Recombinant Factor VIIa for Rapid Reversal of Warfarin Anticoagulation in Acute Intracranial Hemorrhage

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OBJECTIVE: **To assess the effects of recombinant factor VIIa (rFVIIa) on hemorrhage volume and functional outcomes in warfarin-related acute intracranial hemorrhage (ICH), which has a 30-day mortality of more than 50%.**

PATIENTS AND METHODS: **We reviewed the clinical, laboratory, and radiographic features of a consecutive series of 7 patients (median age, 87 years; 5 women) with symptomatic, nontraumatic warfarin-related acute ICH treated with intravenous rFVIIa at St. Luke's Hospital in Jacksonville, Fla, between December 2002 and September 2003. Prestroke baseline functional status was assessed with the modified Rankin Scale. Outcome was assessed with the Glasgow Outcome Scale.**

RESULTS: **The international normalized ratio decreased from a mean of 2.7 before administration of rFVIIa to 1.08 after administration of rFVIIa. The median prestroke score on the modified Rankin Scale was zero. The median presenting score on the Glasgow Coma Scale was 14 (range, 4-15). The mean time from onset to treatment was 6.2 hours. The mean initial dose of rFVIIa was 62.1 μg/kg. One patient underwent placement of an external ventricular drain, and another underwent craniotomy and hematoma evacuation. Five of the 7 patients survived and were dismissed from the hospital with severe disability (Glasgow Outcome Scale, 3); 2 patients died during hospitalization.**

CONCLUSIONS: **Intravenous bolus administration of rFVIIa can rapidly lower the international normalized ratio and appears to be safe for patients with warfarin-related ICH. Prospective controlled studies are needed to determine whether rFVIIa can prevent hematoma expansion and improve neurologic outcomes in patients with warfarin-related ICH.**

***Mayo Clin Proc.* 2004;79(12):1495-1500**

CT = computed tomography; FFP = fresh frozen plasma; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICH = intracranial hemorrhage; INR = international normalized ratio; IVH = intraventricular hemorrhage; rFVIIa = recombinant factor VIIa

Warfarin-related intracranial hemorrhage (ICH) is a medical emergency. Rapid reversal of warfarin anticoagulation is needed to prevent hematoma growth and to facilitate hematoma evacuation. Risk factors for warfarin-related ICH include advanced age, hypertension, intensity of anticoagulation, cerebrovascular disease, and cerebral amyloid angiopathy.[1] Reversing warfarin anticoagulation by conventional methods, such as fresh frozen plasma (FFP) or vitamin K, is time-consuming and requires substantial intravenous volumes. Because these methods of anticoagulation reversal require several hours, they may delay immediate surgical intervention. Intracranial hemorrhage associated with anticoagulation has a high mortality; more than 50% of patients die within 30 days.[2] Patients with supratentorial ICH who take warfarin have twice the 3-month mortality rate of patients with supratentorial ICH who do not take warfarin.[3] Recombinant factor VIIa (rFVIIa) rapidly reverses warfarin anticoagulation[4] and has been reported to be efficacious for patients with various bleeding disorders.[5] However, limited evidence supports its clinical use for warfarin-related ICH.

PATIENTS AND METHODS

We reviewed the clinical, laboratory, and radiographic features of a consecutive series of 7 patients who had symptomatic, nontraumatic, warfarin-related acute ICH treated with rFVIIa at St. Luke's Hospital in Jacksonville, Fla, between December 2002 and September 2003. This study was approved by the Mayo Foundation Institutional Review Board.

Of the 7 patients in our study (mean age, 83.5 years; median age, 87 years; range, 70-92 years), 5 were women. Four patients had intraparenchymal hemorrhage without intraventricular hemorrhage (IVH); 1 had intraparenchymal hemorrhage with intraventricular extension; 2 had isolated IVH; and 1 had an extremely small degree of subarachnoid extension observed on computed tomography (CT) of the head (Figure 1).

Prestroke baseline functional status was assessed with the modified Rankin Scale,[6] which ranges from 0 to 6, with 0 representing no symptoms and 6 representing death. Severity of presenting neurologic deficit was assessed with the Glasgow Coma Scale (GCS).[7] The GCS ranges from 3 to 15 points and assesses best eye opening, best motor response, and best verbal response; lower scores represent

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Presented in part at the 29th International Stroke Conference, San Diego, Calif, February 5 to 7, 2004.

Dr Brott has served on the Data and Safety Monitoring Board of a randomized clinical trial sponsored by Novo Nordisk (Princeton, NJ) of recombinant factor VIIa (NovoSeven) for spontaneous intracerebral hemorrhage.

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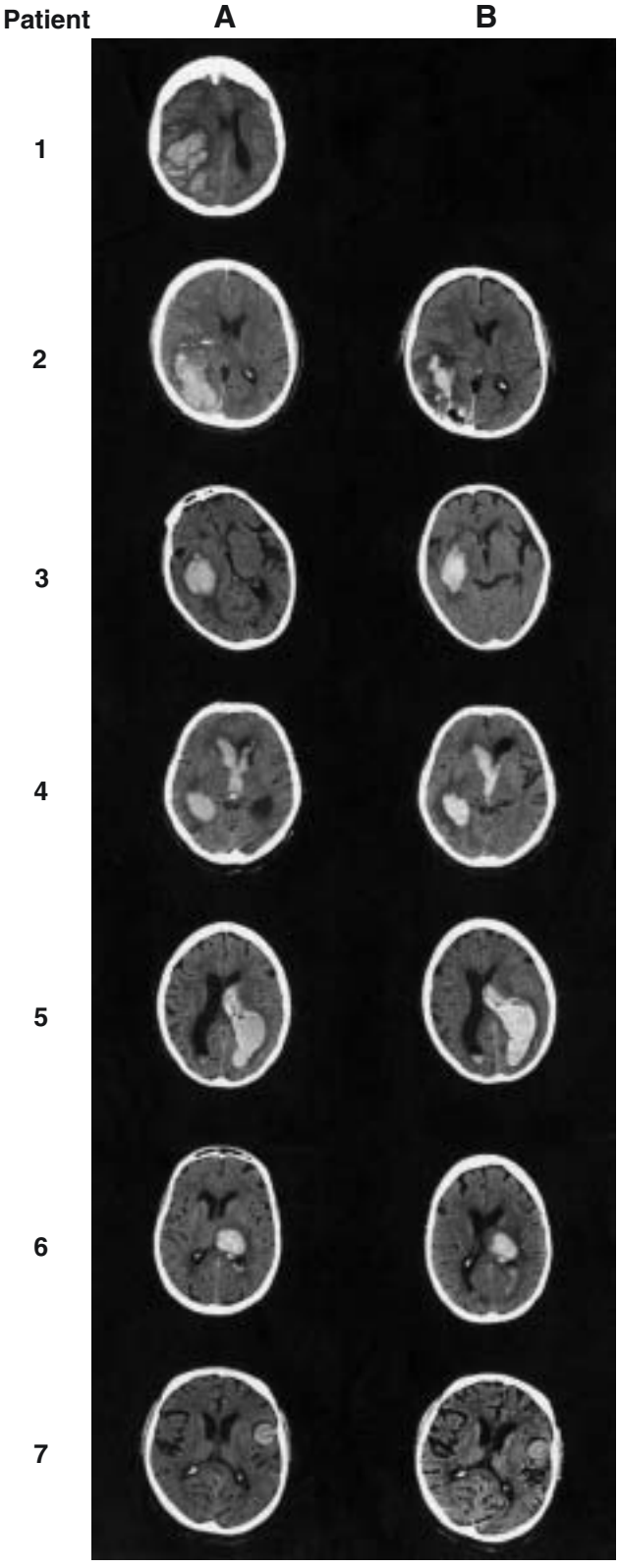

FIGURE 1. Axial computed tomograms of the head without contrast before (A) and after (B) patients received recombinant factor VIIa.

more severe deficits. The severity of ICH was assessed by the method of Hemphill et al.[8] Excluding cases of IVH, we measured ICH volume (cm^3) by the ABC/2 (ellipsoid) method with use of a CT slice interval thickness of 0.5 cm.[9] The percentage of change in ICH volume was calculated by the formula $(F - I)/I \times 100$, in which "F" represents later CT-measured ICH volume (cm^3), and "I" represents the earlier CT-measured ICH volume.[10] Severity of IVH was graded by the method of LeRoux et al[11] in which an IVH score (Table 1[11,12]) is assigned to each lateral ventricle and to the third and fourth ventricles (1 = trace blood, 2 = less than half a single ventricle filled with blood, 3 = more than half a single ventricle filled with blood, or 4 = entire ventricle filled and expanded with blood), with a minimum score of 1 and a maximum score of 16.[11] The hydrocephalus score (Table 1) was calculated by the Diringer method for each frontal horn, atria, temporal horns, and the third and fourth ventricles (0 = none, 1 = mild, 2 = moderate, or 3 = marked).[12] A score of 0 indicates no hydrocephalus, whereas a maximum score of 24 indicates severe hydrocephalus of all 4 ventricles.[12]

We recorded the international normalized ratio (INR) values and the time of each measurement throughout the patients' hospital stay. Also, we recorded the time of onset of ICH symptoms and the time of administration of initial and subsequent doses of rFVIIa. The functional outcome of patients at discharge was assessed with the Glasgow Outcome Scale (GOS).[13] The GOS ranges from 1 (death) to 5 (a good recovery). Length of stay from admission to discharge or death was obtained from medical records. Additional information on the modified Rankin Scale, the GOS, and the GCS can be found on the stroke trials directory of the Internet Stroke Center Web site.[14]

RESULTS

The median prestroke score on the modified Rankin Scale was zero (range, 0-2). Six patients were taking warfarin for chronic atrial fibrillation and 1 patient for deep venous thrombosis and pulmonary embolus. Five patients had a history of hypertension. No patient had a history of ischemic stroke, Alzheimer disease, or mild cognitive impairment. One patient had a history of carcinoma (prostate cancer status after radical prostatectomy with undetectable prostate-specific antigen). The mean INR before administration of rFVIIa was 2.7 (range, 1.6-5.6) (Table 2) and decreased to 1.08 after administration of rFVIIa. The median presenting score on the GCS was 14 (range, 4-15).

The mean time from onset to treatment for rFVIIa was 6.2 hours (range, 1.3-17.6 hours). The mean initial dose of rFVIIa was 62.1 μg/kg intravenously (range, 15-90 μg/kg), and the mean total dose was 4.25 mg (range, 0.68-7.48 mg).

TABLE 1. **Cases of IVH by IVH Pathology, IVH Score, and Hydrocephalus Score***

Patient No.	IVH type	IVH score [11]†	Hydrocephalus score[12]†
4	Primary	13	18
5	Primary	5	17
6	ICH with intraventricular extension	3	11

*ICH = intracranial hemorrhage; IVH = intraventricular hemorrhage.
†Hydrocephalus score was calculated on the initial computed tomogram (within 24 hours).[12]

One patient received a subsequent dose of 1.2 mg rFVIIa 48 hours after the initial dose. Initial decreases in INR values after taking rFVIIa were 0.6 (time interval from last premedication INR to first postmedication INR, 2.5 hours), 0.8 (7.5 hours), 1 (3.5 hours), 1.3 (3 hours), 1.6 (5 hours), 2 (6.3 hours), and 3.5 (4 hours) (Figure 2).

Patient 1 did not receive vitamin K; she died within 24 hours of presentation. The other 6 patients received vitamin K at a mean dose of 11.66 mg (range, 2.5-30 mg). The mean dose of FFP was 7.2 U (range, 0-13 U), with only patient 3 not receiving FFP (but receiving vitamin K). No spontaneous thrombotic complications were observed.

Only 2 patients received surgical intervention: 1 underwent placement of an external ventricular drain (patient 4), and 1 underwent craniotomy and hematoma evacuation (patient 2). At 24 hours, nonsurgical patients 3, 6, and 7 had an increase in ICH volume of 27.15%, 11.76%, and 28.46%, respectively (Table 3). The change in ICH volume from admission to most recent in-hospital follow-up CT was +21.22%, 0%, and –10%, respectively. Patient 2 underwent craniotomy and hematoma evacuation and had a –4.2% change in ICH volume from admission to discharge. At admission, mean systolic blood pressure for all 7 patients was 167 mm Hg, and mean diastolic blood pressure was 94 mm Hg.

Clinical short-term outcomes are shown in Table 4. Mean length of hospital stay was 13.7 days (range, 1-52 days). Two of 7 patients died during hospitalization: 1 on day 1 and 1 on day 6; both deaths were attributed to neurologic injury. The 5 patients who survived to discharge all had a GOS of 3 (severe impairment).

Illustrative Case 1 (Patient 2)

A 77-year-old man with a history of hypertension and atrial fibrillation who was taking warfarin awoke with severe headache and presented within 5 hours to the emergency department with a GCS of 14. His initial blood pressure was 137/99 mm Hg. The patient was disoriented and had a left homonymous hemianopia and left hemiparesis. Acute ICH was seen on CT of the head without contrast (Figure 1, patient 2). The patient was given a 90-μg/kg bolus of rFVIIa. His INR decreased from 2.4 to 1.4. Within the first 24 hours, the patient was given 4 U of FFP and 10 mg of vitamin K subcutaneously. He underwent emergent craniotomy and hematoma evacuation. On the second hospital day, he again was given rFVIIa (1.2 mg) because his INR had increased to 1.8. The patient survived to discharge with a dense left hemiparesis and left homonymous hemianopia (GOS, 3).

Illustrative Case 2 (Patient 6)

An 81-year-old woman with hypertension and atrial fibrillation who was taking warfarin awoke with weakness in her right arm, leg, and face the evening before presentation. Although her husband believed her weakness would "improve with sleep," he realized in the morning that her symptoms had not improved, and he called for emergency assistance. The patient was taken by ambulance to the emergency department. On presentation, neurologic examination revealed an awake patient with global aphasia, dense right hemiparesis, right homonymous hemianopia, and right-sided neglect. The patient's initial GCS score was 14, and blood pressure was 203/108 mm Hg; CT of the head without contrast revealed an acute left thalamic ICH with intraventricular extension (Figure 1, patient 6). Infusion of 4.8 mg of rFVIIa reduced the patient's INR from 2.3

TABLE 2. **Methods of Emergent Reversal of Warfarin Anticoagulation***

Patient No.	Age (y)/ sex	Weight (kg)	Initial INR	rFVIIa Initial dose (μg/kg)	rFVIIa Total given† (mg)	Vitamin K (mg)	FFP (U)
1	89/F	91	1.6	80	7.28	0	6
2	77/M	77	2.4	30	3.60	10	4
3	87/F	47	1.8	15	0.68	2.5	0
4	89/F	52.5	2.5	90	4.73	30	13
5	92/F	62.9	5.6	40	2.40	15	6
6	81/F	59	2.3	80	4.80	5	7
7	70/M	88	2.9	85	7.48	7.5	7

*FFP = fresh frozen plasma; INR = international normalized ratio; rFVIIa = recombinant factor VIIa.
†Total rFVIIa includes approximate initial rFVIIa given and any subsequent rFVIIa dosing.

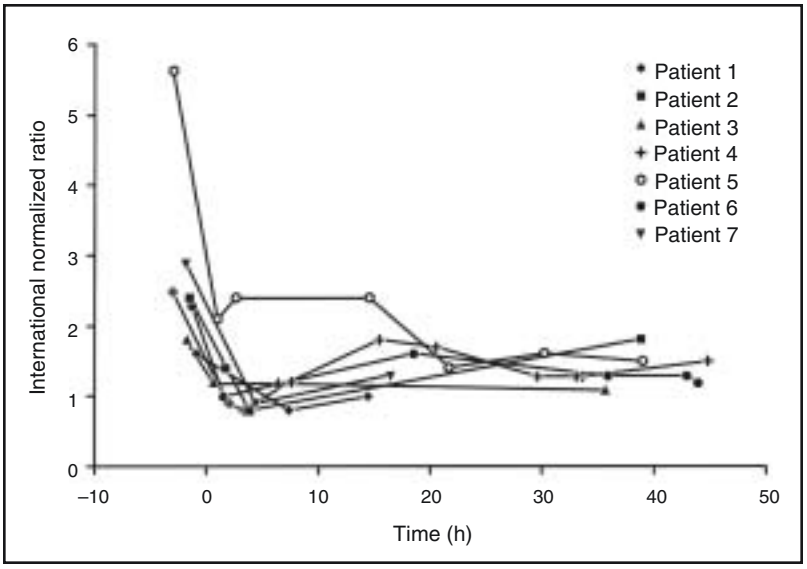

FIGURE 2. International normalized ratios before and as long as 48 hours after administration of recombinant factor VIIa. Time zero is defined as the time of administration of recombinant factor VIIa. Patients also received fresh frozen plasma, vitamin K, or both.

to 1. Four units of FFP and 5 mg of subcutaneous vitamin K were given. The next day, the patient's INR was 1.6, and 3 U more of FFP were given. She survived to discharge with a severe right hemiparesis and aphasia (GOS, 3). The patient died 3.5 months after initial presentation as a result of acute thrombotic occlusion of the left middle cerebral artery observed on magnetic resonance angiography.

DISCUSSION

Factors that predict a worse outcome in ICH include hematoma volume, IVH, and a depressed level of consciousness.[1] Early hemorrhage growth of more than 33% of baseline volume occurs within 24 hours in at least 38% of patients and is associated with neurologic deterioration.[15] No surgical or medical intervention has been proved to reduce morbidity and mortality. Emergent hematoma evacuation (within the first 3-4 hours) is often delayed by standard anticoagulation reversal methods, thereby preventing possible intervention in patients with abrupt clinical deterioration.

Our study showed that rFVIIa rapidly reversed warfarin anticoagulation as measured by the INR. Several units of FFP take longer to infuse than a single bolus of rFVIIa; also, FFP requires checking for blood compatibility, requires thawing, and can induce hypervolemia. The INR of patient 3, who received intravenous vitamin K, did not appear to increase later (Figure 2). This finding reflects the

TABLE 3. **Hematoma Volume Dynamics for Patients With Parenchymal ICH***

Patient No.	ICH volume (cm^3)			ICH score at presentation	Surgical intervention	Relative change in ICH volume (%)	
	Initial	At 24 h	Before discharge†			At 24 h	At discharge
1	197	NA	NA	4	NA	NA	NA
2	86	NA	82.37	1	Craniotomy; hematoma evacuation	NA	–4.2
3	39	49.59	47.24	2	None	+27.15	+21.22
4	NA	NA	NA	3	EVD	NA	NA
5	NA	NA	NA	2	None	NA	NA
6	13.6	15.2	13.6	2	None	+11.76	0
7	13	16.7	11.7	0	None	+28.46	–10

*EVD = external ventricular drain; ICH = intracranial hemorrhage; NA = not applicable.
†Volume of ICH before discharge refers to last computed tomogram before hospital discharge.

ability of intravenous vitamin K to restore warfarin-inhibited coagulation factors within several hours[16] and with minimal risk (3 in 10,000) of anaphylaxis.[17] The rapid-onset action of rFVIIa and the later increase in INR may reflect the short half-life of rFVIIa (2.3 hours[18]) or inadequate amounts of FFP and vitamin K. Lin et al[19] used rFVIIa in 4 patients with warfarin-related hemorrhages of the central nervous system. The initial INR (range, 1.9-5.6) normalized in every patient within 2 hours after administration of rFVIIa. Sorensen et al[20] reported on 7 patients using vitamin K antagonists who had central nervous system bleeding emergencies. Initial INR (range, 1.7-6.6) stabilized to 1.5 or lower within 10 minutes after a single dose (10-40 μg/kg) of rFVIIa. We found that rFVIIa did not permanently normalize the INR in every patient. For 5 patients, a delayed increase in INR was observed that required standard methods such as FFP or additional vitamin K or that required repeated dosing with rFVIIa.

Although rFVIIa can rapidly improve both the prothrombin time and the INR in patients taking warfarin who experience bleeding complications, INR reduction should not be assumed to be an adequate means of monitoring all the effects of rFVIIa when the agent is given at pharmacological doses. High-dose rFVIIa acts independently of tissue factor to enhance platelet-surface thrombin generation.[21] Currently, no widely available laboratory test can optimally measure all the relevant effects of rFVIIa at pharmacological doses.

The 30-day mortality rate of 28.5% (95% confidence interval, 3.7%-71.0%) in our small series of patients treated with rFVIIa appeared to be less than that observed in larger studies,[2,15] which suggests that rFVIIa may have early benefit against neurologic deterioration. No patient had an ICH score of more than 5. The 2 patients who died had an ICH score of 3 or more. All patients with an ICH score of 2 or less survived to discharge. At the doses prescribed, rFVIIa did not eliminate early hemorrhage growth in these patients. However, early use of rFVIIa may have reduced early hematoma growth.

One limitation of our study was that we estimated hematoma volumes using the ABC/2 method, which assumes that the shape of the hematoma approximates an ellipsoid.[9] However, this method cannot be used in patients with ICH with substantial intraventricular extension or primary IVH. Postoperative residual hematomas can have an irregular border and nonellipsoid configuration. The ABC/2 formula does not reliably estimate IVH volume. Therefore, we assessed IVH severity with the IVH score described by LeRoux et al,[11] which was originally described in patients with IVH after blunt head trauma. Two patients with an IVH score of 5 or less survived to discharge. One patient with an IVH score of 13 died, which was predicted from the LeRoux et al description of 3 patients with similar IVH scores who died. Hydrocephalus developed in all 3 of our patients who had relatively high IVH scores.[12] Tuhrim et al[22] showed that ICH with IVH extension and high IVH volume was an important determinant of 30-day outcome. Warfarin-related IVH may increase the risk of hydrocephalus, an independent predictor of mortality.[12]

TABLE 4. **Prestroke Functional Status, Presenting Deficit Severity, and Functional Outcome at Discharge (N=7)**

Patient No.	Prestroke modified Rankin Scale	Initial presenting Glasgow Coma Scale	Glasgow Outcome Scale at discharge or death	Length of hospital stay (d)
1	0	4	1	1
2	0	14	3	10
3	0	15	3	12
4	2	10	1	6
5	0	14	3	5
6	0	14	3	10
7	0	14	3	52

For patients who survive the acute phase of warfarin-related ICH, the question becomes when, if ever, should warfarin anticoagulation be resumed? A limitation of our study is that patients were not monitored for long-term thromboembolic complications after rapid reversal of anticoagulation. Eckman et al[23] used a decision model to determine that most survivors of lobar or deep hemispheric ICH with atrial fibrillation should not be given long-term anticoagulant treatment. However, patients at high risk of thromboembolic stroke or at low risk of recurrent ICH may benefit from anticoagulants. One patient with atrial fibrillation in our study survived to discharge (patient 6) but died 3.5 months later after a massive thromboembolic stroke. Phan et al[24] found the probability of ischemic stroke to be 2.6% to 4.8% at 30 days after discontinuation of anticoagulants in patients at high risk of thromboembolic or ischemic stroke. Pending further research, the decision to resume anticoagulants must be made on a case-by-case basis.

CONCLUSIONS

Compared with conventional treatment with FFP and vitamin K, intravenous bolus administration of rFVIIa clearly leads to rapid correction of the INR in patients taking warfarin without risk of hypervolemia and anaphylaxis. Thus, rFVIIa can expedite safe neurosurgical hematoma evacuation. What is less clear is whether emergent use of rFVIIa can improve neurologic and functional outcomes with or without hematoma evacuation. The therapeutic time window for rapid warfarin reversal is also unclear for

patients with acute spontaneous ICH and IVH. Of note, rFVIIa is costly, and other agents can rapidly normalize the INR. The relative merits of these rapidly reversing agents are unknown. Yasaka et al[25] found that administration of prothrombin complex concentrate rapidly reduced the INR and appeared to prevent hematoma enlargement relative to a nonrandomized control group that received vitamin K or FFP. There is a need for randomized controlled trials of various methods that may rapidly counteract the anticoagulant effects of warfarin in patients with warfarin-related ICH.

We thank Darlene E. Gunsolus for her assistance with the preparation of the submitted manuscript.

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