

Recombinant Factor VIIa Treatment for Acute Intracerebral Hemorrhage

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ABSTRACT

Intracerebral hemorrhage is a lethal stroke type with a high morbidity and mortality. Hematoma growth is one of the independent determinants of neurological and functional outcomes after intracerebral hemorrhage. Attenuation of growth is an important therapeutic strategy. Hemostatic therapeutic intervention, given ultra-early in the course of intracerebral hemorrhage, may thus improve clinical outcomes by arresting ongoing bleeding and limiting in turn the size of the hematoma. Recombinant factor VIIa is a hemostatic drug approved to treat bleeding in hemophilia or other coagulopathy; it has also been reported to arrest bleeding in nonhemophilic cases. We reviewed the published articles specifically addressing clinical trials of recombinant factor VIIa treatment for acute intracerebral hemorrhage and evaluate the safety and feasibility of it. (*Kor J Cerebrovascular Surgery* 8:273-8, 2006)

KEY WORDS : Intracerebral hemorrhage · Recombinant activated factor VII · Hematoma growth · Hemostatic treatment

Introduction

Intracerebral hemorrhage (ICH) accounts for 15% or more of all strokes, but the proportion could have been underestimated in most stroke incidence studies. Primary ICH, in which there is no identifiable underlying cause for the hemorrhage, has a higher early case fatality than ischemic stroke. After primary ICH, only 38% of affected people survive the first year.⁷⁾ Although guidelines for supportive care exist,¹⁾ there is currently no treatment that has been shown in a randomized controlled trial to improve outcome after ICH.

The volume of the hematoma is an important determinant of mortality and functional outcome after ICH and early hematoma growth is an important cause of neurological

deterioration.²⁾³⁾¹²⁾ Approximately one third of ICHs enlarge by a third within three to 24 hours after onset.³⁾ Early ICH growth occurs in the absence of coagulopathy and appears to result from continued bleeding or rebleeding at multiple sites within the first few hours after onset.¹⁷⁾ The only prospective study of this phenomenon revealed a > 33% increase in ICH volume in 26% of patients at 1 hour, and in an additional 12% between 1 and 20 hours.³⁾

Hematoma volume is a critical determinant of mortality and functional outcome after ICH,⁶⁾ and intervention with ultra-early hemostatic therapy in the emergency setting could potentially improve outcome after ICH by arresting ongoing bleeding and minimizing hematoma growth. Apart from attempting to improve ICH outcome by limiting ICH volume with surgical intervention, treating both the perihematomal edema and ischemic penumbra surrounding an acute ICH are other potential therapeutic targets. Steroids have not proven beneficial for the acute treatment of ICH; the trials revealed that the 95% confidence intervals around the overall estimate of treatment effect encompassed clinically significant harm or benefit.⁹⁾ Nor have osmotic diuretics proven beneficial for the treatment of edema due to ICH in a randomized controlled design.¹⁸⁾ Thrombin is thought to be the most potent promoter of perihematomal

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edema, and thrombin inhibitor may counteract this, although they are as yet untested in a randomized controlled design.¹¹⁾

Recombinant factor VIIa (rFVIIa) act at sites of tissue and endothelial injury by binding to both exposed tissue factor and activated platelets, thereby generating thrombin, with a half life of two to three hours. rFVIIa is currently approved to treat bleeding in hemophilia patients with inhibitors to factors VIII or IX, and is approved in Europe for the treatment of factor VII deficiency and Glanzmann thrombasthnia. Furthermore, a large number of case series studies and anecdotal evidences, from patients with different bleeding conditions, have now shown that rFVIIa is actually a valuable general hemostatic agent. Although thromboembolic complications related to rFVIIa administration have occurred, with >400,000 doses administered for a growing number of clinical uses, the frequency of serious adverse events remains <1%.²⁰⁾

Herein, we reviewed of the published articles specifically addressing clinical trials of rFVIIa treatment for acute ICH and evaluate the safety and feasibility of it.

Materials and Methods

The literature used for this review was identified using the Medline database (PubMed, <http://www.ncbi.nlm.nih.gov/PubMed/>). A systematic review of all language literature was carried out. The following English keywords were used for the search: intracerebral hemorrhage and VII. This query yielded 137 results. In advanced search with human study and English in language, 104 results were identified, and title and abstract were carefully reviewed. Seven articles of these was a clinical trial of rFVIIa for acute ICH.^{6,8,10,14-16,21)} Full text articles were procured where possible.

After careful review of the seven articles, there was three randomized, controlled clinical trials and one cohort study. Three randomized, controlled clinical trials (Table 1) was Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators,^{6,14)} Europe/AustralAsia NovoSeven ICH Trial Investigators,¹⁵⁾ and US phase IIA trial.¹⁶⁾ One cohort study was Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study.¹⁰⁾ One article was focused on the intraventricular hemorrhage, not ICH.²¹⁾ Another one article was examined the cost-effectiveness of early treatment with rFVIIa for ICH.⁸⁾

In this review, we analyzed three randomized, controlled

clinical trials and one cohort study.

Results

Results of included studies are summarized on Table 2. Overall, treatment with rFVIIa within four hours after the onset of ICH limits the growth of the hematoma, reduces mortality, and improves functional outcomes at 90 days, despite a small increase in the frequency of thromboembolic adverse events.

Europe/AustralAsia Trial Investigators¹⁵⁾ reported that ICH volume change between baseline and 24 hours was not different and clinical outcome between baseline and 90 days was not significant. However, the method of randomization was not specified and there was imbalance in the baseline ICH volume between placebo and treatment groups.

US phase IIA trials¹⁶⁾ tested the safety of the rFVIIa treatment. 33 patients experienced 186 adverse events, which occurred with similar frequency in each patients and placebo groups. Ten thromboembolic adverse events were composed of one deep thrombosis, one cerebral infarction, one pulmonary embolism, and six ischemic electrocardiogram changes or cardiac enzyme elevation. There were no coagulopathy or dose-related increase in edema-to-ICH volume ratio. However, the method of randomization was not specified on this trial and the participants was too small.

Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study of Canadian Stroke Network¹⁰⁾ revealed that mortality at 90 days among potentially eligible patients was the same as for the placebo group in the rFVIIa trial (29% versus 29%; P=0.99). However, the absolute mortality benefit for rFVIIa patients compared with placebo patients in the trial was 11% (P=0.02). Death or severe disability at 3 months occurred in 69% of placebo patients and 53% of rFVIIa-treated patients (P=0.004). However, this cohort study had several limitations. The inclusion and exclusion criteria of the study were ambiguous and the data collection was retrospective. Values were sometimes missing or not aggressively pursued by attending physicians when deemed irrelevant to patient care.

Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators^{6,14)} was a randomized (4/block, sequentially numbered, identical-appearing containers), placebo-controlled, phase IIB, dose-ranging, 'proof-of-concept' study, regardless of funding by Novo Nordisk. One recent report of this clinical trial⁶⁾ revealed that hematoma growth is an independent

Table 1. Characteristics of included studies

Study	Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators ⁽¹⁴⁾
Methods	Parallel group, randomized (4/block, sequentially numbered, identical-appearing containers), double-blind, placebo-controlled, phase IIB, dose-ranging, 'proof-of-concept' study
Participants	Inclusion criteria: age 18 years or older; spontaneous ICH within three hours of onset Exclusion criteria: GCS 3 to 5; planned surgical evacuation of hematoma within 24 hours after admission; secondary ICH with known underlying cause; known use of oral anticoagulant agents; known thrombocytopenia; history of coagulopathy; acute sepsis; crush injury; DIC; pregnancy; preexisting disability (mRS >2 pre-ICH); symptomatic thrombotic or vaso-occlusive disease within 30 days before onset of ICH
Interventions	Recombinant activated factor VII (NovoSeven) at doses of (40 µg/kg, 80 µg/kg or 160 µg/kg) versus placebo, within one hour of baseline CT and no later than four hours after ICH onset
Outcomes	Percentage change in ICH volume on CT from baseline to 24 hours; mRS 4 to 6 or GOS-E 1 to 4 at 90 days; adverse events in hospital and serious adverse events until day 90
Study	Europe/AustralAsia NovoSeven ICH Trial Investigators ⁽¹⁵⁾
Methods	Parallel group, randomized, placebo-controlled, phase IIA dose escalation safety and feasibility study
Participants	Inclusion criteria: age 18 years or older; spontaneous ICH within three hours of onset Exclusion criteria: GCS 3 to 5; surgical hematoma evacuation planned or performed within 24 hours; secondary ICH with known underlying cause; known oral anticoagulant use; coagulopathy; thrombocytopenia; history or acute evidence of thrombotic, hypercoagulable, or vaso-occlusive disease; acute sepsis or crush injury; pregnancy; known malignant disease or alcohol abuse; preexisting disability (mRS >2 pre-ICH); known or suspected allergy to trial product; participation in another trial
Interventions	Recombinant activated factor VII (NovoSeven) at doses of (10 µg/kg, 20 µg/kg, 40 µg/kg, 80 µg/kg or 160 µg/kg) versus placebo, within one hour of baseline CT
Outcomes	Adverse events at days 1 to 5, 15 (or discharge), and 90; change in ICH +/- IVH volume on CT between baseline and 24 hours; ICH growth (>33% or 12.5 ml); drop of > 1 GCS point or increase of > 3 NIHSS points days 0 to 5; dead versus alive with little disability (Barthel index 95 to 100, GOS-E 8, mRS 0 to 2) versus alive and functionally independent (Barthel Index 60 to 100, GOS-E 5 to 8, mRS 0 to 3) at day 90
Study	US phase IIA trial ⁽¹⁶⁾
Methods	Parallel group, randomized, double-blind, placebo-controlled, phase IIA dose escalation safety study
Participants	Inclusion criteria: age 18 years or older; spontaneous ICH within three hours of onset Exclusion criteria: GCS 3 to 5; planned surgical evacuation of hematoma within 24 hours; secondary ICH with known underlying cause; known use of oral anticoagulant agents; known thrombocytopenia; history of coagulopathy; acute sepsis; crush injury; DIC; pregnancy; preexisting disability (mRS >2 pre-ICH); symptomatic thrombotic or vaso-occlusive disease within 30 days before onset of ICH, known or suspected allergy to trial product; participation in another trial
Interventions	Recombinant activated factor VII (NovoSeven) at doses of (5 µg/kg, 20 µg/kg, 40 µg/kg, or 80 µg/kg) versus placebo, within four hours of ICH onset
Outcomes	Serious adverse events; coagulation parameters; perihematomal edema; ICH volume ratio on CT; change in ICH volume from baseline on CT; change in 'neurological scores'
Study	Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study ⁽¹⁰⁾
Methods	Large, population-based cohort study
Participants	Inclusion criteria: age 18 years or older; spontaneous ICH within three hours of onset, drug administration within one hour of CT scan Exclusion criteria: History of thrombotic or vaso-occlusive disease; GCS 3 to 5; INR ≥1.4 or PTT > 35; Baseline mRS >2; Surgical drainage within 24 hours; ICH from aneurysm or vascular malformation; Platelet count ≤50000; coagulopathy, DIC or hypercoagulable state; pregnancy; crush injury; acute sepsis
Interventions	Recombinant activated factor VII (NovoSeven) at doses of (5 µg/kg, 20 µg/kg, 40 µg/kg, or 80 µg/kg) versus placebo, within one hour of ICH onset
Outcomes	Serious adverse events, Mortality at 90 days

GCS: Glasgow Coma Scale, ICH: intracerebral hemorrhage, DIC: Disseminated intravascular coagulation, mRS: modified Rankin scale, GOS-E: Extended Glasgow Outcome Scale, IVH: intraventricular hemorrhage, NIHSS: National Institutes of Health Stroke Scale, INR: international normalized ratio, PTT: partial thromboplastin time.

determinant of both mortality and functional outcome after ICH. And they concluded that attenuation of growth is an important therapeutic strategy. Another recent report¹⁴⁾ revealed that ultra-early hemostatic therapy with rFVIIa limited the growth of hemorrhage, reduced mortality, and improved functional outcomes after ICH. Hematoma volume increased more in 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 (P=0.01). Growth in the volume of ICH was reduced by 3.3 ml, 4.5 ml, and 5.8ml in

the three treatment groups, as compared with that in the placebo group (P=0.01). Mortality at 90% was 29% for patients who received placebo, as compared with 18% in the three rFVIIa groups combined (P=0.02). Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa-treated patients, as compared with 2% of those given placebo (P=0.12).

Discussion

rFVIIa is a vitamin-K-dependent glycoprotein with a

Table 2. Results of included studies

Study (reference)	Participants	Results
Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators ⁶⁾	Patient: 103 Placebo: 115	<ul style="list-style-type: none"> Percentage of hematoma growth, initial ICH volume, GCS, and IVH were all associated with increased mortality Percentage growth, initial ICH volume, GCS, and age predicted outcome. Gender, location, blood glucose, and blood pressure did not predict outcome.
Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators ¹⁴⁾	Patient: 399 40µg/kg: 108 80µg/kg: 92 160µg/kg: 103 Placebo: 96	<ul style="list-style-type: none"> Hematoma volume: increased more in the placebo group than in rFVIIa group Mean increase: 29% in placebo group, 16%, 14%, and 11% in groups given 40µg/kg, 80µg/kg or 160µg/kg of rFVIIa, respectively (P=0.01) Growth in volume of ICH: reduced by 3.3ml, 4.5ml, and 5.8ml in groups given 40µg/kg, 80µg/kg or 160µg/kg of rFVIIa, respectively (P=0.01) Mortality or Severe disability (mRS 4 to 6): 69% in placebo group, 55%, 49%, and 54% in groups given 40µg/kg, 80µg/kg or 160µg/kg of rFVIIa, respectively (P=0.004) Mortality at 90 days: 29% in placebo group, 18% in rFVIIa group (P= 0.02) Serious thromboembolic adverse events: 7% in rFVIIa group, 2% in placebo group (P=0.12)
Europe/AustralAsia NovoSeven ICH Trial Investigators ¹⁵⁾	Patient: 36 Placebo: 12	<ul style="list-style-type: none"> No significance of baseline ICH volume No difference of percent changes in ICH volume between baseline and 24 hours No difference of total hemorrhage volume (ICH+IVH) No significance of improvement between baseline and 90 days No noticeable difference in types, frequency, or severity of adverse events
US phase IIA trial ¹⁶⁾	Patient: 35 Placebo: 5	<ul style="list-style-type: none"> 33 patients experienced 186 adverse events, which occurred with similar frequency in each five groups 10 thromboembolic adverse events (1 DVT, 1 cerebral infarction, 2 pulmonary embolism, and 6 ischemic ECG changes or cardiac enzyme elevation), No consumption coagulopathy or dose-related increase in edema-to-ICH volume ratio
Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study ¹⁰⁾	Patient: 133 Placebo: 96	<ul style="list-style-type: none"> Mortality at 90 days: no significant difference between two groups (P=0.99) Absolute mortality benefit for rFVIIa patients versus placebo: 11% (P=0.02) Death or severe disability at 3 months (mRS 4 to 6 and e-GOS 1 to 4): 69% of placebo and 53% of rFVIIa-treated patients (P=0.004) Thromboembolic adverse events: 2% of placebo and 7% o rFVIIa patients (P=0.12)

GCS: Glasgow Coma Scale, ICH: intracerebral hemorrhage, IVH: intraventricular hemorrhage, rFVIIa: recombinant activated factor VII, mRS: modified Rankin scale, GOS-E: Extended Glasgow Outcome Scale, DVT: deep vein thrombosis, ECG: electrocardiogram

structure resembling human activated factor VII, manufactured using DNA biotechnology. Being a biotechnology product, it is not derived from human or animal plasma, thus eliminating the risk of human blood-transmitted disease. rFVIIa is usually administered by slow IV bolus injection and it has a predictable, well-characterized pharmacokinetic profile (half-life of 2.7 hours). rFVIIa may be acting locally at the site of tissue and vascular wall injury, by binding to exposed tissue factor to produce thrombin. Even though this amount of thrombin may not be sufficient to cause significant coagulation, it can accelerate platelet activation. The activated platelet accumulating at the site of injury will provide additional surface activate factor X to activated factor X to mediate additional thrombin production. This 'thrombin burst' will ultimately mediate the activation of factor XIII and the conversion of fibrinogen into fibrin, thus enhancing coagulation. In addition, rFVIIa activates thrombin-activatable fibrinolysis inhibitor, thus stabilizing the recently formed blood clot.⁵⁽²²⁾ Moreover, there is increasing evidence showing that rFVIIa, in high concentration, can directly activate factor X on activated platelets, monocytes, or phospholipid vesicles independently of tissue factor.¹³⁾

Although rFVIIa has a good safety profile in patients with hemophilia and other bleeding disorders, experience with rFVIIa in older, monocoagulopathic patients with risk factors for cardiovascular or cerebrovascular disease was considered limited. Accordingly, the investigator's main objective was to focus on treatment-related thrombo-embolic or coagulation-related adverse events. On current situations, randomized and controlled clinical trials (RCT) of this potential hemostatic agent for acute ICH is warranted. The effectiveness and safety of hemostatic drug therapies, compared against placebo or open control, in RCT should be proven the following hypotheses: 1) Do hemostatic drug therapies reduce the risk of a poor clinical outcome after ICH? 2) Are hemostatic drug therapies safe in the treatment of acute ICH? 3) Do hemostatic drug therapies reduce ICH expansion in the first 1 or 2 days?

One review of RCT of hemostatic drugs for acute ICH in published or unpublished databases identified four RCTs (ATICH, rFVIIa EurAsia IIA, rFVIIa IIB, and rFVIIa USA IIA).²³⁾ One of the four RCTs was a phase II RCT of intravenous epsilon-aminocaproic acid (EACA) compared against supportive treatment alone, started within three hours of PICH onset in adults (ATICH). ATICH stopped after the

enrolment of three participants; because recruitment had been slow and the investigators decided that the rationale for rFVIIa was better than EACA, they terminated ATICH and participated in rFVIIa USA IIA and rFVIIa IIB instead. The other three included studies were phase II RCTs, all funded and conducted by Novo Nordisk, comparing the use of various doses of intravenous rFVIIa against placebo, started within four hours of ICH onset in adult. There are ongoing RCTs of rFVIIa: one is a multinational phase III RCT intending to recruit 675 participants and compare two doses of rFVIIa with placebo [rFVIIa III (FAST)], and the other is a phase II RCT intending to recruit 90 Japanese participants and compare rFVIIa with placebo (rFVIIa Japan IIA).

The safety of rFVIIa is surprisingly good considering its mechanism of action, which one might expect to provoke both thromboembolism and worsening of cerebral edema around ICH. A recent summary of thromboembolic complications related to the use of rFVIIa which were reported to the USA Food and Drug Administration's system of passive surveillance of RCTs and everyday clinical practice found that 14% of them occurred during use of rFVIIa for ICH, and over half of thromboembolic events attributed to rFVIIa were due to arterial thromboembolism.¹⁹⁾ The median time from rFVIIa treatment to the event was 24 hours, meaning that half of the events occurred more than 24 hours after rFVIIa treatment.¹⁹⁾ In this review, the incidence of the thromboembolic complications was 7%. There appeared to be a two-fold increase in thromboembolic serious adverse events in the rFVIIa group than in the placebo one. This discrepancy could be explained by underestimation of the hazards of rFVIIa use in all comers with acute ICH, because of the exclusion of adults with a recent history of thromboembolic or vaso-occlusive disease half-way through the largest RCT (rFVIIa IIB).

Most of RCTs did not explore the effect of rFVIIa in pre-specified subgroups possessing any or all of the other well-recognized predictors of PICH outcome (e.g., hematoma size and location, intraventricular extension of ICH, conscious level on admission).²¹⁾ Blood pressure may also be a determinant of outcome, but blood pressure data were not provided over time in any of the studies, nor were they used to explore the effect of blood pressure on the efficacy of rFVIIa.⁴⁾ Standardization of these predictors between placebo group and patient group should be warranted.

The costs of rFVIIa cannot be ignored. No economic analyses have been performed specifically for treatments of ICH. Recently, cost-effectiveness of rFVIIa in the treatment of ICH was analyzed.⁸⁾ They concluded that treatment of ICH with rFVIIa 40 $\mu\text{g}/\text{kg}$ and 160 $\mu\text{g}/\text{kg}$ appeared to be cost-effective. At the 80 $\mu\text{g}/\text{kg}$ dose, rFVIIa was not only cost-effective, but cost saving. Before rFVIIa is recommended for widespread use, its cost-effectiveness must be assessed.

Conclusions

Hematoma growth is one of the independent determinants of neurological and functional outcomes after ICH. Attenuation of growth is an important therapeutic strategy. Hemostatic therapeutic intervention, given ultra-early in the course of ICH, may thus improve clinical outcomes by arresting ongoing bleeding and limiting in turn the size of the hematoma. rFVIIa is a hemostatic drug approved to treat bleeding in hemophilia or other coagulopathy; it has also been reported to arrest bleeding in nonhemophilic cases.

Overall, treatment with rFVIIa within four hours after the onset of ICH limits the growth of the hematoma, reduces mortality, and improves functional outcomes at 90 days, despite a small increase in the frequency of thromboembolic adverse events. More standardized, randomized, and controlled clinical trials are nevertheless warranted. Additionally, its cost-effectiveness must be assessed before rFVIIa is recommended for widespread use.

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