



Recombinant activated factor VII for acute intracerebral hemorrhage

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Acute stroke is the third leading cause of death worldwide, exceeded only by coronary artery disease and cancer.^[1] There are two major subtypes of stroke—ischemic and hemorrhagic with 20-30% of all strokes being hemorrhagic in nature.^[2] The incidence of ischemic strokes has steadily declined by virtue of rigorous risk factor modification, but the same has not been possible for hemorrhagic strokes. Moreover, ischemic strokes can now be effectively treated by thrombolysis with tissue plasminogen activator. On the other hand, the incidence of intracerebral hemorrhage (ICH) is expected to grow, given the aging of the population. The treatment of hemorrhagic strokes remains mainly conservative with a recent large multi-centric study failing to show any benefit from early surgery^[2] and the mortality at 30 days is seven times higher than ischemic strokes (63% vs. 9%).^[3] However, it is believed that strict control of hypertension may significantly decrease the incidence of nonlobar type of ICH.^[4] The above factors clearly point towards the need for newer drugs or treatment modalities for patients with ICH. Recombinant activated factor VII (rFVIIa), as shown in some recent trials, appears to be of promise in the management of ICH.^[5]

Rationale for using rFVIIa in ICH

Historically, bleeding due to a hemorrhagic stroke was considered to be a monophasic event that stopped quickly as a result of clotting and tamponade by the surrounding brain tissue. However, computerized tomography-based studies have demonstrated that the initial

hematoma expands in up to 38% of patients who were initially scanned within 3 hours of the onset of stroke, and in 16% of those scanned between 3 and 6 hours, even in the absence of coagulopathy.^[6] Progressive bleeding of this type has been associated with contrast extravasation on CT angiography^[7] and poor outcome after early (<4 hours) surgical clot evacuation.^[8] On the basis of these observations, it is plausible that ultra-early hemostatic therapy given in the emergency room setting might improve outcome after ICH by arresting ongoing bleeding and minimizing the increase in the volume of the hematoma. rFVIIa is approved to treat bleeding in patients with hemophilia who have antibodies to factor VIII or IX, and it has been reported to reduce bleeding in patients without coagulopathy as well.^[9]

The precise mechanism by which rFVIIa arrests bleeding in patients with acute ICH is not fully understood. It promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. After blood-vessel damage and local initiation of the coagulation cascade, the administration of rFVIIa enhances thrombin generation on the surface of activated platelets, leading to accelerated formation of a fibrin clot.^[10] It seems most likely that the administration of rFVIIa after ICH accelerates thrombosis within ruptured small penetrating arteries or arterioles. Although the half-life of rFVIIa is only 2.6 hours, a sustained hemostatic effect may occur after a single dose because the clot that forms is denser than normal and more resistant to fibrinolysis.^[11]

Current evidence regarding the efficacy of rFVIIa in ICH

rFVIIa for spontaneous ICH in adults

In a recent multi-centre, double-blind, placebo-control-

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led trial, 399 adult patients with CT-documented ICH were randomized to receive either placebo or rFVIIa (at a dose of 40, 80 or 160 µg per kilogram body weight) as a single intravenous dose within four hours of onset of symptoms (within one hour of CT).^[5] There was a greater increase in hematoma volume in the placebo group than in the rFVIIa groups. The mean increase was 29% in the placebo group, as compared with 16%, 14%, and 11% in the groups given 40 µg, 80 µg, and 160 µg of rFVIIa per kilogram, respectively. Growth of the hematoma was reduced by 3.3 ml, 4.5 ml, and 5.8 ml in the three treatment groups, as compared with that in the placebo group. Outcome at 90 days was worse in the placebo group. Sixty-nine percent of placebo-treated patients died or were severely disabled, as compared with 55%, 49%, and 54% of the patients who were given 40, 80, and 160 µg of rFVIIa, respectively. Mortality was 29% for patients who received placebo, as compared with 18% in the three rFVIIa groups combined. This study, therefore, establishes the efficacy of rFVIIa in ICH, if administered within four hours of symptom onset.

Role of rFVIIa in patients with ICH on warfarin thromboprophylaxis

Major bleeding is a frequent and hazardous complication associated with thromboprophylaxis using vitamin-K antagonists (VKA) such as warfarin. Suggested regimens for control of the elevated International Normalized Ratio (INR) and hemorrhagic events during VKA treatment include administration of vitamin K, infusion of fresh frozen plasma or a prothrombin complex concentrate. However, correction of INR by these measures may take 24-48 hours; and for the patients who require an emergent neurosurgical intervention and evacuation of hematoma, early normalization of INR would be a distinct advantage. In a study on seven patients with oral-anticoagulant induced ICH (INR ranging from 1.7 to 6.6) requiring emergency neurosurgical intervention, rFVIIa was administered at a dose of 10-40 µg/kg body weight,^[12] which resulted in a reduction in the INR to 1.5 or less within 10 minutes of administration of rFVIIa. Six patients underwent drainage of the hematoma and survived to hospital discharge.

rFVIIa therapy for ICH in patients with hemophilia A or B with inhibitors

The efficacy of rFVIIa for ICH in hemophilia A patients with inhibitors was demonstrated more than a decade ago in a study on five patients.^[13] More recently, in a

study on 12 patients with hemophilia and life-threatening ICH previously unresponsive to one or more alternate therapies; rFVIIa was administered in an emergency setting,^[14] resulting in effective ICH control in 10 patients.

rFVIIa therapy in thrombocytopenic patients with ICH

Efficacy of rFVIIa in thrombocytopenic patients with ICH has been demonstrated with a few case reports.^[15,16] The clinical settings included patients with refractory thrombocytopenia or idiopathic thrombocytopenic purpura, who required emergency surgery and therapies with platelet rich concentrates or intravenous immunoglobulins had failed.

rFVIIa for cerebral-injury induced coagulopathy

Coagulopathy is common in patients with moderate or severe head injury. In a recent study, thrombocytopenia and coagulopathy were present in 14% and 21% of patients at admission, which increased to 46% and 41% by the third day.^[17] Many patients with head injury require emergency neurosurgical intervention including evacuation of intracerebral hematoma and placement of intracranial pressure monitoring devices. The procedures may get delayed in presence of coagulopathy. In this setting, therapy with rFVIIa could be useful. In a study on three pediatric patients, rFVIIa at a dose of 90 µg/kg body weight was found to be effective in correcting the coagulopathy and allowing the neurosurgical procedures without any complication.^[18]

Adverse events with rFVIIa therapy

The major limitation with rFVIIa therapy is its potential to cause thromboembolic complications. In a recent trial in patients with ICH, serious thromboembolic adverse events occurred in 7% of rFVIIa-treated group as compared to 2% in the placebo-treated group.^[5] Though the difference was statistically insignificant, it remains a cause for concern. The arterial thromboembolic events included myocardial or cerebral infarction and the majority occurred within three days of administration of rFVIIa. There is a report of subdural vein thrombosis developing three weeks after rFVIIa therapy for postnatal ICH in an infant.^[19] These reports suggest a need for careful monitoring of patients receiving rFVIIa therapy.

Dose, availability and cost

rFVIIa is manufactured and marketed by Novo Nordisk, Denmark as NovoSeven. It is supplied as a white, lyophilized powder in single use vials. It is available in two strengths- 1.2 mg and 2.4 mg.^[20] Prior to reconstitution;

it should be kept refrigerated (2-8°C). It needs to be re-constituted with sterile water for injection prior to use. The recommended dose is 40-80 µg/kg body weight and is administered by the intravenous route as a bolus dose. NovoSeven is available in India too, costing approximately Rs. 35,000 and Rs. 75,000 for 1.2 mg and 2.4 mg vials, respectively.

Summary

Recombinant activated factor VII therapy is effective and safe in patients with ICH and seems to be useful in a variety of clinical scenarios. These include spontaneous ICH, warfarin-induced ICH, bleeding associated with thrombocytopenia and coagulopathy occurring in head injury. The only point of concern seems to be its propensity to cause serious thromboembolic adverse events. Further trials are, however, needed to better determine its efficacy and safety.

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