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The Risk of Thromboembolic Events in the Use of Recombinant Activated Factor VII to Control Bleeding in Nonhemophiliac Patients With Spontaneous Intracerebral Hemorrhages: A Systematic Review

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Abstract
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Methods: A systematic review of the past 6 years of English-language published literature was conducted using MEDLINE, CINAHL, and a multi-resource EBM database using keywords rFVIIa, thromboembolic events, intracerebral hemorrhage and subordinate headings. Articles that examined safety with the use of rFVIIa in non hemophiliac patients to manage spontaneous intracerebral hemorrhages were selected. Five studies were analyzed for quality and noteworthy results.

Results: These studies have demonstrated that the risk of thromboembolic events at low doses, <80 μg/kg of rFVIIa, is comparable to that of a placebo. Simultaneously, they have demonstrated that with higher doses, ≥ 80 μg/kg of rFVIIa, in high-risk patients, occurrence of thromboembolic events increases substantially.

Conclusion: These findings suggest that it would be appropriate at this time to pursue further investigations comparing the safety and efficacy of rFVIIa with that of Vitamin K and FFP in well-designed, randomized controlled trials in addition to studies that include patients on oral anticoagulant therapy.

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rFVIIa, thromboembolic events, arterial/venous thromboembolism, spontaneous intracerebral hemorrhage

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The Risk of Thromboembolic Events in the Use of Recombinant Activated Factor VII to Control Bleeding in Nonhemophiliac Patients With Spontaneous Intracerebral Hemorrhages: A Systematic Review

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
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For the Masters of Science Degree, August 14, 2010

Faculty Advisor: Rob Rosenow, PharmD, OD
Clinical Graduate Project Coordinators: Annjanette Sommers, MS, PAC, and Rob Rosenow, PharmD, OD
Biography

Jeanette came to Pacific University from beautiful Salt Lake City Utah, where she worked as an Athletic Trainer for Juan Diego Catholic High School, the University of Utah Men’s Lacrosse Team and a variety of other athletic organizations.

In addition to the more than 350 athletes in her care, at Juan Diego, Jeanette organized and taught a training program for student athletic trainers, many of whom have gone on to medical schools, nursing programs and physical therapy programs. After years of diagnosing and rehabilitating thousands of athletic injuries, intellectual curiosity and a desire to broaden her skills and knowledge led her to into the Physician Assistant Program at Pacific University.
Abstract

Background: Intracerebral hemorrhage is a devastating event that may occur spontaneously or as the result of a trauma. Anticoagulation-related hemorrhages are increasing with the growing number of patients on oral anticoagulation therapy. Off label use of recombinant activated factor VIIa (rFVIIa) is effective in lowering the INR, thus rapidly decreasing the risk of hematoma expansion and allowing for faster response when emergent surgery is indicated. rFVIIa, currently approved by the FDA for use in hemophiliac patients only, has been demonstrated to quickly reverse the effects of anticoagulation therapy, with the additional benefit of reducing further hematoma growth. However, it’s not without complications. rFVIIa has been reported as increasing the occurrence of post treatment thromboembolic events. This review will assess published studies that have evaluated the safety of rFVIIa in non-hemophiliac patients presenting with acute spontaneous intracerebral hemorrhages.

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Results: These studies have demonstrated that the risk of thromboembolic events at low doses, <80 µg/kg of rFVIIa, is comparable to that of a placebo. Simultaneously, they have demonstrated that with higher doses, ≥ 80 µg/kg of rFVIIa, in high-risk patients, occurrence of thromboembolic events increases substantially.

Conclusion: These findings suggest that it would be appropriate at this time to pursue further investigations comparing the safety and efficacy of rFVIIa with that of Vitamin K and FFP in well-designed, randomized controlled trials in addition to studies that include patients on oral anticoagulant therapy.

Keywords: rFVIIa, thromboembolic events, arterial/venous thromboembolism, spontaneous intracerebral hemorrhage,
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To my sweet husband Matt: Without your sacrifices, support and encouragement, none of this would have been possible. Thank you for being Mr. Mom, and for putting your dreams on the back burner to help me achieve mine.

To my kiddos Ian and Grady: Mommy loves you very much and I appreciate your being so flexible and patient with my road warrior year, crazy hours and grumpy mommy moments. Mommy is home for good!

To my Mom who came to the rescue when we needed an extra hand: Thanks for your sacrifices. I smile because you’re my mom. I laugh because there’s nothing you can do about it.

To my amazing friends and family: Without your support and patience, late night phone calls, places to crash when on rotation, proofing of text and general hand holding, we would never have made it. Thank you!
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Table 1: Summary Matrix of Studies Utilized for This Review

List of Abbreviations

rFVIIa ......................................................... Recombinant Activated Factor VIIa
ICH.......................................................... Intracerebral hemorrhage
sICH.......................................................... Spontaneous Intracerebral hemorrhage
TE.............................................................. Thromboembolic event
INR........................................................... International Normalized Ratio
µg/kg ........................................................ microgram per kilogram
SAE........................................................... Serious adverse event
MI............................................................. Myocardial Infarction
DVT.......................................................... Deep Vein Thrombosis
PE............................................................. Pulmonary Embolism
The Risk of Thromboembolic Events in the Use of Recombinant Activated Factor VII to Control Bleeding in Nonhemophiliac Patients With Spontaneous Intracerebral Hemorrhages: A Systematic Review

BACKGROUND

Intracerebral hemorrhage (ICH) is the deadliest, most disabling and least treatable form of stroke. Approximately 40 percent of patients die within one month of ICH onset and 66% of those who do survive never regain functional independence. Patients on oral anticoagulation therapy are at an increased risk for ICH. However, prompt treatment can prevent acute bleeds from becoming chronic disabilities that, in turn, negatively affect functional independence. When an ICH occurs in patients who use an anticoagulation therapy, the prompt reversal of the elevated international normalized ratio (INR), as well as an effective therapy, is required to stop bleeding and prevent hematoma expansion. Additionally, when surgical intervention is mandated, fast reversal of anticoagulation therapy becomes vital for patient survival and positive clinical outcomes.

Current practice includes the utilization of vitamin K and/or fresh frozen plasma (FFP) to reverse anticoagulation. Unfortunately, these agents are slow-acting and potentially risky, as patients may suffer from allergic or transfusion reactions. With so many ICH patients presenting with a history of cardiovascular disease, the additional volume of FFP could result in congestive heart failure, volume overload, or lung damage. An added concern to the use of FFP lies in the fact that while it is has been demonstrated to be effective in reversing the INR; it does not control the growth of the hematoma and is thus not an effective therapy.
Conversely, recombinant activated Factor VIIa (rFVIIa), currently approved by the FDA for use in hemophiliac patients only, has been demonstrated to quickly reverse the effects of anticoagulation therapy, with the additional benefit of reducing further hematoma growth.\textsuperscript{14, 15} Its use has demonstrated better clinical outcomes, allowed for more rapid surgical response,\textsuperscript{11} and has proven to be more cost effective\textsuperscript{16} than vitamin K or fresh frozen plasma alone or in combination. It is not, however, without potential risks, as a small series of studies performed on the effectiveness of rFVIIa has also revealed an increased risk of thromboembolic events secondary to the hemostatic nature of the agent.\textsuperscript{14, 15, 17, 18}

This review will assess published studies that have evaluated the safety of rFVIIa in non-hemophiliac patients presenting with acute spontaneous intracerebral hemorrhages.

METHODS

A search of the literature was performed using Medline, CINAHL, and a multi-resource EBM database. Search terms included: recombinant proteins, rFVIIa, thromboembolic events, blood coagulation, thrombosis, complications, intracerebral hemorrhage, arterial/venous thromboembolism, safety, adverse events, toxicity and warfarin.

Included in this review are cohort studies and randomized placebo-controlled studies that evaluated the safety of rFVIIa in non-hemophiliac patients with spontaneous intracerebral bleeding. Studies were limited to those published from 2004-2010 in English text.
The search term and study results were then compiled and analyzed. Studies that did not fit the criteria were considered for the background and discussion portion of this review.

RESULTS

A total of five studies were published between 2004 and 2010 that met the criteria for assessing the risk of thromboembolic events in spontaneous intracerebral hemorrhage (sICH) patients receiving rFVIIa therapy. (Table 1) These articles addressed the questions relating to the number of thromboembolic events (TEs), the risk factors and the dosing impacts of rFVIIa in comparison to placebo. The number of arterial TEs and the number of venous TEs were noted in all studies as were serious adverse events (SAEs) i.e., MIs and cerebral infarctions. The sample sizes ranged from 48 to 841 with all studies being randomized controlled trials.

The Diringer et al studies\textsuperscript{14, 19} have been in the foreground for research on this topic, presenting two separate trials; one in 2008\textsuperscript{14} and one in 2010 (FAST Trial).\textsuperscript{19} The 2008 study, involving 486 patients, randomized patients into investigation groups including a placebo group, patients who received a single dose of 5 µg/kg – 80 µg/kg rFVIIa , and patients who received a single dose of 120 µg/kg-160 µg/kg rFVIIa. This study excluded high-risk patients with any history of thromboembolic events.\textsuperscript{14}

The study concluded that there was no overall increase in occurrence of total TEs in rFVIIa-treated patients; however, there were more arterial TEs in the high dose group (120 to 160 µg/kg) compared with placebo (5.4% versus 1.7%; $P=0.13$).\textsuperscript{14}

SAEs recorded were specific to arterial events. Myocardial ischemia ($n=9$) and ischemic stroke ($n=9$) occurred in 5.4% of the population receiving rFVIIa vs. 1.7% of
the population receiving placebo. (P=0.13) A regression analysis identified high doses (120 to 160 µg/kg) of rFVIIa as the only factor associated with arterial TEs (OR=6.75; P=0.02).\textsuperscript{14}

Another Diringer et al study was The FAST Trial (Factor Seven for Acute Hemorrhagic Stroke of 2010).\textsuperscript{19} It was a multicenter, randomized, placebo-controlled trial that placed 841 patients presenting within 3 hours of sICH into groups receiving either 20 µg/kg of rFVIIa, 80 µg/kg of rFVIIa, or placebo to define the risk factors and frequency of thromboembolic events when treating sICH with rFVIIa. Patients were excluded from the FAST Trial if they had a glasgow score <5, planned surgery, had received oral anticoagulants, suffered from sepsis, crush injury, pre-existing disability, were pregnant or had a history of TEs within the last 30 days. Risk factors identified by the study included:

a) age >65 years, (OR 1.14/5years; 95% CI 1.03-1.27; P=0.012),

b) prior use of antiplatelet agents, (OR = 1.83; 95% CI 1.04-3.20; P= 0.035),

c) signs of cardiac or cerebral ischemia at presentation, (OR= 4.19; 95% CI 1.46-10.54; P= 0.010), and

d) receiving 80 µg/kg rFVIIa (OR= 2.14; 95% CI 1.09-4.41; P= 0.031).

A total of 225 events were noted: 78 arterial and 47 venous. Venous events were similar across all groups: 17 (6%) placebo, 15 (5%) in 20 µg/kg rFVIIa, and 15 (5%) in 80 µg/kg rFVIIa (P=0.45). The arterial events revealed a marked difference between the placebo and 20 µg/kg groups, as compared to the 80 µg/kg group. In the placebo group, 49 (27%) arterial events occurred, with 47 (26%) in the 20µg/kg group, and 82 (46%) in the 80 µg/kg group (P=0.04).\textsuperscript{19}
Two events were defined within arterial TEs as serious adverse events (SAE): MIs and cerebral infarcts. In the placebo group, 41 (15%) MIs occurred, while the 20 µg/kg group reported 36 (13%) and the 80 µg/kg group reported 64 (22%) (P=0.04). In contrast, cerebral infarctions, possibly related to the study drug, occurred in 7, 5, and 8 patients in the placebo, 20 µg/kg, and 80 µg/kg groups, respectively.¹⁹

The FAST Trial concluded that higher doses of rFVIIa administered in a high-risk population are, in fact, associated with a slight increased risk of what were typically minor cardiac events. They also concluded that this increased risk may be outweighed by the proven effectiveness of rFVIIa in slowing bleeding.¹⁹

Mayer et al conducted three separate studies: Mayer et al January 2005,¹⁸ Mayer et al February 2005¹⁵ and Mayer et al 2008.¹⁷ His later two trials were held in conjunction with the Diringer et al¹⁴ trial of 2008 and the FAST trial¹⁹ published in 2010.

In Mayer et al¹⁸ January 2005, a 48-patient randomized controlled, dose escalation trial found no difference in the occurrence of TEs when comparing all dosing groups with the placebo-controlled group.¹⁸

They listed 6 reported adverse events that were possibly related to rFVIIa but these were limited to rash, headache, vomiting, fever, ECG T-wave inversion, and 2 cases of DVT. Ten patients reported 12 SAEs including neurological deterioration (n=6), unstable angina, pneumonia, urosepsis, dyspnea, av-malformation (n=1 each) and DVT (n=2). The study states that no cases of myocardial ischemia or consumption coagulopathy were found.¹⁸

In the Mayer et al¹⁵ study of February 2005, 399 patients presenting within <3 hours post sICH were randomized into rFVIIa dosage levels of 40 µg/kg, 80 µg/kg, 160
µg/kg and a placebo group. It was found that arterial adverse events in all patient groups receiving rFVIIa were increased 5% vs. 0% increase in the placebo control (p= 0.01), and an increased number of total serious adverse events, mainly myocardial or cerebral infarctions, in all patient groups receiving rFVIIa over those receiving placebo: 7% vs. 2% (P= 0.12).\textsuperscript{15} Mayer also noted, however, that there appeared to be an improvement in neurological outcomes that had not been reported in other studies.\textsuperscript{15}

In the most recent Mayer et al\textsuperscript{17} trial (2008), 841 patients were followed. Patients were excluded if the ICH was secondary to trauma, if there was a known cause of the ICH, if the patients were taking oral anticoagulants, had a history of a thromboembolic event, any coagulopathy disorder, sepsis, or pregnancy. Clinical outcomes were as follows: 21 (8%) arterial TEs occurred in the placebo group, 24 (9%) arterial TEs in the 20 µg/kg group, and 31 (10%) arterial TEs occurred in the 80 µg/kg group. Myocardial infarctions occurred in 8 (3%) of the placebo group, 11 (4%) of the 20 µg/kg group, with 25 (8%) occurring in the 80 µg/kg group. The percentage of patients suffering cerebral infarctions were 1%, 1% and 4% of patients in the placebo, 20 µg/kg and 80 µg/kg groups respectively. The occurrence of venous events was similar in all groups. (Table 1) Results of the trial demonstrated that arterial thromboembolic events were more frequent in the group receiving the 80 µg/kg dose vs. the placebo group (9% vs. 4% P=0.04).\textsuperscript{17}

DISCUSSION

Intracerebral hemorrhage is a devastating event that may occur spontaneously or as the result of a trauma. Anticoagulation-related hemorrhages are increasing with the growing number of patients on oral anticoagulation therapy.\textsuperscript{2} The use of rFVIIa is
effective in lowering the INR, thus rapidly decreasing the risk of hematoma expansion and allowing for faster response when emergent surgery is indicated. It has also shown to help in minimizing the likelihood of a poor long-term outcome.\textsuperscript{2, 5, 13}

However, the currently available published studies are incomplete in several respects. Many questions are left unanswered and concerns have not been addressed about the wisdom of assuming that rFVIIa usage is devoid of negative potential risks. In the studies that have been reviewed, only the FAST trial\textsuperscript{19} included patients that had a thromboembolic event greater than 30 days prior to onset of sICH symptoms and none of them included patients who were currently receiving anticoagulation therapy.\textsuperscript{19} While on the face each study appears to be reporting about different population groups, the patient numbers in the groups are quite similar. This raises questions as to whether or not they were actually studying the same patient populations. Admittedly, the patient acceptance criteria was slightly different, but the total patient numbers are uncomfortably similar as were the overall results.

The available studies have other significant limitations or factors that should be addressed. All studies were performed by the same group of investigators over a period of six years. Each of the authors either was employed by, consulted for, or had received funds from Novo-Nordisc, the manufacturer of the rFVIIa product being used. While not meant to disparage either the investigators or their results, there are no randomized controlled trials, specifically for sICH, conducted by completely independent investigative teams.

Earlier studies eliminated high-risk patients which may have skewed practical application.\textsuperscript{14, 15, 17, 18} The only study that kept higher-risk patients eligible was the
The FAST trial exclusion criteria were identical to that of the previous studies, however, they excluded patients with a thromboembolic event only if said event had occurred within 30 days prior to the ICH. Furthermore, later studies were composite studies of early ones with slight changes to inclusion and exclusion protocols. The Mayer et al 2008 study was conducted specifically to be included in the FAST trial. However, high-risk patients were eliminated from their trial, with the possible net effect that the results appear more promising than they would be in reality.

No trial reviewed included patients that would appear to be the most at risk for sICH, namely those who are taking oral anticoagulants. One study, the Robinson study, did include patients taking oral anticoagulants. It was not included in this review because it was a retrospective cohort study that did not have a well-defined control group. However, Robinson’s trial found that rFVIIa carried a slightly higher risk of thromboembolic complications, though most were minor DVTs without embolism. The study concluded that the risk of thromboembolic events was not higher in anticoagulated populations than in populations reported in the FAST trial, suggesting that it would be safe to compare rFVIIa with FFP in a randomized controlled trial.

Perhaps one of the most significant challenges with each of the studies is that of the placebo group. Each study compared the rFVIIa results to placebo results while not specifying whether placebo was no treatment or whether it was current protocol of Vitamin K and/or fresh frozen plasma (FFP) making them difficult to replicate. No study reviewed overtly compared the three protocol approaches.

On a positive note, the usage of rFVIIa does appear to offer an overall positive protocol choice for the treatment of ICEs, even with the noted adverse events. For
example, the FAST trial\textsuperscript{19} demonstrated more adverse events related to higher doses in higher-risk populations than the other four trials reported. An increase in thrombotic events was also reported, specifically a relative increase in myocardial events in those receiving rFVIIa.\textsuperscript{19}

Surprisingly, the incidence of venous thromboembolic events was consistent among comparison groups in all studies,\textsuperscript{14, 15, 17-19} raising the question of what specifically is occurring physiologically to focus events arterially. It has been considered that age and antiplatelet therapy use were associated with the increased risk of arterial events. These patient populations are more likely to have ulcerated or ruptured atheromatous plaques resulting thromboses.\textsuperscript{7} Still, the overall risk appears to be relatively small when compared to the effectiveness at slowing bleeding.\textsuperscript{19}

Even accounting for potential flaws, the aforementioned studies have established that there is a slight risk of a thromboembolic event, especially at higher doses of rFVIIa or when risk factor are present, as compared to an unnamed placebo. Extensive and long-term studies that compare rFVIIa usage to current practices, such as the use of Vitamin K and FFP, need to be conducted, both in general and high-risk patient populations.

CONCLUSION

The use of recombinant factor VIIa, although currently approved by the FDA for use in hemophiliac patients only, reverses the effects of oral anitcoagulants more expeditiously, allows for rapid surgical response,\textsuperscript{8-10} demonstrates better clinical outcomes,\textsuperscript{2-6, 11, 21} and is more cost effective when compared to placebo, vitamin K and FFP.\textsuperscript{16} Questions of safety, specifically the perceived increased risk of thromboembolic events, have also been the topic of many studies over the last six years.
These studies have demonstrated that the risk of thromboembolic events at low
doses of rFVIIa is comparable to that of a placebo.\textsuperscript{14, 15, 17, 19}

Simultaneously, these studies have also demonstrated that at higher doses, the risk of
thromboembolic events increases substantially.\textsuperscript{19}

In total, these findings suggest that it would be appropriate at this time to pursue
further investigations comparing the safety and efficacy of rFVIIa with that of Vitamin K
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patients on oral anticoagulant therapy.
REFERENCE


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<td>Diringer M. et al, Thromboembolic Events with Recombinant Activated Factor VII in Spontaneous Intracerebral Hemorrhage, Stroke, 2010</td>
<td>841 Pts presenting within &lt;3 hours post spontaneous intracerebral hemorrhage</td>
<td>20 or 80 µg/kg rFVIIa vs. placebo</td>
<td>47 arterial TEs w/20 µg/kg&lt;br&gt;82 arterial TEs w/80 µg/kg&lt;br&gt;49 arterial TEs w/placebo&lt;br&gt;Venous events were similar in all groups</td>
<td>FAST/RCT</td>
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<td>Authors either received consulting fees or were employees of Novo Nordisk</td>
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<td>Mayer S. et al, Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage</td>
<td>841 Pts presenting within &lt;4 hours post spontaneous intracerebral hemorrhage</td>
<td>20 or 80 µg/kg rFVIIa vs. placebo</td>
<td>21 arterial TEs w/placebo&lt;br&gt;24 arterial TEs w/20 µg/kg&lt;br&gt;31 arterial TEs w/80 µg/kg&lt;br&gt;Venous events were similar in all groups</td>
<td>RCT</td>
<td>4</td>
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<td>Diringer M. et al, Risk of Thromboembolic Events in Controlled Trials of rFVIIa in Spontaneous Intracerebral Hemorrhage, Stroke, 2008</td>
<td>486 pts presenting within &lt;3 hours post spontaneous intracerebral hemorrhage</td>
<td>Single dose rFVIIa (5-160 µg/kg) vs. placebo</td>
<td>4 arterial TEs w/5-40 µg/kg&lt;br&gt;3 arterial TEs w/80 µg/kg&lt;br&gt;10 arterial TEs w/&gt;120 µg/kg&lt;br&gt;2 arterial TEs w/placebo&lt;br&gt;Venous events similar in all groups</td>
<td>RCT</td>
<td>5</td>
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<td>Mayer S. et al, Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage, New England Journal of Medicine, 2005</td>
<td>399 Pts presenting within &lt;3 hours post spontaneous intracerebral hemorrhage</td>
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<td>Improved neurological outcomes in patients receiving rFVIIa. Authors received compensation for Novo Nordisk</td>
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<td>Mayer S. et al, Safety and Feasibility of Recombinant Factor VIIa for Acute Intracerebral Hemorrhage, Stroke, 2005</td>
<td>48 Pts presenting within &lt;3 hours post spontaneous intracerebral hemorrhage</td>
<td>10, 20, 40, 80, 120, and 160 µg/kg rFVIIa vs. placebo</td>
<td>No difference noted in SAE or TE</td>
<td>Dose Escalation, RCT, dbl blinded trial</td>
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<td>No neurological change demonstrated in pts, study population too small to be effective.</td>
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