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

Maisha T. Robinson, MD; Alejandro A. Rabinstein, MD; James F. Meschia, MD; William D. Freeman, MD

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;41:1459-1463.)

Key Words: Factor VII ■ intracranial hemorrhage ■ safety ■ warfarin
A known complication of rFVIIa is the precipitation of thromboembolic events secondary to its hemostatic nature.\textsuperscript{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.\textsuperscript{17} Reversing the effects of anticoagulation in patients with anticoagulation-associated ICH might 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 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 should be 40 to 80irms/kg, but we began administering smaller doses adjusted to 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 is >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 electrocardio-

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 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 hemor-
rhages, 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 \(\mu g/kg\) (median 43.9 \(\mu g/kg\); range, 4.4 to 186.8 \(\mu g/kg\)). 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
Table 1. Demographic and Clinical Characteristics of 101 Patients With Warfarin-Associated ICH Treated With rFVIIa

<table>
<thead>
<tr>
<th>Demographics</th>
<th>52/49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>76 (29–94)</td>
</tr>
<tr>
<td>Comorbid conditions, total patients (percentage)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>17 (16.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (14.8)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>17 (16.8)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>12 (11.8)</td>
</tr>
<tr>
<td>None</td>
<td>40 (39.6)</td>
</tr>
<tr>
<td>Warfarin indication, total patients (percentage)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>55 (54.4)</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>DVT</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>14 (13.8)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (18.8)</td>
</tr>
<tr>
<td>INR</td>
<td>3.04 (1.2–16.2)</td>
</tr>
<tr>
<td>Post rFVIIa mean (range)</td>
<td>1.03 (0.7–2.1)</td>
</tr>
<tr>
<td>Type of hemorrhage, total patients (percentage)</td>
<td></td>
</tr>
<tr>
<td>Intracerebral</td>
<td>32 (31.6)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>30 (29.7)</td>
</tr>
<tr>
<td>Intraparenchymal with intraventricular extension</td>
<td>23 (22.7)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>Spinal epidural hemorrhage</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Therapies</td>
<td></td>
</tr>
<tr>
<td>rFVIIa mean (SD)</td>
<td>51.7 μg/kg (±28.99)</td>
</tr>
<tr>
<td>FFP mean (SD)</td>
<td>2.5 U (±2.37)</td>
</tr>
<tr>
<td>Vitamin K mean (SD)</td>
<td>9.5 mg (±7.42)</td>
</tr>
<tr>
<td>Neurosurgical intervention, total patients (percentage)</td>
<td>43 (42.5)</td>
</tr>
</tbody>
</table>

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.
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). Arterial adverse events, primarily non-ST-elevation MIs, predominated. The risk of minor cardiac events was higher in patients treated with 80 μg/kg of rFVIIa. 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 not considered attributable to rFVIIa, 1 patient had a DVT 2 weeks after treatment. 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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*Stroke*. 2010;41:1459-1463; originally published online June 3, 2010;
doi: 10.1161/STROKEAHA.110.581538

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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