. The findings of other physical examinations were unremarkable. Laboratory investigations showed persistent anemia (hemoglobin, 7 g/dL), thrombocytopenia (33×10^3/μL), impaired liver function (total/direct bilirubin, 2.54/1.8 mg/dL; alanine aminotransferase, 1370 U/L; aspartate aminotransferase, 448 U/L) and bleeding tendency (INR, 2.1; activated partial thromboplastin time (aPTT), 55 seconds). Copious blood oozed from the insertion wound of the chest tube, and hemoglobin remained low despite aggressive component therapy. Emergent angiography on the next day showed a bleeder over the lateral portion of the right fifth intercostal artery, and superselective embolization with glue mixed with lipiodol was performed. Postembolization angiography showed no more bleeding (Figure 2). However, hemoglobin remained low despite massive transfusion (2.5 L packed red cells, 2.5 L fresh frozen plasma, 36 units platelets, 30 units cryoprecipitate) after the procedure. On the basis of continuous intrathoracic bleeding in the absence of a major bleeder, two doses of rFVIIa 100 μg/kg/BW (7.2 mg/dose) were administered intravenously at an interval of 2 hours. The bleeding from the chest tube wound stopped immediately, and prothrombin time (PT) returned to normal (INR, 1). No further blood transfusion was required over the next 5 days (Figure 3). Although blood pressure stabilized after admission and dopamine was tapered off on the 2nd day of admission, the patient's liver function deteriorated gradually after the onset of shock. Hepatic failure progressed, and the patient

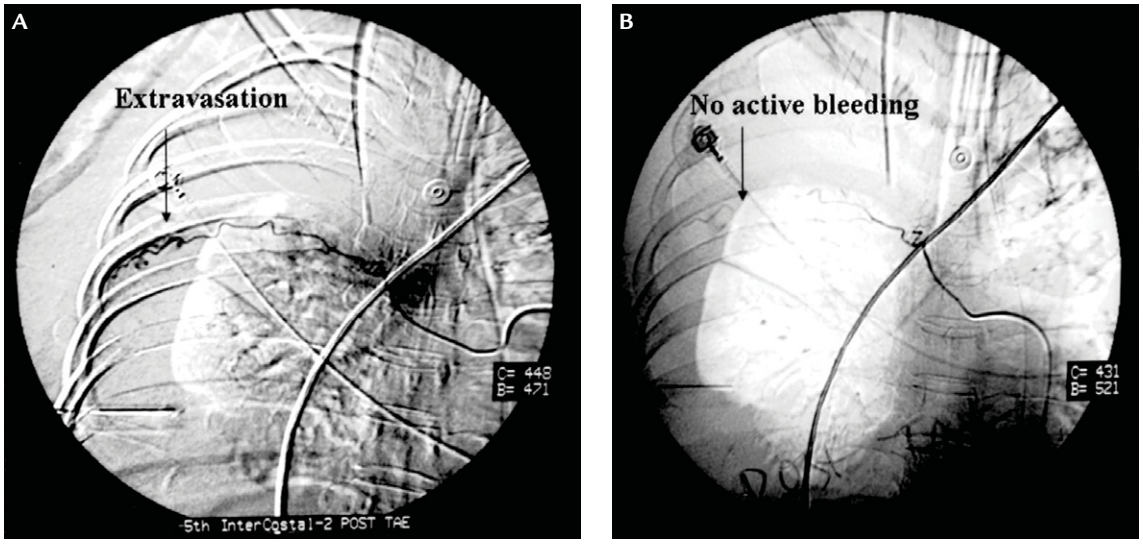

Figure 2. (A) Angiography shows a bleeder over the lateral portion of the right fifth intercostal artery. (B) Postembolization angiography shows no more bleeding.

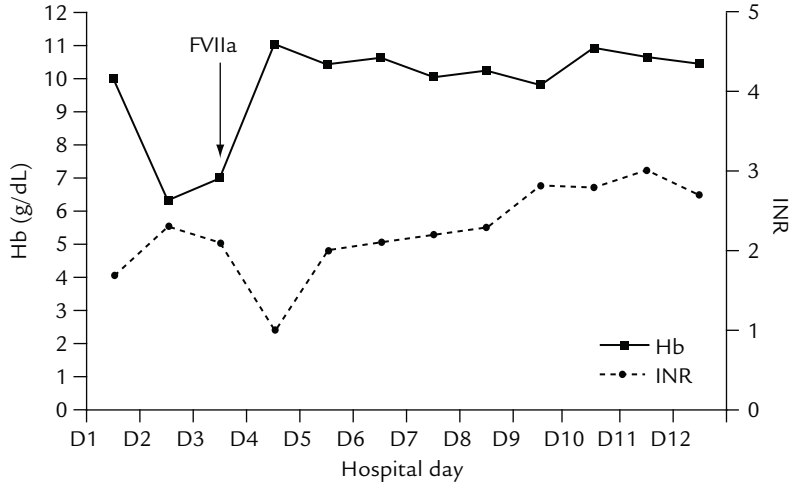

Figure 3. Hemoglobin dramatically recovered and stabilized without transfusion in the 5 days after two doses of rFVIIa administration; coagulation test (international normalized ratio, INR) also transiently normalized during this time.

Transfusion	Units				
Packed red cells	4	4	10		2
Fresh frozen plasma	10	16	10		
Platelet	30	48	36	24	
Cryoprecipitate	18	34	30		
Whole blood	4	8			

died of nosocomial infection and multiple organ failure on the 12th day of hospitalization.

Discussion

The most common cause of hemothorax is trauma. Other etiologies of hemothorax include neoplasm (primary or metastatic), dissecting aortic aneurysm, coagulation disorders, pulmonary embolism with infarction, catamenial and iatrogenic disorders.[6] The most common causes of iatrogenic hemothorax are perforation of a central vein by a percutaneously inserted catheter, followed by thoracentesis and pleural biopsy.[6] Tube thoracostomy, thoracoscopy and thoracotomy

should be considered as needed in patients with iatrogenic hemothorax as in patients with traumatic hemothorax. Angiographic embolization may be an alternative choice to thoracotomy in patients with massive bleeding from an intercostal artery.[7] This patient with massive and persistent hemothorax had a bleeder identified at an intercostal artery, but did not receive surgical intervention because of bleeding tendency. Although selective embolization stopped the bleeding from the intercostal artery, the patient's hemoglobin level did not increase even under aggressive transfusion. However, bleeding ceased dramatically after two doses of rFVIIa administration, and hemoglobin did not decrease thereafter.

rFVIIa was originally used for the treatment of hemophilic patients with inhibitors to either factor VIII (FVIII) or IX (FIX). It is also approved for the treatment of acquired hemophilia, congenital FVII deficiency and Glanzmann's thrombasthenia in Europe.[8] It is interesting to note that there were many reports suggesting that this product is safe and effective in controlling bleeding in nonhemophilic patients.[4] The treatment of hemothorax with rFVIIa in a nonhemophilic patient unresponsive to conventional therapy has not been previously reported. The mechanism of action of rFVIIa is not completely clear. Small quantities of FVIIa in circulation are not biologically active unless bound to TF that is exposed at the site of the vascular injury. The complex of TF and VIIa (TF-VIIa) initiates the coagulation cascade by activating factors X and IX, resulting in the production of a small amount of thrombin. Thrombin leads to platelet activation as well as activation of factors VIII, V and XI. The activated platelets provide the phospholipids surface and the factors necessary for the production of a critical level of thrombin, which in turn allows for the deposition of fibrin and clot formation.[1–3]

The half-life of rFVIIa is 2.60–2.84 hours in adults and is independent of dosage.[9] Based on clinical experience and pharmacokinetic studies, the recommended dosing schedule of rFVIIa for serious bleeding episodes and surgical coverage is 90–120 μg/kg/BW, given at 2-hour intervals in the first 24 hours until bleeding ceases.[10] Most bleeding can be stopped with two to three doses. That is why only two doses were given to this patient. There is still no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa, and shortening of PT and PTT does not necessarily reflect in clinical effectiveness.[11]

rFVIIa has been used for the treatment of bleeding in patients with liver disease.[12] Most patients treated with rFVIIa have maintained hemostasis, including rescue therapy in gastrointestinal or variceal bleeding, during liver transplantation and partial hepatectomy in noncirrhotic patients, and on prophylactic use in patients undergoing laparoscopic liver biopsy or colonoscopic polypectomy.[12] Other uses of rFVIIa include treatment of hereditary clotting factor deficiencies,[8] severe thrombocytopenia,[13] platelet dysfunction,[14] severe trauma,[15] intractable bleeding during surgery,[16] life-threatening postpartum hemorrhage,[17] pulmonary hemorrhage,[18] intracranial hemorrhage[19] and reversal of anticoagulation intoxication.[20] O'Connell et al[21] reported a series of nonhemophilia patients treated with rFVIIa for major hemorrhages. Of the 40 patients who received rFVIIa for uncontrolled hemorrhage, bleeding either stopped or decreased in 32 (80%). However, 23 (57.5%) of the 40 patients died from nonhemorrhagic causes. They concluded that rFVIIa was effective in nonhemophilia patients with bleeding, but there was a high mortality rate from nonhemorrhagic causes.

It is likely that the safety of rFVIIa is due to its selective location at the site of bleeding. The incidence of serious adverse events due to thromboembolism in hemophilic patients with inhibitors is about 1%.[22] The incidence in nonhemophilic patients, however, is not known. Many of the thrombotic events have occurred in patients with a predisposition to thrombotic complications such as diabetes mellitus, obesity, cancer and atherosclerotic cardiovascular disease, and administration of rFVIIa to such patients should be approached with caution.[22] Further study of the safety of rFVIIa use in hemophilic and nonhemophilic patients is warranted.

The available evidence suggests that rFVIIa is both safe and effective in hemophilic and non-hemophilic conditions. This treatment appears to be an attractive option in some patients experiencing life-threatening hemorrhage, although better delineation of its indications, including safety, appropriate dosing and cost-benefit is needed.

References

1. Lisman T, De Groot PG. Mechanism of action of recombinant factor VIIa. *J Thromb Haemost* 2003;1:1138–9.
2. Butenas S, Brummel KE, Branda RF, et al. Mechanism of factor VIIa-dependent coagulation in hemophilia blood. *Blood* 2002;99:923–30.
3. Hoffman M, Monroe DM III. The action of highdose factor VIIa (FVIIa) in a cell-based model of hemostasis. *Semin Hematol* 2001;38:6–9.
4. Roberts HR, Monroe DM III, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol* 2004;41:101–8.
5. Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista F, et al. Recombinant-activated factor VII as hemostatic therapy in eight cases of severe hemorrhage from esophageal varices. *Clin Gastroenterol Hepatol* 2004;2:78–84.
6. Light RW. Hemothorax. In: *Pleural Disease*, 4th edition. Philadelphia: Lippincott Williams and Wilkins, 2001:320–6.
7. Kessel B, Alfici R, Ashkenazi I, et al. Massive hemothorax caused by intercostal artery bleeding: selective embolization may be an alternative to thoracotomy in selected patients. *Thorac Cardiovasc Surg* 2004;52:234–6.
8. Poon MC. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol* 2001;8:312–8.
9. Erhardtsen E. Pharmacokinetics of recombinant activated factor VII (rFVIIa). *Semin Thromb Hemost* 2000;26:385–91.
10. Hedner U. Dosing with recombinant factor VIIa based on current evidence. *Semin Hematol* 2004;41:35–9.
11. Gabriel DA, Carr M, Roberts HR. Monitoring coagulation and the clinical effects of recombinant factor VIIa. *Semin Hematol* 2004;41:20–4.
12. Caldwell SH, Chang C, Macik BG. Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: a break from convention in need of controlled trials. *Hepatology* 2004;39:592–8.
13. Goodnough LT. Experiences with recombinant human factor VIIa in patients with thrombocytopenia. *Semin Hematol* 2004;41:25–9.
14. Almeida AM, Khair K, Hann I, et al. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol* 2003;121:477–81.
15. Martinowitz U, Kenet G, Lubetski A, et al. Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anaesth* 2002;49:S15–20.
16. Tanaka KA, Waly AA, Cooper WA, et al. Treatment of excessive bleeding in Jehovah's witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology* 2003;98:1513–5.
17. Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *Br J Anaesth* 2005; 94:592–5.
18. Pastores SM, Papadopoulos E, Voigt L, et al. Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest* 2003;124:2400–3.
19. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VIIa for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777–85.
20. Deveras RA, Kessler CM. Reversal of warfarin induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002;137:884–8.
21. O'Connell NM, Perry DJ, Hodgson AJ, et al. Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion* 2003;43:1711–6.
22. Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost* 2004;2:899–909.