Use of Activated Recombinant Factor VII in Severe Bleeding – Evidence for Efficacy and Safety in Trauma, Postpartum Hemorrhage, Cardiac Surgery, and Gastrointestinal Bleeding

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Keywords
Factor VII · Coagulation factors · Bleeding complication

Summary
Background: Uncontrolled bleeding continues to be a major cause of mortality in trauma, cardiac surgery, postpartum hemorrhage and liver failure. The aim of this paper is to assess the evidence supporting the efficacy of activated recombinant factor VII (rFVIIa) administration in these settings.

Methods: Electronic literature search.

Results: Numerous retrospective trials have mostly shown a decrease in blood transfusion requirements with no increase in thromboembolic events (TEE), but major limitations in trial design make generalization difficult. In most retrospective reports rFVIIa has been administered as a last-ditch attempt to control bleeding, when acidosis, hypothermia and coagulation factor depletion may not allow optimal rFVIIa effect. Prospective randomized controlled trials have not shown any effect of rFVIIa on mortality or TEE, although some have shown a reduction in RBC requirement.

Conclusion: Stipulated transfusion protocols in prospective trials have reduced anticipated mortality among controls and make future trials for mortality effect unlikely in view of large sample size requirements. Establishment of these protocols and rapid hemostasis are likely to have greater benefits than administration of a single agent.

Schlüsselwörter
Factor VII · Gerinnungsfaktoren · Blutungskomplikation

Zusammenfassung
Hintergrund: Unkontrollierte Blutungen sind nach wie vor ein großes Problem während Trauma, Herzchirurgie, Post-partum-Hämorrhagie und Leberversagen. Das Ziel der vorliegenden Arbeit ist es, die Evidenz für die Effektivität der Verabreichung von aktiviertem rekombinantem Faktor VII (rFVIIa) innerhalb dieser Settings zu bestimmen.

Methoden: Elektronische Literatursuche.


Schlussfolgerung: Festgeschriebene Transfusionsprotokolle in prospektiven Studien haben die erwartete Mortalität in der Kontrollgruppe reduziert und machen zukünftige Studien des Mortalitätseffekts im Hinblick auf die hohe Stichprobengröße unwahrscheinlich. Eine Etablierung derartiger Protokolle und eine schnelle Hämostase bewirken vermutlich einen größeren Benefit als die Verabreichung eines einzelnen Agens.
Introduction

Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) was initially developed for the treatment of hemophilia with coagulation factor inhibitors. It has since also been approved for the treatment of acquired hemophilia and other inherited bleeding diathesis such as Glanzmann thrombasthenia and factor VII deficiency. Its success in these clinical conditions as well as anecdotal reports of dramatic improvements when used as a ‘last ditch’ attempt in the treatment of coagulopathy has resulted in increased usage across various clinical scenarios. In the treatment of severe bleeding in non-hemophiliacs its off-label use persists despite the lack of high-level evidence for efficacy. The aim of this report is to review the evidence for safety and efficacy of rFVIIa usage for severe hemorrhage in the emergency setting. In particular we will review its use in severe trauma, gastrointestinal bleeding associated with liver failure, cardiac surgery and postpartum hemorrhage (PPH). Its use in bleeding prophylaxis and intracranial hemorrhage, while well reported, is beyond the scope of this review.

Mode of Action

rFVIIa appears to act via two separate pathways [1, 2]. The first is a tissue factor(TF)-dependent mechanism in which vascular damage leads to the TF availability. This leads to the formation of a TF-activated factor VII complex on activated platelets which in turn activates factor X and leads to the conversion of prothrombin to thrombin. At pharmacological levels, which is estimated at over 100 times the level of normal circulated FVII, rFVIIa has the additional effect of a TF-independent mechanism which activates factor X in the absence of TF. This pathway explains the ability of rFVIIa to bypass factor VIII and IX in hemophiliacs. rFVIIa at pharmacological levels may also down-regulate the fibrinolytic system through the production of thrombin-activatable fibrinolysis inhibitor (TAFI), a potentially pertinent action in severe trauma given the role of hyperfibrinolysis in acute coagulopathy of trauma (ACOT) [3].

Its mode of action [reviewed in 1, 2, 4] makes rFVIIa appealing as a systemic procoagulant in the treatment of refractory bleeding as TF availability and activated platelets are only available at active bleeding sites and should limit the danger thromboembolic events (TEE). Nevertheless the pharmacological doses involved and the background of elevated TEE risk in patients with severe trauma, PPH and cardiac and liver disease justifies arterial and venous thrombosis as the main focus of studies assessing the safety of rFVIIa use in these clinical settings. O’Connell et al. [5], reporting the incidence of TEEs in the Adverse Events Reporting System (AERS) of the US Food and Drug Administration (FDA), records 185 arterial and venous TEEs in 168 patients, most of whom received rFVIIa for ongoing bleeding. In the 102 reports in which a causality assessment for TEE was available, 81 (79%) were thought to have a probable or possible causal relationship to rFVIIa. This is disconcertingly high rate of TEEs is worrisome especially as the AERS is an open reporting system that consists mainly of voluntary clinician reports and is likely to underreport actual incidence. Nevertheless the lack of a control group and information of baseline risk and concomitant medications hinders any assessment of causality to rFVIIa administration. Where controls are available, a more accurate evaluation of TEEs contributable to rFVIIa dosing is possible. In a review of TEEs in 35 randomized clinical trials for a wide spectrum of clinical scenarios in non-hemophiliacs, subjects administered with rFVIIa in various doses were noted to have in increased risk of arterial TEEs (5.5 vs 3.2%; p = 0.003), most commonly manifesting as coronary events. This increased risk was especially marked in subjects over 65 years of age [6].

The optimal dose and timing of rFVIIa in bleeding non-hemophiliacs has not been determined. Several in vitro and in vivo studies have demonstrated a decrease in rFVIIa activity with increasing acidosis at pH 7.2 and below and a smaller effect of hypothermia [7]. A review of rFVIIa clearance in humans from pharmacokinetic profiling across a variety of clinical uses has also demonstrated rapid clearance with ongoing exsanguinations [8]. These studies support the earlier use of rFVIIa in the course of resuscitation of the bleeding patient and the need for repeated dosing, an approach which has shown to be beneficial in the military setting. Both these factors suggest that retrospective series which assess the use of rFVIIa and mostly consist of last-ditch attempts to secure hemostasis when all other conventional therapies have failed, may not represent optimal rFVIIa performance.

rFVIIa in Severe Trauma

Trauma is the leading cause of death under the age of 45 years in developed countries. Of these, uncontrolled bleeding is the leading cause of preventable in-hospital death. Bleeding from trauma results from two mechanisms which require concurrent therapeutic strategies. ‘Surgical’ bleeding requires expedient control either by rapid surgical or interventional radiology techniques. In additional to rapid hemostasis, bleeding from trauma-related injuries also requires systemic replacement of hemostatic factors. The pathophysiology of trauma-related coagulopathy is multifactorial and has been extensively studied. A useful working model of a ‘bloody vicious triad’ described by Moore et al. [9] illustrates that a combination of the primary injury as well of secondary insults leads to dilution of coagulation products, acidosis, and hypothermia that further compromises clot formation leading to further blood loss. More recently an acute coagulopathy of trauma (ACOT) mediated via hyperfibrinolysis has been described
<table>
<thead>
<tr>
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<th>Inclusion criteria</th>
<th>Study size</th>
<th>rFVIIa dose</th>
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<tr>
<td>Cameron [45]</td>
<td>registry</td>
<td>use of rFVIIa in trauma patients in Australia and New Zealand</td>
<td>108</td>
<td>90 (78–105) μg/kg</td>
<td>–</td>
<td>clinician assessment of bleeding control, blood transfusions before and after rFVIIa dosing</td>
<td>significant decrease in bleeding by 59%; significant reduction in blood transfusion requirements</td>
<td>3 % TEE</td>
<td>wide variation in timing of rFVIIa dosing and massive transfusion practices</td>
</tr>
<tr>
<td>Spinella [14]</td>
<td>registry</td>
<td>combat casualties with ISS&gt;16 receiving &gt;10 units RBC/24 h</td>
<td>49 study patients and 75 controls</td>
<td>1.20 μg/kg</td>
<td>within 2 h of admission</td>
<td>24-hour and 30-day mortality and TEE</td>
<td>significant decrease in 24-hour (14% vs. 35%; p = 0.01) and 30-day mortality (31% vs. 51%; p = 0.03)</td>
<td>no increase in TEE</td>
<td>early administration of rFVIIa decreases mortality in combat casualties with massive transfusions</td>
</tr>
<tr>
<td>Geeraedts Jr [46]</td>
<td>retrospective</td>
<td>life-threatening uncontrolled bleeding due to blunt trauma</td>
<td>8</td>
<td>55–90 μg/kg</td>
<td>9–38</td>
<td>blood product requirement, bleeding control</td>
<td>all cases obtained hemostasis, reduction in blood transfusion requirement</td>
<td>3 deaths not related to bleeding or TEE</td>
<td>beneficial in blunt trauma with uncontrolled bleeding</td>
</tr>
<tr>
<td>Dutton [47]</td>
<td>retrospective</td>
<td>uncontrolled bleeding from trauma, exceeding 10 units RBC</td>
<td>46</td>
<td>100 μg/kg</td>
<td>5.5 (1–37) days</td>
<td>blood transfusion requirement, coagulation profile</td>
<td>28/46 responders</td>
<td>no TEE</td>
<td>use should be considered for patients who have coagulopathic hemorrhage in which surgically accessible bleeding has been controlled</td>
</tr>
<tr>
<td>Zaman Khan [48]</td>
<td>retrospective</td>
<td>trauma and postoperative bleeding with intractable life threatening bleeding</td>
<td>13</td>
<td>7.56 ± 9.6 μg/kg</td>
<td>–</td>
<td>transfusion requirements and correction of coagulation profiles</td>
<td>significant decrease in blood transfusion requirements</td>
<td>–</td>
<td>to be considered in cases with intractable bleeding</td>
</tr>
<tr>
<td>Martinowitz [49]</td>
<td>retrospective</td>
<td>intractable bleeding following blunt or penetrating trauma</td>
<td>7</td>
<td>median 120 (120–212) μg/kg</td>
<td>median after 40 (25–49) units RBC</td>
<td>control of bleeding, coagulation profile</td>
<td>significant decrease in blood transfusion requirements</td>
<td>–</td>
<td>may have beneficial role in severe uncontrolled bleeding</td>
</tr>
<tr>
<td>Harrison [50]</td>
<td>case-cohort</td>
<td>cases of trauma patients receiving NovoSeven, controls matched for age, ISS and mechanism of injury</td>
<td>29 patients with 72 matched control</td>
<td>median dose 60 μg/kg</td>
<td>–</td>
<td>blood transfusion requirement, mortality</td>
<td>significant decrease in blood transfusion requirements, no difference in mortality</td>
<td>6.9% TEE in rFVIIa vs 19.7 in controls (p = 0.2)</td>
<td>lower than hemophilia doses may suffice, no increase in TEE</td>
</tr>
</tbody>
</table>
by Brohi et al. [10], resulting in early coagulation defects even before the onset of hypothermia and massive fluid resuscitation. Present in 25% of severely injured patients with acidosis even in the pre-hospital phase, it suggests the importance of early intervention with systemic procoagulants in this population of patients.

Since the first report of its use in the successful treatment of a severely injured young soldier [11], increasing off-label use in both in civilian and military settings have been reported. Since then numerous studies have reported on the efficacy of rFVIIa in the setting of trauma-associated coagulopathy. Given the relative rarity of exsanguinating hemorrhage in trauma, accounting for less than 5% of patients requiring blood transfusions, these studies have taken the form of retrospective case reports (table 1). A wide range of inclusion criteria, timing and dosing of rFVIIa, outcome measures, and statistical validity have been reported. Given the need for early and repeated doses of rFVIIa to maintain adequate levels in exsanguinating hemorrhage, whether all these trials represent optimal use is debatable.

Inherent biases limit the validity of these retrospective series in assessing the efficacy and safety of rFVIIa in the trauma setting. There is a wide variation in the dose and timing of rFVIIa administration. Furthermore, the lack of a control group in the majority of studies does not permit the contribution of rFVIIa for TEE in a population inherently at risk for TEE. While decrease in blood transfusion requirements is consistently used as a surrogate to estimate bleeding control, this may also be as a result of correction of coagulopathy by standard methods, surgical or radiologic control, or even death.

Prospective clinical data on the use of rFVIIa in trauma are available from two randomized controlled trials. Boffard et al. [12] have reported on the single completed randomized controlled trial on rFVIIa in trauma-associated bleeding refractory of standard management. The study arm received 400 µg of rFVIIa in three divided doses over a 2-hour period after the 4th RBC unit. A statistically significant reduction in RBC requirement was reported in the study arm. Criticisms of this trial include heterogeneity of treatment as 39 centers in 19 countries were included with no formalized transfusion protocols. Deaths prior to 48 h were not included in the analysis, and decreases in morbidity outcomes including multiple organ failure, ARDS, and sepsis were only conducted as a post-hoc analysis. No increase in TEE was noted.

The following CONTROL study [13] had planned to accrue 1,507 patients in order to demonstrate mortality benefit with rFVIIa administration, with a 30% anticipated mortality based on the previous trial and registry data. At the interim analysis following 573 randomized subjects, a mortality of only 11% and 18% in treatment arms for blunt and penetrating trauma patients, respectively, was recorded, with no significant difference to controls. The trial was terminated on grounds that it was unlikely to meet significant sample size for the primary endpoint for mortality benefit. A significant improvement from the previously reported trial was the institution of strict treatment protocols on ventilator weaning as well as blood product and fluid transfusions across all recruiting centers. It is likely that adherence to such evidence-based protocols may have a higher effect on survival than any intervention with a single agent such as rFVIIa.

While clinical data supporting a reduction in trauma mortality with rFVIIa is unlikely to be forthcoming, these randomized controlled trials do appear to suggest a comparable TEE rate to controls in this study population [14]. While the first randomized trial has been criticized for insufficient prospective observation for complications [13], in the CONTROL trial the 12% overall incidence of TEEs is higher than that reported by previous retrospective series as well as the 3% reported among similarly injured patients in the National Trauma Data Bank, with no increase in TEE in rFVIIa subjects versus controls.

### rFVIIa in Bleeding Associated with Postpartum Hemorrhage

Severe PPH is traditionally defined as estimated blood losses exceeding 1 l after caesarian delivery or 500 ml following vaginal delivery. Although encountered in less than 1% of deliveries, PPH persists as a significant contributor to maternal fatalities worldwide, contributing to about 25% of peripartum mortality [15, 16]. Common causes are uterine atony, placental abnormalities, genital tract injury, and coagulation disorders. Accordingly, conventional treatment consists of fluid transfusion, oxytocin, misoprostol, and prostaglandin administrations, frequently followed by escalation to surgical maneuvers including ligation of ovarian and uterine arteries, B-Lynch suturing, bilateral internal iliac artery ligation, arterial embolization, and finally hysterectomy.

Studies reporting the use of rFVIIa have largely been based on retrospective reports (table 2) with wide variations in timing and dosing of rFVIIa. Generally rFVIIa has been administered as a last-ditch attempt after liters of blood loss to prevent hysterectomy, although occasionally administration post hysterectomy for intractable nonsurgical bleeding has also been reported. In almost all cases, rFVIIa has been administered in the absence of any formal guidelines for its clinical indications, and reporting bias is likely. On the whole, however, a subjective reduction in bleeding and blood transfusion requirement has been observed in about two thirds of cases, suggesting its potential benefit in patients with PPH intractable to standard treatment.

The largest retrospective series is presented by the Australian and New Zealand Haemostasis Registry (ANZHR) which documented 110 patients in whom rFVIIa was administered for intractable PPH [17]. It appears that in most cases this was used as a ‘last ditch’ to avoid death from exsanguin-
## Table 2. rFVIIa in PPH

<table>
<thead>
<tr>
<th>First author</th>
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<th>Inclusion criteria</th>
<th>Sample size</th>
<th>rFVIIa dose</th>
<th>Outcome measures</th>
<th>Response</th>
<th>Adverse effects</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hossain [51]</td>
<td>retrospective cohort</td>
<td>severe PPH</td>
<td>18 rFVIIa; 16 controls</td>
<td>70 μg/kg, repeated in persistent bleeding (3 cases)</td>
<td>mortality, transfusion requirement, improved coagulation profile, hysterectomy rate</td>
<td>significant improvement in mortality, transfusion rate, coagulation profile, no difference in hysterectomy</td>
<td>nil</td>
<td>rFVIIa can be life-saving in PPH</td>
</tr>
<tr>
<td>Ahonen [20]</td>
<td>case report</td>
<td>severe PPH</td>
<td>12</td>
<td>42–93 μg/kg</td>
<td>clinical assessment of bleeding response</td>
<td>partial response (6), good response (5), no response (1)</td>
<td>nil</td>
<td>the use of rFVIIa may be of benefit in life-threatening PPH. A selective arterial embolization may be needed</td>
</tr>
<tr>
<td>Phillips [17]</td>
<td>retrospective cohort</td>
<td>rFVIIa use for PPH in Australia and New Zealand</td>
<td>110</td>
<td>median total dose 92 (58–108) μg/kg, single and multiple dosing</td>
<td>clinician impression of hemostasis, hysterectomy rate</td>
<td>positive for 76% with 64% responding to the first dose; 41% required hysterectomy before rFVIIa, 13% of remainder required hysterectomy after rFVIIa</td>
<td>1 case each of DVT and PE</td>
<td>suggests earlier use may reduce hysterectomy rate</td>
</tr>
<tr>
<td>Bouma [18]</td>
<td>retrospective questionnaire</td>
<td>all cases of rFVIIa use in the Netherlands</td>
<td>27</td>
<td>mean 79 (16–128) μg/kg</td>
<td>clinical chart record of reduced or cessation of bleeding; need for hysterectomy</td>
<td>successful in 16 cases (76%) in prevention of hysterectomy; significant reduction or complete cessation of bleeding after rFVIIa was noted in 24/27 cases (89%).</td>
<td>1 TEE (pulmonary embolism) was diagnosed in one case 10 days postpartum</td>
<td>rFVIIa can be helpful and avoid an emergency hysterectomy</td>
</tr>
<tr>
<td>Ahonen [19]</td>
<td>open nonrandomized comparison with standard treatment</td>
<td>PPH with blood loss over 1.5 l circulated blood volume</td>
<td>26 rFVIIa cases vs. 22 controls</td>
<td>blood transfusion requirement after rFVIIa, coagulation profiles</td>
<td>good/moderate response in 19 patients (76.9%), poor in 6 (23.1%)</td>
<td>1 PE (patient has AT3 deficiency)</td>
<td>no superiority of rFVIIa over standard treatment</td>
<td></td>
</tr>
</tbody>
</table>
rFVIIa in Postcardiac Surgery Bleeding

Intractable postcardiac surgery has been variously defined as ongoing bleeding that precludes sternal closure, surgical drains with blood loss exceeding 100 ml/h, or the need for large-volume transfusions to maintain clinical stability, with or without repeat operations to exclude a surgical cause for ongoing blood losses. Constituting between 5 and 7% of the cardiac operations [22], these patients are at significantly higher risk for postoperative morbidity than the general cardiac surgery population, with mortality between 19 and 40% [23].

Several studies have reported the effect of rFVIIa on postcardiac surgery, but their findings are difficult to translate into clinical recommendations. The majority are observational studies without controls. Subjects in these studies consist of a wide range of patients undergoing coronary bypass, valve surgery, aortic root surgery, or a combination of operations, making generalizations difficult. The larger of these studies have been summarized in table 3. Perhaps more than other clinical subgroups commonly associated with massive bleeding, cardiac patients are at especially high risk for the adverse event associated with systemic procoagulants such as rFVIIa, including myocardial infarction, ischemic strokes, and other TEE [24]. This and the absence of control groups in these studies have made the safety aspects and efficacy especially difficult to determine.

Consistent across almost all retrospective series is the reduction of blood loss after rFVIIa administration. This has occasionally been measured directly by surgical drains but most commonly by blood transfusion requirements pre and post dosing. The largest experience of rFVIIa usage in this setting comes from registry data. The ANZHR examined the efficacy of rFVIIa for intractable bleeding following cardiac surgery in 304 patients, 83% of whom received a single median dose of 93 μg/kg [25]. Hemostatic response was assessed by pre- and post-rFVIIa blood transfusion requirements and clinicians’ assessment of response. Moderate to complete cessation of bleeding was assessed in 84% of patients with substantial reduction in blood transfusion requirements. TEE were noted in 4% of patients, which is consistent with previous reports of similarly complex cardiac surgery although no formal comparison was made. A later analysis of an expanded ANZHR study population by Willis et al. [26] found no difference in reduction in bleeding or 28-day mortality across different rFVIIa dosage groups from <40 to >100 μg/kg, suggesting that a lower dose may be adequate. A review of off-label rFVIIa use in 503 Canadian patients by Karkouti et al. [27] showed a reduction in blood transfusion requirements post dosing. Adverse events were compared with controls drawn from consecutive cases from the participating centers, with no significant difference in mortality or serious adverse events. In both Australian and Canadian registries rFVIIa administration was associated with a delay in the end of cardiopulmonary bypass – in the Canadian series the median delay was 280 min, suggesting that
### Table 3. rFVIIa in postcardiac surgery bleeding

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<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Willis [26]</td>
<td>registry uncontrolled bleeding</td>
<td>associated with cardiac surgery</td>
<td>804</td>
<td>18–141 μg/kg</td>
<td>hemostasis, mortality and TEE</td>
<td>no correlations between outcomes and dose of rFVIIa</td>
<td>--</td>
<td>recommends lowest possible effective dose for economic and possible dose depend complication rates</td>
</tr>
<tr>
<td>Masud [52]</td>
<td>retrospective single center</td>
<td>uncontrolled bleeding associated with cardiac surgery</td>
<td>93</td>
<td>median 552 μg/kg</td>
<td>RBC transfusion required in 6 h pre and post rFVIIa use; need for massive transfusion; correction of INR, TEE, assessed across different rFVIIa doses</td>
<td>significant reduction in blood transfusion requirement and correction of INR; no dose response effect in doses &gt;30 μg/kg</td>
<td>no TEE</td>
<td>no difference in outcomes across different dosing quartiles suggest doses of &lt;90 μg/kg may be effective in this population</td>
</tr>
<tr>
<td>Gelsomino [30]</td>
<td>retrospective with propensity score-based greedy matched controls</td>
<td>refractory bleeding following negative re look cardiac surgery</td>
<td>40</td>
<td>median 18 μg/kg</td>
<td>RBC requirement, ICU stay</td>
<td>improved RBC requirement; shortened MV and ICU stay; no difference in overall morbidity and mortality</td>
<td>no increase in TEE</td>
<td>low dose may be adequate</td>
</tr>
<tr>
<td>Von Heymann [29]</td>
<td>retrospective single center</td>
<td>refractory bleeding following cardiac surgery matched with historical controls</td>
<td>24</td>
<td>most patients (92%) received one or two doses with median cumulative doses of 60 μg/kg and 116 μg/kg respectively</td>
<td>blood transfusion, estimated blood loss, adverse events, in-hospital and 6-day mortality</td>
<td>reduction in blood loss and transfusion requirements but no difference in mortality</td>
<td>no difference in TEE or renal failure</td>
<td>no increase in TEE but may not improve mortality</td>
</tr>
<tr>
<td>Dunkley [25]</td>
<td>registry</td>
<td>rFVIIa given for postcardiac surgery bleeding</td>
<td>304</td>
<td>93 μg/kg</td>
<td>hemostasis, blood transfusion requirements, mortality</td>
<td>reduction in all blood transfusion requirements, responders had improved survival</td>
<td>4% TEE, no micrograft thrombosis</td>
<td>as improved response was correlated with fewer blood transfusions before rFVIIa dosing, earlier administration to be considered</td>
</tr>
<tr>
<td>Karkouti [27]</td>
<td>registry with historical controls</td>
<td>rFVIIa given for cardiac surgery bleeding</td>
<td>503</td>
<td>62</td>
<td>blood transfusion requirements before and after rFVIIa, morbidity and mortality</td>
<td>reduction in blood transfusion requirements, no change in mortality or adverse events</td>
<td>no significant increase in TEE</td>
<td>lack of response related to abnormal INR and &gt;15 units RBC transfusion pre rFVIIa administration suggests earlier dosing may be more beneficial</td>
</tr>
<tr>
<td>Gill [31]</td>
<td>dose escalation RCT</td>
<td>postcardiac surgery intractable bleeding</td>
<td>172</td>
<td>40 μg/kg vs. 80 μg/kg vs placebo</td>
<td>critical severe adverse events (mainly death cardiac and TEE); secondary endpoints of blood transfusion requirements, volume blood loss, re operation rates</td>
<td>no increase in severe adverse events. Reduction in blood loss, transfusion requirements and re operations</td>
<td>nonsignificant increase in TEE</td>
<td>caution and further clinical trials required in view of numerically larger number of TEEs in the rFVIIa arms</td>
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Table 3. Continued

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<thead>
<tr>
<th>First author</th>
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<th>Median rFVIIa dose</th>
<th>Sample size</th>
<th>Median rFVIIa dose</th>
<th>Condition</th>
<th>Outcome measures</th>
<th>Response</th>
<th>Adverse effects / complications</th>
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<tbody>
<tr>
<td>Karkouti [28]</td>
<td>retrospective observational</td>
<td>51 patients</td>
<td>70 μg/kg for severe bleeding and 35 μg/kg for less severe bleeding</td>
<td>70 μg/kg for severe bleeding and 35 μg/kg for less severe bleeding</td>
<td>70 μg/kg for severe bleeding and 35 μg/kg for less severe bleeding</td>
<td>postcardiac surgery</td>
<td>significant reduction in blood product transfusions</td>
<td>moderate</td>
<td>increased incidence of renal compromise, longer ICU stay, and numerically increased stroke rates non statistically significant</td>
</tr>
<tr>
<td>Raivio [53]</td>
<td>retrospective observational</td>
<td>15 patients</td>
<td>median 65 μg/kg (34–192 μg/kg)</td>
<td>15 patients</td>
<td>median 65 μg/kg (34–192 μg/kg)</td>
<td>postcardiac and thoracic aorta surgery</td>
<td>reduction in blood transfusion requirements, adverse events</td>
<td>no TEE</td>
<td>caution in use in patients at high risk for TEE</td>
</tr>
<tr>
<td>Bishop [54]</td>
<td>retrospective observational</td>
<td>12 patients</td>
<td>100 μg/kg (5–490 μg/kg)</td>
<td>12 patients</td>
<td>100 μg/kg (5–490 μg/kg)</td>
<td>postcardiac and thoracic aorta surgery</td>
<td>significant reduction in blood volume and TEE</td>
<td>significant reduction in blood product requirements and TEE</td>
<td>no TEE</td>
</tr>
<tr>
<td>McCall [55]</td>
<td>retrospective observational</td>
<td>53 patients</td>
<td>90 μg/kg</td>
<td>53 patients</td>
<td>90 μg/kg</td>
<td>postcardiac surgery bleeding</td>
<td>significant reduction in blood volume and TEE</td>
<td>no TEE</td>
<td>significant reduction in blood product requirements, subjective assessment of response</td>
</tr>
</tbody>
</table>

rFVIIa was truly a last-ditch attempt to achieve bleeding control. As the number of blood units transfused prior to rFVIIa administration was demonstrated as a predictor of lack of response to rFVIIa and mortality, both studies suggest earlier administration for maximum efficacy. Also notable in this large experience of off-label use is the absence of coronary micrograft thromboses.

Prior to the availability of adequately powered prospective randomized controlled trials, retrospective studies with some variation in approach have been used to determine the efficacy and safety of rFVIIa in this setting. Karkouti et al. [28] matched 51 postcardiac surgery patients with an equal number of controls selected by a propensity score for massive bleeding as determined by preoperative hemoglobin levels, weight, age, and gender. A significant reduction in blood product requirement was noted in the rFVIIa group although this was offset by an increased length of ICU stay and renal compromise, with a nonsignificant increase in the incidence of stroke. A possible confounding temporal effect may compromise this analysis, as the timing of rFVIIa administration was not taken into account in calculating its effect on bleeding complications. To correct for this potential bias, von Heymann et al. [29] matched 24 postcardiac patients with an equal number of historical controls matching for volume of bleeding and other co-morbidities and the blood transfusion required up to and after the 24-hour postoperative mark, the median time in which rFVIIa was administered in the study group. Although blood loss and transfusions were reduced in the immediate period hours post rFVIIa infusion compared to controls, there was no difference in blood transfusions at the 24-hour mark, nor in the in hospitalization and mortality at 6 months. Reflecting the concerns for cost and TEE in this high-risk population, Gelsomino et al. [30] reported the effectiveness of a 1.2 mg rFVIIa dose (providing a median dose of 18 μg/kg) in 40 cardiac patients with persistent blood loss compared to a control group with equal a priori probability of bleeding based on a propensity score analysis. Significant reductions in blood loss and transfusion requirements, length of mechanical ventilation, and hospital stay were noted.

Prospective data on the efficacy and safety of rFVIIa in the clinical setting of postcardiac surgery is limited to a phase II multicenter prospective randomized controlled trial reported by Gill et al. [31]. Patients admitted with severe bleeding following cardiac surgery in 30 participating centers were randomized in two separate cohorts to receive either rFVIIa 40 μg/kg or placebo or 80 μg/kg or placebo. Primary endpoints consisted of severe adverse events (SAEs) of interest, mainly myocardial and TEE complications, with secondary endpoints of volumes of blood requirement and re-operation rates. Unlike previous registry data from off-label rFVIIa use as a last-ditch effort to control bleeding, patients received trial drugs relatively early.
Table 4. rFVIIa in gastrointestinal bleeding

<table>
<thead>
<tr>
<th>First author</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Sample size</th>
<th>RFVIIa dose</th>
<th>Outcome measure</th>
<th>Response</th>
<th>Adverse effects / complications</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejersen [39]</td>
<td>retrospective</td>
<td>active variceal bleeding, Child-Pugh class B and C</td>
<td>10</td>
<td>80 μg/kg</td>
<td>reversal of PT and bleeding response</td>
<td>reversal of PT in 30 min, bleeding controlled in all patients</td>
<td>no TEE</td>
<td>potential for use in bleeding varices</td>
</tr>
<tr>
<td>Romero-Castro [40]</td>
<td>retrospective</td>
<td>active variceal bleeding, uncontrolled with standard therapy</td>
<td>8</td>
<td>4.8 mg</td>
<td>control of bleeding, mortality</td>
<td>all had initial bleeding controlled, 2 re-bled, 4 died</td>
<td>no TEE</td>
<td>potential for use in uncontrolled bleeding varices</td>
</tr>
<tr>
<td>Flowers [41]</td>
<td>registry</td>
<td>upper gastrointestinal bleeding with liver failure</td>
<td>38</td>
<td>90 μg/kg (IQR 64–102)</td>
<td>transfusion requirements pre and post dosing, 28 day mortality</td>
<td>67% had decrease in blood transfusion requirements, 60% 28-day mortality</td>
<td>1 patient had acute myocardial infarct, possible protein C insufficiency</td>
<td>not recommended for use in variceal bleeding intractable to standard treatment</td>
</tr>
<tr>
<td>Bosch [42]</td>
<td>RCT</td>
<td>suspected variceal bleeding in cirrhotic patients</td>
<td>121 study arm / 121 controls</td>
<td>100 μg/kg in eight repeated doses within 30 h vs. controls</td>
<td>composite endpoint of control of bleeding within 24 h, bleeding control and mortality in 5 days</td>
<td>no difference in primary endpoints overall although more severely cirrhotic patients with confirmed variceal bleeding had significant improvement in composite outcomes</td>
<td>no difference in TEE</td>
<td>may benefit more severe cirrhotic patients (Child – Pugh B and C) with variceal bleeding</td>
</tr>
<tr>
<td>Bosch [43]</td>
<td>RCT</td>
<td>active variceal bleeding, Child-Pugh class B and C</td>
<td>placebo 89, lower dose rFVIIa 88, higher dose rFVIIa 88</td>
<td>300 μg/kg or 600 μg/kg</td>
<td>composite endpoint as above, secondary endpoints of 42-day mortality and SAE</td>
<td>no difference and primary endpoints, decrease mortality at 42 days in higher dose group</td>
<td>no difference in TEE</td>
<td>routine use of rFVIIa not supported by this study</td>
</tr>
</tbody>
</table>
in their postoperative course, on average after just 2.8 h after arrival at the ICU, with control groups requiring a median of only 825 ml of blood transfusion. Consistent with retrospective data, there was a significant decrease in blood transfusion requirement and estimated blood losses. However, patients receiving either dose had a numerically higher, statistically non-significant incidence of complications (4 cases of cerebral infarction vs. nil in placebo group, and 3 cases of other TEEs vs. nil in placebo group). rFVIIa given earlier in the course of postcardiac surgery appears to be efficacious, but the real correlation with TEE may require larger sample sizes.

rFVIIa in Upper Gastrointestinal Bleeding and Liver Failure

The liver plays a major role in maintaining hemostasis by the synthesis and regulation of most pro- and anti-thrombotic factors. Cirrhosis leads to a loss of this controlled regulation and can lead to both hyper- or hypocoagulable states. A bleeding diathesis is traditionally thought to arise from thrombocytopenia secondary to hypersplenism from portal hypertension, a loss of function of vitamin K-dependent clotting factors, and loss of platelet function from decreased thromboxane A2 [32, 33]. Conversely hypercoagulability may ensue following an impaired fibrinolytic pathway secondary to decreased plasminogen and antiplasmin [34, 35].

Bleeding from esophageal and gastric varices is a common complication and cause of mortality of cirrhotic patients. Despite recent developments in the treatment of bleeding varices, there is a persistent 40% rate of re-bleeding, and mortality for initial bleeding and each re-bleeding episode is approximately 30% [36]. The potential of rFVIIa in treating cirrhosis-associated coagulopathy was first reported in studies which showed that single doses could reverse prolonged prothrombin time (PT) and correct international normalized ratios (INRs) [37, 38].

Two retrospective noncomparative trials assessed the efficacy of single doses of rFVIIa in patients with bleeding esophageal varices. Ejersen et al. [39] administered a single dose of 80 μg/kg to 10 Child-Pugh class B and C patients diagnosed with bleeding esophageal varices. Normalization of PT levels was obtained in 30 min and sustained over 7 h. Bleeding in all cases was controlled with no increase in TEE. In a similar study Romero-Castro et al. [40] administered a single dose of 4.8 mg of rFVIIa in 8 patients in whom active bleeding esophageal varices persisted despite treatment with endoscopy, vasopressors, and balloon tamponade. Hemostasis was obtained in all patients although 2 re-bleed within 1 week and 4 deaths occurred during the observation period. Flower et al. [41], reporting for the ANZHR, assessed the efficacy of rFVIIa in 38 cases of upper gastrointestinal bleeding associated with liver failure. Although 67% of patients were assessed to have reduced blood transfusions after rFVIIa administration, there was still a 60% 28-day mortality rate which was not different from that of non-responders. Notably as with other studies reporting off-label use, experience with rFVIIa in the ANZHR appeared to be mainly as a last-ditch effort, with 32% of patients already receiving more than 10 units of RBCs prior to rFVIIa administration. These patients appear to have a significant mortality regardless of whether bleeding is controlled or not.

Two randomized controlled trials by the European Study Group on rFVIIa on Upper GI Bleeding assess the feasibility of rFVIIa over and above standard treatment. The first was reported by Bosch et al. [42] in which patients with suspected variceal bleeding were randomized to either placebo or eight doses of 100 μg/kg of rFVIIa over a 30-hour period post randomization. The primary outcome measure was a composite endpoint consisting of control of bleeding within 24 h and re-bleeding and death within 5 days of administration. No difference in the composite endpoint was noted in the rFVIIa compared to control patients. It should be noted that patients were often randomized on clinical diagnosis of variceal bleeding which was subsequently diagnosed in about two thirds of patients at endoscopy, during which about 45% had already shown no active signs of bleeding. On post-hoc analysis, patients with Child-Pugh class B and C cirrhosis with variceal bleeding receiving rFVIIa treatment had a significant decrease in failures in the composite endpoint, suggesting that rFVIIa may be of benefit in a more specific patient population with more severe liver disease. Of interest, the 5-day mortality of the intervention and control arms were 3% and 6%, respectively, and thus much lower than the anticipated 30% seen in historical reports. This suggests that the strict adherence to optimal treatment protocols of vasoactive treatment, blood product transfusions, and therapeutic endoscopy in participating centers may have a larger effect on outcomes that the rFVIIa intervention. In a following study using the same endpoints with the additional secondary endpoints of adverse events and 42-day mortality, Bosch et al. [43] targeted 256 severely cirrhotic patients (Child-Pugh B and C) with endoscopically confirmed active variceal bleeding to receive either rFVIIa in divided doses of 300 μg/kg or 600 μg/kg, or placebo within 1 h of diagnosis. Again no differences in the composite endpoints and 5-day mortality were noted; however, there was a significant decrease of 42-day mortality in the 600 μg/kg group compared to placebo, with death from bleeding significantly being reduced from 12 to 2%. In neither of these RCTs a difference in TEE or SAEs between rFVIIa and placebo groups could be found (table 4).

Conclusions

Our review of the efficacy and safety of rFVIIa in emergency situations of massive blood loss suggests that with the present published evidence rFVIIa cannot be recommended as part of...
standard care for the treatment of massive bleeding in trauma, PPH, cardiac surgery or gastrointestinal bleeding associated with liver failure. Concordant with the meta-analysis presented by Lin et al. [44], all RCTs carried out in these clinical situations have yielded a relative risk for mortality where 95% confidence intervals have included 1.0. It is unlikely that class I data for mortality benefit, which would require an estimated sample size of about 12,000 patients (based on an anticipated mortality in control groups of about 20%) will ever be undertaken. Aside from mortality outcomes, efficacy of rFVIIa has also been assessed with pooled blood transfusion requirements as a surrogate for hemostatic effect. Again the meta-analysis does not show conclusive evidence of a significant reduction in blood transfusion requirement. A consistent finding across randomized trials involving massive blood losses is the decrease in anticipated mortality and blood requirements in studies in which a transfusion protocol was provided and enforced [13]. These would stipulate the administration of early RBCs, high RBC to plasma volumes, cryoprecipitate, fibrinogen, and other coagulation factor concentrates as well as expedient surgical and radiological hemostasis. It would appear that such comprehensive measures of optimizing bleeding control would have a larger efficacy in the treatment of these severely ill patients than can be expected by the intervention with a single agent.

Disclosure Statement

The authors did not state a conflict of interest statement.

References


