PERSPECTIVE

Use of Recombinant Factor Seven (rFVIIa) in the treatment of severe bleeding from trauma

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Introduction

Recombinant factor seven (rFVIIa) has been approved for the treatment of acquired hemophilia and other inherited bleeding diathesis such as Glanzmann thromboaesthenia and factor VII deficiency. Although initial studies in severe trauma had shown promise, prospective trials have failed to show its benefit in decreasing mortality. Use of rFVIIa is now recommended to be only within the setting of clinical trials. Nevertheless off label use still continues and accounts for over 20% of rFVIIa sales. The aim of this editorial is to give an overview of rFVIIa trials in the setting of severe trauma and provide information for optimal use in trauma related coagulopathy

Mode of action

At physiological levels rFVIIa acts within a tissue factor (TF) dependent pathway [1], leading 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 an additional TF independent pathway leads to direct activation of factor X [2], and possibly also downregulates the fibrinolyic system through the production of thrombin activation 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 makes rFVIIa appealing as a systemic pro coagulant in the treatment of refractory bleeding as TF availability and activated platelets are available only at active bleeding sites and should limit the danger thromboembolic events (TEE). Nevertheless multiple injured patients are at notably increased risk with TEE, which has been the main safety consideration in rFVIIa trials. O'Connell et al [4], 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 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 under-report actual incidence. Nevertheless the lack of a control group and information of baseline risk and concomitant medications hinder any assessment of causality to rFVIIa administration.

Factors affecting the biological activity of rFVIIa have been extensively studied in in-vivo and in-vitro models [5]. Significant decreases in efficacy have been demonstrated in severe acidosis below pH7.2, with a smaller effect from hypothermia. Pharmacokinetic studies have also shown increased clearance with ongoing bleeding [6]. 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 benefit in the military setting. Furthermore, they would also suggest that the use of rFVIIa as a "last ditch" measure when all other measures have failed may not lead to

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maximal efficacy and that earlier dosing before reversible acidosis and hypothermia would be more reasonable.

rFVIIa in severe trauma

Numerous retrospective studies have shown impressive results in the use of rFVIIa in severe trauma, with a variety of inclusion criteria, dosing and dosing intervals, outcome measures and statistical validity (Table 1). Mostly, these have been given late in the course of trauma resuscitation and publication bias is likely. Furthermore, the lack of a control group in the majority of studies does not permit the assessment of the contribution of rFVIIa for TEE in a population inherently at elevated risk. Blood transfusion requirements pre- and post-dosing, is consistently used as a surrogate to estimate bleeding control. While this may be a surrogate indicator of rFVIIa efficacy, a decrease in transfusion requirements may also be as a result of correction of coagulopathy by standard transfusion methods, surgical or radiological haemostasis, or even death.

Prospective clinical data on the use of rFVIIa in trauma are available from two randomized controlled trials. Boffard et al [7] have reported on the single completed randomized controlled trial on rFVIIa in trauma associated bleeding refractory of standard management. The study arm received 400ug of rFVIIa (some four times higher than the recommended dose for treatment of bleeding in hemophilia) in three divided doses over a two hour period after the fourth packed red blood cell (RBC) tranfusion. A statistically significant reduction in RBC requirement was reported in the study arm. Criticisms of this trial include heterogeneity of treatment as 39 centres in 19 countries were included with no formalized transfusion protocols. Deaths prior to 48 hours 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 follow on CONTROL [8] study had planned to accrue 1507 patients in order to demonstrate mortality benefit with rFVIIa administration, with a 30% anticipated mortality based on the previous trial and German 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 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, blood product and fluid transfusions across all recruiting centres. Early availability of massive transfusion protocols was required. It is likely that adherence to such evidence based protocols and the early availability of blood products in large volumes may have a higher effect on survival than 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 patient population [9]. While the first randomized trial has been criticized for insufficient prospective observation for complications, 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.

Conclusions

The efficacy and safety of rFVIIa in severe trauma suggests that with the present published evidence rFVIIa cannot be recommended as part of standard care. Concordant with the meta analysis presented by Lin et al [10], all RCTs carried out in trauma and other situations of massive blood loss in non-haemophiliacs 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. A consistent finding across randomized trials involving massive blood loss is the decrease in anticipated mortality and blood requirements in studies in which a transfusion protocol was provided and enforced [8]. These would stipulate the administration of early

Table 1. Studies comparing the value of rFVIIa in treatment of bleeding.

First author	Study type	Inclusion criteria	Study size	rFVIIa dose	Timing of dose (hr)	Outcome measures	Response	Adverse events	Conclusions/ recommendations
Cameron(7)	Registry	Use of rFVIIa in trauma patients in Australia and New Zealand	108	90ug/kg (78 – 105)	-	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 (8)	Registry	Combat casualties with ISS>16 receiving >10 units rbc/24 hours	49 study patients and 75 controls	120ug/kg	Within 2 hours of admission	24 hr 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(9)	Retrospective	Life threatening uncontrolled bleeding due to blunt trauma	8	55-90 ug/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(10)	Retrospective	uncontrolled bleeding from trauma, exceeding 10 units rbc	46	100 ug/ kg	5.5 days (range 1 - 37 days)	Blood transfusion requirement, coagulation profile	28/46 responders	No TEE	Use should be considered for patients who have coagulopathic haemorrhage in which surgically accessible bleeding has been controlled
A Zaman Khan(11)	Retrospective	Trauma and post operative bleeding with intractable life threatening bleeding	13	75.6 ± 9.6ug/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(12)	Retrospective single centre	Intractable bleeding following blunt or penetrating trauma	7	Median 120 ug/kg (120 - 212ug/kg)	Median after 40 units rbc (range 25 – 49)	Control of bleeding, coagulation profile	Significant decrease in blood requirements, improvement in PT. PTT	-	May have beneficial role in severe uncontrolled bleeding
T Daniel Harrison(13)	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 60ug/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

RBC transfusions, high RBC:plasma volumes, cryoprecipitate, reversal of hypothermia and surgical or radiological hemostatic interventions. It would appear that such comprehensive measures to optimize bleeding control would have a larger efficacy on the treatment of these severely ill patients than can be expected by intervention by a single agent.

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