Safety of Recombinant Activated Factor VII in Patients With Warfarin-Associated Hemorrhages of the Central Nervous System

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Background and Purpose—Recombinant Factor VIIa decreases hematoma growth after spontaneous intracerebral hemorrhage (ICH) and rapidly decreases international normalized ratios in patients on warfarin but is also associated with an increased risk for thromboembolic complications. In this study, we assessed the risk of thromboembolic events in patients receiving recombinant Factor VIIa after ICH associated with warfarin treatment.

Methods—We reviewed the medical charts, laboratory data, and radiological findings of consecutive patients with anticoagulation-related hemorrhages of the central nervous system who received recombinant Factor VIIa at Mayo Clinic Rochester and Mayo Clinic Florida between 2002 and 2009. The primary end point was the frequency of new thromboembolic events, including myocardial infarction, deep vein thrombosis, ischemic stroke, and pulmonary embolism.

Results—We identified 101 patients; 54% had ICH and 30% subdural hematomas. The most common indications for anticoagulation were atrial fibrillation, deep vein thrombosis, and prosthetic valve. Thirteen patients (12.8%) had new thromboembolic events (10 deep vein thromboses and 3 ischemic strokes) within 90 days after recombinant Factor VIIa administration. Eight of these adverse events occurred within 2 weeks of treatment. In patients with ICH, the rate of thromboembolic complications was 5% and all events were venous.

Conclusion—The risk of thromboembolic events in patients who received recombinant Factor VIIa for anticoagulation-associated ICH was not higher than that seen in patients treated for spontaneous ICH in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial. Spontaneous deep vein thrombosis was the most common complication in our series. (Stroke. 2010;41:00-00.)

Key Words: Factor VII • intracranial hemorrhage • safety • warfarin

Intracerebral hemorrhage (ICH) associated with oral anticoagulation is a significant and growing problem that is associated with increasing hematoma size and poor outcome.1–3 The manner in which anticoagulation increases the risk of ICH is not absolutely clear, but it is thought to exacerbate underlying, subclinical hemorrhages.4 The rate of hematoma growth is rapid, primarily occurring within the first 3 hours.5 Therefore, anticoagulation should be reversed promptly,6,7 and effective therapies to stop immediate bleeding and hematoma expansion are necessary.8 In addition, other forms of intracranial hemorrhage such as subdural hematomas, epidural hematomas, and subarachnoid hemorrhage can also be more severe and worsen more rapidly in anticoagulated patients. When emergency neurosurgical interventions are necessary, ultrafast reversal of anticoagulation becomes paramount.

Medical treatments such as fresh-frozen plasma (FFP) and vitamin K are efficacious in reversing anticoagulation. However, reversal with these agents is both slow and potentially risky.9 Efficacy of FFP is limited by the hazard of allergic and transfusion reactions (such as transfusion-related acute lung injury) and thawing and processing times. Many anticoagulated patients have cardiovascular disease and the administration of large volumes of FFP could precipitate volume overload or lung injury in these patients. These limitations and concerns may delay full reversal of anticoagulation with FFP.7 Additionally, hematoma growth may continue despite full reversal of the international normalized ratio (INR) with FFP.10 Recombinant Factor VIIa (rFVIIa) has been shown to be a rapidly acting hemostatic agent that works at the bleeding site.5 It is effective at lowering the INR11–16 and reducing hematoma growth,17–19 although it has not been shown to improve outcome in patients with spontaneous ICH.19 Previously published experience using rFVIIa for warfarin-associated intracranial hemorrhage has been limited to small series.11–14,20
A known complication of rFVIIa is the precipitation of thromboembolic events secondary to its hemostatic nature.17–19 In patients who received rFVIIa for spontaneous ICH, the risk of thromboembolic events was 5.4% versus 1.7% in the placebo group across 3 randomized studies.17 Reversing the effects of anticoagulation in patients with anticoagulation-associated ICH may be riskier because these patients have a known risk of thromboembolic events. On the other hand, patients who receive rFVIIa for spontaneous ICH may become prothrombotic, whereas patients who receive rFVIIa for anticoagulation-associated ICH may only return to their normal coagulation state. Therefore, it may actually be less risky to administer rFVIIa to this group of patients. The aim of this study was to determine the risk of thromboembolic complications in patients who received rFVIIa for anticoagulation-related intracranial hemorrhage.

Methods
We reviewed the medical charts of all patients with warfarin-associated intracranial and intraspinal hemorrhages who received rFVIIa at Mayo Clinic Rochester and Mayo Clinic Florida between December 22, 2002, and February 16, 2009. Recombinant Factor VIIa has been approved in our institutions for compassionate use in patients with anticoagulation-associated hemorrhages. The study was approved by the Mayo Foundation Institutional Review Board.

Recombinant Factor VIIa is used in our hospitals according to internal guidelines. The administration of rFVIIa is considered in patients with acute intracranial hemorrhages (and in selected cases of intraspinal hemorrhage) associated with warfarin use and an INR >1.4 within 6 hours of symptom onset. Exclusion criteria for rFVIIa use include end-stage renal disease, previous allergic or adverse reaction to the drug, or moribund condition. Administration of rFVIIa is decided on a case-by-case basis by the treating neurologist or neurosurgeon. Patients are treated with a single bolus of intravenous rFVIIa administered over 2 to 5 minutes. Initially we agreed that the dose would be 40 to 80 mg/kg; however, this dose was adjusted with a smaller dose at the initial INR in Rochester since 2007. All patients also receive 5 to 10 mg of intravenous vitamin K on first evaluation. FFP is often initiated at the referring hospital or in our emergency department before consultation with neurology or neurosurgery. FFP infusion is not continued after rFVIIa administration unless INR >1.4. INR is rechecked 15 to 30 minutes after rFVIIa administration and every 4 to 6 hours thereafter, at least for the first 24 hours. Repeat doses of rFVIIa are used only in cases of neurosurgical emergency. An INR ≤1.4 is deemed safe to proceed with neurosurgical interventions.

Inclusion criteria included radiologically documented symptomatic intracranial or intraspinal hemorrhages, treatment with warfarin, and administration of rFVIIa. A data retrieval system was used to identify patients with intracerebral hemorrhage and matched with patients who received rFVIIa by the pharmacy registry. Medical records and brain CT scans were reviewed and the type of hemorrhage was identified. The 6 types of hemorrhages were ICH, ICH with intraventricular extension (ICH with intraventricular hemorrhage), subdural hemorrhage (SDH), intraventricular hemorrhage, epidural hemorrhage, and subarachnoid hemorrhage.

We collected clinical information, including hemorrhage type, age, sex, warfarin indication, comorbidities (coronary artery disease, stroke history, deep venous thrombosis or pulmonary embolus), initial INR, post rFVIIa INR, rFVIIa dose, weight, FFP dose, vitamin K dose, neurological intervention, thromboembolic complications, timing of thromboembolic events, and survival to dismissal. We also documented whether electrocardiogram, troponin levels, or Doppler ultrasounds were obtained and their results.

Thromboembolic complications were defined as myocardial infarction (MI), deep venous thrombosis (DVT), pulmonary embolism (PE), and ischemic stroke. Criteria were based on the electrocardiogram and cardiac biomarkers for coronary events (troponin T elevation >0.1 ng/mL with significant delta over 6 hours), venous ultrasounds for DVT (obtained because of clinical suspicion), or chest CT angiogram for PE and brain imaging for stroke. We relied on the interpretation of electrocardiogram by a cardiologist and the report of the imaging studies by a radiologist to ascertain the end points of MI and DVT/PE, respectively. For patients with a history of stroke before receiving Factor VIIa, a recurrent stroke (after the infusion of Factor VIIa) was defined as a stroke involving a vascular territory distinct from the prior stroke based on neurological examination and brain imaging. We reviewed all brain imaging scans independently for this study. Patients who experienced a thromboembolic event were stratified into 4 categories based on the temporal relationship between the event and the hemorrhage. The categories were 2 weeks, 30 days, 60 days, and 90 days posthemorrhage. All of the complications were reviewed by at least 2 of the investigators to confirm each thromboembolic event and final ascertainment were reached by consensus.

Data are presented primarily through descriptive analysis. Statistical analyses were performed to assess for predictors of thromboembolic events. Age, initial INR, common indications for anticoagulation (atrial fibrillation, mechanical valve, and history of DVT or PE), dose of rFVIIa, dose of FFP, and hemorrhage type (intraparenchymal versus extraparenchymal) were the variables included in the analysis. Categorical data were analyzed using the 2-tailed Fisher exact test and continuous variables using the Student t test.

Results
We identified 101 consecutive patients who were eligible for the study (Table 1). Fifty-two patients (51.4%) were women and the average age was 76 years (range, 29 to 94 years). Forty patients (39.6%) had no history of coronary artery disease (CAD), stroke, DVT, or PE. Seventeen patients (16.8%) had a documented history of CAD, 15 patients (14.8%) had a history of stroke, and 17 patients (16.8%) had a history of either DVT or PE. Twelve patients (11.8%) had >1 of these previous diagnoses. Indications for anticoagulation therapy were atrial fibrillation, prosthetic valve, congestive heart failure, DVT, PE, pulmonary hypertension, left ventricular thrombus, internal carotid artery stenosis, patent foramen ovale and transient ischemic event, aortic thrombi, and stroke.

The most common indications were atrial fibrillation in 55 patients (54.4%), DVT in 7 patients (6.9%), and prosthetic valve in 6 patients (5.9%). Fourteen patients (13.8%) had >1 indication for oral anticoagulation and in 1 patient (0.9%), the indication was unknown. The mean (range) INR at admission was 3.04 (1.2 to 16.2). The mean (range) INR after rFVIIa was 1.03 (0.7 to 2.1). Six patients (5.9%) did not have an INR checked or recorded after administration of rFVIIa because of poor prognosis leading to withdrawal of life support, death, or emergency neurosurgical intervention.

Thirty-two (31.6%) patients had intraparenchymal hemorrhages, 23 (22.7%) patients had intraparenchymal hemorrhages with intraventricular extension, 30 (29.7%) patients had subdural hematoma, 7 (6.9%) patients had subarachnoid hemorrhages, 6 (5.9%) patients had intraventricular hemorrhages, and 3 (2.8%) patients had an epidural hematoma (2 intraspinal). The mean total dose of rFVIIa was 51.7 μg/kg ± 28.99 (median 43.9 μg/kg; range, 4.4 to 186.8 μg/kg). The mean dose of FFP was 2.5 U ± 2.37 (median 2 U; range, 0 to 13). The mean dose of vitamin K was 9.5 mg ± 7.42 (median, 10 mg; range, 0 to 41). INR was ≤1.4 after the initial dose of rFVIIa in 91 of 95 patients in whom a
follow-up INR was obtained. Forty-three (42.5%) patients had neurosurgical intervention, including placement of an external ventricular drain, craniotomy with evacuation of the hematoma, or placement of an aneurysm clip (in only 1 patient). No patients were excluded from surgery because of delayed or insufficient reversal of anticoagulation.

Sixty-seven patients (66.3%) survived until dismissal from the hospital. Seventy-one patients (70.2%) had troponin levels drawn and 79 patients (78%) had at least 1 electrocardiogram during the first 24 hours after rFVIIa administration. Thirty-five patients had (34.6%) extremity ultrasounds performed during their hospitalization.

Thirteen patients (12.8%) had new thromboembolic events (10 DVTs and 3 ischemic strokes) over a 90-day period after administration of rFVIIa (Table 2). Eleven patients (10.8%) had events within the first 30 days, including 7 acute DVTs and 1 ischemic stroke, which occurred within the first 2 weeks. Two of these early DVTs (Patients 1 and 2) were associated with Peripherally Inserted Central Catheter lines. One of the DVTs (Patient 3) was associated with a radial head fracture and 1 DVT occurred in a parietic leg (Patient 4). Three early DVTs occurred in patients with a history of DVT (Patients 5, 6, and 7). Five days posthemorrhage, 1 patient with a mechanical valve had a stroke that was deemed likely cardioembolic (Patient 8). At the time of dismissal, this patient had mild distal left upper extremity weakness. At 30 days posthemorrhage, 3 additional patients had thromboembolic events (2 DVTs and 1 stroke). Patient 11 had multiple embolic strokes 1 month after receiving rFVIIa, resulting in akinesis mutism. The family withdrew life support measures and the patient subsequently died. The stroke was classified as cardioembolic due to atrial fibrillation. At 60 days, Patient 12 had a stroke in the middle cerebral artery distribution causing hemiparesis; the brain infarction was deemed related to his atrial fibrillation. The patient recovered without any significant, permanent deficits. At 90 days, Patient 13 had a DVT. In total, 7 DVTs affected an upper extremity and 3 DVTs were associated with Peripherally Inserted Central Catheter lines. No patients in our study had PE or MIs.

Statistical analysis showed no association between the occurrence of thromboembolic events and the presence of any of the variables analyzed, including age ($P=0.87$), initial INR ($P=0.40$), atrial fibrillation ($P=0.53$), mechanical valve ($P=0.61$), DVT or PE ($P=0.95$), initial or total rFVIIa dose ($P=0.82$ and 0.98), FFP dose ($P=0.60$), intraparenchymal hemorrhage ($P=0.24$), or extraparenchymal hemorrhage ($P=0.74$).

### Discussion

In this study of patients with warfarin-associated intracranial and intraspinal hemorrhages who received rFVIIa, the risk of thromboembolic complications was slightly higher than previously reported in patients with spontaneous ICH.\(^17,19\) However, most of our patients had minor DVTs without embolism. The difference between this patient population and those included in prior studies is that at baseline, our patients may have had a higher risk of developing thromboembolic events due to the pre-existent conditions that led to the anticoagulation. Despite this baseline risk, there were no fatal or incapacitating thromboembolic complications within the first month. Delayed strokes, which occurred several weeks after rFVIIa administration, were most likely related to unprotected atrial fibrillation rather than a direct consequence of rFVIIa use.

Anticoagulation-related hemorrhages are becoming an increasingly concerning public health problem because of the exponential growth in the number of anticoagulated patients in the general population.\(^21\) In addition, anticoagulation increases the risk of hematoma expansion and poor outcome.\(^22\) Rapid reversal of anticoagulation might decrease this risk. Recombinant Factor VIIa can reverse the INR quickly.\(^11,13–15\) Our results indicate that rFVIIa therapy rapidly reduces the INR and carries a relatively low risk of thromboembolic complications in patients who were prescribed warfarin because of pre-existing thromboembolic disease. In theory, the thromboembolic complications might be lowered further by using smaller doses of rFVIIa, which proved to be sufficient in some of our patients.
Table 2. Detailed Information of Patients With Thromboembolic Events After Administration of rFVIIa*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Medical History (CAD, DVT/PE, Stroke)</th>
<th>Indication for Anticoagulation</th>
<th>Type of Hemorrhage</th>
<th>Pre-rFVIIa INR</th>
<th>Post-rFVIIa INR</th>
<th>Dose of rFVIIa, μg/kg</th>
<th>Dose of FFP, U</th>
<th>Type of Event</th>
<th>Timing of Event (Days After rFVIIa)</th>
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<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>None</td>
<td>Atrial Fibrillation</td>
<td>ICH</td>
<td>2.3</td>
<td>0.8</td>
<td>45.6</td>
<td>3</td>
<td>DVT</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>M</td>
<td>Stroke</td>
<td>Atrial Fibrillation</td>
<td>SAH</td>
<td>5.3</td>
<td>2.1</td>
<td>44.1</td>
<td>0</td>
<td>DVT</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>M</td>
<td>CAD, stroke</td>
<td>Atrial fibrillation, stroke</td>
<td>SAH</td>
<td>2.6</td>
<td>0.8</td>
<td>86</td>
<td>1</td>
<td>DVT</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>M</td>
<td>CAD</td>
<td>Atrial fibrillation</td>
<td>ICH</td>
<td>1.7</td>
<td>1.1</td>
<td>52.2</td>
<td>4</td>
<td>DVT</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>F</td>
<td>DVT</td>
<td>DVT</td>
<td>ICH with IVH, SAH, SDH</td>
<td>1.2</td>
<td>0.8</td>
<td>78.8</td>
<td>6</td>
<td>DVT</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>F</td>
<td>DVT</td>
<td>Atrial Fibrillation</td>
<td>SDH</td>
<td>2</td>
<td>1.3</td>
<td>33.8</td>
<td>3</td>
<td>DVT</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>F</td>
<td>DVT</td>
<td>DVT</td>
<td>SDH</td>
<td>1.9</td>
<td>0.8</td>
<td>90.9</td>
<td>4</td>
<td>DVT</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>92</td>
<td>F</td>
<td>Stroke</td>
<td>Atrial fibrillation, mechanical valve</td>
<td>SDH</td>
<td>5.5</td>
<td>0.9</td>
<td>11.1</td>
<td>4</td>
<td>Stroke</td>
<td>5</td>
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<tr>
<td>9</td>
<td>86</td>
<td>M</td>
<td>CAD, PE</td>
<td>Mechanical valve</td>
<td>SDH</td>
<td>2.6</td>
<td>0.8</td>
<td>49.1</td>
<td>4</td>
<td>DVT</td>
<td>21</td>
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<tr>
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<td>75</td>
<td>M</td>
<td>None</td>
<td>Atrial fibrillation</td>
<td>ICH</td>
<td>3.1</td>
<td>0.9</td>
<td>62.3</td>
<td>7</td>
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<td>30</td>
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<tr>
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<td>Atrial Fibrillation</td>
<td>SAH</td>
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<td>1.1</td>
<td>19.2</td>
<td>0</td>
<td>Stroke</td>
<td>30</td>
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<tr>
<td>12</td>
<td>58</td>
<td>M</td>
<td>None</td>
<td>Atrial fibrillation</td>
<td>EDH</td>
<td>2.1</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>Stroke</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>86</td>
<td>M</td>
<td>None</td>
<td>Atrial fibrillation</td>
<td>ICH and EDH</td>
<td>2.1</td>
<td>0.9</td>
<td>39.7</td>
<td>0</td>
<td>DVT</td>
<td>90</td>
</tr>
</tbody>
</table>

*Clinical data for patients with thromboembolic complications.
M indicates male; F, female; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; EDH, epidural hematoma.

In the Factor VII for Acute Hemorrhagic Stroke (FAST) trial, the rate of thromboembolic events was 22% in the 20-μg/kg group and 32% in the 80-μg/kg group (versus 25% in the placebo group). In contrast with the FAST study, the majority of our patients with thromboembolic events had venous thromboembolic complications, which are known to be prevalent in hospitalized patients with ICH, especially with limb immobility. Of the 10 patients with DVTs, 3 were possibly associated with Peripherally Inserted Central Catheter lines and may not have been directly related to rFVIIa because they all occurred >1 week after rFVIIa administration. Although 3 patients in our study had strokes, 2 of them took place several weeks after rFVIIa infusion in patients with atrial fibrillation who had remained off warfarin since the bleeding. Only 5 of the thromboembolic complications in our series (all venous) occurred in patients with ICH at baseline (ie, the group of our population that can be compared more directly with the FAST trial); consequently, the rate of thromboembolism in this subgroup was 5%. The remainder of the adverse events occurred in patients with extraparenchymal hemorrhages.

In the FAST trial, age and prior use of antiplatelet agents were determined to be risk factors for serious thromboembolic events. In our study, no predictors of thromboembolic events were identified in an analysis that included age, initial INR, common indications for anticoagulation (mechanical valve, atrial fibrillation or history of DVT or PE), dose of rFVIIa, dose of FFP, or location of hemorrhage (intraparenchymal versus extraparenchymal).

Previous smaller series of patients with warfarin-associated intracranial hemorrhage treated with rFVIIa have been published. In 1 study comparing 15 patients treated with FFP alone with 12 patients who also received rFVIIa, those treated with rFVIIa showed faster anticoagulation reversal and no complications except in patients with dialysis-dependent end-stage renal failure (2 patients had very slow INR correction and 1 of them developed disseminated intravascular anticoagulation after receiving 3 doses of rFVIIa and large volumes of FFP). Although not considered attributed to rFVIIa, 1 patient had a DVT 2 weeks after treatment with the hemostatic agent. In another study of 54 patients presenting with warfarin-associated intracranial hemorrhage, correction of INR was achieved faster and requiring less FFP volume in the 30 patients treated with rFVIIa. One patient had an acute MI after receiving rFVIIa but recovered uneventfully.

Prothrombin complex concentrate is another alternative for rapid reversal of warfarin anticoagulation. It contains high concentrations not only of Factor VII, but also of Factors II, IX, and X. The total fluid volume administered is much lower than with FFP, thus reducing the risk of cardiopulmonary complications. The risk of thromboembolic complications in patients treated with prothrombin complex concentrate appears to be relatively low but remains to be examined in a large population. Thus far, experience with the use of prothrombin complex concentrate for anticoagulation reversal in patients with anticoagulation-associated intracranial hemorrhages is very limited.

Our study has several limitations. The patients were not routinely followed to assess for thromboembolic events and, thus, asymptomatic DVTs, PEs, MIs, or strokes could have been missed. Diagnostic studies were performed based on clinical suspicion. Consequently, not all patients had ultrasound, cardiac biomarkers, electrocardiograms, chest CTs, or serial brain imaging scans. Additionally, patients in this study were selected to receive rFVIIa based on the need for emergency invasive intervention, the size of the hemorrhage, the concern for hematoma expansion, and the risk of complications related to the volume of FFP. This selection bias must
be taken into account when interpreting our results. Our patients also received vitamin K and FFP and it is not possible to determine with certainty in our population if the observed cases of thromboembolism were related to rFVIIa, these other hemostatic agents, or unrelated to all. In fact, venous thromboembolism is a relatively common complication after ICH in the absence of hemostatic agent use; rates of asymptomatic DVT between 4% and 40% have been reported.24,31,32 All patients were not followed for 90 days posthemorrhage and therefore, some thromboembolic events beyond the acute hospitalization or rehabilitation periods could have been missed. Our ability to assess for predictors of thromboembolic complications was limited by the low number of events.

Conclusion

The risk of thromboembolic complications in patients with anticoagulation-associated central nervous system hemorrhages treated with rFVIIa was not higher than that reported in the FAST trial. Most of the thromboembolic events in our patients were minor DVTs. These results suggest that it would be safe to compare rFVIIa versus FFP for reversal of warfarin-associated ICH in a randomized controlled trial.

Disclosures

None.

References

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