

CASE REPORT

Acute Intracranial Hemorrhage in a Cirrhotic Controlled with Recombinant Factor VIIa

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Human factor VIIa is a vitamin K-dependent glycoprotein consisting of 406 amino acids having a molecular weight of 50 kDa (1). Factor VIIa is the initiating factor in the conversion of prothrombin to thrombin via the extrinsic pathway (1). Specifically, factor VIIa forms a complex with tissue factor that activates factor X and factor IX, which in turn forms a multimolecular complex with factor V, which then converts prothrombin to thrombin on the surface of platelets with the resultant production of fibrin monomers. The resultant fibrin undergoes self-polymerization until a critical size is achieved and the protein becomes insoluble as the hemostatic plug or clot.

Recently, recombinant human factor VIIa (rhFVIIa) has become commercially available for the treatment of hemophiliacs with antibodies to factor VIII or factor IX and individuals who are congenitally factor VII-deficient (1). Even more recently, rhFVIIa has been used to control bleeding in cases of trauma in both hemophiliacs as well as nonhemophiliac patients (2–9). This use of rhFVIIa in surgical and trauma units has raised the possibility that rhFVIIa might also be clinically useful in other medical situations.

Herein, we report a case of a 68-year-old man with a severe coagulopathy due to alcohol-associated cirrhosis, who experienced a spontaneous acute intracranial hemorrhage and was treated with rhFVIIa with cessation of the intracranial bleeding with clinical and radiological stabilization of his intracranial injury.

CASE REPORT

This 68-year-old male was admitted to hospital for the treatment of cellulitis of his legs. His past medical history was significant for alcohol-associated cirrhosis, a severe coagulopathy, esophageal varices, hepatic encephalopathy, and paroxysmal atrial fibrillation. He had had a cancer of the tongue, which had been resected 12 years earlier. He had no prior history of transient ischemic attacks, facial palsy, or stroke. On the 11th hospital day, he was found in bed complaining of not being able to move his extremities and face on the left. On examination, his temperature was 37.9°C. His blood pressure was 156/70 mm Hg with a regular pulse of 120/min. His respiratory rate was 20/min. His oxygen saturation on room air was 94%. He was alert and oriented as to person, place, and time. His speech, however, was slurred. His pupils were equal and responded equally to light. Both corneal reflexes were present. His resting gaze was rightward. He had a left-sided central facial paralysis with decreased sensation on the left. Muscle strength was graded as 0/5 for the left upper and lower extremities. Strength on the right side was normal. No sensory deficits were evident. The Babinski reflex was positive on the left side. Laboratory analysis revealed a prothrombin time (PT) of 19.9 sec, international normalized ratio (INR) of 2.5, an activated partial thromboplastin time (aPTT) of 51.5 sec, a fibrinogen level of 93 mg/dl, and fibrin split products at a level of 10 µg/ml. A computed tomographic (CT) scan of the head without contrast demonstrated a right parietal intraparenchymal hematoma (Figure 1A, B).

In order to stabilize the intracranial bleeding, he was given 90 µg/kg of rhFVIIa as an intravenous infusion that was repeated again after 6 hr, with the first dose being given approximately 6 hr after the onset of the hemorrhage. His PT, INR and aPTT were determined at times 0, 2, 4, and 6 hr after the first infusion of rhFVIIa and time 0, 30 min and 2 and 4 hr after the second infusion of rhFVIIa. An immediate correction of the coagulopathy that persisted for at least 6 hr was observed after the first infusion and for at least an additional 4 hr after the second infusion (Figure 2A, B). A second CT scan was obtained 7 hr after the first CT scan (Figure 3A, B).

There was no change in the size of the intraparenchymal hematoma. More importantly, the patient's neurologic deficit stabilized and no additional neurologic deficit was detected.

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Fig 1. Two representative computed tomographic scans (A and B) obtained initially of the central nervous system hemorrhage experienced in the patient reported.

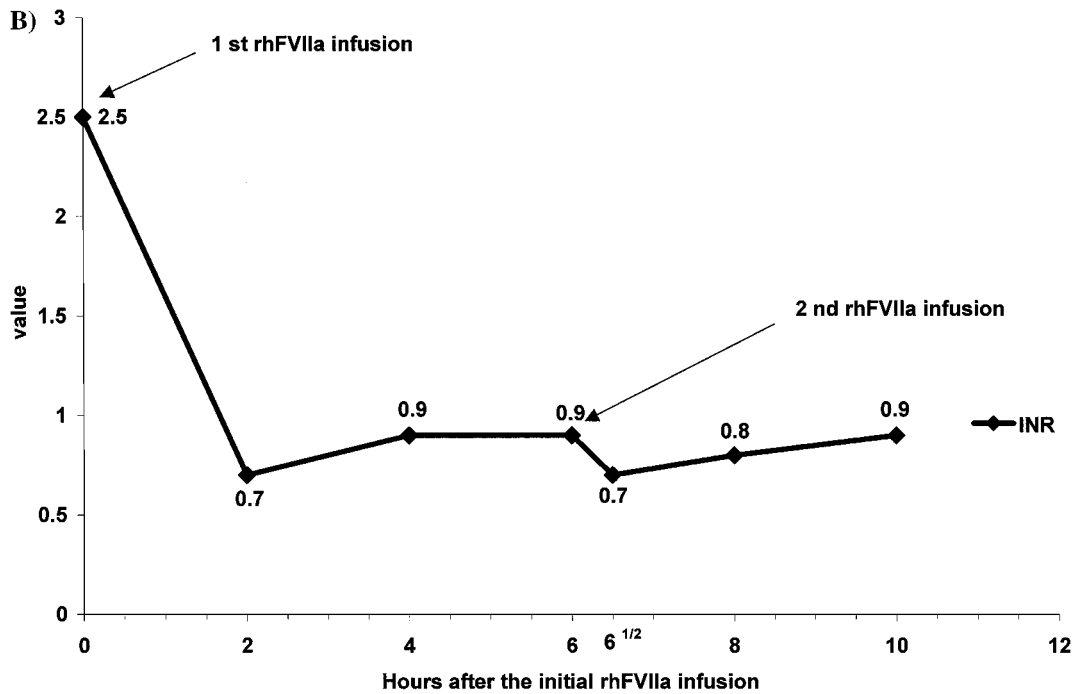
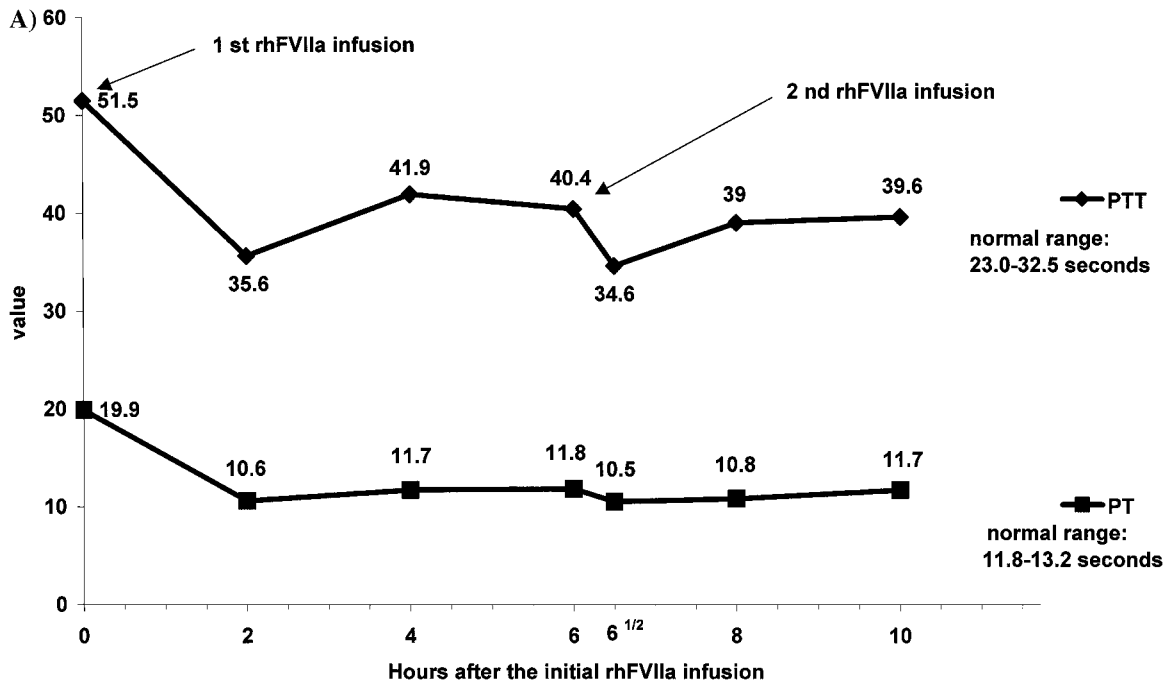


Fig 2. (A) Sequential changes in PT and aPTT before and after the infusion of 90 $\mu\text{g}/\text{kg}$ of rhFVIIa in the patient reported. The arrows denote when the infusions were given. (B) Sequential changes in INR before and after the infusion of 90 $\mu\text{g}/\text{kg}$ of rhFVIIa in the patient reported. The arrows denote when the infusions were given.

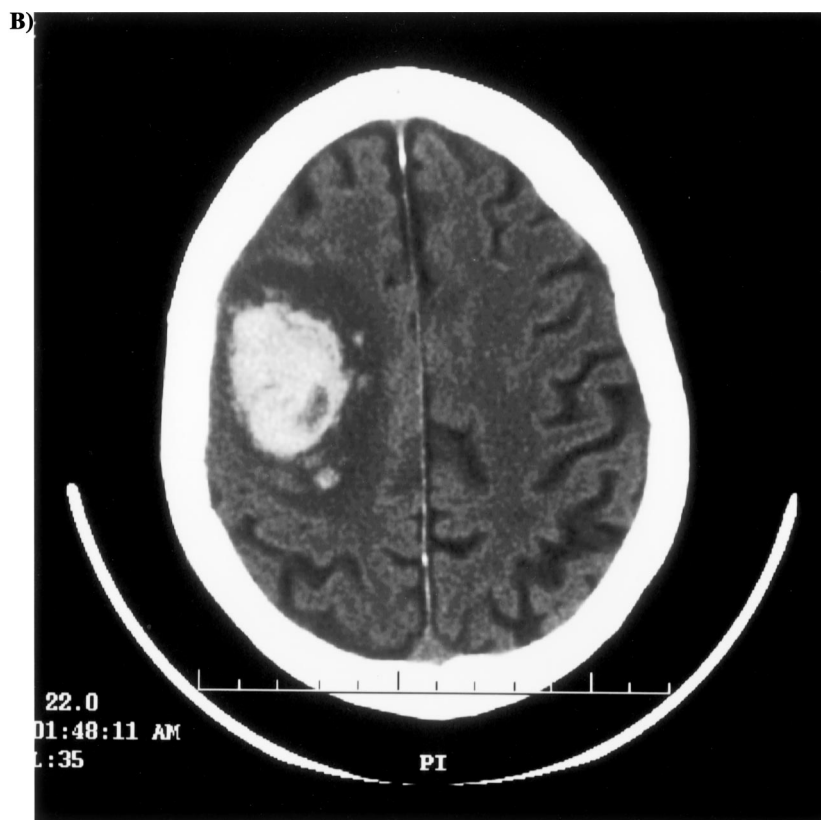


Fig 3. Two representative computed tomographic scans of the central nervous system hemorrhage obtained 7 hr after the first scan (Figure 1A, B). Note stabilization of the lesion.

DISCUSSION

Patients with advanced cirrhosis have a potential for spontaneous bleeding due to a combination of acquired coagulation defects and thrombocytopenia (10–12). Specifically, they are well known to be at risk for variceal as well as other types of gastrointestinal bleeding (peptic ulcer disease, gastric antral vascular ectasias, atraumatic hemobilia, etc) (13–16). They are known also to have an increased risk of intracranial bleeding as a result of even minor often unrecognized trauma (15–17). Bleeding in an individual with cirrhosis can be difficult to manage and is associated with a significant morbidity risk as well as mortality. Often large volumes of fresh frozen plasma, multiple units of platelets, and similarly large doses of cryoprecipitate are required before the bleeding stops. The transfusion of large volumes of fresh frozen plasma, platelets, and cryoprecipitate can cause volume overload, increase the risk for variceal bleeding, and carry the risk of transmission of blood-borne infections such as hepatitis C (18,19). The use of recombinant human Factor VIIa has significant advantages over the use of fresh frozen plasma and cryoprecipitate in such cases. Specifically, it carries no risk of infection and it provides immediate control of bleeding with infusion of a small volume of fluid.

This case documents the immediate correction of a severe coagulopathy in a cirrhotic male with an acute intracranial hemorrhage given rhFVIIa. This report is the first such case in the English literature. A somewhat similar case of a neonate with a congenital deficiency of factor VII has been reported (6). As a result of the immediate correction of his coagulopathy, the intraparenchymal hemorrhage stabilized in size. Specifically, it clotted and remained stable for the rest of his hospital stay. This ability to correct a serious coagulopathy in a bleeding cirrhotic patient within minutes is anticipated to markedly improve the outcome of such patients. Not only can cirrhotic individuals with intraparenchymal hemorrhage be treated with this agent but the more frequently seen cirrhotic patient with a subdural hematoma might also benefit from such therapy. It is important to note that the severe coagulopathy in the present case corrected rapidly within minutes after the infusion of the rhFVIIa was started. More importantly, the hemostatic effect observed, as measured by the correction in the PT, INR, and aPTT, which were markedly abnormal before the infusion of rhFVIIa, corrected immediately and persisted for at least 6 hr. This prolonged improvement in hemostatic status was unexpected and has not been reported previously either in normals or hemophilic children (9, 20). We suspect that the effect persisted so long in this case because of the underlying liver disease of the

patient and the reduced hepatic clearance of the infused hemostatic product.

Other investigators have reported the use of rhFVIIa in cirrhotics prior to liver biopsy, alcohol injection of a hepatoma, and cholangiography (21, 22) as well as under unstressed basal conditions (23, 24). A single pilot study in liver transplantation has reported a reduced transfusion requirement in patients given rhFVIIa preoperatively (25). The present case is the first where rhFVIIa has been given to a cirrhotic, who had an intracranial bleed, in an effort to control the bleeding and prevent progressive tissue injury. Thus, the present case adds substantially to the knowledge base accumulating concerning the use of rhFVIIa in a cirrhotic patient by defining the time course, suggesting that hepatic disease, as a result of reduced hepatic clearance of the agent, is associated with a prolongation of the achieved hemostatic effect, and finally that not only can it be used prophylactically to prevent bleeding problems, as has been reported previously, but it can also be used to control bleeding and reduce tissue injury as a result of bleeding once it has occurred.

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