

Recombinant Activated Factor VII for Coagulopathy in Fulminant Hepatic Failure Compared With Conventional Therapy

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Severe coagulopathy in fulminant hepatic failure (FHF) is difficult to correct by conventional means. Recombinant activated factor VII (rFVIIa) is an antihemophilic factor that has shown promise in treating coagulopathy in liver disease. Our aim is to review our experience with rFVIIa in treating the coagulopathy of FHF and compare these results with those of conventional therapy. Fifteen patients with FHF who met King's College criteria for orthotopic liver transplantation were studied. All were ascertained from our liver disease registry. Eight consecutive patients were administered fresh frozen plasma (FFP) alone, whereas seven consecutive patients were administered FFP and rFVIIa (40 μ g/kg intravenous bolus). The two groups, with similar demographic characteristics, were compared in terms of measured parameters of coagulopathy (prothrombin time and international normalized ratio), amount of plasma infused, development of anasarca, ability to undergo intracranial pressure (ICP) transducer placement, bleeding complications, ability to undergo transplantation, and survival. All patients administered rFVIIa (after a single dose) versus none administered FFP alone had temporary (2- to 6-hour) correction of coagulopathy ($P < .0002$). All patients administered rFVIIa versus 38% administered FFP alone were able to have an ICP transducer placed ($P = .03$). The rFVIIa group had less anasarca ($P = .04$). An equal number of patients underwent transplantation from each group, but overall survival was slightly better in the rFVIIa group ($P = .04$). Five of seven patients in the rFVIIa group were administered one or more subsequent doses of rFVIIa after placement of the ICP monitor (two patients, for additional procedures; three patients, prophylactically in the first 24 hours after ICP transducer placement) at the discretion of the attending physicians. We conclude that rFVIIa is effective in transiently correcting laboratory parameters of coagulopathy in patients with FHF. It facilitates the performance of invasive procedures and is associated with less frequent anasarca compared with conventional therapy. Our preliminary experience supports the need for further studies to define the optimal dosing, safety, and efficacy of rFVIIa in patients with FHF. (*Liver Transpl* 2003;9:138-143.)

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With the exception of bioartificial liver support, which remains experimental, little has changed in the management of fulminant hepatic failure (FHF) since the advent of liver transplantation. Mortality figures remain high even in the modern era.¹ Severe coagulopathy is a prominent clinical finding in FHF.² Although precise guidelines for safe coagulation parameters in patients with FHF for the performance of invasive procedures do not exist, the presence of coagulopathy is widely believed to increase the risk for procedure-related bleeding. Common invasive procedures in this setting include placement of catheters for dialysis or ultrafiltration or placement of intracranial pressure (ICP) monitors that, although still controversial,³ are considered valuable tools in many centers.

Conventional treatment with fresh frozen plasma (FFP), usually aimed at producing a locally defined safe level of coagulation indices, often is unsuccessful and may require large quantities of plasma, producing volume overload and anasarca. Other means of managing this problem have not become established because of moderate efficacy, excessive complexity, or thrombotic complications. These include plasma exchange, promoters of platelet aggregation (DDAVP [desmopressin acetate]; Aventis Pharmaceuticals, Bridgewater, NJ), prothrombin-complex concentrate administration, inhibitors of fibrinolysis (ϵ -aminocaproic acid), and combination infusions of plasma and heparin.^{2,4-6} The wide variety of interventions aimed at correcting this deficit attest to the clinical importance attached to correction of this problem in practice.

Normal coagulation is initiated by the formation of a tissue factor (TF)-activated factor VII complex.⁷ This complex activates factors IX and X, leading eventually to formation of a hemostatic fibrin plug. Recombinant activated factor VIIa (rFVIIa; NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) was approved in the United States as an antihemophilic agent in 1999 and has shown encouraging results in early studies of the coagulopathy of chronic liver disease.^{8,9} Factor VII has a key role in initiating normal clot formation and is the first coagulation factor to have decreased levels in patients with FHF.² It is reasonable to believe that the administration of exogenous rFVIIa should promote hemosta-

sis in FHF. In 1999, we began using rFVIIa in patients with FHF to facilitate placement of ICP transducers. We review our experience with the first seven patients treated with rFVIIa and compare these results with conventional therapy in eight consecutive historic controls treated before we began using this agent.

Methods

Patients with FHF were ascertained from a liver disease registry maintained by one of the authors (S.H.C.). Since our initial use of rFVIIa in December 1999, all subsequent patients with this diagnosis have been administered rFVIIa. Because this date provided a breakpoint in our management of this disorder, we compared our first seven patients treated with rFVIIa with eight previous consecutive patients with FHF ascertained from our registry. Selection criteria for liver transplantation in patients with FHF remain unsettled, but all patients were transplant eligible by traditional criteria of the King's College Hospital.^{10,11}

Available clinical material, including hospital records and computerized databases, were reviewed for abstraction of specific information. This included age, sex, cause of FHF, coagulation parameters, ability to place an ICP transducer (based on the ability to correct coagulation parameters), number of units of plasma infused (from the time of admission until stabilization of the clinical course, early signs of recovery, death, or liver transplantation), development of anasarca, and short-term survival with discharge from the hospital. These data are listed in Table 1.

Because placement of an ICP transducer is considered a part of optimal management of these patients in our institution, the ability to perform this procedure (i.e., achieving the target for correction of the coagulopathy) provided both a target for therapy and an end point of treatment efficacy. The minimal goal of therapy with FFP and/or rFVIIa is to produce

a prothrombin time (PT) international normalized ratio (INR) less than 1.6 and/or PT less than 4 seconds above normal. Patients in the rFVIIa group were administered 40 $\mu\text{g}/\text{kg}$ as an intravenous bolus. Our choice of this dose was derived from past hemophilia studies (in which 90 $\mu\text{g}/\text{kg}$ is typically administered),^{12,13} early studies of cirrhotic patients (in which 5, 20, and 80 $\mu\text{g}/\text{kg}$ appeared to be effective),⁸ and reports of patients with liver failure undergoing liver transplantation (in which 80 to 100 $\mu\text{g}/\text{kg}$ was administered).^{9,14} Plasma administration was at the discretion of the attending physician in both groups of patients. Coagulation parameters were measured again after plasma and/or rFVIIa were administered (within 30 minutes).

rFVIIa was readministered after the procedure at the discretion of the attending physicians and consultants after placement of the ICP transducer. Five of seven patients were administered additional postprocedure doses of rFVIIa (20 to 40 $\mu\text{g}/\text{kg}$ as intravenous bolus) in the first 24 hours after placement of the ICP monitor; two patients for additional procedures and three patients for post-ICP monitor placement prophylaxis. Of these five patients, one patient was administered a single additional dose, two patients were administered two subsequent doses, and two patients were administered four subsequent doses of rFVIIa in this period.

The study was approved by the University of Virginia Institutional Review Board (Charlottesville, VA). Data were analyzed using Fisher's exact test for binary data and Wilcoxon's rank-sum test for continuous data. *P* less than .05 is considered statistically significant.

Results

Results are listed in Table 1. PT and/or PT INR normalization was seen in 100% of patients administered rFVIIa as opposed to none of the patients administered plasma alone (*P* = .0002). All patients administered

Table 1. Patient Demographics and Results

	Plasma Alone (N = 8)	rFVIIa (N = 7)	<i>P</i>
Median age (yr)	28 (7-45)	34 (16-64)	.10
Gender (% women)	5/8 (63)	6/7 (86)	.57
Acetaminophen-induced FHF	4/8 (50)	4/7 (57)	1.00
Baseline PT (s)	29.5 \pm 7	33.4 \pm 14	.50
PT correction	0/8 (0)	7/7 (100)	.0002
Ability to place ICP transducer	3/8 (38)	7/7 (100)	.03
Average units of FFP	19	13	.35
Anasarca	7/8 (88)	2/7 (29)	.04
Bleeding	2/8 (25)	0/7 (0)	.47
Liver transplantation	3/8 (38)	3/7 (43)	1.00
Time to end point (d)	4.2 \pm 2	3.2 \pm 1	.07
Death*	6/8 (75)	1/7 (14)	.04

NOTE. Values expressed as median (range), of number/total number (percent), or mean \pm SD.
*Six of the seven deaths were in the control group, and five of these were caused by cerebral edema.

rFVIIa were able to have an ICP transducer placed compared with 38% of those administered plasma alone ($P = .03$). Because placement of the ICP monitor is part of our general management strategy for these patients, failure to place this device was directly attributable to failure to achieve coagulation criteria. In all patients administered rFVIIa, correction of the coagulopathy was rapid (Fig. 1).

The interval from admission to stabilization, transplantation, or death varied and ranged from 2 to 6 days. Mean duration of assessment was 3.2 ± 1 days for the rFVIIa group and 4.2 ± 2 days for the control group. The difference, although not statistically significant, reflected the typically longer time required to reach a clinical end point in the plasma-treated group.

We could not detect a statistically significant difference in number of FFP units administered between the two groups. However, in the group administered plasma alone, seven of eight patients were administered greater than 10 units of FFP during the observation period, whereas in the rFVIIa group, only three patients were administered greater than 10 units, and in three patients, coagulation parameters were corrected completely with 4 or fewer units. We also noted that as our experience with rFVIIa increased, substantially less plasma was administered to subsequent patients. Anasarca, attributable to volume expansion with plasma, was significantly less evident in the rFVIIa group compared with the plasma group ($P = .04$).

Bleeding complications developed in two patients administered FFP alone compared with none of the rFVIIa group, although this did not reach statistical significance. Likewise, we did not observe a significant difference in number of patients eventually undergoing

transplantation. Overall, seven patients died; five patients, of cerebral herniation, and two patients, of multiorgan failure. Mortality was greater in the group administered plasma alone (six of eight versus one of seven patients; $P = .04$). We did not note complications related to the administration of rFVIIa.

Discussion

Management of patients with FHF is one of the most challenging and complex tasks of the liver disease or critical care specialist. Coagulopathy in this setting further complicates patient management because of attendant bleeding risks, increased risks of procedures, alterations of risk assessment for transplant selection, and complications related to treatment of the coagulopathy.² Although hyperfibrinolysis^{2,15,16} and disseminated intravascular coagulation¹⁷ are important considerations, the most common coagulation abnormality in these patients is prolongation of the PT because of decreased synthesis of vitamin K–dependent coagulation factors (factors II, VII, IX, X).^{2,4} Although laboratory abnormalities do not allow absolute prediction of bleeding risks, it is widely accepted that severe prolongation of the PT or INR carries increased risks for bleeding in patients with FHF. This is supported specifically by a report from Boks et al¹⁶ showing a correlation between mucosal and puncture-site bleeding and laboratory measurements of coagulopathy in patients with FHF.

Factor VII is the initiator of coagulation when TF has been exposed at the site of injury. rFVIIa is believed to act mainly by binding to TF-bearing cells, predominantly monocytes, at the site of injury.^{17,18} Factors IX and X then are activated and generate a critical amount of thrombin (thrombin burst), which activates platelets and other coagulation factors.¹⁹ rFVIIa does not act as a replacement factor alone, but initiates a site-specific burst of coagulation activity. This mechanism explains the activity of rFVIIa in a variety of coagulopathies, including thrombocytopenia, type III von Willebrand's disease, and warfarin-treated individuals.²⁰ Thus, high FVIIa levels can initiate thrombin generation because of high local concentrations of coagulation factors despite low systemic concentrations.

Bernstein et al⁸ showed that rFVIIa is effective in transiently reversing the coagulopathy of cirrhosis at all three doses tested (5, 20, and 80 $\mu\text{g}/\text{kg}$). Duration of response varied from 2 hours with the lowest dose (5 $\mu\text{g}/\text{kg}$) to 12 hours with the highest dose (80 $\mu\text{g}/\text{kg}$). It was calculated from their study that a 20- $\mu\text{g}/\text{kg}$ bolus of rFVIIa increases mean plasma FVIIa concentration

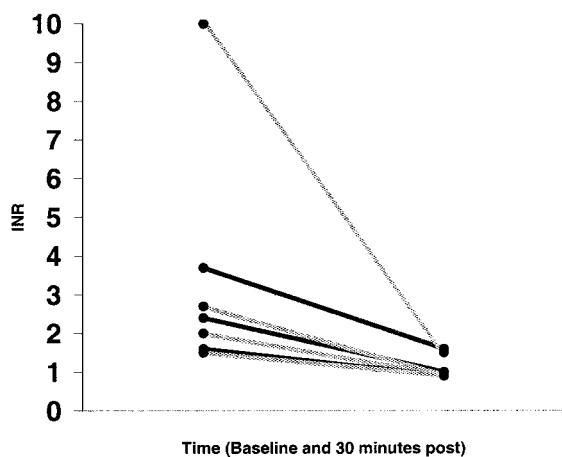


Figure 1. PT INR before and 30 minutes after administration of 40 $\mu\text{g}/\text{kg}$ of rFVIIa.

from a baseline of 0.03 U/mL to 8 U/mL (1U = 100% activity) in patients with cirrhosis. It is believed that this increases the number of FVIIa-TF complexes that form at the site of injury, thus enhancing the ability to generate factor Xa and compensating for the depressed levels of other factors that influence PT (factor X, factor V, prothrombin). Platelet function also is enhanced.^{7,18}

Performance of invasive, but potentially life-saving, procedures in patients with FHF carries the risk for bleeding complications. Although bleeding could occur at any point during or after a procedure, the initial break in the skin and breach of the vascular barrier is believed to carry the greatest risk, especially with the placement of ICP monitors. Management of patients with FHF frequently involves a multidisciplinary team, and in the United States, these devices are most often placed by neurosurgeons. As mentioned, there are no uniformly accepted coagulation parameters for the placement of an ICP monitor, but it is our experience that neurosurgical consultants always have cutoff values above which they will not perform the procedure. Thus, practically speaking, if placement of these devices is sought, correction of the coagulopathy is typically undertaken as part of procedure preparation. Transient correction of the PT and PT INR, achieved uniformly by rFVIIa administration in our experience, thus is of practical value in allowing ICP monitor placement.

The need to readminister rFVIIa in patients with FHF is unknown. Three patients were readministered rFVIIa after ICP monitor placement as a precautionary measure to prevent later bleeding, whereas two patients were readministered rFVIIa after ICP placement to perform other invasive procedures, such as liver biopsy or central catheter placement. With our experience, we now believe that readministration of rFVIIa is probably of limited utility unless there is recurrence of the coagulopathy and associated bleeding or recurrence of the coagulopathy and the need for additional invasive procedures.

Any intervention to correct the coagulopathy in patients with liver failure carries the risk for thrombosis or disseminated intravascular coagulopathy. rFVIIa has been proven relatively safe in common forms of hemophilia,²¹ and Bernstein et al⁸ reported no major complications in a small series of patients with cirrhosis. Similarly, concerns over exacerbation of fibrinolysis have not been supported in recent studies,²² and none of our seven patients in this series had adverse effects. However, the complexity of coagulation defects in liver disease warrants caution. It is possible that a hypercoagulable state may be more likely in cirrhotic patients with

active circulating TF present, such as that is seen in gram-negative sepsis.^{23,24}

The apparent benefit in mortality should be viewed cautiously given the small number of patients and use of historic controls. Substantiation of our findings requires larger prospectively controlled trials. If proven, it is uncertain whether a survival benefit derives from the greater use of invasive monitoring per se or the avoidance of volume expansion and anasarca. Previous studies of ICP monitoring in patients with liver failure suggested that the greatest benefit of these devices occurs intraoperatively, during transplantation, when wide volume swings increase the risk for cerebral edema.²⁵ This observation, along with the decreased occurrence of anasarca with rFVIIa use, may explain the infrequent need for intervention to treat intracranial hypertension in our patients treated with rFVIIa. Unfortunately, because we were unable to place ICP monitors in most of the control (plasma-treated) patients, we were unable to directly compare the incidence of intracranial hypertension in the two groups. Although a relationship between anasarca and cerebral edema has not been established, the high number of deaths from cerebral edema in our control group (most of whom developed anasarca) supports an association between these processes.

Since assembling this series, we have successfully administered rFVIIa to an additional 12 patients with FHF. Results in these latter patients were very similar to our initial experience, with one exception. An 18-year-old student presented with acetaminophen toxicity in the setting of alcohol and suspected recreational drug use with coagulopathy, acidemia, and severe hypotension requiring multiple adrenergic medications. Administration of rFVIIa corrected the coagulopathy, and she underwent uncomplicated ICP monitor placement. However, she subsequently experienced a myocardial infarction (see Food and Drug Administration MedWatch) after multiple postprocedure doses of rFVIIa and while being administered high-dose intravenous α -adrenergic therapy (norepinephrine and phenylephrine). No thrombus was shown on urgent cardiac catheterization; thus, vasospasm is favored as the mechanism, but caution is warranted, particularly in a patient requiring high-dose α -adrenergic agents. Consequently, the authors caution against multiple doses of rFVIIa after a successful procedure, especially if α -adrenergic agents are required, unless there is bleeding.

Resource utilization is another concern in this setting. In our pharmacy, the approximate cost of a 1.2-mg vial is \$972. Administration of 2.4 mg to a

60-kg individual (40 $\mu\text{g}/\text{kg}$) would cost \$1,944. Conversely, the average cost of a unit of FFP is \$50 to \$100. This translates to \$850 to \$1,900 for the average number of units administered to the plasma-alone group in our study. Thus, incremental costs of using rFVIIa seem reasonable. In addition, some institutions now prophylactically initiate hemofiltration to prevent problems with fluid overload. This intervention (or plasma exchange) is estimated to add an additional \$1,200 to \$1,500 per day to the costs of patient care. Thus, avoidance of fluid overload and quick correction of the coagulopathy allowing important and sometimes life-saving intervention may more than offset the added pharmacy costs of rFVIIa.

Our results are limited by the use of historic controls. Nonetheless, similar to a recent report of the relative safety and efficacy of rFVIIa in liver biopsy patients,²⁶ it offers encouragement to further investigations of the use of this agent in patients with liver disease and associated coagulopathy. The prospect of avoiding severe volume overload in patients with FHF while facilitating potentially beneficial interventions is very attractive. Severe volume expansion exacerbates portal hypertension,²⁷ and anasarca probably exacerbates cerebral edema. Although it remains to be seen whether correction of the coagulopathy without volume expansion results in improved overall outcomes, we can safely conclude that rFVIIa is effective in transiently correcting the major laboratory parameters of coagulopathy in patients with FHF. Its use facilitates the performance of invasive procedures and is associated with less frequent development of anasarca compared with conventional therapy with plasma alone. Our preliminary experience supports the need for further studies to define the safety and efficacy of this agent in patients with FHF.

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