

# Successful Use of Activated Recombinant Factor VII in Traumatic Liver Injuries in Children

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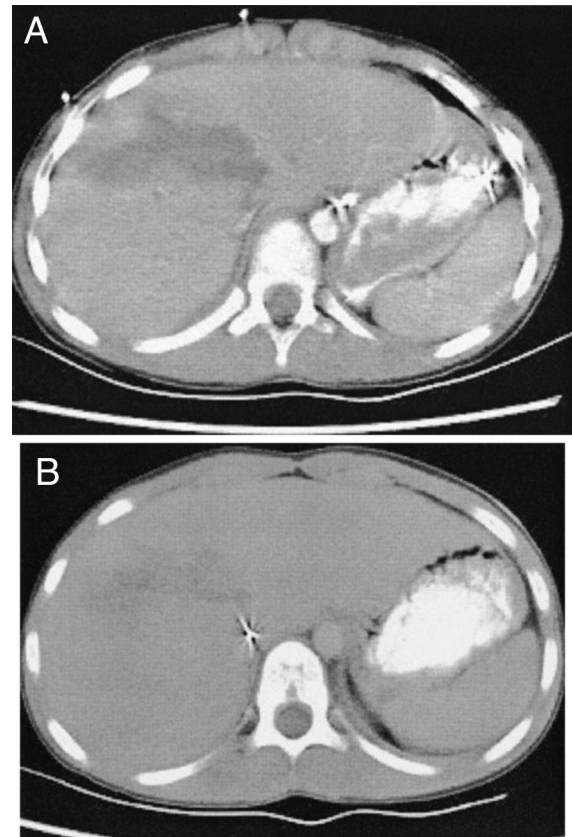
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**A**ctivated recombinant factor VII (rFVIIa) is an effective hemostatic agent in the management of bleeding episodes in hemophiliacs with and without inhibitors. It has also been used in nonhemophilic individuals with life-threatening hemorrhages. We describe its safety and efficacy in two pediatric nonhemophilic patients with liver lacerations secondary to blunt abdominal trauma.

## CASE REPORTS

### Case 1

A 7-year-old white boy with attention deficit hyperactivity disorder fell 16 feet from a windowsill to a concrete floor. He was taken to a local hospital, where he was found on computed tomographic (CT) scanning and radiography to have a laceration of the right lobe of the liver; a right frontal subdural hematoma; and fractures of the right frontal bone, right orbit, basal skull, and bilateral wrist bones. The Glasgow Coma Scale (GCS) score was 15. He was airlifted to the tertiary care hospital. At admission, his GCS score was 12, his blood pressure was 146/72 mm Hg, and he weighed 27.2 kg. He had bilateral periorbital hematomas, tenderness of the right upper quadrant of the abdomen, and casts on both forearms. A repeat CT scan of the abdomen revealed a large hepatic laceration (grade III–IV) extending from the diaphragm to the porta hepatis involving the anterior segment of the right lobe of the liver (Fig. 1A). A small amount of free fluid was seen adjacent to the inferior aspect of the right lobe of the liver and extending to the paracolic gutter that was slightly more than on the previous film (at the local hospital). There was no free air in the peritoneal cavity, and the spleen, kidneys, gallbladder, ureters, and bladder were normal. Chest radiography showed patchy atelectasis in the lower lobes bilaterally, on left more than on the right. His complete blood count showed a steady drop in the hemoglobin from 10.5 g to 8.6 g and in the platelets from  $217$  to  $122 \times 10^3$ . Hemostasis



**Fig. 1.** A, CT scan showing hepatic laceration extending from the diaphragm to the porta hepatis involving the anterior segment of the right lobe of the liver. B, CT scan obtained 5 days after admission showing a decrease in the size of the laceration.

was achieved using rFVIIa 50  $\mu$ g/kg intravenously every 2 hours for two doses for 3 days. Pre- and post-rFVIIa prothrombin times (PT) were 14.7 and less than 8 seconds, respectively. D-dimers were positive 1:4 before and after institution of rFVIIa. There was no decrease in platelet count, hemoglobin, or fibrinogen after treatment. Table 1 lists the coagulation profiles and hemoglobin and platelet counts during his stay. A repeat CT scan (Fig. 1B) obtained 5 days after admission showed a decrease in the size of the laceration. The patient was discharged on day 8. A coagulation profile and a complete blood count obtained approximately 2 months later

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**Table 1** Pre- and Post-rFVIIa Infusion Duration and Relevant Laboratory Parameters (Case 1)

	PT (11–13.5 s)	aPTT (27–27 s)	Fibrinogen (150–400 mg/dL)	D-Dimer Negative	Hemoglobin (g/dL)	Platelet Count (/mm <sup>3</sup> )
Admission (day 0)	13.0	27.6	228	1:4	10.5 8.6	217,000
Day 1						
Pre-rFVIIa	14.7	20.0	351	1:4	Packed cell transfusion	122,000
Post-rFVIIa	<8.0	27.6	443	1:2		116,000
Day 2						
Pre-rFVIIa	9.3	29.6	428	1:4	12.7	138,000
Post-rFVIIa	<8.0	29.6	477	1:4	13.2	121,000
Day 3						
Pre-rFVIIa	10.3	31.0	517	1:8	12.6	121,000
Post-rFVIIa	<8.0	30.4	517	1:4	12.5	126,000

rFVIIa, recombinant activated factor VII; PT, prothrombin time; aPTT, activated partial thromboplastin time.

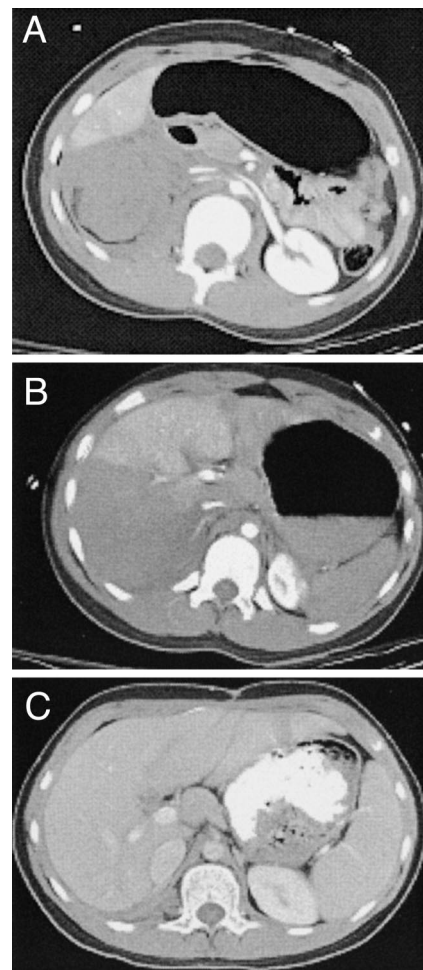
were normal, with negative D-dimers. Factor VII levels remained greater than 100%.

## Case 2

A 13-year-old white boy was thrown off his dirt bike while riding at a high speed. He was brought to the emergency department pale but conscious; breath sounds were decreased on the right side. In addition, he had an obvious right upper thigh deformity, and a large abrasion over his right shoulder and chest and right flank area. Cranial nerves II to XII were grossly intact and extremities were cool bilaterally. CT scan of the head was normal. Radiographs of the chest and extremities revealed a fragmented inferior right scapula and a fracture of the right femur. CT scan of the chest showed small bilateral pneumothoraces with a pulmonary contusion of the right lower lobe. Abdominal CT scan revealed a lacerated liver involving more than 50% of the liver volume and retroperitoneal hemorrhage without visualization of the right kidney; only a clot on the right side by the renal artery was noted (Fig. 2A).

A complete blood count showed a hemoglobin of 10.8 g/dL, a hematocrit of 32.2%, and a platelet count of  $212 \times 10^3$ . His PT was 16.6 seconds, his activated partial thromboplastin time (aPTT) was 32.4 seconds, and his fibrinogen was 199 mg/dL. The patient received packed red blood cells and fresh frozen plasma.

A repeat coagulation profile showed a PT of 21.7 seconds, an aPTT of 55.7 seconds, and a fibrinogen of 117 mg/dL. An exploratory laparotomy was undertaken to determine the extent of liver and kidney injury. During surgery, despite multiple packed red blood cell, fresh frozen plasma, and cryoprecipitate transfusions, the patient continued to bleed and experienced hemorrhagic shock; he had a weak aortic pulse and his blood pressure dropped to 50/20 mm Hg. He required cardiopulmonary resuscitation. He was then administered two doses of rFVIIa, 50  $\mu$ g/kg intravenously, 1½ to 2 hours apart. The bleeding visibly ceased and his aortic pulse improved. The exploratory laparotomy revealed a right avulsed kidney, a grade IV liver laceration, and a grade II



**Fig. 2.** A, Right abdominal CT scan shows greater than 50% of liver lacerated with hematoma. Left CT scan shows left kidney with contrast; however, the right kidney did not take up contrast secondary to being avulsed. B, Hepatic hematoma improved. Liver was repaired with fibrin glue and Dexon mesh was placed around the liver and rFVIIa was administered. C, CT scan of the abdomen obtained 6 months after admission showing residual scarring in the posterior aspect of the right lobe of the liver, a normal left kidney, and an absent right kidney.

**Table 2** Pre- and post-rFVIIa Infusion Duration and Relevant Laboratory Parameters (Case 2)

Day/Time	PT (11–13.5 s)	aPTT (27–37 s)	Fibrinogen (150–400 mg/dL)	Comments
Day 1, hour 0				
Pre-rFVIIa	21.7	55.7	117	Fluids, PRC, FFP, cryoprecipitate transfusion rVIIa q-2-h bolus intravenously
Post-rFVIIa	11.2	78.4	100	
Hour-6 Pre-rFVIIa	12.6	91	92	
Post-rFVIIa	9.7	44.9	284	
Day 2	9.8–12.2	29.2–33.4	269–327	rFVIIa q 4 h
Day 3	8.3–12.6	29.8–55.7	279–597	rFVIIa q 6 h
Day 4	9.1–10.9	26.3–37	402–477	rFVIIa q 6 h
Day 5	9.2–13.4	24.9–25.5	443–459	rFVIIa q 6 h
Days 6–12	13.4–15.9	24.4–26.5	443–631	rFVIIa stopped
1 mo	15.1	27.1	477	Positive for lupus anticoagulant
6 mo	13.6	28.2	289	D-dimer negative, FVII 93%

rFVIIa, recombinant activated factor VII; PT, prothrombin time; aPTT, activated partial thromboplastin time; PRC, packed red cell; FFP, fresh frozen plasma.

splenic laceration. The avulsed kidney was removed and a Dexon (polyglycolic acid) mesh compression of the right hepatic lobe and hepatic packing were performed. Approximately 20 mL of fibrin glue was applied to the raw liver surface. A repeat coagulation profile obtained 1 hour after the second dose of rFVIIa revealed a PT of 11.2 seconds, an aPTT of 78.4 seconds, and a fibrinogen of 100 mg/dL.

After surgery, he was started on rFVIIa (50 µg/kg) every 2 hours for 18 hours. Post-rFVIIa PT ranged from 11.2 to 9.7 seconds (Table 1). On the following day, because the patient remained hemodynamically stable, the dosing interval of rFVIIa was increased to every 4 hours. The patient underwent reexploration for removal of sponges and reassessment of possible abdominal compartment syndrome. During the inspection of the hepatic and renal areas, it was found that the posterior aspect of the right hepatic region was hemorrhaging. Fibrin glue (15 mL) was administered to the posterior portion, and the area of bleeding was held together with Dexon mesh. In addition, the area around the right kidney did not show any bleeding. The abdominal cavity was partially closed and the patient continued on rFVIIa every 4 hours for 16 hours and then every 6 hours for the next 3 days, after which rFVIIa was discontinued (Table 2). Recombinant FVIIa was given for a total of 6 days. The patient remained hemostatically and hemodynamically stable and was taken to the operating room for closure of his abdominal wall on day 3. From day 2 to day 38 of admission, the patient was on hemodialysis for acute renal failure. He was transferred to the pediatric floor on day 33 and continued hemodialysis and physical therapy and was discharged from the hospital on day 59. Repeat abdominal CT scans (Fig. 2B) a month later showed improvement of liver laceration and 6 months later revealed residual scarring in the posterior aspect of the right lobe of the liver, normal left kidney, and an absent right kidney.

The PT continued to be mildly prolonged and the aPTT was normal during the entire period that the patient was on the ward. The patient tested positive for a lupus anticoagu-

lant. Continued outpatient monitoring of the coagulation profile showed a progressive decrease of PT from 15.8 to 14.8 seconds. Repeat coagulation profile obtained 6 months later was negative for lupus anticoagulant and D-dimers; PT was 13.6 seconds, aPTT was 28.2 seconds, fibrinogen was 289 mg/dL, and factor VII assay was 93%.

## DISCUSSION

Severe blunt liver injury is a life-threatening condition, has a mortality of 13%, and is often accompanied by concurrent chest and skeletal injuries.<sup>1</sup> Operative mortality in grade III to IV blunt hepatic trauma is 6% to 16%; in grade V blunt hepatic trauma, operative mortality ranges from 67% to 80%.<sup>2</sup> The mortality rate of patients with severe abdominal trauma increases if major blood vessels are involved to greater than 50%.<sup>1</sup> Nonoperative management is the treatment of choice for hemodynamically stable patients with mild to moderate liver injury;<sup>3</sup> however, there is no consensus regarding optimal treatment for children with severe hepatic injuries.<sup>4</sup> The first patient showed a low GCS score, dropping hemoglobin and platelet count, coupled with a prolonged PT, all indications of an impending hemostatic and hemodynamic instability. The second patient sustained a right avulsed kidney, grade IV to V lacerated liver, and a hemorrhaging right renal artery and vein. The severity of patient injury coupled with abnormal coagulation profile placed the mortality rate at the time of surgery at greater than 50%. A major cause of mortality in high-grade liver injury is exsanguinations accompanied by shock. Patients frequently require transfusions of large amounts of fluids and blood products. Dilution of coagulation factors, platelet dysfunction, and impaired production of clotting factors because of tissue hypoxia caused by hypotension may contribute to the “diffuse coagulopathic bleeding.” Other contributory causes of coagulopathy that accompany trauma include consumption coagulopathy, excessive fibrinolysis, hypothermia, tissue hypoperfusion, and acidosis.<sup>5,6</sup>

The use of rFVIIa as an adjunct in hemorrhage control in patients with trauma has been the subject of recent studies.<sup>6,7</sup> Recombinant FVIIa, a panhemostatic agent, is devoid of blood products and is indicated in the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to factor VIII or IX.<sup>8,9</sup> Its off-label use has included the treatment of bleeding in nonhemophilic patients with a variety of bleeding disorders, including those secondary to liver disease.<sup>10,11</sup> Recombinant FVIIa complexes with tissue factor and activates factor Xa at the site of injury. High levels of circulating rFVIIa can directly activate factor X on the surface of activated platelets in the absence of tissue factor.<sup>11</sup> The role of hemostasis is important in severe liver damage because liver plays a key role in the regulation and synthesis in most of the coagulation factors in blood. The above two cases demonstrate the successful use of rFVIIa in controlling clinical bleeding in traumatic liver injuries in children. The dose of rFVIIa was lower than the standard recommended dose of 90 µg/kg for hemophilia with inhibitors. We have shown the effectiveness of this dose in the treatment of intrapulmonary hemorrhage in newborns.<sup>12</sup>

In both of the cases presented, rFVIIa was a low-volume alternative to blood and blood products. The first case received only a single unit of packed red cell; his hemoglobin stabilized, surgery was avoided, and the patient was managed conservatively. In the second case, after administration of rFVIIa during surgery, bleeding visibly ceased. A reduced transfusion requirement has been reported after the use of rFVIIa in orthotopic liver transplantation.<sup>13</sup> The combination of systemically administered rFVIIa that promoted a local “thrombin burst” along with the local application of fibrin glue to the lacerated liver surface conceivably enhanced hemostasis at the site of injury. According to Martinowitz et al.,<sup>6</sup> the advantage of the fibrin glue is in its formation of “superclot” by initiation and forming a strong and resistant clot. However, fibrin glue, by itself, is ineffective in massive bleeds because it is washed away. Prior administration of rFVIIa, perhaps, has the advantage of promoting hemostasis at the site of liver injury, thereby allowing the fibrin glue to form a firm clot.

No evidence of disseminated intravascular coagulation or adverse thromboembolic episode were seen in our cases, despite the fact that the first case had a subdural hematoma. Recombinant FVIIa has not been reported to induce hypercoagulability; on the contrary, it has been used in individuals with disseminated intravascular coagulation, cirrhosis, trauma, pulmonary hemorrhage, and so forth. The safety of rFVIIa has been studied in the hypothermic coagulopathic swine animal model with grade V liver injury.<sup>7</sup> Our results correlate well with published reports of hemostasis using rFVIIa for abdominal surgeries in individuals without any known history of coagulopathy.<sup>14</sup> Shortening of the PT after administration of rFVIIa was noted in both patients and correlated with correction of hemostasis and, in case 2, recovery from hemorrhagic shock. A similar effect has been

reported in a swine model of trauma.<sup>15</sup> Recombinant FVIIa has also been reported to normalize PT in liver disease and Coumadin-treated individuals.<sup>15,16</sup>

## CONCLUSION

Recombinant FVIIa is a safe and effective hemostatic agent for the control of hemorrhage associated with pediatric blunt liver trauma. Although expensive, the cost of rFVIIa must be balanced against the potential risk of transmission of blood-borne pathogens, the cost of surgery, and the cost of blood and plasma products. Further clinical studies are needed to determine the safety profile and optimum therapeutic dosages as well as its effectiveness in reducing the use of a large volume of blood products in cases of severe trauma.

## REFERENCES

1. Sanchez J, Paidas N. Childhood trauma, now and in the new millennium. *Surg Clin North Am.* 1999;79:1503–1535.
2. Chen RJ, Fang JF, Lin BC, Hsu YP, Kao JL, Chen MF. Factors determining operative mortality of grade V blunt hepatic trauma. *J Trauma.* 2000;49:886–891.
3. Knudson MM, Maull KI. Nonoperative management of solid organ injuries: past, present, and future. *Surg Clin North Am.* 1999; 79:1357–1371.
4. Pryor JP, Stafford PW, Nance ML. Sever blunt hepatic trauma in children. *J Pediatr Surg.* 2001;36:974–979.
5. Gubler DK, Gentilello LM, Hassantash A, Maier RV. The impact of hypothermia on dilutional coagulopathy. *J Trauma.* 1994;36:847–851.
6. Martinowitz U, Kenet Gili, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma.* 2001; 51:431–439.
7. Martinowitz U, Holcomb JB, Pusateri AE, et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma.* 2001;50:721–729.
8. Arkin S, Cooper HA, Hutter JJ, et al. Activated recombinant human coagulation factor VII therapy for intracranial hemorrhage in patients with hemophilia A or B with inhibitors: results of the Novoseven emergency use program. *Haemostasis.* 1998;28:93–98.
9. Shapiro AD, Gilchrist GS, Hoots WK, et al. Prospective, randomized trial of two doses of rFVIIa (Novoseven) in hemophilia patients with inhibitors undergoing surgery. *Thromb Haemost.* 1998;80:773–778.
10. Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teeraratkul S, Hongeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis.* 2000;11:S101–S105.
11. Hedner U. NovoSeven as a universal haemostatic agent. *Blood Coagul Fibrinolysis.* 2000;11:S107–S111.
12. Olumu I, Kulkarni R, Manco-Johnson M. Treatment of intrapulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight (VLBW) infants on mechanical ventilation in a community level III neonatal intensive care unit (NICU). *Blood.* 2001;98:262A–263A.
13. Hendriks HG, Meijer K, de Wolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation.* 2001;71:402–405.
14. Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol.* 2001;114:174–176.

15. Lynn M, Jerokhimov I, Jewelewicz D, et al. Early use of recombinant factor VIIa improves mean arterial pressure and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. *J Trauma*. 2002;52:703–707.
16. Erhardtsen E, Nony P, Dechavanne M, French P, Boissel JP, Hedner U. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. *Blood Coagul Fibrinolysis*. 1998;9:741–748.