

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Safety and Efficacy of Recombinant Factor VIIa in Patients With Liver Disease Undergoing Laparoscopic Liver Biopsy

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Background & Aims: Activated recombinant factor VII (rFVIIa) has been shown to be effective in correcting prolonged prothrombin time (PT) in cirrhotic patients. The main objective of this study was to evaluate the effect of 4 (5, 20, 80, and 120 $\mu\text{g}/\text{kg}$) doses of rFVIIa on correction of PT and the time to achieve hemostasis in cirrhotic patients with coagulopathy who are undergoing laparoscopic liver biopsy. **Methods:** Seventy-one patients (parts I and II) with advanced liver disease (Child-Turcotte B or C), platelet count $\geq 60,000/\text{mm}^3$, and PT in the range of 3–15 seconds above normal were included in the study. Efficacy endpoints were normalization of PT and time to hemostasis. **Results:** PT was corrected to normal levels (<13.1 seconds) in the majority of patients. The duration of normalization of PT was longer in patients treated with higher doses of rFVIIa. Forty-eight (74%) of 65 patients (part II) achieved hemostasis within 10 minutes. No correlation between the time to hemostasis and duration of correction of PT was observed. None of the patients required operative intervention or transfusion of blood/blood products to control bleeding. One thrombotic event and one case of disseminated intravascular coagulation were reported, but both events were considered by the investigator as unlikely to be related to treatment with rFVIIa. **Conclusions:** The results of this study suggest that treatment with rFVIIa may offer benefit for patients with liver disease undergoing laparoscopic biopsy.

The liver is the principal site for the synthesis and clearance of many of the vitamin K–dependent coagulation factors, plasminogen activators, and anticoagulants involved in the maintenance of hemostasis.^{1–4} Patients with liver disease frequently present with reduced serum levels of vitamin K–dependent coagulation factors II, VII, IX, X, and prothrombin.^{2,5–7} Of these, factor VII has the shortest half-life (approximately 3–6 hours in plasma) and is therefore the first factor to show decreased levels when hepatic synthesis is impaired.^{8,9}

Patients with liver disease have various types or degrees of hematological abnormalities that may lead to clinical manifestations such as thrombocytopenia, a prolonged prothrombin time (PT), and hyperfibrinolysis.^{2,10} Although spontaneous bleeding is not common in these patients, they are at an increased risk of bleeding from the gastrointestinal (GI) tract, as well as having increased bleeding risk during common surgical and medical procedures such as dental extractions and liver biopsy.^{5,11–13} In addition, patients who are undergoing liver transplantation may experience significant blood loss as a result of the underlying coagulopathy, which can lead to increased mortality and morbidity.^{4,14–17}

There are important clinical concerns in current treatment modalities for managing hemostatic disorders in patients with liver disease. Transfusion of fresh frozen plasma or administration of prothrombin-complex concentrates (PCC), etc., is currently used to manage hemostatic disorders, but these products are associated with possible risk of viral transmission, variable effectiveness, and volume overload.^{18–20}

Activated recombinant factor VII (rFVIIa; NovoSeven [Novo Nordisk A/S, Copenhagen, Denmark]) was developed for treatment of hemophilia A or B patients with inhibitors against factor VIII or IX, respectively. rFVIIa was cloned from the human FVII gene and is identical in sequence to the naturally occurring protein.²¹ No materials of human origin are used in the manufacturing process. The clone is expressed in baby hamster kidney cells, and rFVII is then purified from the culture medium

Abbreviations used in this paper: DIC, disseminated intravascular coagulation; GI, gastrointestinal; NPT, normalization of PT; PCC, prothrombin-complex concentrates; PT, prothrombin time; rFVIIa, activated recombinant factor VII; SAE, serious adverse event.

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through multiple steps including filtration, viral inactivation, ion exchange chromatography, and affinity chromatography. During ion exchange chromatography, autoactivation of rFVII occurs via cleavage at amino acid 152 resulting in the final product, rFVIIa.^{22,23}

Studies conducted in warfarin-treated rats and in healthy human volunteers pretreated with anticoagulants have suggested that rFVIIa could enhance hemostasis in situations that mimic the coagulopathy of liver disease.^{24,25} A preliminary study in non-bleeding patients with advanced liver disease has shown a dose-related effect of rFVIIa on duration of normalization of PT (NPT).¹⁰ rFVIIa has also reportedly been used to treat patients with fulminant liver failure.^{26,27} The aim of this study was to evaluate the overall safety and efficacy of rFVIIa in patients with coagulopathy caused by liver disease who were undergoing a scheduled liver biopsy.

Patients and Methods

Study Design

This multicenter, randomized, double-blind trial was designed to evaluate the efficacy and safety of 4 different doses of rFVIIa (5, 20, 80, and 120 $\mu\text{g}/\text{kg}$ body weight) on specific laboratory and clinical hemostatic parameters in patients with liver disease who were undergoing laparoscopic liver biopsy.

A total of 71 patients were enrolled, with the first 5 patients as part of an open label pilot run-in (part I) and the remaining 66 patients in the randomized, double-blind part (part II) of the study. In the pilot run-in, 5 patients were treated at the University of Miami School of Medicine, Jackson Memorial Medical Center (UM-JMMC). The 66 randomized patients were treated at 3 United States centers (UM-JMMC, Miami, FL; Louisiana State University School of Medicine, Memorial Hospital, New Orleans, LA; and Indiana University Medical Center, Indianapolis, IN). Appropriately convened individual institutional review boards approved the protocol, and the trial was conducted according to good clinical practice. All subjects provided written informed consent before the start of the trial.

Patients

Male or female patients were considered eligible for the study if they were scheduled for a liver biopsy and met the following inclusion criteria: age ≥ 18 years; advanced liver disease or presumed liver cirrhosis (defined as Child-Turcotte score B or C); PT between 3 to 15 seconds above normal value; and a platelet count $\geq 60,000/\text{mm}^3$. Patients with known malignant disease (other than facial basal cell carcinoma); myocardial infarction or stroke within the last 6 months; advanced atherosclerosis; renal dysfunction (serum creatinine levels >1.5 mg/dL); treatment (within 7 days) with blood products (including PCC, desmopressin acetate, or antifibrinolytic agents); and inadequate or abnormal blood flow in the hepatic vein, portal vein, or mesenteric venous circulation were

not included in the trial. On the study day, patients who were actively bleeding, showed signs of infection, or used nonsteroidal anti-inflammatory drugs, including aspirin, within the previous 2 weeks were not included in the study.

Treatment Regimen

The 5 patients in the pilot run-in (part I) received a single dose of rFVIIa (5 $\mu\text{g}/\text{kg}$) administered as a slow intravenous injection over 2 minutes. The remaining 66 patients were randomized (part II) in blocks of 8 and sequentially assigned to 1 of the 4 treatment groups (5, 20, 80, and 120 $\mu\text{g}/\text{kg}$ body weight). To ensure blinding, the injection volume (in milliliters) per kilogram body weight was the same regardless of the rFVIIa dose administered. This was achieved by dosing patients from vials containing either rFVIIa or vehicle. For example, a patient weighing 80 kg randomized to the 120 $\mu\text{g}/\text{kg}$ dose group received the same injection volume (16 mL) as an 80-kg patient randomized to any of the other 3 dose groups. All patients received a single dose of rFVIIa 10 minutes before the start of the biopsy procedure.

Biopsy Procedure

Laparoscopy is not the most commonly used procedure for liver biopsy in patients with increased PTs. However, it was used in this trial because it enabled the visual assessment of hemostasis by the investigators. In addition, the laparoscopic procedure is not routinely performed in patients with Child's C cirrhosis. However, the rationalizations for performing liver biopsies in patients with Child's C cirrhosis in this trial were: (1) in patients with alcoholic liver disease, a biopsy was performed as part of a transplant evaluation to assess liver damage and determine if the patient's alcohol consumption had ceased or was active; (2) as part of a transplant evaluation in patients with hepatitis C and/or excessive alcohol consumption to determine if liver damage was caused by hepatitis C virus (HCV) or alcoholic cirrhosis, as well as determine if the patient's alcohol consumption had ceased or was active; (3) evaluate for hepatocellular carcinoma in the presence of suspicious mass/nodules in the liver or elevated α fetal protein; (4) in the case of idiopathic cirrhosis, to evaluate as the etiology of disease (i.e., autoimmune in origin).

The biopsy procedure was performed under monitored anesthesia care. An area on the abdominal wall approximately 2 cm above and 2 cm to the left of the umbilicus was anesthetized with 1% lidocaine without epinephrine. The patient was dosed with rFVIIa 10 minutes before insertion of the Veress needle through the skin. After an appropriate pneumoperitoneum was obtained, a 5-mm trocar was inserted into the abdomen and the abdominal cavity was explored. An area on the anterior surface of the left lobe of the liver, at least 2 cm from the liver edge, was chosen as the site for liver biopsy.

After an adequate site for the second puncture was determined in the left upper quadrant, a 16-gauge biopsy gun with a needle in position was inserted through the skin and a liver biopsy was performed. The biopsy needle was removed, and the adequacy of the biopsy was assessed. A second 3-mm trocar

was inserted through the skin in the left upper quadrant. The biopsy site was then observed, and hemostasis was assessed at 2, 4, 7, and 10 minutes after biopsy by means of flushing the biopsy wound with saline through the second inserted trocar.

Assessments

The trial included a screening visit, treatment day visit, and a follow-up visit. Patients underwent a physical examination, and hematology, blood chemistry, urinalysis, and coagulation parameters were assessed. Patients who met the inclusion/exclusion criteria underwent a laparoscopic liver biopsy (study day visit) within a week of the screening visit.

The first 5 patients were assessed for laboratory (PT correction) and clinical response (hemostasis), and safety of rFVIIa. Efficacy in the randomized patients was evaluated by the time to achieve and maintain hemostasis, duration of NPT, and measuring serum levels for FVII:C, and FVIIa:C (level of activated FVII activity) at 10, 30, and 60 minutes, and 2, 4, 6, 8, and 12 hours.

Time to hemostasis. Hemostasis at the biopsy site was assessed visually at 2, 4, 7, and 10 minutes post-biopsy. No other hemostatic treatment was administered during this time period. If hemostasis was not achieved within the first 10 minutes, the investigator selected alternative treatment. If hemostasis was achieved within 10 minutes after the biopsy, its maintenance was assessed for 18 hours by monitoring rebleeding and blood loss. Blood loss was defined as the number of transfusions required by a patient within 18 hours of the start of the procedure. Rebleeding was defined as having achieved hemostasis and then presenting with a 2-g decrease in hemoglobin at any time between 6 hours after biopsy until discharge from the clinic (18 hours). Blood was drawn at 12 and 18 hours after infusion to assess laboratory coagulation parameters. If significant bleeding occurred at any time, the investigator had the option of administering a rescue dose (80 $\mu\text{g}/\text{kg}$) of rFVIIa or treating the patient with standard therapy.

Duration of NPT. The duration of NPT was measured as the time interval from the time-point when PT values first dropped into the normal range to the time-point when PT values changed from normal to above normal. These 2 time points were calculated by linear extrapolation. Patients who did not achieve hemostasis within 10 minutes and received a rescue dose were not included in the evaluation of duration of NPT because their PT was altered by the extra dose of rFVIIa.

Safety assessment. Safety was assessed by measuring hematological, biochemical, and laboratory coagulation parameters as well as vital signs. Routine hematological and biochemical variables were measured before and at 12 hours after rFVIIa infusion. Coagulation-related variables (aPTT, fibrinogen, D-dimer, F_{1+2} , and platelets) were measured before rFVIIa administration and 12 hours after infusion. In addition, activated partial thromboplastin time was measured at 10, 30, and 60 minutes, and 2, 4, and 8 hours after rFVIIa infusion. Fibrinogen, D-dimer, platelets, and F_{1+2} were also measured at 30 minutes, and 2, 4, and 6 hours after rFVIIa infusion. Vital signs were continuously monitored from the time of rFVIIa

infusion to 6 hours post-infusion, and again at 8-, 12-, and 18-hour time points. Adverse events were recorded throughout the study period, and all patients were asked to return to the clinic within 4 weeks for a follow-up visit.

Data analysis. Statistical analysis was performed using the SAS version 6.12 software package (SAS Institute Inc., Cary, NC). For duration of NPT, the Kruskal-Wallis test was used with no *P* value adjustment made for multiple comparisons. This study was designed to detect a difference of 190 minutes of NPT between the 5 and 20 $\mu\text{g}/\text{kg}$ dose groups with 80% power. Data on 14 patients (13 patients received a rescue dose of rFVIIa, and 1 patient received the drug but did not undergo biopsy) were excluded from the analysis of duration of NPT. For time to hemostasis, the number and percentage of subjects who reached hemostasis at 2, 4, 7, or 10 minutes after the biopsy procedure were summarized in a frequency table, and the treatment effect was tested using the Fisher exact test. Missing data were excluded from the analysis, and patients who withdrew from the study were not replaced or permitted to reenter the study.

Materials

The trial product (rFVIIa; NovoSeven) was supplied by Novo Nordisk A/S in vials containing 2.4 or 4.8 mg lyophilized powder per vial. Before use, rFVIIa was reconstituted with sterile water for injection, United States Pharmacopeia, to a final concentration of 0.6 mg/mL.

Results

Patient Characteristics

Baseline characteristics and demographic data for the 71 patients (5 in the pilot run-in; 66 in the randomized part) enrolled in the study are listed in Table 1. Patients in the 120 $\mu\text{g}/\text{kg}$ treatment group had higher baseline PT values as compared with the other 3 (5, 20, and 80 $\mu\text{g}/\text{kg}$ body weight) treatment groups.

All 5 patients completed the pilot run-in. Sixty-two patients completed the randomized part of the study, and 4 patients were discontinued from the study. Three patients died before the follow-up visit, and 1 patient received the drug but did not undergo the biopsy procedure because of intraperitoneal adhesions.

Efficacy

PT. In the pilot run-in (part I), PT was corrected to normal or near-normal for all 5 patients after treatment with rFVIIa at a dose of 5 $\mu\text{g}/\text{kg}$. In the randomized part of the study (part II), a dose-related effect on duration of NPT was observed for 3 treatment groups (5, 20, and 80 $\mu\text{g}/\text{kg}$) (Figure 1 and Table 2). The maximum reduction in PT values was observed at 30 minutes after dosing, and patients treated with 80 and 120 $\mu\text{g}/\text{kg}$ showed significantly longer duration of NPT as com-

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	5 µg/kg (pilot run-in) (N = 5)	5 µg/kg (N = 16)	20 µg/kg (N = 14)	80 µg/kg (N = 17)	120 µg/kg (N = 19)
Age (yr)	46.4 ± 6.9	50.7 ± 10.0	48.9 ± 7.2	51.8 ± 8.6	50.3 ± 12.5
Sex (n; M/F)	4/1	15/1	11/3	10/7	12/7
Race—n (%)					
White	3 (60)	9 (57)	6 (43)	10 (59)	8 (42)
Black	1 (20)	1 (6)	1 (7)	4 (24)	2 (11)
Hispanic	1 (20)	6 (38)	7 (50)	3 (18)	9 (47)
Height (cm)	175 ± 16.4	171.2 ± 10.1	175.4 ± 11.6	168.3 ± 9.4	168.2 ± 9.0
Weight (kg)	82.4 ± 10	84.3 ± 15.0	86.7 ± 24.0	79.2 ± 16.3	79.5 ± 14.7
Prothrombin time (s)	21.8 ± 2.1	19.4 ± 2.1	19.7 ± 2.6	20.8 ± 5.5	22.3 ± 4.62
Child-Turcotte classification (n)					
B	3	4	9	10	8
C	2	12	5	7	11

NOTE. Values are expressed as mean ± SD except where otherwise noted.

pared with patients in the 5 and 20 µg/kg treatment groups. A weak association between baseline PT and bilirubin levels and duration of NPT was found. A direct correlation between duration of NPT and the time to achieve hemostasis was not observed.

Time to hemostasis. Of the 65 patients evaluated in the randomized phase (part II) of the study, 48 (74%) achieved hemostasis within 10 minutes (Table 3) and maintained it for 18 hours. Eighty percent (30 of 48) of these patients achieved hemostasis within 7 minutes post-biopsy, although a direct correlation between rFVIIa treatment and the time to achieve hemostasis was

not observed ($P > 0.05$). Seventeen of 65 (26%) patients did not achieve hemostasis within 10 minutes, and 13 of these 17 received a rescue dose of (80 µg/kg) rFVIIa at 45 to 65 minutes after the biopsy procedure. The administration of the rescue dose was at the sole discretion of the investigators at each site, who were given the option of administering a rescue dose of rFVIIa or standard hemostatic therapy (mainly fresh frozen plasma) in patients that did not achieve hemostasis within 10 minutes. Because of the large volumes of fresh frozen plasma that are often needed to induce hemostasis, this treatment option was not desirable in this patient population

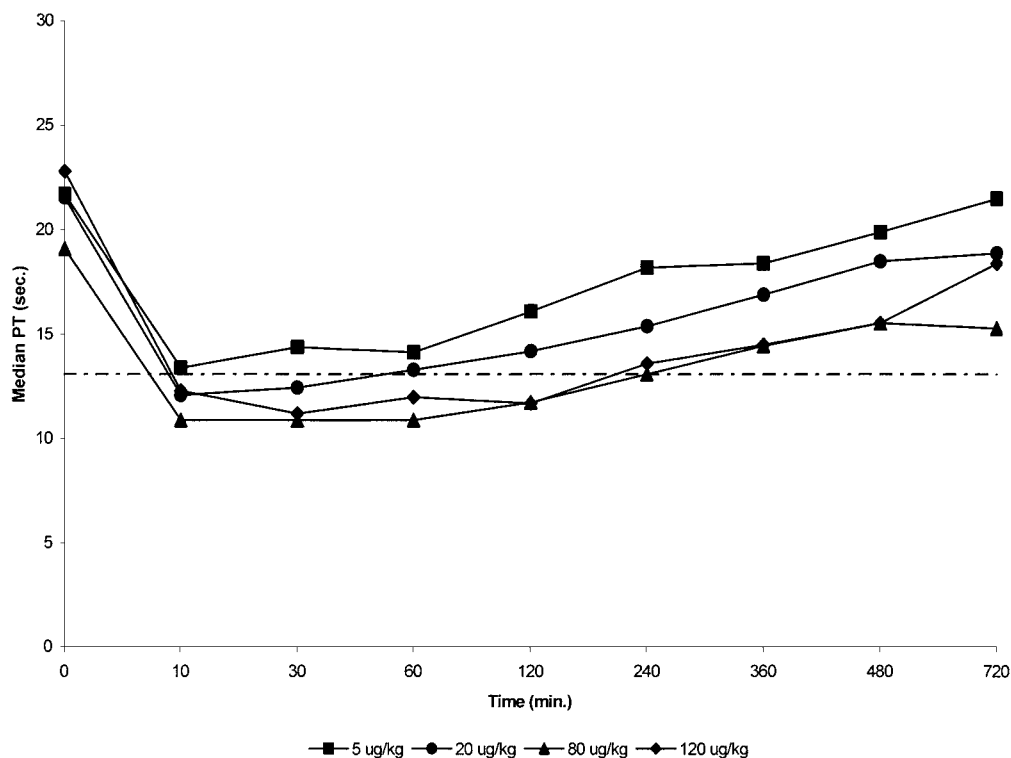


Figure 1. The median PT correction (seconds) observed after administration of 4 dose levels (5, 20, 80, and 120 µg/kg) of rFVIIa to patients with liver disease undergoing laparoscopic liver biopsy. Reference value for normal PT (13.1 seconds) indicated by broken line.

Table 2. Duration of NPT

Dose	N	Duration (min) of PT correction to normal (<13.1 s)	
		Median (range)	
5 µg/kg	11	9.6 (0–76)	
20 µg/kg	12	29.4 (0–143)	
80 µg/kg	13	280.7 (0–454)	
120 µg/kg	16	83.7 (0–714)	
		P values ^a	
Overall treatment effect		0.005	
High dose (80 and 120 µg/kg) vs. low dose (5 and 20 µg/kg)		0.001	
80 µg/kg vs. 120 µg/kg		0.523	

^aP values are from Kruskal–Wallis test.

because of the possibility of volume overload. The patients receiving a rescue dose were distributed among all 4 treatment groups. None of the patients receiving a rescue dose required transfusion or operative intervention for blood loss. No association between disease severity and time to hemostasis was found.

Safety

No clinically significant changes in coagulation laboratory parameter values from baseline to the end of the treatment were observed (Figure 2A–D). Three patients in the pilot run-in with below normal baseline values of platelet count ($<150\text{--}400 \times 10^9/\text{L}$) did not show any further decrease after rFVIIa dosing. In the randomized part of the study, 29 patients had baseline fibrinogen values below normal, ($<200\text{--}400 \text{ mg/dL}$), which did not decrease any further after a single dose of rFVIIa.

In the pilot run-in, one patient experienced a serious adverse event (SAE). The patient was hospitalized with a leakage of ascitic fluid caused by dehiscence of the wound after a laparoscopic procedure. In the randomized part of the study, adverse events did not show a dose-related correlation between treatment groups. Eighteen patients experienced SAEs (28 events). The most frequently observed SAEs were hepatic failure, and bleeding (hemorrhage involving the GI tract or hematoma) that may be

associated with underlying disease of this patient population (Table 4). Other SAEs were ascites, sepsis, and pneumonia, which are commonly observed complications in this patient population.^{7,11,28} One case of disseminated intravascular coagulation (DIC) was observed in a 43-year-old white female admitted for acute liver failure secondary to the use of Duract (Wyeth Ayerst Laboratories, St. Davids, PA) (bromfenac sodium). This patient was infused with 80 µg/kg rFVIIa, and DIC was suspected post-biopsy after a drop in hematocrit with no obvious signs of overt bleeding. The patient's baseline coagulation parameters were suggestive (but not conclusive) of DIC. This event was not considered by the investigator to be related to rFVIIa treatment, and the patient recovered after a successful liver transplantation.

Seven deaths occurred in patients with SAEs, but these deaths occurred at times between 4 days to 8 months after treatment with rFVIIa. A thrombotic event (portal vein thrombosis) was reported in a 38-year-old white male 6 days after receiving a single (5 µg/kg) dose of rFVIIa before laparoscopic liver biopsy. The patient expired 13 days after treatment, and the cause of death was determined to be a result of peritoneal sepsis. A review of this case by an independent panel of 3 physicians determined that the thrombotic event was not related to treatment with rFVIIa.

Discussion

A number of factors such as viral hepatitis infection (type B or C), alcohol abuse, or exposure to chemical agents can lead to cirrhosis or hepatocellular carcinoma resulting in a progressive degeneration of liver function. HCV is a major cause of chronic liver disease worldwide, affecting 175 million people globally.²⁹ The sequelae of HCV-induced chronic liver disease account for 8000–10,000 deaths annually in the United States and are currently the leading cause of liver transplantation. To date, there are no accurate noninvasive markers of liver disease activity and fibrosis. Liver biopsy is usually the most specific test to assess the nature and severity of the disease and provides an accurate diagnosis in approxi-

Table 3. Time to Hemostasis

Dose	N	Hemostasis achieved (min)—N					Total	Hemostasis > 10 minutes
		2	4	7	10	N		
5 µg/kg	16	0	4	6	1	11	5	
20 µg/kg	14	2	4	2	2	10	4	
80 µg/kg	16	0	5	4	4	13	3	
120 µg/kg	19	0	3	8	3	14	5	
Total (%)	65	2 (3)	16 (25)	20 (31)	10 (15)	48 (74)	17 (26)	

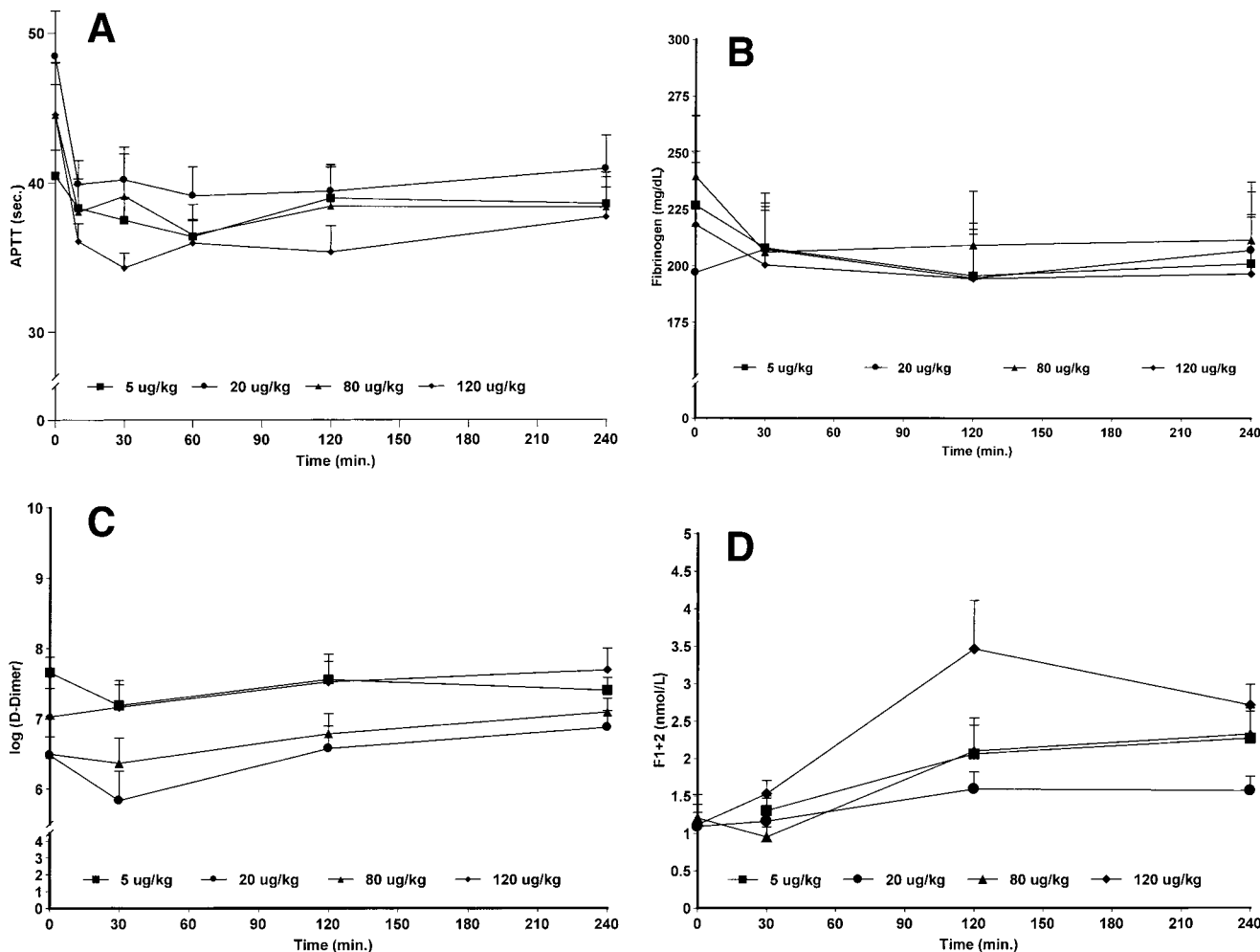


Figure 2. The effect of 4 dose levels (5, 20, 80, and 120 µg/kg) of rFVIIa on (A) activated partial thromboplastin time; (B) fibrinogen; (C) D-dimer; and (D) fragment 1+2 in patients with liver disease undergoing laparoscopic liver biopsy. Values are mean ± SE.

mately 90% of patients with unexplained abnormalities revealed on liver function tests.³⁰

Patients with liver disease are at an increased risk of bleeding during surgical procedures such as dental extractions, liver biopsy, or liver transplant.³¹ Recently, rFVIIa has reportedly been used to treat patients with fulminant liver failure.^{26,27} However, safety parameters have not been clearly evaluated. This study was conducted to evaluate the safety and effect of rFVIIa treatment on bleeding and PT correction in patients with liver disease undergoing scheduled laparoscopic liver biopsy.

Patients with cirrhosis and a prolonged PT have been shown to have significantly lower levels of FVII, which is the major initiator of the tissue factor-dependent coagulation pathway.^{5,7} Treatment intended to replace FVII in these patients should therefore reduce bleeding complications. In this study, 48 of 65 (74%) patients achieved (within the first 10 minutes) and subsequently

maintained (for 18 hours) hemostasis after treatment with a single dose of rFVIIa. Thirteen of the remaining 17 patients did not achieve hemostasis within the first 10-minute time frame and received a single rescue dose (80 µg/kg) of rFVIIa. None of these patients required any surgical intervention or blood transfusion to control excessive bleeding. No correlation between bleeding time and severity of the disease was observed in patients undergoing laparoscopic liver biopsy, which is in agreement with previously reported studies.³²

Garrison et al.³³ emphasized the significance of preoperative correction of PT in a study that described the outcome of 100 celiotomies performed in patients with cirrhosis for reasons other than portal decompression. Patients with a prolonged PT had a mortality rate of 47% as compared with 7% in patients with a normal PT. In addition, in patients whose PT was >1.5 seconds above normal, the mortality rate was 63%. Previous studies have shown that treatment with rFVIIa was

Table 4. SAEs by Occurrence (Randomized Patients)

Event	5 $\mu\text{g}/\text{kg}$ (n = 16)	20 $\mu\text{g}/\text{kg}$ (n = 14)	80 $\mu\text{g}/\text{kg}$ (n = 17)	120 $\mu\text{g}/\text{kg}$ (n = 19)	Total (n = 66)
Hepatic failure	1	1	1	2	5
Bleeding (hemorrhage/hematoma)	1	1	1	2	5
Pneumonia	0	2	0	1	3
Sepsis	1	1	0	0	2
Ascites	1	0	1	0	2
Thrombophlebitis	1	0	0	0	1
DIC	0	0	1	0	1
Pulmonary edema	0	0	0	1	1
Hepatic function abnormal	0	1	0	0	1
Peritonitis	0	0	1	0	1
Abdominal pain	0	0	1	0	1
Atrial fibrillation ^a	0	0	0	1	1
Myocardial ischemia ^a	0	0	0	1	1
Pulmonary hypertension ^a	0	0	0	1	1
Encephalopathy	0	0	0	1	1
Diabetes mellitus	0	0	1	0	1

DIC, disseminated intravascular coagulation.

^aThese 3 cardiac-related events occurred in the same patient.

effective in correcting the PT in warfarin-treated rats and healthy volunteers.^{24,25} Bernstein et al.¹⁰ reported the dose-dependent effect of rFVIIa treatment on the PT correction in nonbleeding patients with severe liver disease. Results of the present study showed that treatment with 80 and 120 $\mu\text{g}/\text{kg}$ of rFVIIa resulted in significantly higher duration of NPT as compared with the 5 and 20 $\mu\text{g}/\text{kg}$ doses of rFVIIa. The lack of significant difference in duration of NPT between the 2 higher dose groups (80 vs. 120 $\mu\text{g}/\text{kg}$) might be attributed to the higher baseline values of PT in patients dosed with 120 $\mu\text{g}/\text{kg}$ rFVIIa. The results of this study also showed a correlation between the dose of rFVIIa and the PT correction, which may be a good therapeutic tool for achieving a targeted level of PT in these liver disease patients.¹⁰ Although PT is a laboratory measure and should be used with caution, the report by Garrison et al.³³ suggests that correction of this parameter in this patient population may be an important variable in determining successful outcome of surgical interventions.

No clinically significant safety concerns were observed in the first 5 patients in the pilot run-in. Therefore, the study continued to enroll patients for the double-blind, randomized part of the study. In this part of the study, the safety profile formed no clear pattern, and no dose-related relationship for adverse events was observed. Most adverse events were considered by the investigators as not related to treatment with rFVIIa, and may have been attributable to the underlying conditions of the patients.

The most frequently reported SAE was hepatic failure, which is consistent with the advanced liver disease of this

patient population. GI bleeding was reported in 4 patients, which is one of the most frequent causes of morbidity and mortality in patients with liver cirrhosis.¹² According to Boyer et al.,³⁴ 80%–90% of patients with liver cirrhosis develop some degree of esophageal varices; 25% of these bleed and 65% re-bleed within a year. Upper GI variceal bleeding is a medical emergency, with a mortality rate as high as 30% within 6 weeks, depending on the severity of the underlying liver disease and the age of the patient.^{12,13,35} Both incidence and types of SAEs reported in this study are within expected range observed in this patient population.⁷

One of the major concerns with the administration of activated coagulation factors is the potential risk of initiating the coagulation cascade, possibly leading to DIC. Indicators of DIC, such as elevated levels of fibrinopeptide A, fragment 1+2, and D-dimers, have been shown to increase in cirrhosis.^{7,36} In the present study, no clinically relevant changes from baseline values for activated partial thromboplastin time, fragment 1+2, and D-dimer were observed. Patients with low levels of baseline values of fibrinogen or platelets did not show any further decline after a single dose of rFVIIa.

Treatment with rFVIIa seems to offer several advantages over the current treatment modalities available to treat patients with liver disease. Because no human components are used during manufacturing of rFVIIa, the risk of viral transmission should be negligible. The local hemostatic effect of rFVIIa should result in a decreased risk for DIC, and the low volumes of rFVIIa used should eliminate concerns of volume overload in this population. Finally, the presence of consistent/defined levels of

FVII present in rFVIIa should lead to more consistent efficacy using this treatment.

Liver biopsy is an essential diagnostic tool in the management of patients with acute and chronic liver disease. The results of this study indicate that rFVIIa use may be feasible in patients with liver disease undergoing laparoscopic liver biopsy. Further controlled dose exploratory studies will be necessary to evaluate the effect on hemostasis of single or multiple doses of rFVIIa on bleeding in this patient population.

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