

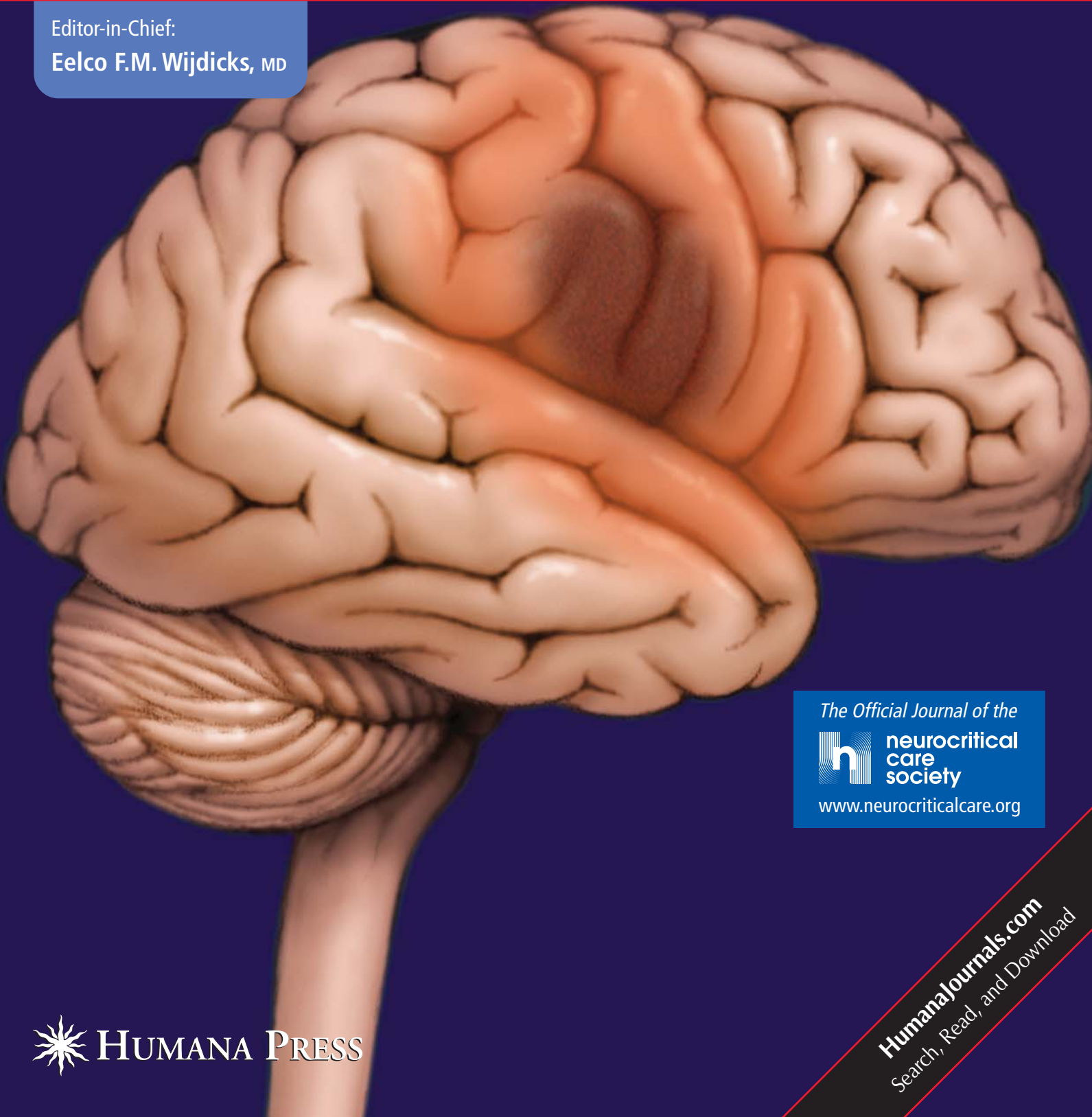
Inaugural Issue

Neurocritical Care

Volume 1 • Number 1 • 2004 • ISSN 1541-6933

A Journal of Acute and Emergency Care

Editor-in-Chief:
Eelco F.M. Wijdicks, MD



The Official Journal of the

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The Emerging Role of Recombinant-Activated Factor VII in Neurocritical Care

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Abstract

Recombinant-activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Denmark) was developed specifically for the management of bleeding in hemophiliacs with inhibitors to factors VIII or IX. Several recent case reports and small clinical studies also suggest that rFVIIa may be useful as a general hemostatic agent in nonhemophilic patients. The mechanism by which rFVIIa acts is controversial with both tissue factor-dependent and -independent mechanisms proposed. Regardless of the specific mechanism, rFVIIa enhances hemostasis at the site of injury without systemic activation of the coagulation cascade. Several features make rFVIIa an ideal candidate for reversal of coagulopathy in central nervous system (CNS) hemorrhage. It acts almost immediately, requires negligible volume for infusion, poses no risk of transfer of blood-borne pathogens, and has few apparent complications. To date, clinically proven efficacy for rFVIIa by randomized controlled trials has been accomplished mainly for hemophilic patients. However, there are ongoing or planned clinical trials for rapid reversal of coagulopathy in trauma and liver disease, as well as CNS hemorrhage associated with oral anticoagulation and minimization of hematoma expansion after intracerebral hemorrhage. These trials will hopefully answer unresolved questions regarding risk-benefit ratio, therapeutic index, efficacy, safety, indications, optimal dosing, monitoring, and cost-effectiveness of rFVIIa in nonhemophilic patients.

Key Words: Recombinant-activated factor VII; NovoSeven; coagulopathy; intracranial hemorrhage.

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Introduction

Recombinant-activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Denmark) was developed in the late 1980s specifically for the management of bleeding in patients with hemophilia and inhibitors to factors VIII or IX. Approved in Europe in 1996 and in the United States in 1999 by the Food and Drug Administration (FDA), rFVIIa is now registered in more than 50 countries worldwide for the treatment of spontaneous and surgical bleeding episodes in hemophiliacs with inhibitors. A number of case reports and data from small clinical studies also suggest that rFVIIa may be effective as a general hemostatic agent in nonhemophilic patients. This article provides a brief background on rFVIIa, explains the rationale for its use outside of hemophilia, reviews the existing literature, including applications to neurocritical care, and suggests other potential indications for its use.

Background and Rationale for Use of rFVIIa

An open knee-joint synovectomy in 1988 at the Karolinska Hospital in Stockholm was the first major surgical procedure performed in a hemophilic patient with inhibitors using rFVIIa (18). Initial clinical trials with rFVIIa in hemophilia demonstrated an 80–90% efficacy in attaining hemostasis in spontaneous bleeding episodes (3,42). A number of major procedures were subsequently performed safely in hemophilic patients as part of a compassionate use program, including one patient who underwent craniotomy for evacuation of an epidural hematoma (24,25,55).

A growing body of evidence supports the safety and efficacy of rFVIIa to rapidly correct a variety of nonhemophilic coagulopathies (12,20). Published reports have described successful use of rFVIIa in platelet disorders, such as Glanzmann's thrombasthenia (49,59,62), Bernard-Soulier syndrome (47), and von Willebrand's disease (17,35), as well as thrombocytopenia (31,64), and coagulopathy associated with oral anticoagulant therapy (9,10,34,57), trauma (29,36,41,44), and liver disease (21,40).

rFVIIa has also been successfully used in non-coagulopathic patients with intractable surgical bleeding (32), difficult surgical bleeding in heart valve repair (1,22), and postsurgical intra-abdominal hemorrhage (65). Administration of rFVIIa decreased perioperative blood loss in patients who underwent transabdominal retroperitoneal prostatectomy (13) and reduced transfusion requirements during orthotopic liver transplantation (21). These initial reports have provided the impetus for investigational trials of rFVIIa outside hemophilia (12).

Mechanism of Action

In the normal cell-based model of coagulation, tissue factor (TF) is present in the media and adventitia of vessel walls (20). With vessel injury, TF-bearing cells become exposed to the circulating blood and are bound by endogenous FVIIa which is normally present at low levels. The cell-bound TF-FVIIa complex then cleaves factor X (FX) to FXa which complexes with FVa to form small amounts of thrombin as well as activate platelets. The TF-FVIIa complex also cleaves FIX to FIXa which diffuses to activated platelets and binds with FVIIIa. The platelet-bound FIXa-VIIIa complex then promotes additional cleavage of FX to FXa. The production of FXa on the platelet surface by FIXa-VIIIa is the key step in generating the large amounts of thrombin required for hemostasis.

This cell-based model of coagulation, however, does not readily explain the observed efficacy of rFVIIa in hemophilia B patients deficient in FIX. Consequently, several investigators have proposed a modified mechanism of action for rFVIIa (15). In this proposal, rFVIIa in a supra-physiologic concentration is able to directly cleave FX to FXa on the platelet surface to generate thrombin, thus bypassing the need for FVIII or FIX (23). This modification in the cell-based model of coagulation would also account for the lack of systemic activation of the coagulation cascade with use of rFVIIa because its action would be specific to activated platelets, which are generally present only at sites of vessel injury (26).

Pharmacokinetics

Pharmacokinetics have been evaluated in adult and pediatric patients with hemophilia, as well as in adults with acquired FVII deficiency, healthy volunteers treated with acenocoumarol (Sintrom®; Novartis, East Hanover, NJ), and patients with liver cirrhosis (10,11,26). The reported half-life values for adults vary from 2.4 to 3.2 hours with bolus administration of rFVIIa compared to 1.3 hours in children (11,26,56). rFVIIa is intended to be given by intravenous bolus administration over 2–5 minutes. Onset of action appears to be almost immediate with clinically apparent hemostasis noted within 10 min.

Dosage

Clinical dose-finding trials have been performed in hemophiliacs and patients with acquired factor deficiencies. In one multicenter study, no significant difference was found between 35 and 70 µg/kg per dose. However, in a randomized trial of two doses of rFVIIa in hemophilic patients with inhibitors undergoing surgery, a dose of 90 µg/kg was found to be more effective than 35 µg/kg (55). In a dose-ranging study on normal volunteers taking acenocoumarol, even the smallest dose of 5 µg/kg was found to normalize the prothrombin time (PT) and international normalized ratio (INR) (10). A 5 µg/kg dose normalized the PT/INR for 2 to 4 hours, whereas a dose greater than 80 µg/kg was required for correction more than 6 hours. Repeated dosing by intravenous bolus or even continuous infusion of rFVIIa may be used if necessary.

Monitoring rFVIIa Treatment

Clinical hemostasis is the ultimate measure of efficacy of rFVIIa. Laboratory coagulation parameters have shown no direct correlation with achieving clinical hemostasis and do not necessarily reflect the effectiveness of rFVIIa. Although administration of an 80–110 µg/kg dose typically normalizes the PT, the activated partial thromboplastin time (aPTT) is shortened by about 35%, and has no effect on the meas-

ured platelets, fibrinogen, or D-dimer (24,25). Using the plasma level of FVIIa has not been possible because the level needed for hemostasis is unknown. One method which has been proposed is determining the plasma factor VII-coagulant levels (FVII:C) (25). The PT has a negative correlation with plasma levels of FVII:C and may be used as a surrogate marker to verify that a hemostatic level of FVII:C is present (19). More data is needed to ensure that rFVIIa not only normalizes coagulation parameters, but also hemostatic conditions, especially during surgical procedures such as for central nervous system (CNS) hemorrhages.

Safety

rFVIIa appears to have an excellent safety profile and only rare serious thromboembolic complications have been reported including acute myocardial infarction (46), pulmonary embolism (53), and disseminated intravascular coagulation (58). As of 2001, more than 180,000 standard doses of rFVIIa have been administered with only 17 thrombotic adverse events reported (12). Most of these adverse events (11 arterial thrombosis, 6 venous thrombosis) could be attributed to improvements in the clotting mechanism in individuals with underlying prothrombotic conditions rather than a direct effect of rFVIIa itself (51).

No conclusions regarding the comparative safety or efficacy of rFVIIa to other coagulation products can be made as no clinical trials with direct comparisons have been conducted. It should not be administered to patients with hypersensitivity to mouse, hamster, or bovine proteins. Patients with known hypercoagulability, those with a history of thromboembolic events, and those with clinical conditions which predispose to thromboembolic events may be at increased risk of developing adverse events with rFVIIa use.

Cost of rFVIIa

One criticism of rFVIIa is its cost. rFVIIa is available in 1.2-mg, 2.4-mg, and 4.8-mg vials.

At our institution, the cost of one 1.2-mg vial is \$1369. However, in those coagulopathic patients requiring emergent neurosurgical intervention for life-threatening CNS hemorrhages, we feel the benefit derived from rapid correction justifies this cost. In addition, it is our experience that patients treated with rFVIIa require fewer transfusions with blood products. At least one report has shown that a single dose of rFVIIa might actually represent a cost savings when compared to unsuccessful standard therapy of multiple fresh frozen plasma (FFP) infusions (41).

rFVIIa in Neurocritical Care

Investigational uses of rFVIIa are being evaluated in a number of ongoing clinical trials (12). The following section reviews the existing literature regarding rFVIIa in areas of importance to physicians involved in neurocritical care.

rFVIIa in CNS Hemorrhage During Oral Anticoagulation Therapy

Oral anticoagulant medication is now commonly used for an expanding number of medical indications, including hypercoagulable conditions, atrial fibrillation, deep venous thrombosis, prosthetic heart valves, and preventing acute myocardial infarction and stroke. Oral anticoagulants have a narrow risk-to-benefit ratio, with the most common complication being adverse bleeding. Nontraumatic intracranial hemorrhage in patients receiving warfarin is estimated to occur at a rate of approximately 1%/year with a mortality of nearly 80% (37).

Several standard treatments are available for reversal of oral anticoagulation, including FFP, vitamin K, prothrombin complex concentrate, and factor IX complex. All have limitations such as variations in doses, volumes, and rates of reversal, as well as potential complications of anaphylaxis, fluid overload, transmission of infective agents, and thromboembolism (8,30).

The optimal coagulation parameters at which neurosurgical procedures can be performed has not been determined in any randomized trial, however, most authors suggest an INR of at least 1.4 or less (4,37). In a small series of patients with warfarin-related intracranial hemorrhage,

the average time to correction was nearly 9 hours with standard FFP administration. Factor IX complex administration in conjunction with FFP shortened the reversal time to an average of 2.95 hours (4). Kawamata et al. were unable to sufficiently reverse any of their patients with warfarin-related acute subdural hematomas and cerebral contusions (27).

The ability of rFVIIa to rapidly reduce the INR in healthy volunteers treated with oral anticoagulant has been demonstrated in a randomized study (10). The lowest dose of 5 µg/kg normalized the INR for 2 hours, whereas doses above 120 µg/kg corrected the INR for 24 hours. In a series of 13 patients, rFVIIa was used to rapidly reverse excessive warfarin-induced anticoagulation (9). An initial dose of 90 µg/kg was subsequently lowered when it became apparent that even doses of 15–20 µg/kg were effective for reversal.

rFVIIa may be the best candidate to date for reversal of coagulopathy in CNS hemorrhage. It appears to act almost immediately, requires negligible volume for infusion, poses no risk of transfer of human blood-borne pathogens, and has an excellent safety profile.

rFVIIa in CNS Hemorrhage in Hemophilia

Mortality is 20–50% in hemophiliacs who present with CNS hemorrhage (50). A number of studies have reported successful use of rFVIIa to control bleeding in hemophiliacs with intracranial hemorrhages (54). Data from two compassionate-use clinical trials of rFVIIa reported cessation of bleeding in 84% of CNS hemorrhages after administration of rFVIIa (80–100 µg/kg) with only one fatality (4.8% mortality) and no major adverse events (50). Another compassionate use program of rFVIIa in Australia and New Zealand included one patient with a subdural hematoma (SDH) evacuated by craniotomy and one with a SDH that did not require surgery (39). Ingerslev et al. reported 12 hemophilic patients undergoing major surgery using rFVIIa, including evacuation of an epidural hematoma in one patient (24). In another series, rFVIIa effectively controlled life-threatening intracranial hemorrhage in 10

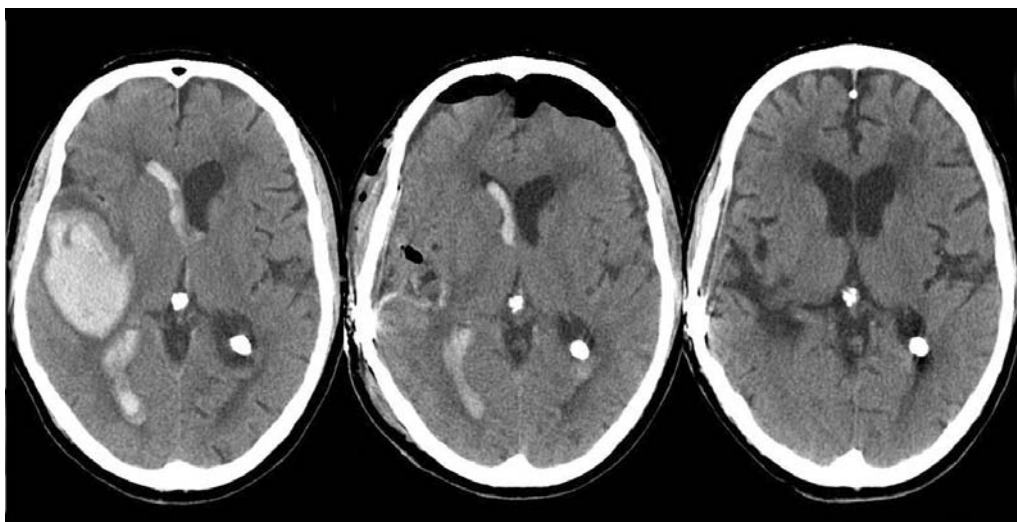


Fig. 1. A 78-year-old man taking coumadin for atrial fibrillation presented with a right temporal-parietal intracerebral hemorrhage. Initial coagulation parameters were a PT of 28, INR of 2.8, and aPTT of 36. After a 90 $\mu\text{g}/\text{kg}$ dose of rFVIIa, the values immediately corrected to a PT of 9.6, INR of 0.9, and aPTT of 32.0. The patient then underwent an uncomplicated craniotomy for clot evacuation. (Left) Axial noncontrast CT obtained at presentation. (Middle) Axial CT obtained 1 day postoperatively. (Right) Follow-up CT obtained 6 weeks postoperatively.

of 12 patients (3). rFVIIa has been effectively used to treat an extensive spinal epidural hematoma in a patient with hemophilia A and a CNS hemorrhage in a patient with severe neonatal FVII deficiency (33,66).

Given the historically high mortality rate of CNS bleeds in hemophiliacs, the data presented above argues that rFVIIa should be considered as first line treatment for CNS hemorrhages in all hemophiliacs.

rFVIIa in Neurosurgical Procedures

Coagulopathy is a significant contraindication to neurosurgery. Unfortunately, many coagulopathic patients require urgent neurosurgical intervention. For these patients, potentially life-saving surgery is often delayed or deferred altogether because of the inability to correct the coagulopathy rapidly with infusions of standard blood products.

Table 1 summarizes the existing literature regarding use of rFVIIa in nonhemophilic coagulopathic patients undergoing neurosurgical intervention. This initial experience in neurosurgical practice comprises a total of 25 patients

who received rFVIIa doses ranging from 10 to 120 $\mu\text{g}/\text{kg}$ for a variety of coagulopathic conditions (16,34,41,45,57,63). Overall, these preliminary results have been excellent with no procedural complications and no adverse postoperative hemorrhages or thromboembolic events.

Gerlach et al. were the first to report use of rFVIIa in the neurosurgical literature (16). They described rFVIIa (120 $\mu\text{g}/\text{kg}$) for hemostasis in uncontrollable intraoperative bleeding during transfacial resection of a giant skull base hemangiopericytoma after standard surgical methods and massive blood product transfusion failed to stop diffuse bleeding. rFVIIa has been effectively used for surgical management of warfarin-induced intracranial and spinal hemorrhages (34,57,63), as well as severe cerebral injury-induced coagulopathy (41).

We have recently reported our own experience using rFVIIa for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients (45). Nine coagulopathic patients requiring urgent neurosurgical intervention received rFVIIa (40–90 $\mu\text{g}/\text{kg}$) to correct their

Table I
Summary of rFVIIa Use in Nonhemophilic Coagulopathic Patients Undergoing Neurosurgical Intervention

<i>Authors</i>	<i>n</i>	<i>Cause of coagulopathy</i>	<i>Indication for surgery</i>	<i>Procedure</i>	<i>Dose (µg/kg)</i>	<i>Complications</i>
Gerlach et al., 2002 (16)	1	Uncontrolled surgical bleeding	Giant skull base hemangiopericytoma	Transfacial resection	120	None
Veshchev et al., 2002 (63)	1	Warfarin	SDH	Craniotomy	120	None
Morenski et al., 2002 (41)	3	Cerebral trauma	Closed head injury (3)	ICP monitor (3)	90	None
Lin et al., 2002 (34)	4	Warfarin	SDH (2), spinal hemorrhage (2)	Craniotomy (2), spinal hemorrhage evacuation (2)	16–22	None
Sorenson et al., 2003 (57)	7	Warfarin	ICH (3), SDH (2), spinal SAH (1), spinal stenosis (1)	Not detailed other than drainage of hematomas (6)	10–40	None
Park et al., 2003 (45)	9	Warfarin (3), liver disease (3), dilutional after trauma (3)	Hepatic encephalopathy (3), ICH (2), EDH (2), SAH (1), IVH (1)	Craniotomy (4), ventriculostomy (2), ICP monitor (3)	40–90	None

SDH, subdural hematoma; ICH, intracerebral hematoma; SAH, subarachnoid hemorrhage; EDH, epidural hematoma; ICP, intracranial pressure.

coagulopathy, and then underwent their appropriate neurosurgical procedure. These patients presented with varied etiologies for their coagulopathy including warfarin anticoagulation, liver dysfunction, and dilutional coagulopathy after trauma. Neurosurgical procedures performed were craniotomy for evacuation of epidural and intraparenchymal hemorrhages, ICP monitor placement, and ventriculostomy (Fig. 1). Since our initial report, we have treated six additional coagulopathic patients successfully with rFVIIa, including one Jehovah's witness patient with a large cerebral abscess who refused standard blood products, but did accept rFVIIa use.

rFVIIa in Subarachnoid Hemorrhage

Rebleeding following aneurysmal subarachnoid hemorrhage is a major factor contributing to poor outcomes in these patients. Antifibrinolytic agents have been shown to reduce the rate of rebleeding, but at the expense of increased risk of infarct and exacerbation of vasospasm (52). In an effort to prevent rebleeding following aneurysmal subarachnoid hemorrhage while addressing the theoretical concern that rFVIIa might increase the risk of vasospasm and cerebral ischemia, a dose escalation study was undertaken in collaboration with the UK Spontaneous Intracranial Haemorrhage Group (48).

The first nine patients treated with rFVIIa showed no evidence of cerebral ischemia, however, the tenth patient developed multiple branch occlusions of the middle cerebral artery contralateral to the aneurysm. This occurred on day 4 in a patient who had received a single 80 µg/kg dose of rFVIIa followed by continuous infusion at 7 µg/kg per hour. It is not clear from this preliminary study, however, that the ischemic complication was a result of treatment with rFVIIa. This study was suspended pending review of the potential adverse effects by an independent panel. Based on this limited initial experience, the usefulness of rFVIIa for prevention of rebleeding following aneurysmal subarachnoid hemorrhage is uncertain.

rFVIIa in Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes in the United States and Europe and 20–30% in Asian populations. ICH has a higher mortality rate than either ischemic stroke or subarachnoid hemorrhage. Of the estimated 37,000 Americans who suffered an ICH in 1997, nearly half were dead at 1 month, and only 20% were living independently at 6 months (5). Hematoma volume is one of the strongest predictors of 30-day mortality following ICH (6). Several recent prospective and retrospective studies have evaluated the rate of hematoma enlargement after initial presentation and report rates ranging from 14% to 38% within the first 24 hours of admission (7,14,28). Many of these patients experience further neurological deterioration and poor clinical outcome.

Mayer has proposed using rFVIIa as ultra-early hemostatic therapy in ICH in an attempt to minimize hematoma expansion and late deterioration related to secondary effects of edema, ischemia, and inflammation (38). This use of rFVIIa to promote early hemostasis after ICH can be viewed as a counterpart to thrombolytic intervention for acute ischemic stroke. To that end, the NovoSeven ICH trial is a randomized, double-blind, placebo-controlled, dose-ranging study that will investigate the use of rFVIIa as an ultra-early hemostatic agent in ICH patients with normal coagulation (38). Two dose-escalation phase IIa studies are currently in progress to determine the safety and feasibility of using rFVIIa in patients with acute ICH. A multicenter phase IIb dose-ranging trial will investigate the change in ICH volume as measured from baseline computed tomography (CT) scan to 24-hour CT scan in 240 patients randomized to receive placebo or rFVIIa in doses ranging from 10 to 120 µg/kg (12). Anecdotal evidence exists in the literature to support this use of rFVIIa (40).

rFVIIa in Liver Disease

Liver disease and cirrhosis can result in coagulopathy from decreased clotting factor synthesis and altered platelet metabolism. Factor VII has the shortest half-life of the clotting fac-

tors and is, therefore, the most susceptible in liver disease to impaired production. A single case of ICH in a cirrhotic managed without surgery using rFVIIa (90 µg/kg) has been reported (40). A few small trials and case reports indicate that rFVIIa may be an effective hemostatic agent in patients with liver disease and in those undergoing liver transplantation (21). Several trials are investigating the ability of rFVIIa to decrease transfusion requirements in cirrhotic patients with upper gastrointestinal bleeding and those undergoing partial hepatectomy or liver transplantation.

rFVIIa in Trauma

Multiple factors are involved in the coagulopathy observed in trauma patients. These include hypothermia, excessive fibrinolysis, and dilutional coagulopathy from massive transfusions and volume resuscitation. Three reports have been published which describe successful use of rFVIIa in controlling hemorrhage after failure of conventional measures in patients experiencing blunt or penetrating trauma (29,36,44). A large randomized controlled trial is currently underway to recruit 280 patients with severe blunt and/or penetrating trauma (12). Transfusion requirements will be compared in patients randomized to receive standard therapy or standard therapy and three doses of rFVIIa.

Future Indications

If the safety and efficacy of rFVIIa as a universal hemostatic agent is substantiated in the ongoing clinical trials, several other clinical situations might represent potential opportunities for investigation. Spinal fusions, especially in pediatric patients with scoliosis, can be associated with large blood loss that may equal or exceed the patient's blood volume. Successful use of rFVIIa in two children with scoliosis who developed dilutional coagulopathy during posterior spinal fusion has been reported (61). Uncontrollable intraoperative bleeding, such as seen with certain tumors, is fortunately a rare event in neurosurgery. In pediatric patients and those adults who might tolerate large volume

losses and transfusions poorly, a perioperative dose of rFVIIa may serve to decrease blood loss.

As with spontaneous ICH, progression of hemorrhage can be seen in traumatic brain contusions and hematomas. In a study of 142 patients with hemorrhagic brain trauma, early progressive hemorrhage occurred in almost 50% of patients (43). Intraparenchymal contusions were more likely (51%) to demonstrate progression, than epidural hematomas (22%), subarachnoid hemorrhages (17%), or subdural hematomas (11%). Similar to the rationale for ultra-early hemostatic therapy in ICH proposed by Mayer, rFVIIa has the same theoretical potential to prevent or minimize hematoma growth and neurological deterioration in traumatic hemorrhages (38). With an estimated 1.5 million traumatic brain injuries and 50,000 deaths as a result of these injuries annually in the United States alone, traumatic brain hemorrhages represent a large clinical pool for investigation of rFVIIa (60).

Conclusion

rFVIIa has proven effectiveness for obtaining hemostasis in hemophiliacs undergoing various surgical procedures and is currently indicated for bleeding episodes in hemophiliacs with inhibitors. A growing body of evidence indicates that rFVIIa has the potential to act as a general hemostatic agent in a variety of coagulopathic conditions. In particular, rFVIIa may be the most promising treatment for reversal of coagulopathy in CNS hemorrhage secondary to oral anticoagulation. It acts quickly, requires negligible volume for infusion, poses no risk of transfer of human blood-borne pathogens, and has an excellent safety record to date.

There are criticisms of rFVIIa. First, it is expensive. Although we believe the benefits of near immediate hemostasis and fewer potential side effects in certain patient groups outweigh this cost, this has not been proven in any formal manner. Cost may limit the use of rFVIIa for routine oral anticoagulation reversal in patients without neurosurgical indications. Second, repeated dosing may be necessary due to the short

half-life, especially in hemophiliacs. Third, no laboratory test predicts its efficacy and monitoring rFVIIa therapy can be problematic. Finally, clinically proven efficacy by randomized controlled trials has been accomplished only for hemophilia. Caution must, therefore, be used before extrapolating case reports and anecdotal evidence to general clinical practice (2). Several randomized controlled trials are underway for investigational uses of rFVIIa to hopefully answer some yet unresolved questions regarding risk/benefit ratio, therapeutic index, efficacy, indications, optimal dosing, monitoring, and cost-effectiveness.

Disclaimer

None of the authors have any financial interest in rFVIIa.

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