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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. **Ergebnisse:** Eine Vielzahl retrospektiver Studien zeigte zumeist einen Rückgang des Bluttransfusionsbedarfs, ohne dass es zu einer Zunahme von thromboembolischen Ereignissen (TEE) kam; allerdings machten schwerwiegende Mängel beim Studiendesign eine Generalisierung schwierig. In den meisten retrospektiven Berichten wurde rFVIIa als letzter verzweifelter Versuch eingesetzt, um die Blutung zu kontrollieren, wenn eine Azidose, eine Hypothermie und ein Gerinnungsfaktormangel möglicherweise einen optimalen rFVIIa-Effekt verhindern. Prospektive randomisierte kontrollierte Studien zeigten keinen Effekt von rFVIIa auf die Mortalität oder TEE, obwohl einige eine Reduzierung des Erythrozytenbedarfs nachweisen konnten. **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.

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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 fibrinolyic 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. 1. rFVIIa in trauma

First author	Study type	Inclusion criteria	Study size	rFVIIa dose	Timing of dose, h	Outcome measures	Response	Adverse events	Conclusions / recommendations
Cameron[45]	registry	use of rFVIIa in trauma patients in Australia and New Zealand	108	90 (78–105) µg/kg	–	clinician assessment of bleeding control, blood transfusions before and after rFVIIa dosing	significant decrease in bleeding in 59%; significant reduction in blood transfusion requirements	3% TEE	wide variation in timing of rFVIIa dosing and massive transfusion practices
Spinella [14]	registry	combat casualties with ISS>16 receiving >10 units RBC/24 h	49 study patients and 75 controls	120 µg/kg	within 2 h of admission	24-hour and 30-day mortality and TEE	significant decrease in 24-hour (14% vs. 35%; p = 0.01) and 30-day mortality (31% vs. 51%; p = 0.03)	no increase in TEE	early administration of rFVIIa decreases mortality in combat casualties with massive transfusions
Geeraedts Jr [46]	retrospective	life-threatening uncontrolled bleeding due to blunt trauma	8	55–90 µg/kg	9–38	blood product requirement bleeding control	all cases obtained hemostasis, reduction in blood transfusion requirement	3 deaths not related to bleeding or TEE	beneficial in blunt trauma with uncontrolled bleeding
Dutton [47]	retrospective	uncontrolled bleeding from trauma, exceeding 10 units RBC	46	100 µg/ kg	5.5 (1–37) days	blood transfusion requirement, coagulation profile	28/46 responders	no TEE	use should be considered for patients who have coagulopathic hemorrhage in which surgically accessible bleeding has been controlled
Zaman Khan [48]	retrospective	trauma and postoperative bleeding with intractable life threatening bleeding	13	75.6 ± 9.6 µg/kg initial dose; 7 patients required repeat dosing	-	transfusion requirements and correction of coagulation profiles	significant decrease in blood transfusion requirements	–	to be considered in cases with intractable bleeding
Martinowitz [49]	retrospective single center	intractable bleeding following blunt or penetrating trauma	7	median 120 (120–212) µg/kg	median after 40 (25–49) units RBC	control of bleeding, coagulation profile	significant decrease in blood requirements, improvement in PT. PTT	–	may have beneficial role in severe uncontrolled bleeding
Harrison [50]	case-cohort	cases of trauma patients receiving NovoSeven, controls matched for age, ISS and mechanism of injury	29 patients with 72 matched control	median dose 60 µg/kg	–	blood transfusion requirement, mortality	significant decrease in blood transfusion requirements, no difference in mortality	6.9% TEE in rFVIIa vs 19.7 in controls (p = 0.2)	lower than hemophilia doses may suffice, no increase in TEE

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 its 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 large 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

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

ation as over two thirds of patients had received over 15 units of RBCs before rFVIIa dosing and 41% had already undergone hysterectomy. Of the patients that had not undergone hysterectomy prior to rFVIIa dosing, this was required in 21% of cases, suggesting that earlier rFVIIa may improve uterine preservation. Bouma et al. [18], reporting on the experience of rFVIIa use for PPH in the Netherlands, found similar improvements in bleeding control. Again almost all patients had an estimated blood loss of over 3 l before rFVIIa administration. Given how rFVIIa action may be compromised by acidosis, thrombocytopenia, hypothermia, and low fibrinogen levels attendant with this volume of blood loss [7], it is unlikely that these registry findings represent optimal rFVIIa performance. Despite an increased risk of TEE in this group of patients, these were rarely reported following rFVIIa use.

One prospective nonrandomized single center trial has been reported by Ahonen et al. [19]. Based on their previous experience in the use of rFVIIa in PPH [20], 26 patients were prospectively managed with rFVIIa using an institution protocol that included a rFVIIa dose of 90–120 μg/kg, optimal platelet and fibrinogen levels, factor XIII support, and repeated rFVIIa dosing in refractory bleeding. When blood product and coagulation profiles were compared with 22 controls managed without rFVIIa over the same period, rFVIIa use was associated with poorer outcomes. The validity of these conclusions is debatable. rFVIIa was only considered when patients had lost at least 1.5 times their circulating blood volume. In the rFVIIa arm a mean of 9.9 l of blood loss (range 4.2–19.7 l) had occurred before rFVIIa administration, which is greater than the mean total loss of 8.0 l (range 5.0–19.0 l) in control patients. That poorer outcomes were seen in the rFVIIa arm is therefore not surprising.

No prospective randomized trials are available to conclusively assess the efficacy of rFVIIa in severe PPH. Given the rarity of PPH intractable to standard therapy, it is highly unlikely that this will ever be available and treatment may have to be determined on retrospective data. Given the high cost of rFVIIa, the inherent selection bias of these reports is inevitable as clinicians are likely to reserve and report the action of rFVIIa with a higher likelihood of response. In a review of available retrospective trials with 10 or more accrued subjects, Franchini et al. [21] observed that, with these reservations notwithstanding, over 85% of reported subjects had significant reduction in blood losses after a median administration of 81.5 μg/kg of rFVIIa, suggesting a clinically relevant role. For the treatment of refractory life-threatening PPH, the authors recommended optimization of conditions for rFVIIa action, including correction of hypothermia, thrombocytopenia, acidosis and hypofibrinogenemia, and a 90 μg/kg loading dose, with repeated dosing if no clinical response is observed in 20 min. Should there be no response after the second dose, a hysterectomy should be considered.

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 stokes, 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

First author	Type of paper	Inclusion criteria	Sample size	Median rFVIIa dose	Outcome measures	Response	Adverse effects / complications	Conclusions
Willis [26]	registry	uncontrolled bleeding associated with cardiac surgery	804	18–141 μg/kg	hemostasis, mortality and TEE	no correlations between outcomes and dose of rFVIIa	–	recommends lowest possible effective dose for economic and possible dose depend complication rates
Masud [52]	retrospective single center	uncontrolled bleeding associated with cardiac surgery	93	median 55.2 μg/kg (IQR 30.4–76.2)	RBC transfusion required in 6 h pre and post rFVIIa use; need for massive transfusion; correction of INR, TEE, assessed across different rFVIIa doses	significant reduction in blood transfusion requirement and correction of INR; no dose response effect in doses >30 μg/kg	no TEE	no difference in outcomes across different dosing quartiles suggest doses of <90 μg/kg may be effective in this population
Gelsomino [30]	retrospective with propensity score-based greedy matched controls	refractory bleeding following negative re look cardiac surgery	40	median 18 μg/kg	RBC requirement, ICU stay	improved RBC requirement, shortened MV and ICU stay, no difference in overall morbidity and mortality	no increase in TEE	low dose may be adequate
Von Heymann [29]	retrospective single center	refractory bleeding following cardiac surgery matched with historical controls	24	most patients (92%) received one or two doses with median cumulative doses of 60 μg/kg and 116 μg/kg respectively	blood transfusion, estimated blood loss, adverse events, in-hospital and 6-day mortality	reduction in blood loss and transfusion requirements but no difference in mortality	no difference in TEE or renal failure	no increase in TEE but may not improve mortality
Dunkley [25]	registry	rFVIIa given for postcardiac surgery bleeding	304	93 μg/kg	hemostasis, blood transfusion requirements, mortality	reduction in all blood transfusion requirements, responders had improved survival	4% TEE, no micrograft thrombosis	as improved response was correlated with fewer blood transfusions before rFVIIa dosing, earlier administration to be considered
Karkouti [27]	registry with historical controls	rFVIIa given for cardiac surgery bleeding	503	62	blood transfusion requirements before and after rFVIIa, morbidity and mortality	reduction in blood transfusion requirements, no change in mortality or adverse events	no significant increase in TEE	lack of response related to abnormal INR and >15 units RBC transfusion pre rFVIIa adminstration suggests earlier dosing may be more beneficial
Gill [31]	dose escalation RCT	postcardiac surgery intractable bleeding	172	40 μg/kg vs. 80 μg/kg vs placebo	critical severe adverse events (mainly death cardiac and TEE); secondary endpoints of blood transfusion requirements, volume blood loss, re operation rates	no increase in severe adverse events. Reduction in blood loss, transfusion requirements and re operations	nonsignificant increase in TEE	caution and further clinical trials required in view of numerically larger number of TEEs in the rFVIIa arms

Table 3 continued on next page

Table. 3. Continued

First author	Type of paper	Inclusion criteria	Sample size	Median rFVIIa dose	Outcome measures	Response	Adverse effects / complications	Conclusions
Karkouti [28]	retrospective with propensity score controls	postcardiac surgery massive bleeding where surgical cause excluded	51 study patients and propensity-matched controls	70 μg/kg for severe uncontrolled bleeding and 35 μg/kg for less severe controlled bleeding	blood product transfusions and adverse events; mortality	significant reduction in BLOOD losses	increased incidence of renal compromise, longer ICU stay and numerically increased stroke rates non statistically insignificant	reduces uncontrollable blood loss but greater complication rate
Raivio [53]	retrospective observational	postcardiac and thoracic aorta surgery intractable bleeding	15	median 65 (24–192) μg/kg	blood transfusion requirements, adverse events	reduction in blood transfusion	25% TEE	caution in use in patients at high risk for TEE
Bishop [54]	retrospective observational	postcardiac surgery bleeding intractable to uncontrollable	12	100 μg/kg	BL<OOD requirements and TEE	significant reduction in blood volumes	no TEE	safe for post cardiac surgery bleeding
McCall [55]	retrospective observational	uncontrolled bleeding preventing chest closure in operating room	53	90 μg/dl	blood transfusion requirements, subjective surgeons assessment of response	significant reduction in blood volumes, 83% responses graded either moderate to excellent	19% mortality, no assessment on rFVIIa causation	effective for treatment of refractory bleeding, uncertain contribution to significant morbidity and mortality in these patients

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 in account in calculating its effect on blood transfusion requirements. 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

First author	Study type	Inclusion criteria	Sample size	RFVIIa dose	Outcome measure	Response	Adverse effects / complications	Conclusions
Ejersen [39]	retrospective	active variceal bleeding, Child-Pugh class B and C	10	80 µg/kg	reversal of PT and bleeding response	reversal of PT in 30 min, bleeding controlled in all patients	no TEE	potential for use in bleeding varices
Romero-Castro [40]	retrospective	active variceal bleeding, uncontrolled with standard therapy	8	4.8 mg	control of bleeding; mortality	all had initial bleeding controlled, 2 re-bled, 4 died	no TEE	potential for use in uncontrolled bleeding varices
Flowers [41]	registry	upper gastrointestinal bleeding with liver failure	38	90 µg/kg (IQR 64–102)	transfusion requirements pre and post dosing, 28 day mortality	67% had decrease in blood transfusion requirements, 60% 28-day mortality	1 patient had acute myocardial infarct, possible protein C insufficiency	not recommended for use in variceal bleeding intractable to standard treatment
Bosch [42]	RCT	suspected variceal bleeding in cirrhotic patients	121 study arm / 121 controls	100 µg/kg in eight repeated doses within 30 h vs. controls	composite endpoint of control of bleeding within 24 h, bleeding control and mortality in 5 days	no difference in primary endpoints overall although more severely cirrhotic patients with confirmed variceal bleeding had significant improvement in composite outcomes	no difference in TEE	may benefit more severe cirrhotic patients (Child – Pugh B and C) with variceal bleeding
Bosch [43]	RCT	active variceal bleeding, Child-Pugh class B and C	placebo 89, lower dose rFVIIa 88, higher dose rFVIIa 88	300 µg/kg or 600 µg/kg	composite endpoint as above, secondary endpoints of 42-day mortality and SAE	no difference and primary endpoints, decrease mortality at 42 days in higher dose group	no difference in TEE	routine use of rFVIIa not supported by this study

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 nonsignificant 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 hypercoagulobility 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 at 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 rebleeding 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 at 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 provide a conflict of interest statement.

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