

# Expert Opinion

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## The emerging role of recombinant activated Factor VII (rFVIIa) in the treatment of blunt traumatic haemorrhage

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Recombinant activated Factor VII (rFVIIa; eptacog alpha [activated], NovoSeven<sup>®</sup>) is currently used for the management of a subgroup of haemophilia patients with inhibitors to Factors VIII or IX, and is under investigation as an adjuvant therapy for critical bleeding from other causes, including trauma. rFVIIa has a mode of action founded on physiological coagulation processes, and causes localised haemostasis at injury sites, both spontaneous and traumatic, with the capacity to correct the systemic coagulopathy associated with massive blood loss and its management. This review charts the development of rFVIIa as a new and potent adjuvant therapy for severe bleeding and coagulopathy caused by blunt trauma, where it is reported to produce rapid and significant haemostasis, reducing transfusion requirements and improving clinical outcome.

**Keywords:** blunt trauma, coagulopathy, haemorrhage, recombinant activated Factor VII, transfusion

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### 1. Introduction

Recombinant activated coagulation Factor VII (rFVIIa) (eptacog alpha [activated], NovoSeven<sup>®</sup> [Novo Nordisk A/S, Bagsvaerd, Denmark]) was first developed for the treatment of bleeding in haemophilia patients with inhibitors (antibodies) against Factors VIII or IX, following reports of the successful use of plasma-derived activated Factor VII to control clinical bleeds in these patients [1,2]. In addition to the management of bleeding episodes in haemophilia patients with inhibitors, rFVIIa has also been effective as a haemostatic agent for the management of other coagulation deficiencies characterised by impaired thrombin generation and life-threatening bleeding [3]. This article briefly reviews the development of rFVIIa as a biological agent, before focusing on evidence from clinical investigations, which show rFVIIa to have localised pro-haemostatic activity that helps reduce and control severe bleeding following blunt traumatic injury.

#### 1.1 Chemistry

The amino acid sequence of rFVIIa is identical to that of human, plasma-derived FVIIa (pdFVIIa) and the activities of rFVIIa and pdFVIIa are indistinguishable [3]. Recombinant FVIIa is a serine protease of 406 residues, which is manufactured via a transfected baby hamster kidney cell line, using human FVII cDNA as the source, and purified through three ion-exchange steps and one immunoaffinity chromatography step, where this latter stage ensures completion of the auto-activation of rFVII to activated rFVII (rFVIIa) [3].

### 1.2 Mode of action

According to the accepted cell-based model of coagulation, the process of clot formation and eventual haemostasis begins with vessel injury and the subsequent interaction between cell-derived tissue factor (TF) and blood-borne FVIIa [4,5]. This initial interaction and the formation of a TF/FVIIa complex allows activation of Factors IX and X, and is crucial in generating the first small amounts of thrombin essential to the amplification and propagation phases of coagulation. During amplification, FXa complexes with FVa to generate thrombin and subsequently activate Factors V and VIII, and platelets. Thereafter, activated platelets at the site of bleeding provide the template for further thrombin generation and the full 'thrombin burst' needed for the formation of a stable fibrin plug. At supraphysiological or pharmacological doses, rFVIIa also directly activates FX on the surface of locally activated platelets, helping to generate thrombin and further augment the coagulation process (Figure 1). However, rFVIIa does not bind to resting platelets. Instead, the effect of rFVIIa is localised to the sites of vessel injury where TF is exposed and platelets are activated [3]. Hence, rFVIIa has a unique mode of action, and works by producing a stable fibrin clot directly at the site of vascular injury both dependently and independently of TF [4,6-8].

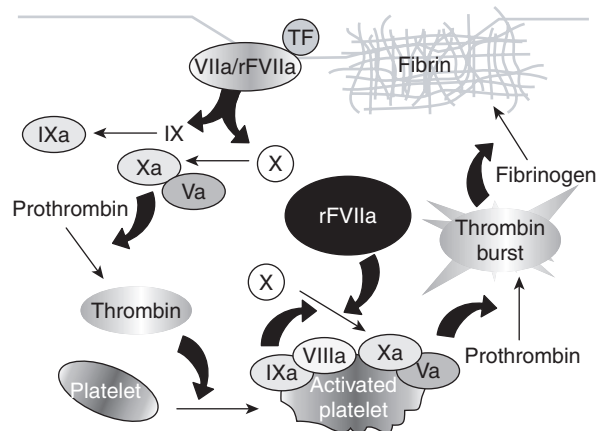
### 1.3 Pharmacokinetics and pharmacodynamics

The pharmacokinetics of rFVIIa have been studied extensively in adult and paediatric haemophilia patients, as well as in adults with acquired FVII deficiency (healthy adult volunteers pretreated with acenocoumarol and patients with liver cirrhosis) and healthy Caucasian and Japanese adults [9,10]. The clearance and half-life values of rFVIIa after bolus drug administration range from 2.4 to 3.2 h in adults, are slightly different in children where half-life is shorter (1.3 h) and clearance higher, but are not otherwise affected by patient gender or ethnic origin [9-12].

### 1.4 Safety and tolerability

Since the launch in 1996 of rFVIIa for use in patients with serious bleeding disorders, there have been well over 700,000 doses of rFVIIa given to several thousand patients, and the serious adverse event rate reported to date during use of this treatment is in the range of 1 – 2% [13-15]. Data from the Hemophilia and Thrombosis Research Society Register in the US also describe rFVIIa for treatment of haemophilia bleeds at doses up to 346 µg/kg as a treatment with a wide safety margin [16].

Under normal physiological conditions, only 1% of endogenous FVII circulates as FVIIa [3]. Administration of rFVIIa effectively elevates the level of activated FVII by 1000-fold; however, as described in the mechanism of action section above, even this amount of circulating activated FVII should not result in clotting in the absence of functional TF to initiate the process of coagulation. Thus, the mechanism of therapeutic rFVIIa-induced coagulation and haemostasis is



**Figure 1. The mode of action of rFVIIa – effecting local haemostasis at injury sites.** The mechanism of action includes the binding of endogenous Factor VIIa to exposed tissue factor. This complex activates Factor IX into Factor IXa, and Factor X into Factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and Factors V and VIII at the site of injury and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of rFVIIa activate Factor X directly on the surface of activated platelets, localised to the site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor.

rFVIIa: Recombinant activated Factor VII; TF: Tissue factor.

effectively localised at sites of vessel injury and is not typically associated with systemic or diffuse clotting [5].

Although thromboembolic complications due to the use of rFVIIa are rarely seen in clinical practice, these remain the most frequent and serious complications following the administration of rFVIIa [15] and include myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism and other forms of thrombotic occlusion. Such events have typically occurred in patients with underlying pathological conditions predisposing to thromboembolic complications, where it is assumed plaque rupture and activation of platelets at pathological sites predisposes to thrombosis during the attempt to correct the patient's concomitant hypocoagulable state using rFVIIa [13]. Risk factors for thromboembolic events include increased age, atherosclerosis, postsurgical immobility, crush injury and septicaemia.

In a recently published clinical study of rFVIIa in acute intracerebral haemorrhage (ICH), the overall frequency of fatal or disabling thromboembolic serious adverse events did not differ significantly between the rFVIIa and the placebo groups. Arterial thromboembolic serious adverse events occurred significantly more frequently with rFVIIa treatment than with placebo [17]. These adverse events were primarily in the form of myocardial ischaemic events and cerebral infarction within 3 days after the study drug was given. The

majority of patients recovered from these complications. The authors subsequently stated that in a preliminary analysis of all 485 patients with ICH enrolled in three Phase II trials conducted to date [17-19], a previous history of thromboembolic disease did not predict acute thromboembolic complications when rFVIIa was administered [20].

Thus, although there are concerns over diffuse thrombosis during clinical use of rFVIIa, there is positive support for its safety profile [13] and, indeed, a recent report on the use of rFVIIa in the management of bleeding associated with traumatic injury [21] and meta-analyses of data for patients with severe bleeding managed by rFVIIa, where adverse events have been recorded [15], suggest no increase in the rate of thromboembolic complications with the use of rFVIIa for traumatic bleeding.

### 1.5 Current approved clinical indications

Highly purified recombinant coagulation factors, free of human viruses and any added human protein, have greatly improved the safety and convenience of treatment for congenital and acquired haemophilia. In 1999 the US Food and Drug Administration approved rFVIIa for the treatment of spontaneous bleeding in patients with haemophilia A or B, with known inhibitors to FVIII or FIX. In the EU, rFVIIa is also licensed for the treatment of spontaneous and surgical bleeding in haemophilia A and B patients with inhibitors against FVIII and FIX, respectively, as well as for use in acquired haemophilia, in patients with congenital Factor VII deficiency undergoing surgery or invasive procedures, and in patients with Glanzmann's thrombasthenia with antibodies to blood platelets, glycoprotein IIb/IIIa and/or human leukocyte antigen [22-35].

### 1.6 Preclinical studies of rFVIIa in traumatic bleeding

Animal models for the study of the haemostatic effects of rFVIIa are limited by interspecies differences in coagulation molecule interactions [36,37]. Changes in coagulation parameters seen with the use of human rFVIIa in animals may not correlate with haemostatic end points, and little can be drawn from such studies regarding optimal dosing of rFVIIa in humans [3]. However, in the investigation of rFVIIa as a potential treatment for haemorrhage following injury, a number of animal models have been developed and used to assay the efficacy and safety of rFVIIa. Trauma models using swine, which attempt to mimic liver injury, have shown that treatment with rFVIIa administered immediately after injury is associated with statistically significant reductions in blood loss and mortality, even in animals where a coagulopathic state was induced [38-42].

## 2. Clinical application of rFVIIa – the context for study in trauma

As mentioned previously, rFVIIa has been used in haemophilia for a number of years, where it is associated with prompt,

effective haemostasis, offering 84 – 97% efficacy when used as home treatment for bleeding episodes [14,16,22,24]. Treatment of haemophilia with inhibitors using rFVIIa, in the hospital and in home settings, is cost-effective when compared with the use of activated prothrombin concentrate [43-45].

Successful use of rFVIIa in management of haematological diseases has prompted investigation of this biological agent in other clinical settings where uncontrollable bleeding poses morbid and lethal threats. For example, rFVIIa has been investigated as a treatment for the excessive bleeding that often follows orthotopic liver transplantation. A recent open-label dose-finding study found that intravenous injection of 80 µg/kg 10 min before the start of transplantation significantly reduced transfusion requirements and blood loss [46], and larger-scale, double-blinded studies also support the efficacy of single-dose preoperative rFVIIa in reducing patient requirement for transfusion products without any increase in the incidence of thromboembolic complications [47-48].

Another area of high unmet clinical need where treatment with rFVIIa has recently been found to have a significant effect on haemorrhage with resultant improvements in clinical outcome is in the management of acute, non-traumatic ICH [17]. In a double-blind, placebo-controlled, study in patients with acute ICH, the effects of treatment with 40 µg/kg (108 patients), 80 µg/kg (92 patients) or 160 µg/kg (103 patients) rFVIIa versus placebo (96 patients) given within 1 h of a diagnostic CT scan were compared in terms of haemorrhage growth at 24 h, deaths and functional outcome at 3 months. Compared with a 29% haematoma growth in placebo-treated patients, ICH volume growth in the rFVIIa treatment groups was 16, 14 and 11%, respectively. Thus, pooled data for all doses of rFVIIa showed that treatment resulted in a 52% relative reduction in haemorrhage growth compared with placebo ( $p = 0.01$ ). Three months after ICH, mortality was 29% in the placebo group versus 18% in the three rFVIIa treatment groups combined, a relative reduction in patient mortality of 38% ( $p = 0.02$ ). The lower mortality rate in the rFVIIa group was not associated with an increase in severe disability. Acute rFVIIa treatment effected an absolute reduction in risk of death or severe disability by 16% (95% confidence interval [CI] 5 – 27;  $p = 0.004$  all doses versus placebo), and more than doubled a patient's chances of improving one level on the modified Rankin Scale.

## 3. Severe haemorrhage following blunt trauma

Perhaps one of the most challenging areas in which severe critical bleeding is recognised to be a major contributor to high rates of morbidity and mortality is that of traumatic injury. Trauma is a growing burden to society, accounting for 10% of worldwide deaths, remaining the number one killer among people aged 15 – 44 years and accounting for half of all deaths in this age group [49-51]. Early, uncontrolled haemorrhage is responsible for ~ 40% of all trauma fatalities [49,52-54].

Trauma affects a young, productive and otherwise healthy section of the population. The costs of traumatic injury extend much beyond that measured by the number of deaths.

There is a long-lasting burden on the survivors in terms of pain, suffering, permanent physical and/or mental disability, altered quality of life and loss of productive work years. Although the study of the economic impact of trauma is complex, it can be summarised as follows: the more severe the injury, the greater the health economic and social burden [55,56].

Well-established principles of haemorrhage management include prompt control of the source of bleeding – with surgery and/or angiographic embolisation – accompanied by replacing circulating volume losses, red blood cells (RBC) and coagulation factors. In combination with the body's natural haemostatic responses, these management principles hold the key to managing traumatic bleeding. However, despite strict adherence to these principles, many patients still die from traumatic bleeding, revealing the limitations of the existing management strategies [60]. Many of these deaths are potentially preventable [54,57].

Severe multiple injuries, blood losses and consumption of coagulation factors can lead to rapid exhaustion of the coagulation system [21,57,58], resulting in diffuse bleeding [21,54,57-60]. Resuscitation with large volumes of crystalloids, colloids and packed RBC also conspire to aggravate the haemorrhage and coagulopathy by diluting platelets and coagulation factors essential for clotting and systemic haemostasis [61]. Hypothermia and acidosis further impair coagulation enzyme activity and platelet function. The combination of coagulopathy, acidosis and hypothermia is referred to as the 'lethal triad' [57,60]. Once patients enter the 'lethal triad', even aggressive rewarming and massive blood product administration (fresh plasma, platelets, cryoprecipitate) are sometimes insufficient to correct the coagulopathy and prevent death.

Although blood products are a mainstay in the management of blood loss, their use is not without risks [62]. In patients with severe traumatic injury, there is a known correlation between rising transfusion requirements and an increased risk of multiple organ failure (MOF) and worsened clinical outcome [63,64]. More than 50% of massively transfused (> 50 units of blood products) trauma patients do not survive their hospital stay [65]. MOF and transfusion-related acute respiratory distress syndrome (ARDS) increase the trauma patient's length of stay both in the intensive care unit and in hospital [66,67]. Hence, effective management of bleeding in trauma has the potential to decrease both morbidity and mortality [68,69].

These facts point to the urgent need for new approaches to the current standard management of haemorrhage. A number of agents are under investigation at present for use as adjunct therapy in haemorrhage control, including local haemostatic agents, such as fibrin sealants, and systemic pro-coagulant/antifibrinolytic agents, such as aprotinin, tranexamic acid, DDAVP (1-deamino-8-D-arginine vasopressin) and aminocaproic acid. To date, clinical studies with these agents have

demonstrated less than satisfactory haemostatic effects in trauma. A recent Cochrane review reported insufficient evidence from randomised controlled trials (RCTs) of antifibrinolytic efficacy in acute traumatic bleeding [70].

### 4. rFVIIa for management of haemorrhage following trauma

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#### 4.1 Current evidence

Since the first report documenting the successful use of rFVIIa to manage trauma coagulopathy following a gunshot wound [71], interest has been fuelled in the potential for a role for rFVIIa in the management of haemorrhage associated with traumatic injury [15,21,57,58,61,72-74].

Traumatic injuries can be broadly categorised as either penetrating or blunt. Penetrating traumatic haemorrhage commonly involves large vessels and is often successfully managed by prompt surgical intervention. In contrast, blunt trauma frequently compromises several systems and organs concomitantly, with different sources of bleeding that are less readily correctable by surgery alone. Given our understanding of both the pathophysiology of traumatic haemorrhage and the known mechanism of action of rFVIIa, it is logical to consider that rFVIIa would have the most impact in the management of bleeding caused by blunt traumatic injury. However, the benefits of rFVIIa have also been demonstrated in patients with penetrating trauma. Hence, cases may present where it might be appropriate to attempt control of penetrating traumatic haemorrhage with rFVIIa.

There have been a number of case reports and case series in recent years describing the use of rFVIIa for the management of severe traumatic haemorrhage, including blunt trauma [21,61,75-78]. Wide ranges of doses of rFVIIa have been described, with the initial rFVIIa doses varying in the range of 40 – 212 µg/kg. The most recent report of a case series by Martinowitz *et al.* [21] recorded successful cessation of bleeding in 26 of 36 patients (72%) with rFVIIa. Forty-four per cent of the entire cohort had a penetrating injury, 42% blunt injury and 14% blast injury, and all patients were critically ill, suffering massive, life-threatening bleeds. Patients had received a median of 21 units of packed RBC prior to administration of rFVIIa. The survival rate of 61% (22 of 36) at 90 days was favourable compared with published series of trauma patients with massive bleeding treated only with blood products (range 30 – 57%). The large case series of Dutton *et al.* [61], reported data for 81 patients, 46 of whom had acute traumatic haemorrhage (other causes of bleeding were traumatic brain injury [20], warfarin use [9], congenital Factor VII deficiency [2] and acquired haematological defects [4]). Patients had received at least 10 units of RBC prior to rFVIIa administration. Correction of coagulopathy was achieved in 75% of patients in the entire series with a dose of ~ 100 µg/kg. Thirty-four patients (43%) survived to hospital discharge (20 of 46 traumatic haemorrhage, 5 of 20 traumatic brain injury, 9 of 15 other). Although 18 of

20 patients with traumatic brain injury responded to rFVIIa therapy, with sustained cessation of haemorrhage, the long-term outcome in this patient group was poor. This was most likely due to the severity of brain trauma, as coagulopathy in these patients generally indicates significant pathology.

Another interesting point in the current literature is the suggestion that the actual extent of injury-related coagulopathy is often underestimated due to limitations of the coagulation tests (such as PT, PTT, platelet count and brinogen levels) [21]. Laboratory tests are carried out at a standard temperature of 37°C, thus failing to detect hypothermia-related coagulopathy. Furthermore, they may take 60 min from blood sampling to availability of results. As the haemostatic status of trauma patients with massive bleeding changes rapidly, the results, therefore, might not reflect the patient's current status [21].

#### 4.2 The first randomised controlled trial in trauma

Two parallel, multi-centre, double-blind studies (one in blunt trauma, one in penetrating trauma) were conducted simultaneously to evaluate the efficacy and safety of rFVIIa in patients with severe traumatic bleeding, defined as the transfusion of 6 units of RBC within 4 h of admission to a trauma or emergency care centre. The first dose of the trial product was administered after transfusion of the eighth unit of RBC. Eligible patients received either three infusions of rFVIIa, 200 µg/kg, 100 µg/kg and 100 µg/kg administered at entry and 1 and 3 h later, respectively, or placebo, in addition to local standard surgical treatment to manage haemorrhage. Key exclusion criteria included gunshot wound to the head, Glasgow Coma Score below 8, base deficit > 15 mEq/l or severe acidosis with pH < 7, and injuries sustained ≥ 12 h before randomisation. The primary outcome was a reduction in RBC transfusion requirement during the first 48 h after treatment dosing. The secondary outcome consisted of clinical outcomes and safety [79-81].

Even though the RCT demonstrated that rFVIIa is efficacious in both blunt and penetrating traumas, its beneficial effects were more apparent in blunt trauma patients. Among the entire cohort of patients with blunt trauma who received rFVIIa treatment (143 patients), there was a trend towards a decrease in RBC transfusion ( $p = 0.07$ ) in the first 48 h after treatment. When patients who died within the first 48 h were excluded from the primary end point analyses (an *a priori* decision to exclude possible unpreventable deaths), the reduction in RBC requirement was significant, producing an estimated reduction of 2.6 total RBC units per patient (90% CI, 0.7 – 4.6;  $p = 0.02$ ).

In this same cohort of blunt trauma patients, the need for massive transfusion – defined as > 20 units of RBC – was significantly reduced by rFVIIa treatment. Whereas 33% of patients with blunt trauma in the placebo group required massive transfusion, this figure was reduced to 14% for the group given rFVIIa ( $p = 0.03$ ), a relative risk reduction of 56% (95% CI, 9 – 79%). There were also significant reductions in the 48-h requirement for fresh frozen plasma and

platelets in the rFVIIa treatment arm. The improved haemostasis in patients receiving rFVIIa was followed by a significant reduction in ARDS from 18 to 5% ( $p = 0.047$ ) and a significant decrease in the risk of MOF and/or ARDS (from 25 to 9%;  $p = 0.047$ ) [79,82]. There was also a trend towards more intensive care unit-free days in the treated patients.

It should be noted that in this study the selection criteria were specifically targeted at severely bleeding trauma patients who had already received 6 units of RBC within a 4-h period at randomisation, that is, a selected target population most likely to benefit from rFVIIa treatment. In addition, bias in investigator assessments may have been introduced in cases where routine monitoring of prothrombin time could have potentially revealed whether a patient had received rFVIIa or placebo. Differences in patient management across regions and trial centres were also expected, despite adherence to the study protocol, because of the complexity of the study and diversity of choices faced by trauma teams, although the effect of treatment was shown to be independent of site ( $p = 0.24$  for site versus treatment interaction).

The rFVIIa dose used for this trial (200 µg/kg followed by two additional doses of 100 µg/kg) is frequently debated as it is higher than the doses used in most reports to date. This dose was based in pharmacokinetic models designed to achieve mean plasma levels proven effective in haemophilia patients or 40 U.ml.kg<sup>-1</sup>.h<sup>-1</sup>, but in patients that are actively bleeding. A full pharmacokinetic analysis was performed as part of this study to determine whether this dose achieved the desired FVIIa plasma coagulation levels. This analysis has been submitted for publication and the results are eagerly awaited.

#### 4.3 Conclusions from the current evidence

The findings reported in case series and on the RCT offer some guidance for clinical practice. They suggest that prompt treatment with rFVIIa in trauma patients with severe bleeding, often coagulopathic and unresponsive to conventional treatment, results in effective and safe control of haemorrhage, particularly in blunt trauma. Recombinant FVIIa significantly reduces transfusion requirements and, in particular, the need for massive blood transfusion and the associated risks to patients in critical care settings. rFVIIa rapidly controls critical bleeding in trauma patients. The evidence, to date, in blunt trauma patients continue to support the observation that rFVIIa has a good safety profile, associated with no reported increase in serious adverse events such as thromboembolic events.

#### 5. Expert opinion

More than 80% of all trauma patients admitted to the authors' institution, Sunnybrook and Women's College (SW), are victims of blunt trauma. While 55% of the 1100 traumatised adult patients treated at SW require blood transfusions soon after admission, 6% are massively transfused (> 20 U of RBC transfusion), not infrequently compromising the entire city blood supply.

Haemorrhage is common in trauma and is a major cause of death. Blunt trauma patients are among the largest consumers of blood. In a time when blood products are scarce, costly and increasingly recognised as risk factors for organ dysfunction and sepsis, there is a pressing need for improvements in haemorrhage management in trauma. Recombinant FVIIa has been proposed as a new therapy for traumatic haemorrhage.

We recently reviewed the SW experience with the 'off-label' use of rFVIIa in trauma to investigate both its efficacy and guidelines for its use. Over 5 years, rFVIIa has been administered to 45 severely injured (mean Injury Severity Score 42.7; 95% CI, 40.6 – 44.9) trauma patients at SW – two-thirds were blunt trauma victims.

In our experience, rFVIIa was often used late as a 'last resort' therapy, when conventional therapies failed. By the time rFVIIa was used, all patients were coagulopathic (mean International Normalised Ratio [INR] 2.7; 95% CI, 1.1 – 4.2), acidotic (mean base deficit 9.8 mmol/l; 95% CI, 7.4 – 12.2) and hypothermic (mean temperature 33.7°C; 95% CI, 32.7 – 34.7) – a condition called the 'lethal triangle' for a reason. On a few occasions rFVIIa was administered to patients with no chances of survival. Even considering that rFVIIa may not have always been appropriately used – due to the absolute lack of guidelines on its use in trauma until now – the haemostatic effects of rFVIIa were still impressive. Haemorrhage was controlled in two-thirds of these *in extremis* patients, with a marked reduction in the need for RBC, fresh plasma and platelet transfusion after rFVIIa. The reduction in the need for transfusion remained statistically significant even after deaths were excluded. The results were always superior in blunt trauma patients compared with penetrating trauma patients.

Over time, we gradually increased the initial doses of rFVIIa (from ~ 40 to 130 µg/kg), with a subjective improvement in haemostasis and without any apparent increase in side effects, including thromboembolic complications. The doses were repeated up to 3 times, but only 30% of the patients required > 1 dose.

For the sake of comparison, we identified a similar group of trauma patients admitted to SW during the same time period and matched by Injury Severity Score and number of RBC transfusion in the first 24 h but not receiving rFVIIa. The characteristics of this group of patients were also similar to the group treated with rFVIIa in gender, mechanism of injury, presence of head injury, coagulopathy, arterial pH, base deficit, lactate and body temperature.

As no bleeds are the same, patients were classified according to the rate of blood transfusion, or the number of units of RBC transfused per hour. Whereas 27% of the control patients being transfused < 2 U/h died, there were no deaths in the rFVIIa group ( $p < 0.05$ ). Among those transfused 2.1 – 4 U/h, the mortality in the rFVIIa group was approximately half that of the control group ( $p < 0.05$ ). The mortality was equally high in both groups for the patients bleeding extremely fast

(rate of transfusion > 4 U/h). The same comparison was performed including only blunt trauma. Among blunt patients, the survival with rFVIIa was significantly higher than control for all rates of transfusion, even above 4 U/h, thus confirming the suspicion that rFVIIa has a more pronounced effect in blunt trauma. Logistical regression analysis revealed that head injury, blood pH and the use of rFVIIa were independent predictors of survival in our population.

## 6. Expert recommendations

Based on the current evidence and our own experience, we believe that rFVIIa is both efficacious and safe as an adjuvant therapy for the treatment of severe traumatic haemorrhage, particularly in blunt trauma, where both the reduction in the need for blood transfusion and survival rates are higher than in penetrating trauma.

Recombinant FVIIa is an additional tool and not a substitute to the existing principles of haemorrhage management. Surgical control of the bleeding, replacement of circulating volume, RBC and clotting factors must be vigorously pursued while preventing and/or treating acidosis, hypothermia and coagulopathy. Suggested targets are to maintain the haemoglobin > 70 g/l, INR < 1.5, platelets >  $50 \times 10^9/l$  and fibrinogen > 1 g/l. We also suggest using bicarbonate to elevate the serum pH > 7.1, as rFVIIa seems to be much less effective below this level – a concept that remains unproven. It should be noted that bicarbonate has not been shown to provide benefits to patients in haemorrhagic shock.

Published evidence suggests that rFVIIa should be considered early, for any patient that continues to bleed after 6 – 8 units of RBC transfusion and/or have diffuse coagulopathy. The initial 100 µg/kg dose appears sufficient if repeated in 15 – 30 min when the bleeding persists. The RCT results are compelling with a much higher initial dose, 200 µg/kg followed by two 100 µg/kg doses 1 and 3 h later [79]. In practice, an initial dose of 100 µg/kg repeated in minutes differs little from the proposed initial 200 µg/kg dose. Considering the strength of the evidence, the higher initial dose is justifiable. However, the authors believe that subsequent doses should only be given when the bleeding persists. All reports to date, including our own experience, suggest that rFVIIa is a safe drug for use in trauma.

It may seem obvious, but a final recommendation when using this new, potent, safe and fascinating therapy is to ascertain that it will be used in patients with chances of survival.

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