ENTRAL nervous system hemorrhages are associated with high risks of morbidity and death. Recombinant FVIIa is a unique, promising agent designed to stop hemorrhage (Table 1). Many reports have shown that rFVIIa is both safe and effective for treating hemorrhage across the spectrum of medical specialties. Despite the severe risks of morbidity and death associated with CNS hemorrhage, the use of rFVIIa in neurosurgery has lagged behind its use in other fields, although there is a growing body of literature on such uses. In this article the authors review the history and science of rFVIIa as well as dosing and safety information. Various uses pertinent to the neurosurgeon are reviewed, including the treatment of patients with coagulation disorders, those suffering trauma, and those with perioperative hemorrhage, intracerebral hemorrhage, or subarachnoid hemorrhage. Based on their review of the uses of rFVIIa, the authors conclude that rFVIIa is a safe and effective agent with the potential to revolutionize the treatment of neurosurgical patients with hemorrhage. Cost is a major impediment to the widespread use of rFVIIa, and there is some evidence that its use in the neurosurgical population may be subject to higher risk than in other populations studied thus far. Although further study is needed to better delineate the safety and efficacy of the drug in many nonlicensed uses, it is clear that rFVIIa is an agent with tremendous promise.

KEY WORDS • recombinant activated factor VII • hemostasis • neurosurgery • intracerebral hemorrhage • hemorrhagic stroke • subarachnoid hemorrhage

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The role of recombinant activated factor VII in neurosurgery: hope or hype?

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Recombinant activated factor VII (rFVIIa) is a relatively new pharmaceutical agent developed for use in patients with hemophilia in whom inhibitors to clotting factors VIII or IX have developed. Use of this drug has become common in recent years because of its efficacy and safety in patients with coagulation disorders as well as in patients who are at high risk for thromboembolism, even when other means of establishing hemostasis have failed. The use of rFVIIa in neurosurgery has lagged behind its use in other fields, although there is a growing body of literature on such uses. In this article the authors review the history and science of rFVIIa as well as dosing and safety information. Various uses pertinent to the neurosurgeon are reviewed, including the treatment of patients with coagulation disorders, those suffering trauma, and those with perioperative hemorrhage, intracerebral hemorrhage, or subarachnoid hemorrhage. Based on their review of the uses of rFVIIa, the authors conclude that rFVIIa is a safe and effective agent with the potential to revolutionize the treatment of neurosurgical patients with hemorrhage. Cost is a major impediment to the widespread use of rFVIIa, and there is some evidence that its use in the neurosurgical population may be subject to higher risk than in other populations studied thus far. Although further study is needed to better delineate the safety and efficacy of the drug in many nonlicensed uses, it is clear that rFVIIa is an agent with tremendous promise.

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Background rFVIIa Data

History of FVIIa

Led by the impetus to avoid the development of neutralizing antibodies in patients with hemophilia, purified donor FVIIa was developed in 1980 and first used in 1981. To address the limited supply of FVIIa and the risk of infectious disease associated with donor-derived FVIIa, Novo Nordisk began manufacturing a recombinant form in 1988. The description of the first clinical trial of this agent was published in 1993 and showed that rFVIIa was effective in patients with hemophilia A or B who had acquired inhibitors to factors VIII or IX, or who had a factor VII deficiency. Recombinant FVIIa was approved by the European Union in 1996 and by the US Food and Drug Administration in 1999. It is licensed for the treatment of bleeding episodes and surgical prophylaxis in patients who have hemophilia A or B, inhibitors to factor VIII or IX, factor VII deficiency, or Glanzmann thrombasthenia. There has also been a strong movement toward its use in patients without preexisting coagulopathy.

Molecular Biology

Isolation of the gene responsible for factor VII from chromosome 13 and its transfection into a hamster cell line facilitated purification of the protein product. The recombinant form of FVIIa is a 406–amino acid protein that is structurally similar and enzymatically identical to human FVIIa. Hydrolysis of a peptide bond between amino acids 152 and 153 is the only change required to convert factor...
normally only 1% of factor VII is normally circulating in the plasma and it has been suggested that a platelet thrombectomy is necessary for rFVIIa to be effective. It has proven to be a safe, effective general hemostatic agent in the management of hemophilia & other indications.

**What dose do I use?**
Dosing is controversial. The generally accepted range is 40–120 μg/kg. The lowest effective dose described is 5 μg/kg, & low doses may be effective even in severe hemorrhage. Effects of rFVIIa do not appear to be dose dependent, except perhaps at higher doses that may be more effective. Doses of 20 μg/kg & 80 μg/kg are being assessed in ongoing ICH trials.

**How fast does it work?**
A dose of rFVIIa should take effect in 10–20 mins if conditions for use are right. Repeated dosing is suggested if efficacy is not apparent after this duration.

**How safe is it?**
Adverse events have been infrequent in previously healthy patients. Caution is warranted in patients w/ thromboembolism risks such as recent DVT or MI, those administered PCC, & possibly those with CNS hemorrhage or advanced age.

**What are the licensed indications?**
Licensed uses for rFVIIa vary slightly among countries. Uses include treatment of bleeding episodes & surgical prophylaxis in patients w/ hemophilia A or B & inhibitors to factor VIII or IX, factor VII deficiency, & Glanzmann thrombasthenia.

**What are the neurosurgical indications?**
Randomized controlled trial evidence suggests that rFVIIa improves outcome in ICH. It may also be useful in coagulation reversal, ICH patients w/ traumatic injury, & perioperative hemostasis.

**What dose does it cost?**
A single 90-μg/kg dose in a 70 kg individual costs $12,600, based on the wholesale price in US dollars. Multiple doses may be required.

* DVT = deep vein thrombosis; MI = myocardial infarction.

**Mechanisms of Action**
Recombinant FVIIa is extravadated at sites of vessel damage where it complexes with exposed TF. Figure 1 provides a graphic representation of the mechanism by which rFVIIa affects coagulation. The drug has been shown to be 79 to 92% effective for this purpose.

Recombinant FVIIa may also improve coagulation in the face of defective platelets or thrombocytopenia. Supporting this effect, rFVIIa has been shown to decrease bleeding time in rabbits and humans. Platelets may be essential to the action of rFVIIa, and it has been suggested that a platelet count of 50,000 is necessary for rFVIIa to be effective.

**Pharmacokinetics of rFVIIa**
The pharmacokinetics of rFVIIa have been well described. Recombinant FVIIa is only available in an intravenous form and has a half-life of 2.3 hours. Dosing is based on the weight of the patient: the lowest reported effective dose is 5 μg/kg, although a minimal effective dose has not been formally established. Onset of an effect is observed 10 to 20 minutes after administration.

Evidence from both in vitro and in vivo studies has shown that acidosis, and to a lesser extent hypothermia, decrease the function of rFVIIa. This likely explains why patients with prolonged hemorrhagic shock respond poorly to the drug. There has been a push, therefore, to administer rFVIIa to patients who have suffered trauma early in the treatment plan, rather than as a “last-ditch” effort. The increased effectiveness of early treatment may also allow for smaller doses to be administered.

Recombinant FVIIa may produce different effects in patients at the extremes of age. The drug may have a faster rate of clearance in children than in adults; the half-life in children has been recorded as only 1.3 hours, perhaps necessitating more frequent or higher doses. Regardless of this difference in clearance rate, no difference in safety or efficacy has been found between adult and pediatric populations. Use of rFVIIa in the geriatric population has not been specifically studied, but there is evidence of a possible increased risk that is likely related to the higher prevalence of preexisting vascular comorbidities.

**Patient Monitoring**
Standard clotting measures do not accurately reflect the efficacy of rFVIIa. The biological activity of rFVIIa is more directly measured by examining the FVII clotting activity, however, this test is not currently widely available and a therapeutic range has not been established. Clinical assessment may be the best guide to therapeutic decisions.

Thrombelastography, first described in 1948 by Harttert, may be a useful tool for assessing reversal of anticoagulation by rFVIIa. This technique can elucidate the rate of polymerization as well as overall clot strength; thrombelastography is designed for bedside use and generates results in 30 minutes.

**Dosing and Cost of rFVIIa**

**Dosing of rFVIIa**
A review of the literature shows that dosing of rFVIIa has been highly varied and has changed appreciably with time. According to the package insert, a dose of 90 μg/kg (which corresponds to 300 to 500 times the amount of this factor normally circulating in the plasma) is suggested with repeat dosing every 2 hours until hemostasis is achieved. Although a dose range of 90 to 120 μg/kg has been considered standard, recently a shift to lower doses has been seen. The optimal dose of rFVIIa has yet to be established. Although responses proportional to the dose have been seen, no clear relationship to efficacy and adverse events has been established. Complicating matters further, patients are thought to vary greatly in their responses to equivalent doses of the agent.

Though inconsistent, higher doses of rFVIIa may establish hemostasis more quickly and benefit patients not helped by smaller doses. Furthermore, during surgery higher doses may be required for a full thrombin burst to occur. The results of several studies support these conclu-
In the Hemophilia Research Society study, investigators found that doses higher than 200 μg/kg were of statistically significant greater efficacy. Overall there was 97% effectiveness in the higher-dose group compared with 84% efficacy in lower-dose groups. Kenet and colleagues found that with rFVIIa megadoses of 300 μg/kg, response was faster than with conventional dosing. A more overt dose–response relationship may occur with higher doses as well. Further information on these issues will come from an ongoing randomized, multicenter, three-way crossover, double-blind study in the US that is designed to examine the efficacy and safety of a higher dose of rFVIIa (90 μg/kg or 270 μg/kg).

At the same time that some physicians are proposing higher dosing regimens, it should be noted that there are numerous reports that a single, small dose is often very effective in controlling even serious hemorrhage. These reports may be part of the reason that the focus of the Phase III rFVIIa trials is on doses of 20 and 80 μg/kg instead of higher doses. Considering the high cost of this agent, higher doses may not be justified given the questionable and inconsistent gains previously seen.

Dosing of rFVIIa in patients following the establishment of hemostasis is controversial. For severe hemorrhages, the manufacturer recommends repeated dosing at 3- to 6-hour intervals to maintain the integrity of the hemostatic plug, but warns that limited data are available to guide such usage. Some investigators recommend continued dosing for the first 24 hours for serious hemorrhages and to cover the duration of surgery; this method has been shown to induce and maintain hemostasis in 83% to 95% and 90% to 100% of cases, respectively.

One source suggests rounding the dosage to the nearest whole vial to avoid waste given the expense of the agent. Recombinant FVIIa is available in 1.2-, 2.4-, and 4.8-mg vials, and thus for an average 70-kg adult receiving a 60 μg/kg dose (4.2 mg) a single vial of 4.8 mg would suffice. Furthermore, some clinicians have recommended additional doses after 15 to 20 minutes rather than the traditional 2 to 4 hours. Because clinical efficacy should be apparent within this time period, it seems sensible to administer additional doses at shorter intervals if the response is inadequate despite the patient’s normal temperature, serum pH, and levels of calcium and magnesium, and a platelet count greater than 50,000. Ideally, in an emergency a patient with a coagulopathic condition should be given FFP just before or simultaneous with rFVIIa if possible.

**Availability of rFVIIa**

Recombinant FVIIa is widely available and its administration is determined generally on a case-by-case basis at the discretion of the treating physician. Many hospitals and insurers have chosen not to make the agent available or to restrict its availability pending the results of Phase III trials as well as further delineation of the risks associated with its use.
Cost of rFVIIa

Similar to other recently developed therapeutic agents, a very important issue concerning rFVIIa is its expense. The average wholesale price (in US dollars) of a 4.8-mg vial of rFVIIa is $9795 and that for a 1.2-mg vial is $2449, prices equivalent to approximately $2 per microgram. For a 70-kg adult, the approximate cost of a very small single dose, 5 μg/kg, would be $700; the cost of a 90-μg/kg dose would be $12,600; and the cost of a 270-μg/kg dose would be $37,800. The cost to administer a dose of 90 μg/kg in the same patient every 2 hours for a 24-hour period would be approximately $150,000. In a recent paper in which the use of this drug was described in patients suffering trauma, the cost per each life saved was $39,324.44

It is uncertain to what extent these costs may be offset by preventing blood transfusions, operations, and other adverse events.13 The cost of a unit of blood is approximately $500, and some have suggested that rFVIIa may become cost-effective when the need to transfuse 10 units of blood can be averted.41 Other factors specific to neurosurgery include the extra cost of rehabilitation or lost potential income due to neurological disability. These factors must be included in any cost-effectiveness data, which has yet to be done to our knowledge.

In Canada a patent for rFVIIa was issued on April 27, 1999, and expires on April 27, 2016. In personal communications, Novo Nordisk informed us that the expected date of patent expiration in the US is November 2010. Although it might be assumed that patent expiration will allow greater competition and result in lower prices, this is unlikely to occur, because rFVIIa is considered a biological rather than a pharmacological agent, and any competing agent would be required to go through the clinical trials process again. Even a modification of the protocol that Novo Nordisk uses to produce rFVIIa in its current form would mandate a trial to test the new manufacturing process. It is therefore unlikely that appreciable changes in the cost of this agent will occur.

Safety

Contraindications to rFVIIa Use

Hypersensitivity to rFVIIa or its components is a contraindication to rFVIIa use. Sepsis, which is associated with high levels of monocyte-derived TF, and disseminated intravascular coagulation are also contraindications, despite a lack of evidence for an increased risk for these conditions with rFVIIa use.13,54

Safety of rFVIIa

The safety of rFVIIa has come under close scrutiny because of the theoretical risk of thrombotic side effects due to excessive activation of the clotting system.41 Some of this concern likely originates from the fact that activated prothrombin complex concentrates, which contain FVIIa, have been found to cause disseminated intravascular coagulation and adverse thrombotic complications.39 Recombinant FVIIa also has a considerably longer half-life than other activated factors,54 allowing greater opportunity for thrombotic complications.

In general, the literature indicates that rFVIIa is a safe therapeutic agent. It has been deemed safe enough for home use.11,49 Activated factor VII is not known to react with other drugs; however, concomitant use of PCC or activated PCC is discouraged and there is a basis to suspect that this may be a potentially fatal combination.13,54

Numerous factors likely contribute to the apparent safety of rFVIIa. Systemic activation of coagulation has never been noted with this agent,42 and its site specificity probably relates to the localized release of TF at sites of injury, as well as the localization of activated platelets to these areas.11,49 Another undoubtedly important regulator is TF pathway inhibitor.32 It is a strong inhibitor of the FVIIa–TF enzymatic complex as well as factor Xa. The actions of this inhibitor may explain the apparent safety of rFVIIa in patients who have high levels of circulating TF, such as those undergoing cardiac bypass.61 Antifibrinolytics increase the levels of TF pathway inhibitor,32 perhaps explaining why simultaneous use of antifibrinolytics and rFVIIa has been described in more than 50 instances without adverse events.

Even high doses of rFVIIa have been well tolerated.50 In the Hemophilia Research Society study, in which a median dose of 360 μg/kg was administered, four of the 38 patients experienced a total of nine adverse events, but eight of these were decreased therapeutic responses. Even gross overdosing may not lead to complications as shown in a patient given doses between 246 and 986 μg/kg on 5 consecutive days without any adverse effects.

Complications

Recombinant FVIIa is associated with low rates of thrombogenic complications. Although perhaps subject to underreporting, as of 2003 500,000 to 700,000 doses of rFVIIa had been given with 24 associated thrombotic adverse events.1,52 One third of these events occurred in patients older than 70 years of age, many of whom had conditions such as atherosclerosis, diabetes, or hypertension, which undoubtedly increased their risks.10,13,42,52,54 Additionally, approximately one third of these patients had been treated previously with activated PCC or antifibrinolytic agents, which made it more difficult to determine the cause of the adverse effect.54 In three patients (12.5%), the thrombotic event occurred either more than 10 days before or 10 days after the administration of rFVIIa, making a causative relationship to the use of rFVIIa after 10 days unlikely.53

There are several theoretical concerns regarding the use of rFVIIa in patients undergoing neurosurgery. These patients are often subject to prolonged immobility or paralysis, increasing their risks of experiencing clotting events. Furthermore, it has been hypothesized that the thrombin generated by rFVIIa may exacerbate brain edema, although this does not seem to be the case clinically.43 Microvascular thrombi in the brains of patients with traumatic brain injuries may hypothetically be made worse with rFVIIa treatment, but again supporting data are lacking.46 Tissue thromboplastin, a procoagulant released from the damaged brain, is also a theoretical concern. In addition, a safety trial of rFVIIa use in patients with SAH was aborted because there was a thromboembolic complication.51

A large trial of rFVIIa use in ICH undertaken by Mayer and colleagues also raised concerns of interest to neurosurgeons—concerns that are based on Level I evidence rather than theory. Although the rate of serious adverse thromboembolic events possibly or probably related to treatment
That were fatal or disabling occurred at an equal rate of 2% among patients given placebo or rFVIIa. Serious adverse thrombotic events were seen in 7% of rFVIIa-treated patients and 2% of those treated with placebo. This is a significantly higher adverse event rate than has been reported previously. Of greater concern is that these rates are high despite the fact that patients with thromboembolic risk factors were excluded from the trial. Unfortunately, the authors did not provide any details regarding comorbidities of patients with thromboembolic complications. This higher risk may originate from an elderly study population, which has been associated with elevated thromboembolic risk, or perhaps ICH itself leads to a higher risk. It is also possible that this is a more accurate picture of the risks than has previously been available, given the high quality of this study compared with others published.

Neurosurgical Uses of rFVIIa

A summary of the pertinent published literature on the neurosurgical uses of rFVIIa is provided in Table 2.

Patients With Coagulopathic Disorders

Surgeons frequently need to reverse coagulopathies to facilitate safe surgery. The general hemostatic properties of rFVIIa have proven effective for preventing or treating hemorrhage in a wide range of patients with coagulopathic disorders, such as liver disease or thrombocytopenia. Iatrogenic coagopathy caused by anticoagulation, as is frequently seen in patients with prosthesis heart valves or atrial fibrillation, is also readily corrected with rFVIIa. Furthermore, rFVIIa has some distinct advantages in this patient population. First, it works much more quickly than PCC, FFP, or vitamin K, minimizing the time away from anticoagulation therapy. Recent data from Oberlander, et al., suggests that it may facilitate emergency surgery 3 hours earlier than if it were not used. Second, by avoiding the large fluid loads associated with FFP, rFVIIa may also decrease the incidences of morbidity and death in elderly patients and those with heart failure. Furthermore, rFVIIa is often effective after agents such as vitamin K, FFP, and PCC have failed. Reports of the use of rFVIIa for this purpose in neurosurgery are beginning to accumulate. The first report of rFVIIa use to facilitate a neurosurgical procedure was published in 2002 in a case in which a single dose of 120 μg/kg was used effectively to normalize an International Normalized Ratio of 6.39 in a patient with an acute subdural hematoma. Morenski, et al., later described using rFVIIa to make possible the insertion of intracranial monitors in three children with head injuries and concomitant coagulopathy disorders. In 2003 Sorensen and colleagues performed an in vitro and ex vivo study of seven patients with CNS bleeding emergencies. A small dose (10–40 μg/kg) of the drug normalized International Normalized Ratios within 10 minutes, and a neurosurgeon determined that the level of hemostasis was better than expected in all seven patients. Lin and colleagues reported using 16 to 22 μg/kg of rFVIIa in two patients with spinal hemorrhage and two patients with acute intracranial subdural hematomas, all of whom were receiving coumadin therapy. Acceptable hemostasis was achieved within 2 hours in all patients. Szabo, et al., reported using rFVIIa to facilitate emergency surgery in a 59-year-old woman with an extensive spinal epidural hematoma and neurological compromise following administration of an epidural block. In this patient, rFVIIa administration was believed to be a useful adjunct. Park, et al., described a retrospective review of nine cases involving the use of rFVIIa for the rapid reversal of various coagulopathies in emergency neurosurgical procedures. All but one case was judged to have acceptable hemostasis. No thrombotic complications were described in any of the aforementioned cases. There is thus a growing body of evidence for the safety and efficacy of the use of rFVIIa in facilitating neurosurgery in patients with coagulopathic disorders.

Recombinant FVIIa Use in Patients With Trauma

A review of the trauma literature demonstrates a number of case series highlighting the uses of rFVIIa in patients with trauma without premorbidity coagulopathy. There are data suggesting that rFVIIa may decrease the need for blood transfusion. Early administration of the drug may be essential, however; “last-ditch” use of rFVIIa in patients with hemorrhage greater than 10 units may not significantly alter outcomes. Some physicians have thus advocated the use of earlier, faster infusion or even prehospital use of rFVIIa. Timing is critically important in neurosurgery, in which small volumes of hemorrhage can have devastating consequences in short periods of time.

A number of studies provide data on rFVIIa use in trauma and neurotrauma. Barletta and colleagues summarized studies comprising 117 patients without coagulopathy, including 26 patients with systemic trauma, who were treated with rFVIIa. The number of doses of rFVIIa administered ranged from 1 to 10 (mean 2, mode 1), with an overall efficacy rate of 85%. In the subset of patients with systemic trauma, the overall efficacy rate (77%) was slightly lower. A substantial decrease in the need for blood transfusion in these patients was demonstrated. There were two deaths (1.7%) possibly related to rFVIIa administration in this study population, one of which occurred during coadministration of activated PCC. A 1% incidence of thromboembolic events was noted in the patients with systemic trauma compared with 4% in the entire population. The patients with systemic trauma were younger, which may be further evidence for an increasing risk of thromboembolic events with increasing age.

In a recent case series of 81 patients with trauma suffering from various coagulopathies, rFVIIa treatment showed 75% efficacy, and a significant reduction in transfusion requirements was demonstrated in those who responded to rFVIIa. Twenty-five percent of the patients in this study did not respond, however, and the authors stated that further study was needed to delineate which patients may benefit from rFVIIa therapy. They also found that hemorrhagic shock tended to need repeated rFVIIa dosing more often than other indications. Thrombotic complications were noted in three patients (3.7%) although it was not clear whether rFVIIa therapy was causative. A study from Dutton and coworkers also investigated the use of rFVIIa in 20 patients with traumatic brain injury. These patients were an average age of 40.3 years old with severe injuries; six patients had injuries identified in other locations, and 15 of the 20 patients died. Administered doses of rFVIIa ranged from 41 to 178 μg/kg and 18 of the 20
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>No. of Patients</th>
<th>Study Type</th>
<th>Study Design &amp; Significance</th>
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<tr>
<td>Veshchev, et al., 2002</td>
<td>1</td>
<td>case report</td>
<td>1st report of rFVIIa in the preop management of warfarin-induced ICH; found rFVIIa safe &amp; effective</td>
</tr>
<tr>
<td>Lin, et al., 2003</td>
<td>4</td>
<td>retrospective case series</td>
<td>found rFVIIa safe &amp; effective; no thromboembolic complications, blood loss &lt; 100 ml for all operations; found that rFVIIa “may be safe and effective”</td>
</tr>
<tr>
<td>Morenski, et al., 2003</td>
<td>3</td>
<td>retrospective pediatric case series</td>
<td>patients with post-TBI coagulopathy; administration facilitated intracranial device placement w/o complication; authors suggested rapidity of reversal &amp; efficacy make it superior to FFP</td>
</tr>
<tr>
<td>Park, et al., 2003</td>
<td>9</td>
<td>retrospective case series</td>
<td>INR reversal for various coagulopathies to facilitate urgent neurosurgical intervention; no associated thromboembolic complications noted; believed that rFVIIa is promising for this purpose but further studies needed</td>
</tr>
<tr>
<td>Sorensen, et al., 2003</td>
<td>7</td>
<td>retrospective case series</td>
<td>in vivo and ex vivo study documenting normalization of all INRs in 10 mins w/ small rFVIIa doses to facilitate neurosurgical intervention; no biochemical or clinical evidence for thrombosis; suggested rFVIIa might substitute for infusion of FFP or PCC in acute reversal of warfarin treatment</td>
</tr>
<tr>
<td>Szabo, et al., 2004</td>
<td>1</td>
<td>case report</td>
<td>rFVIIa used as adjunct to FFP and vitamin K reversal of anticoagulation in patient w/ spinal epidural hematoma after epidural block; rFVIIa useful in facilitating emergency surgery</td>
</tr>
<tr>
<td>Oberlander, et al., 2005</td>
<td>8</td>
<td>retrospective case series</td>
<td>found an average reduction in delay to surgery of 3 hrs when rFVIIa was used instead of traditional methods; authors believed the time savings justified the cost</td>
</tr>
<tr>
<td>May, et al., 1997</td>
<td>26</td>
<td>retrospective case series</td>
<td>assessed prevalence of coagulopathy in patients with severe closed head injuries to see if empirical treatment was warranted; 81% of the patients with a GCS score ≤6 were judged to be candidates for empirical treatment</td>
</tr>
<tr>
<td>Dutton, et al., 2004</td>
<td>81</td>
<td>retrospective case series</td>
<td>81 patients w/ coagulopathic, systemic trauma treated using rFVIIa compared w/ controls from a trauma registry from the same time period; immediate reduction in coagulopathic hemorrhage noted in most cases; authors suggested use of rFVIIa should be considered for any patient w/ coagulopathic hemorrhage in which surgically accessible bleeding has been controlled</td>
</tr>
<tr>
<td>Martinowitz, et al., 2004</td>
<td>N/A</td>
<td>review</td>
<td>discussed the role of hemorrhage in the morbidity of injuries sustained in combat &amp; proposed a role for rFVIIa because of limitations of medical care in combat</td>
</tr>
<tr>
<td>Barletta, et al., 2005</td>
<td>117</td>
<td>literature review</td>
<td>examined rFVIIa use for refractory bleeding in adult, nonhemophilic, surgical patients; rFVIIa was effective in 85% of all patients &amp; &lt; 7% of the 26 patients identified w/ trauma; 4% had thromboembolic events; found rFVIIa to be effective, but acidosis affected efficacy</td>
</tr>
<tr>
<td>Gerlach, et al., 2002</td>
<td>1</td>
<td>case report</td>
<td>rFVIIa was effective following failure of standard surgical hemostatic methods during resection of a recurrent skull base hemangiopericytoma</td>
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<tr>
<td>Tobias, 2002</td>
<td>2</td>
<td>retrospective pediatric case series</td>
<td>rFVIIa used effectively to treat dilutional coagulopathy refractory to FFP</td>
</tr>
<tr>
<td>Kanidmov, et al., 2003</td>
<td>3</td>
<td>retrospective case series</td>
<td>small doses of rFVIIa rapidly achieved hemostasis after conventional hemostatic techniques had been exhausted; believed rFVIIa prevented use of hemostatic techniques that may result in long-term sequelae</td>
</tr>
<tr>
<td>Al-Otibi, et al., 2004</td>
<td>2</td>
<td>retrospective case series</td>
<td>documented perioperative rFVIIa use that effectively stopped hemorrhage in 2 patients</td>
</tr>
<tr>
<td>ICH</td>
<td></td>
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<td>used rFVIIa for ICH refractory to at least 1 other therapy in 12 patients w/ congenital coagulopathy; found effective in 10 of the 12 patients; extremely high doses were given &amp; adverse events were considered to be unrelated to rFVIIa therapy; found rFVIIa an effective &amp; well-tolerated therapeutic option</td>
</tr>
<tr>
<td>Mayer, et al., 2005</td>
<td>48</td>
<td>randomized controlled trial</td>
<td>phase II study documenting that percentage change in ICH &amp; total hemorrhage volume did not differ significantly from control group though there was a nonsignificant trend toward improvement at 90 days; 6 adverse events were considered possibly treatment related, although authors concluded there were no major safety concerns</td>
</tr>
<tr>
<td>Mayer, et al., 2005</td>
<td>399</td>
<td>randomized controlled trial</td>
<td>a landmark study providing Level I evidence that rFVIIa improves outcome in patients w/ ICH; Serious thromboembolic adverse events occurred in 7% of rFVIIa-treated patients, compared w/ 2% of those given placebo</td>
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<tr>
<td>SAH</td>
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<td>safety trial studying rFVIIa vs placebo in the prevention of rebleeding in patients w/ good grade aneurysmal SAH; trial suspended when the 10th patient developed middle cerebral artery branch thrombosis contralateral to the aneurysm</td>
</tr>
<tr>
<td>Schilling, et al., 2004</td>
<td>1</td>
<td>case report</td>
<td>case of multiple cerebral aneurysms &amp; factor VII deficiency; a possible combined genetic defect is postulated</td>
</tr>
</tbody>
</table>

* GCS = Glasgow Coma Scale; INR = international normalized ratio; N/A = not applicable; TBI = traumatic brain injury.
patients responded to therapy. None of these patients had evidence of thromboembolic complications, even in those patients for whom autopsy data were available. The authors also noted a potential role for rFVIIa in preventing death long enough to allow organ donation in this severely head-injured population. A number of shortcomings of this trial support the need for further study in trauma patients. Military uses of rFVIIa are now being reported. Hemorrhage is the leading cause of death in combat casualties; therefore rFVIIa treatment may be very effective in this setting in which there may be delays to medical care, as well as limited resources such as restricted volumes of blood available for transfusion. The first reported military use of rFVIIa was in March 2005 to treat a pelvic fracture.

Perioperative Hemorrhage

In 1988, an open knee synovectomy conducted at the Karolinska Institute was the first surgical procedure performed using rFVIIa. Subsequent early experience was with the use of rFVIIa to control intra- and perioperative hemostasis in patients with hemophilia. There are many reports of the apparently life-saving intraoperative administration of rFVIIa. Blood loss is generally reduced by 50% or greater with only small doses of rFVIIa, without producing more serious adverse effects than placebo.

There are few reported uses of rFVIIa for intraoperative hemorrhage in the neurosurgical literature, despite the fact that its use is generally less damaging than other measures needed to control severe hemorrhage in the brain. Gerlach and colleagues reported the life-saving use of rFVIIa during the resection of a hemangiopericytoma. Administration of FFP and PCC was ineffective in the patient, but a combination of rFVIIa and compression resulted in successful life-saving hemostasis. A second case report described the use of 4.8 mg of rFVIIa for hemostasis attainment in three neurosurgical patients with intractable hemorrhage, in whom attempts to use other methods such as packing, FFP, plasma, and fibrinogen were unsuccessful. Hemorrhage ceased in all cases within 12 to 20 minutes following administration, no adverse reactions were noted, and clamping and compressing brain tissue were avoided. Tobias reported the successful use of a 90 μg/kg dose of rFVIIa in two children with dilutional coagulopathy during spinal fusion after FFP treatment failure. Al-Otibi, et al., reported two patients were treated successfully with a dose of 90 μg/kg rFVIIa: one patient was a 50-year-old woman in whom a tumor bed hematoma developed following resection of a recurrent malignant glioma, and the second patient had an epidural hematoma and brain contusion. The use of rFVIIa stabilized the hemorrhages in both patients, as confirmed by repeated CT scans. We will likely see more frequent neurosurgical use of rFVIIa for intractable hemorrhage because of its promising efficacy and safety.

Intracerebral Hemorrhage

Intracerebral hemorrhage is associated with poorer outcomes than cerebral infarction or SAH. Hematoma volume, which can be reliably measured by the ABC/2 method, is a strong predictor of a 30-day mortality rate. For example, a hematoma volume of 80 cm³ is almost always associated with death. Intracerebral hematomas may continue to accumulate in some cases for several hours after their initiation. Even in the absence of coagulopathy, hematoma expansion of approximately 33% is found in possibly more than 38% of patients within 3 hours of onset. Clearly this expansion is undesirable and is associated with a worse outcome, as has been documented in a prospective trial. In patients with ICH, one third die within 1 month, and only 20% return to functional independence. Prior to the advent of rFVIIa, no effective treatment for ICH has been shown to improve outcome, and thus the management of ICH in patients is conservative in many centers. As noted, however, rFVIIa may become the first therapy to improve outcome in these patients.

Treatment with rFVIIa was first used for ICH in a study of patients with congenital coagulopathy. Arkin and coworkers described a series of 11 patients with hemophilia and one patient who was factor VII-deficient with life-threatening ICH unresponsive to one or more alternative therapies, who all received large doses of rFVIIa. Patients in the study received an average of 96.9 rFVIIa injections over 14.7 days, with a mean total administration of 153.3 mg, and rFVIIa was well tolerated and effective in 83% of hemorrhages.

After these reports of the safe treatment of ICH in patients with coagulopathies, a clinical trial was initiated to establish the safety of using rFVIIa to treat patients with spontaneous ICH not associated with coagulopathy. Forty-eight patients from 14 centers were enrolled. The primary outcome measure was adverse events within 15 days or until discharge from hospital, or severe adverse events until completion of the trial at Day 90. The percentage change in ICH and total hemorrhage volume was examined between baseline and 24 hours. Neither percentage differed significantly from the percentage in the control group, although there was a nonsignificant trend toward improvement with rFVIIa treatment at 90 days. Forty-seven of the patients experienced adverse events, including five thromboembolic or ischemic events and six potentially treatment-related events. Two patients experienced deep vein thrombosis, and two had clinically significant electrocardiography changes without troponin I elevation. Two of the 11 patients treated with placebo and 3 of the patients treated with rFVIIa died during the trial. All deaths were due to ICH and all occurred within 7 days. This study emphasized rapid treatment to prevent early clot expansion and provided evidence for the safety of rFVIIa across a wide variety of doses when used in ICH.

A more recent larger, randomized, double-blind, placebo-controlled, dose-escalation trial by Mayer and colleagues examined the efficacy of using rFVIIa for treating acute ICH. This landmark trial included 399 patients in whom ICH was diagnosed using CT within 3 hours of illness onset, and randomly assigned patients to receive placebo, 40, 80, or 160 μg/kg doses of rFVIIa. The primary outcome measure in the study was the percentage change in ICH volume at 24 hours. Clinical outcome was also assessed after 90 days. A dose–response relationship was demonstrated among the four groups: the placebo group showed a 29% hematoma expansion, whereas the 40, 80, and 160 μg/kg rFVIIa dosage groups showed a 16, 14, and 11% hematoma expansion, respectively. The probability value was 0.01 when the three groups treated with rFVIIa were pooled and
compared with the placebo group. The corresponding reductions in hematoma volumes were 3.3, 4.5, and 5.8 ml in the three treatment groups (40, 80, and 160 μg/kg, respectively; p = 0.01). The number of patients who died or were severely disabled was 69% in the placebo group compared with 55, 49, and 54% in the respective treatment groups (p = 0.004, placebo group compared with the three treatment groups combined). The 90-day mortality rate was 29% in patients receiving placebo, compared with 18% in the treatment groups after a combined analysis (p = 0.02). The number needed to treat to prevent one unfavorable outcome was demonstrated to be slightly more than six, and according to the authors this treatment may reduce death by one third. It is important to note that in this study statistical significance was achieved only for the highest dose (160 μg/kg) group, as well as for the pooled treatment groups compared with placebo. It should also be noted that the dose–response relationship apparent in this study has not been consistently demonstrated in the literature. This study raised questions regarding the safety of this agent in the ICH population as discussed previously; however, rFVIIa treatment appears to be the first therapeutic intervention capable of improving prognosis in this affliction.

Subarachnoid Hemorrhage

Preventing repeated hemorrhage following aneurysmal SAH using pharmacologic means is not new. Theoretical support for this approach comes from data showing that coagulopathy has been associated with increased risk of rebleeding and poorer outcome.

Epsilon-aminocaproic acid, a competitive inhibitor of the activation of plasminogen to plasmin, has been shown to decrease the incidence of rebleeding in this circumstance. Drawbacks to this approach include requiring 24 to 48 hours of therapy prior to reaching effectiveness, as well as an increased incidence of hydrocephalus, vasospasm, and cerebral infarction. The result of this approach is no net benefit of epsilon-aminocaproic acid therapy.

Similarly, rFVIIa treatment has been postulated as a therapeutic tool for preventing rehemorrhage. Concern was expressed that rFVIIa could have harmful side effects similar to those seen with antifibrinolytics. Results of an open-label, dose-escalation safety study of rFVIIa in preventing rehemorrhage were published in April of 2000. The trial was designed to include 15 adult patients with SAH and monitor their treatment using clinical observation, laboratory variables, positron emission tomography, and transcranial Doppler ultrasonography. Ten patients were recruited into the study. Two patients received an 80 μg/kg single bolus; two received an 80 μg/kg single bolus followed by continuous infusion at 3.5 μg/kg/h; one patient received an infusion of 7 μg/kg/h; and five patients received a control infusion. There was no evidence of treatment complications in the first nine patients, but the last patient developed middle cerebral artery branch thrombosis contralateral to the aneurysm resulting in suspension of the study.

To our knowledge, no other publications specifically discuss the use of rFVIIa in SAH; a Ukrainian study describes the treatment of a patient with SAH using rFVIIa; however, the use of rFVIIa was in the context of idiopathic thrombocytopenic purpura. There is clearly a need for further study of rFVIIa treatment in SAH.

Future Directions

Further and better quality studies will help to define the role of rFVIIa in neurosurgery more precisely. Refining the dosing indications and the monitoring requirements is also needed. Several ongoing studies will help to answer these questions.

Building on the data from the paper by Mayer and coworkers, investigators are currently conducting a Phase III trial to examine the use of rFVIIa in ICH. This study is a multicenter, randomized, double-blind, placebo-controlled trial comparing rFVIIa doses of 20 μg/kg and 80 μg/kg with placebo. Interestingly, this study is designed to examine lower doses than those previously used. A study enrollment target of 500 patients is planned, and completion is anticipated in 2006.

A few current studies are designed to establish a role for rFVIIa in neurotrauma. Protocol F7CBI-1587 is a multicenter observational study, designed to evaluate the incidence and magnitude of hemorrhagic progression of cerebral contusions, as well as safety issues, in patients with greater than or equal to 5 ml of intraparenchymal hemorrhage as a result of traumatic brain injury diagnosed within four hours using head CT and clinical examination. The volume of intraparenchymal hemorrhage required for inclusion in the study was decreased to 2 ml to facilitate increased enrollment. This study has just ended and results are pending. A complementary ongoing study—Protocol F7CBI-1600—is a randomized, double-blind, placebo-controlled, multicenter dose-escalation trial of rFVIIa in patients with brain contusions. This study is designed to examine the safety and preliminary efficacy of rFVIIa and is accruing patients very well.

A current Phase II study—Protocol F7SPIN-2180—is designed to evaluate the safety of rFVIIa as a hemostatic agent in large spine surgeries that are frequently associated with large hemorrhage volumes. Patients must not be coagulopathic, and must be undergoing a posterior spine fusion of four or more vertebrae. Results from this trial may allow the use of rFVIIa in patients without coagulopathy who undergo elective surgeries associated with substantial hemorrhage. These studies have the potential to expand the indications for this drug, and we look forward to the data that they will provide.

Conclusions

The use of rFVIIa has the potential to change the practice of neurosurgery. After nearly 10 years of use, rFVIIa has proven to be safe and effective in several clinical settings relevant to neurosurgery. Treatment with rFVIIa is indicated in patients with congenital coagulopathy, the specific condition for which it was approved. It may also have a role in other coagulopathies, early in the course of spontaneous or traumatic ICH, or intraoperatively as a life-saving measure. Present and future studies will help to refine such indications.

There is no question that rFVIIa use has risks that may be higher in neurosurgical patients, the elderly, or in those patients simultaneously receiving PCC. Although the risks could be greater with neurological uses, the possible benefits may also be greater. Considering the potentially disabling or fatal consequences of CNS hemorrhages, rFVIIa is an agent that could revolutionize neurosurgical practice.
Role of recombinant activated factor VII in neurosurgery

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Disclaimer

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