Multiple Ischemic Strokes Associated With Use of Recombinant Activated Factor VII

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Background: Intracerebral hemorrhage is associated with a high rate of mortality and functional disability. For most patients, no treatment other than supportive care has been shown to improve outcome. Preliminary studies suggest that recombinant activated factor VII may limit early hematoma growth and improve functional outcome. However, ischemic complications may occur in some patients.

Objective: To report a case of severe cerebral ischemic complications associated with the use of recombinant activated factor VII.

Design: Case report.

Setting: Tertiary care medical center.

Patient: We describe a patient with ischemic stroke who developed hemorrhagic conversion following tissue plasminogen activator administration.

Interventions: Treatment with recombinant activated factor VII, in addition to standard treatment with cryoprecipitate and platelets.

Main Outcome Measure: Brain imaging showing multiple ischemic strokes.

Results: The patient subsequently developed multiple acute cerebral infarcts in different vascular distributions.

Conclusion: Although the exact relationship between treatment with recombinant activated factor VII and the development of multiple ischemic strokes remains uncertain, this case suggests that a cautious approach to treatment with this agent is warranted until more data are available.

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INTRACEREBRAL HEMORRHAGE (ICH) is a devastating stroke subtype, with no treatment conclusively proved effective. Early enlargement of the hematoma occurs relatively frequently and is a strong predictor of neurologic deterioration. Treatment with recombinant activated factor VII (rFVIIa) has been shown to decrease hematoma growth and possibly to result in improved clinical outcome. However, the use of rFVIIa may also result in ischemic complications. The risk-benefit ratio of treatment with rFVIIa, particularly in populations other than those with primary ICH, is not yet known.

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REPORT OF A CASE

A 55-year-old right-handed African American man presented with acute left-sided numbness and paresthesia. His initial neurologic examination showed mild left-sided hemiparesis, moderate left-sided ataxia affecting the arm and leg, and a dense sensory deficit on the left to pinprick and proprioception. Initial computed tomography (CT) of the head showed small chronic lacunes in the left caudate nucleus and left lentiform nucleus as well as moderate chronic periventricular white matter changes, without any evidence of acute infarction. He was enrolled in an acute stroke protocol comparing a conventional dose of intravenous tissue plasminogen activator (tPA) vs low-dose intravenous tPA combined with eptifibatide (a glycoprotein IIb/IIIa platelet receptor antagonist). Several hours later, the patient deteriorated neurologically, with severe left hemiplegia, severe dysarthria, left hemineglect, and dense left gaze palsy. Repeated CT of the head showed a large right frontal lobar hematoma, about 5.6 cm at the greatest diameter, with moderate mass effect and edema. There was an evolving, acute right-sided thalamiccapsular infarct, about 1 cm in diameter. He was treated with cryoprecipitate, platelets, and rFVIIa (80 µg/kg). He was taken to the operating room, and the hematoma was evacuated. Repeated CT scans of the head showed significant resolution of the hematoma, with scattered small amounts of subarachnoid hemorrhage but with low density surrounding the previous hemorrhage, suggestive of...
a possible subacute infarct in the anterior cerebral artery (callosomarginal) distribution. During the next 2 days, he showed neurologic improvement: opening his eyes, following 1-step commands, and moving his right side purposefully but with a dense left hemiplegia. On the third day postoperatively, his level of consciousness deteriorated, and he could not be aroused even by noxious stimuli. The pupils were approximately 2 mm in diameter and nonreactive to light. The corneal reflexes were markedly diminished bilaterally. His eyes were at times in the primary position and at other times showed bilateral exodeviation, and the oculocephalic reflexes were consistently absent. There was no spontaneous movement and no movement or grimace in response to noxious stimuli. Repeated CT scans of the head showed an overall decrease in the right frontal hemorrhagic component of the infarct and multiple subacute infarcts involving the cortical and subcortical regions bilaterally. Magnetic resonance imaging of the brain showed innumerable acute and subacute infarcts (bright on diffusion-weighted imaging and showing restricted diffusion on the apparent diffusion coefficient map) involving both hemispheres as well as throughout the brainstem (Figure). There was no evidence of systemic infarcts, and the infarcts appeared to be isolated to the brain. Results of transesophageal echocardiography, collagen vascular screening, and lumbar puncture were normal. Pathologic examination of the craniotomy surgical specimen showed a blood clot. His neurologic condition remained unchanged for the next 2 weeks, at which time he died of cardiopulmonary arrest. A request for an autopsy was refused by the family.

**COMMENT**

Recombinant activated factor VII appears to decrease the degree of hematoma volume expansion and possibly improves clinical outcome in patients with intracerebral hemorrhage. In the trial by Mayer et al, thromboembolic events occurred in 2% of the placebo-treated patients compared with 7% of the rFVIIa-treated patients. There were 7 myocardial ischemic events and 9 cases of ischemic stroke. Two of the stroke cases were “massive and fatal,” and 5 were “moderate in severity and disabling.” No specific information was provided regarding arterial distribution or the multiplicity of the lesions. Recombinant activated factor VII enhances the coagulation cascade and therefore contributes to thrombogenesis. In a case series of patients with ICH, 10% of patients treated with rFVIIa developed troponin elevation compared with 3% of nontreated patients, and 10% of treated patients developed symptomatic myocardial infarction vs 1% of untreated patients. The patient in our report developed ICH following treatment of an ischemic stroke with tPA and was subsequently treated with rFVIIa in addition to cryoprecipitate and platelets. He developed multiple acute infarcts in different vascular distributions. Of course, we cannot infer causality between the administration of rFVIIa and the development of multiple cerebral infarcts. It is possible that the cerebral ischemic events were related to some other undiagnosed mechanism. However, a cardiac source of embolism is unlikely in the setting of normal transesophageal echocardiography results. We did not specifically check for disseminated intravascular coagulation, but the patient’s platelet count remained normal throughout his clinical course, and there was no evidence of systemic ischemia or hemorrhage during his hospitalization. It is therefore unlikely that he had disseminated intravascular coagulation. If rFVIIa can be implicated, it remains unknown whether this substance might have been acting in isolation or whether the combination of rFVIIa and other hemostatic treatments (eg, cryoprecipitate or platelet...
lets) might be responsible. The patients in the phase 2 rFVIIa trial did not receive any additional treatments (eg, cryoprecipitate, platelets, or fresh frozen plasma), whereas our patient received a combination of rFVIIa and other traditional treatments. Of note, our patient differs from the neurologic population being studied most closely for possible benefits from treatment with rFVIIa; that is, those with ICH. Our patient presented with ischemic stroke only to develop hemorrhagic complications after being treated with a thrombolytic agent with or without a platelet receptor antagonist. This constitutes an off-label use of rFVIIa in the setting of an investigational trial (including possible treatment with eptifibatide) after the administration of cryoprecipitate and platelets, and there are no safety data regarding the use of this drug in this context. It is also conceivable that patients presenting with different manifestations of vascular disease (eg, ischemia or the consequences of atherosclerosis) may have a significantly different risk of ischemic complications compared with patients presenting with ICH. Allowing for these uncertainties, we wish to echo the message of an editorial by Greenberg and, if not to wave the red “stop” flag, at least to signal a possible “hazard on the track.” We would urge careful consideration of the possible risks of rFVIIa therapy until more data are available from randomized trials regarding this treatment.

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REFERENCES


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