

Successful Hemostasis with Recombinant Activated Factor VII in a Patient with Massive Hepatic Subcapsular Hematoma

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Key Words

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Abstract

Recombinant activated coagulation factor VII (rFVIIa) is known to be effective in the management of acquired deficiencies of factor VII and platelet function defects. But recently, rFVIIa has been successfully used to treat ongoing bleeding in disseminated intravascular coagulopathy (DIC) condition. The patient reported here was suspected to be suffering from toxic hepatitis on admission. After percutaneous liver biopsy, bleeding occurred and did not stop even after right hepatic artery embolization. The patient developed a severe hemorrhage that resulted in hypovolemic shock, hemoperitoneum, and a massive subcapsular hematoma. The patient then developed DIC due to massive transfusion, as well as acute liver necrosis. The patient was given 400 µg/kg of rFVIIa. Recombinant factor VIIa was administered in an attempt to control the bleeding. This stabilized the hemoglobin levels of the patient. The patient gradually recovered in 4 months. In conclusion, this case suggests that rFVIIa can be successfully used for the hemostasis of uncontrolled bleeding in DIC.

Introduction

Although recombinant factor VII activated form (rFVIIa; NovoSeven[®], Novo Nordisk A/S, Bagsvaerd, Denmark) was initially developed for the treatment of bleeding associated with inhibitors to factor VII and IX, most recently it has been used effectively in the management of acquired deficiencies of factor VII and platelet function defects. A cell-based model of hemostasis can explain why it can work in the disseminated intravascular coagulopathy (DIC) condition [1].

The worst complication of liver biopsy is bleeding. While this complication resolves spontaneously in a normal hemostatic condition in most cases [1], massive subcapsular hematoma of the liver can occur after percutaneous transhepatic liver biopsy [2]. Such hematomas are usually more commonly seen after major blunt trauma or liver transplantation [3, 4] or in amyloidosis patients [5].

We recently treated a patient who was admitted because of alleged toxic hepatitis. She was subsequently suspected to have an autoimmune hepatitis. To differentiate between these two disease conditions, we performed a percutaneous liver biopsy. As a consequence, the patient suffered continuous bleeding for 4 days and a subcapsular hematoma developed. We report here that this complication was successfully managed by using rFVIIa.

Case Report

A 40-year-old woman presented to our medical center with the chief complaint of jaundice. The patient felt weakness, loss of appetite, and nausea. The patient had drunk an extract made by boiling down arrowroot for 1 month. Her medical history only revealed a 2-year history of hypertension. There was no family history of hepatobiliary disease. Apart from her jaundice, the patient's physical examination was unremarkable. Her vitals were as follows: blood pressure, 100/80 mm Hg; heart rate, 80/min; respiratory rate, 20/min; body temperature, 36.5°C. Complete blood count (CBC) revealed white blood cell (WBC) counts of 8,790/ μ l, hemoglobin (Hb) levels of 12.9 g/dl, and platelet counts of 284×10^3 / μ l. Liver function test results revealed AST levels of 765 IU/l, ALT levels of 463 IU/l, alkaline phosphatase levels of 248 IU/l, total bilirubin levels of 20.1 mg/dl, and direct bilirubin levels of 15.2 mg/dl. The patient was treated conservatively with hydration for a week, and her laboratory results improved to AST levels of 462 IU/l, ALT levels of 358 IU/l, and total bilirubin levels of 7.4 mg/dl. However, since the patient had weakly positive serum anti-nuclear antibody levels (1:80), we decided to conduct an ultrasonography-guided percutaneous liver biopsy to differentiate autoimmune hepatitis from toxic hepatitis.

On the ninth day in hospital, the liver biopsy was performed at 1:00 p.m. We marked the biopsy site on the skin during ultrasonography and shot an 18-gauge spring-loaded liver biopsy needle (Angiomed Autovac biopsy needle; Bard, Karlsruhe, Germany) at the biopsy site twice. On the first shot, we obtained a 0.7 cm-sized tissue piece and the patient did not complain of any symptoms. On the second shot, a 3 cm-sized liver tissue was obtained. The patient then complained that she felt a twinge-like pain in her right chest that radiated into the right shoulder. The patient also reported light dyspnea. Analgesics were administered, after which the pain and dyspnea gradually subsided. At that time, the patient's vitals were stable and further sequelae were not expected. On the same day, at 11:30 p.m., the patient complained of dizziness and abdominal distension. She then became confused and lost consciousness. Her systolic blood pressure was 80 mm Hg and diagnostic paracentesis revealed bloody ascites. We suspected the patient was suffering from hemorrhagic shock due to bleeding from an iatrogenic liver injury. Abdominal CT showed that the right lobe of the liver was severely compressed by a huge subcapsular hematoma (fig. 1). Packed red blood cells (RBCs) and crystalloid were administered and inotropics were infused. At the same time, an emergency angiography was performed which revealed that the bleeding came from the right hepatic artery. Consequently, we embolized the culprit vessel by intravascular coiling. The patient's blood pressure remained relatively stable after the procedure, but began to fall when we tried to taper off the dose of inotropics. A second angiogram obtained on the tenth day in hospital showed no evidence of arterial bleeding.

The patient was admitted to the intensive care unit (ICU). Despite being transfused with 10, 3, 3, and 2 units of packed RBC on days 10, 11, 12, and 13, respectively, the patient's hemoglobin levels gradually decreased from 13.1 to 8.8 g/dl. In total, 18 units (4,500 ml) of packed RBC were transfused prior to the infusion of rFVIIa. On the eleventh day in hospital, the patient was given 500,000 units of aprotinin (Rotinin inj; Han Lim Pharm, Seoul, Korea) over 15 min as the loading dose, after which 200,000 units were infused continuously each hour for 5 h as the maintenance dose. Despite the injection of aprotinin, the patient's hemoglobin levels decreased persistently. On the twelfth day in hospital, the patient was given 2.4 mg (40 µg/kg) of rFVIIa 4 times every 2 hours, and then 4.8 mg (80 µg/kg) 3 times every 2 hours. On day 13, the blood pressure and hemoglobin levels of the patient stabilized in the absence of transfusion (fig. 2). On day 13, the patient's laboratory results revealed that her prothrombin time was 20.7 s (INR 2.03), her activated partial thromboplastin time was 82.0 s, her fibrin degradation product level was 17.5 µg/ml, and her D-dimer level was 6,245 ng/ml. The patient was treated in the ICU for 2 months because of the intra-abdominal and the intrathoracic hematoma and its complications, namely DIC due to massive transfusion, acute renal failure, acute respiratory failure, and liver failure due to liver necrosis.

The patient recovered gradually from these complications in terms of liver injury and jaundice (fig. 3) and was discharged 4 months after her admission. A follow-up CT scan showed a considerable reduction in the size of the subcapsular hematoma. The results of the liver biopsy were compatible with toxic hepatitis, but we remained unable to exclude autoimmune hepatitis completely.

Discussion

We describe here a patient with subcapsular hematoma that developed after percutaneous liver biopsy. To obtain hemostasis, we attempted embolization of the right hepatic artery and intravenous injections with aprotinin. These methods failed to stem the gradual decrease in hemoglobin levels that persisted despite the transfusion of large amounts of packed RBCs. Finally, four 40 µg/kg doses and three 80 µg/kg doses of rFVIIa were administered intravenously. Ten hours later, the hemoglobin levels stabilized in the absence of further transfusion.

Clinically significant intraperitoneal hemorrhage is the most serious bleeding complication of percutaneous liver biopsy [1]. The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10,000 to 1 in 12,000 [1, 6]. The mortality rate is highest among patients who undergo biopsies of malignant lesions. Cirrhosis is another risk factor for fatal bleeding after liver biopsy.

Two cases of subcapsular hematoma have been reported, one in a patient receiving a liver graft and the other in a patient with cholestatic liver disease. The present case had severe cholestasis associated with toxic hepatitis, but no underlying chronic liver disease [3, 7].

If hemorrhage is suspected, the administration of IV fluids and blood products should be performed immediately to improve the patient's hemodynamic status, and a surgeon and an angiographer should be kept on standby. If hemodynamic instability persists for a few hours despite the use of aggressive resuscitative measures, angiography and embolization or surgical exploration are indicated [2]. It is generally believed that timely percutaneous external drainage of the large hematoma is needed to prevent the compression of functioning hepatocytes, which may harm the liver, although some authors insist that it may remove the tamponade effect of the hematoma on the bleeding focus [3]. We frequently performed paracentesis after confirming complete hemostasis from the liver.

While rFVIIa was developed to manage bleeding in hemophilic patients who express inhibitors of clotting factors, it was unclear why rFVIIa but not endogenous FVII could overcome coagulopathy in hemophilic patients. A cell-based conceptual model of

hemostasis that focuses on the roles of specific cell surfaces in controlling the coagulation process may shed light on this phenomenon. FVIIa can bind to activated platelets and, once bound to the activated platelet surface, can activate factor X. The cell-based model suggests that while the low levels of endogenous FVIIa cannot induce thrombin generation on the platelet surface, when rFVIIa is added to the system, thereby elevating the total FVIIa levels, the thrombin-generating function of the platelet surface can be restored [8]. In the present case, rFVIIa was administered after we identified and embolized the bleeding focus in the course of right hepatic artery because the bleeding did not stop, even though there was no obvious bleeding point after embolization, as indicated by the second angiography. After administration of rFVIIa, there was no evidence of further bleedings. Thus, we can presume that the administration of rFVIIa successfully controlled the undisclosed bleeding from the site where the biopsy was performed.

Which dose of rFVIIa is appropriate for a bleeding patient who does not have deficiency of coagulation factor VII? One study showed that when patients with chronic liver disease are given 80 µg/kg rFVIIa prior to surgical incision during orthotopic liver transplantation, it is both safe and effective [9]. Another study showed that the decline in hematocrit during an operation undergoing liver resection was smallest in the group receiving 80 µg/kg of rFVIIa, and that this was associated with a significant overall improved effect of treatment [10]. In our patient, we administered a half dose of rFVIIa 3 times on the twelfth day. On the thirteenth day in hospital, we administered the full dose of rFVIIa 3 times because the half dose was suboptimal for hemostasis, totaling 400 µg/kg.

rFVIIa is effective for hemostasis not only in hemophiliac patients [11], but also in patients with thrombocytopathies [12], liver transplantation [9, 13], and hemophiliac patients undergoing orthopedic surgery [14]. We would like to report the successful use of rFVIIa in a DIC patient with potentially fatal iatrogenic bleeding. We also suggest that DIC should be omitted from the contraindication list of rFVIIa use.

Fig. 1. The presence of a subcapsular hematoma is shown on the pre-enhanced image (left), while massive hepatic necrosis is revealed by the post-enhanced image (right).

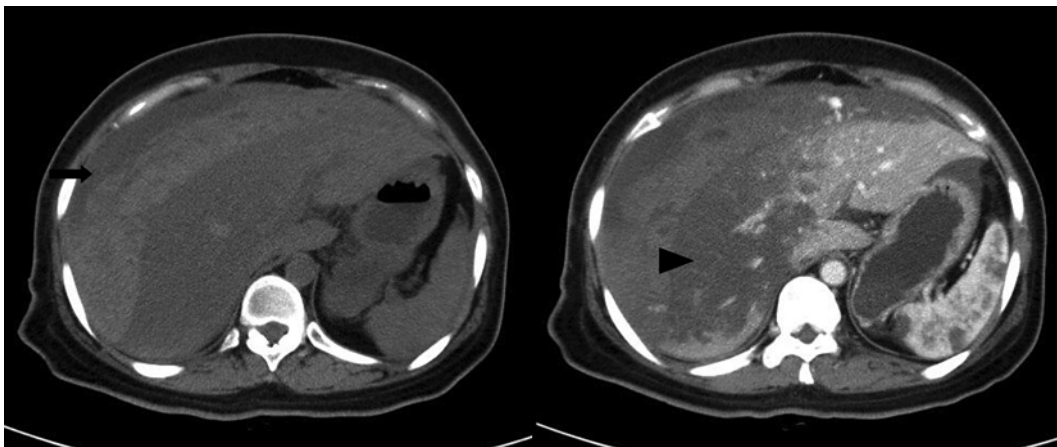


Fig. 2. Blood pressure (BP) and hemoglobin (Hb) profiles of the patient before and after rFVIIa administration. PRC = Infusion of packed red blood cells. The hemoglobin level was stable after rFVIIa without PRC transfusion.

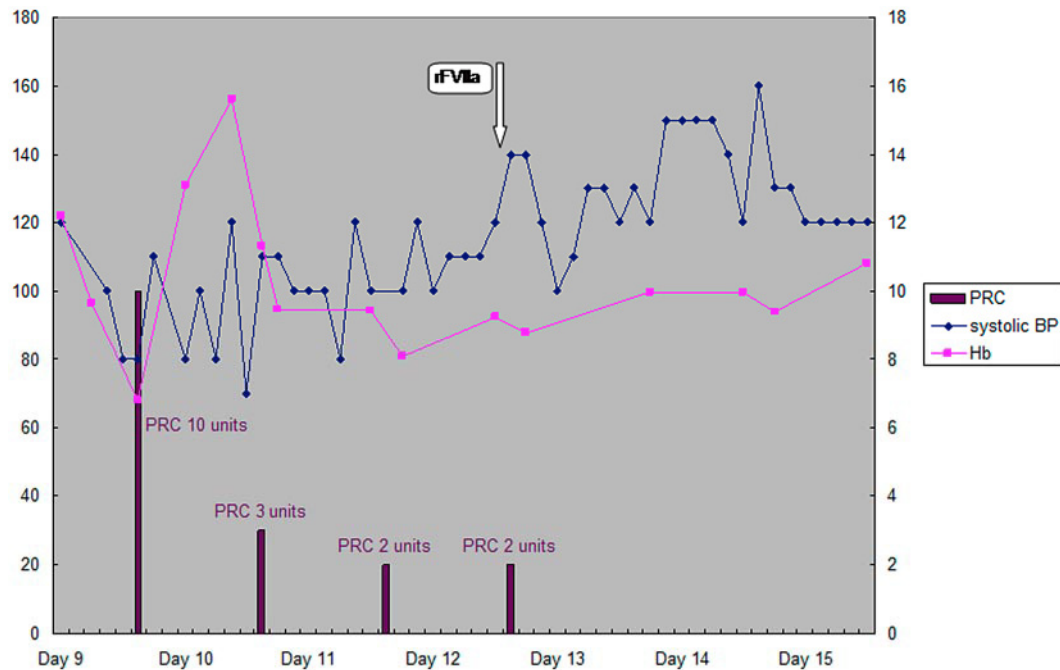
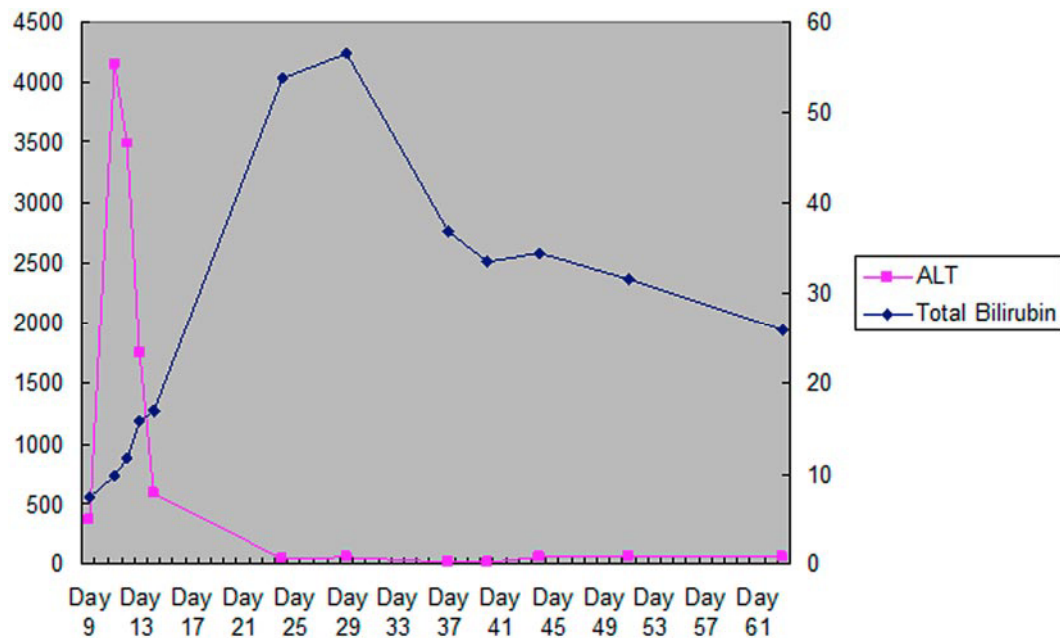


Fig. 3. Serum ALT and bilirubin profiles during hospitalization. After skyrocket increase of ALT and total bilirubin due to right lobe infarct, the ALT and total bilirubin became normal 3 months after liver biopsy.



References

- 1 McGill DB, Rakela J, Zinsmeister AR, Ott BJ: A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990;99:1396–1400.
- 2 Bravo AA, Sheth SG, Chopra S: Liver biopsy. *N Engl J Med* 2001;344:495–500.
- 3 Moon DB, Lee SG, Hwang S, Park KM, Kim KH, Ahn CS, Chu CW, Lee YJ, Na YW, Ha TY, Cho SH, Oh KB: Massive subcapsular hematoma of liver graft after living donor liver transplantation: a case report. *Transplant Proc* 2003;35:1469–1472.
- 4 Mistry BM, Solomon H, Garvin PJ, Durham RM, Turnage S, Bacon BR, Galvin N, Varma CR: Spontaneous rupture of the liver upon revascularization during transplantation. *Transplantation* 2000;69:2214–2218.
- 5 Bujanda L, Beguiristain A, Alberdi F, Cosme A, Ruiz de la Hermosa J, Gutierrez-Stampa MA, Arenas JI: Spontaneous rupture of the liver in amyloidosis. *Am J Gastroenterol* 1997;92:1385–1386.
- 6 Hederström E, Forsberg L, Florén CH, Prytz H: Liver biopsy complications monitored by ultrasound. *J Hepatol* 1989;8:94–98.
- 7 Sakamoto H, Suga M, Ozeki I, Kobayashi T, Sugaya T, Sasaki Y, Azuma N, Itoh F, Sakamoto S, Yachi A, Imai K: Subcapsular hematoma of the liver and pylethrombosis in the setting of cholestatic liver injury. *J Gastroenterol* 1996;31:880–884.
- 8 Hoffman M, Monroe DM 3rd: The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. *Dis Mon* 2003;49:14–21.
- 9 Planinsic RM, van der Meer J, Testa G, Grande L, Candela A, Porte RJ, Ghobrial M, Isoniemi H, Schelde PB, Erhardtsen E, Klintmalm G, Emre S: Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 2005;11:895–900.
- 10 Lodge JP, Jonas S, Oussoultzoglou E, Malago M, Jayr C, Cherqui D, Anthuber M, Mirza DF, Kuhlman L, Bechstein WO, Diaz JC, Tartiere J, Eyraud D, Fridberg M, Erhardtsen E, Mimoz O: Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005;102:269–275.
- 11 Key NS, Aledort LM, Beardsley D, Cooper HA, Davignon G, Ewenstein BM, Gilchrist GS, Gill JC, Glader B, Hoots WK, Kisker CT, Lusher JM, Rosenfield CG, Shapiro AD, Smith H, Taft E: Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 1998;80:912–918.
- 12 d’Oiron R, Ménart C, Trzeciak MC, Nurden P, Fressinaud E, Dreyfus M, Laurian Y, Négrier C: Use of recombinant factor VIIa in 3 patients with inherited type I Glanzmann’s thrombasthenia undergoing invasive procedures. *Thromb Haemost* 2000;83:644–647.
- 13 Hendriks HG, Meijer K, de Wolf JT, Klomp maker IJ, Porte RJ, de Kam PJ, Hagens AJ, Melsen T, Slooff MJ, van der Meer J: Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation* 2001;71:402–405.
- 14 Rodriguez-Merchan EC, Wiedel JD, Wallny T, Hvid I, Berntorp E, Rivard GE, Goddard NJ, Querol R, Caviglia H: Elective orthopaedic surgery for inhibitor patients. *Haemophilia* 2003;9:625–631.

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