

ORIGINAL PAPERS

Clinical experience with recombinant activated factor VII in a series of 45 trauma patients

M Felfernig on behalf of the European rFVIIa Trauma Study Group

Abstract

Aim: Haemorrhage control is a major priority in the care of trauma patients in military as in the civilian setting. About 50% of combat deaths are due to fatal bleeding. The aim of this analysis was to assess the efficacy and safety of recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) when used to treat trauma-related blood loss

Patients and methods: Forty-five patients aged 5–81 years (mean age 30.5 years) received rFVIIa (mean dose 73.6 µg/kg) for the management of trauma-related bleeding. Trauma was classified as blunt (n = 42) or penetrating (n = 3). The primary outcome measure was reduction of transfusion requirements; improvements in coagulation status post-rFVIIa were also noted.

Results: Haemostatic efficacy was achieved in 43/45 (95.6%) patients following rFVIIa administration, and transfusion requirements (defined as median units of packed red blood cells administered in the 24-hour period following rFVIIa administration) were reduced from 10 to 3 units (P < 0.001). Coagulation status also showed improvement (median values for activated partial thromboplastin time and prothrombin time decreased from 43 to 37 s [P < 0.001] and from 19 to 12 s [P = 0.026], respectively). No safety concerns were raised by the available data.

Conclusions: As this analysis has several limitations that are unavoidable when using global registries to collect and analyse data, our findings are not conclusive. However, these preliminary observations especially in those patients who underwent very early rFVIIa treatment offer further support for the use of rFVIIa in trauma.

Keywords: rFVIIa; Trauma; Haemorrhage; Blood transfusion; Haemostasis

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Introduction

Trauma represents a major cause of mortality in both military action and civilian life, ranking among the leading causes of death in all regions and countries across the globe (1, 2). Indeed uncontrolled bleeding represents the leading cause of preventable combat related deaths (3). In the global setting, recent statistics show that injuries kill more than five million people each year, accounting for almost 1 in every 10 deaths worldwide (4).

Uncontrolled blood loss is the second most common cause of mortality in trauma victims (5–7), accounting for approximately one-third of all such fatalities (8). Importantly, haemorrhage also represents the leading cause of potentially preventable death in trauma (9), and is responsible for many early and immediate deaths following injury (10, 11). In the classical trimodal distribution of trauma mortality (12), blood loss is a major contributor to deaths in the first and second mortality peaks (at the scene and within 1 to 4 hours of the event, respectively) (13). By triggering inflammatory cascades, uncontrolled bleeding also contributes to late deaths that result from sepsis and multiple organ failure during the third

mortality peak (>4 hours after the event) (14, 15). Furthermore, the development of trauma-related coagulopathy can be a life-threatening complication in patients with significant injuries and blood loss (16). The pathogenesis of traumatic coagulopathy is complex and multifactorial (16), involving a combination of haemodilution, consumption of coagulation factors and platelets, metabolic derangements, and the development of disseminated intravascular coagulation (9, 16, 17). Thus, early control of haemorrhage and coagulopathy is vital to improve the clinical scenario and reduce the risk of mortality and morbidity in trauma victims (5, 18). In contrast to civilian blunt trauma patients who may have a “golden hour”, casualties with penetrating combat trauma often have a much shorter window for successful intervention. Failure to achieve haemorrhage control can exacerbate hypothermia, acidosis, and coagulopathy; this so-called ‘lethal triad’ (19) worsens haemostatic dysfunction and often leads to exsanguination (9).

The treatment of haemorrhage and haemorrhagic shock in trauma victims typically involves surgical intervention and compression or tamponading of the bleeding area, along with simultaneous transfusion of red blood cells (RBCs) and blood-derived products (fresh frozen plasma [FFP], platelet concentrates, and cryoprecipitate) (1, 5). However, several drawbacks to the use of blood and blood products have been identified. Numerous reports suggest that transfusion of RBCs significantly increases the risk of postoperative immunosuppression and infection (18,

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20–24), and administration of most fluids will reduce blood viscosity and dilute clotting factors, potentially leading to the development or worsening of coagulopathy (1).

These observations suggest that there remains a need for effective haemostatic treatment strategies that can rapidly minimise blood loss in trauma patients, thus reducing mortality from exsanguination and avoiding the need for massive transfusion. One such approach for the acute management of trauma victims may involve the use of procoagulant interventions to induce and maintain haemostasis (1).

Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Demark) is well established as an effective haemostatic therapy for spontaneous and/or surgical bleeds in haemophilia patients with antibodies to factors VIII or IX (25), and has recently been approved in Europe for the additional indications of Glanzmann's thrombasthenia and factor VII deficiency. A growing number of studies and anecdotal reports indicate that rFVIIa may also be effective in a variety of other coagulopathies (26–29) and in previously non-coagulopathic patients with surgery- or trauma-related haemorrhage (7, 30–37). Although there are no controlled studies, case reports about the use of rFVIIa in military settings have been published (38,39).

Here, we report our experience of rFVIIa use in the management of trauma-related haemorrhage in 45 patients from multiple institutions in various countries.

Patients and methods

This analysis included 45 trauma patients from Austria (n = 7), Australia (n = 5), Bulgaria (n = 2), the Czech Republic (n = 14), the Netherlands (n = 3), Poland (n = 11), Sweden (n = 1), and the UK (n = 2). All patients received rFVIIa between September 2000 and August 2003, and their details were reported on the rFVIIa extended-use database—Haemostasis.com. Inclusion criteria were trauma-related blood loss and clinician agreement for inclusion in the analysis. Some clinicians wished to report their cases of rFVIIa-treated trauma victims independently, and these cases are therefore excluded from this analysis. All other cases of rFVIIa-treated traumatic haemorrhage registered on the database between September 2000 and August 2003 were included.

Haemostasis.com is an anonymised, web-based repository for data on the experimental use of rFVIIa. The database is organised by Novo Nordisk A/S, the manufacturer of rFVIIa, but is administered by an independent third party under the supervision of an academic steering committee. These activities are supported by an unrestricted grant from Novo Nordisk A/S.

Efficacy

The main efficacy outcome was a reduction in blood loss, as measured by decreased transfusion requirements (packed RBCs [PRBCs], FFP, and platelets) in the 24-hour period following rFVIIa administration. A secondary outcome measure was improved coagulation status assessed via activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen levels.

Safety

Treatment safety was determined by the number of serious adverse events that were considered to be possibly or probably related to rFVIIa administration.

Statistical analysis

The transfusion requirement data and coagulation status data did not conform to a Gaussian distribution and were therefore described by median values and 90% ranges (calculated from the 5th and 95th percentiles of the distribution) rather than arithmetic means. Paired comparisons between pre- and post-

treatment data were made using the nonparametric Wilcoxon test. All patients were included in the analysis. Further data summaries were produced for patients with blunt versus penetrating trauma to determine whether treatment efficacy was influenced by trauma type. However, owing to the small sample size of the penetrating trauma group (n = 3), the data could not be formally compared between the groups. A P value of less than 0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 11; SPSS Inc., Chicago, IL, USA).

Results

Patients

Patient characteristics and status on admission to hospital, including the cause/location of trauma and blood loss, are shown in Table 1. The majority of patients (37/45 [82.2%]) were male. Forty-two patients (93.3%) had blunt injuries while three patients (6.7%) had penetrating trauma. The mean patient age was 30.5 years (range, 5–81 years). Of patients for whom data are available, 21/43 (48.8%) had low blood pressure (systolic pressure \leq 90 mmHg) on admission to hospital, and 17/38 (44.7%) had hypothermia (body temperature \leq 35°C) (Table 1).

rFVIIa dose

Overall, the mean total dose of rFVIIa administered was 73.6g/kg (SD, 27; range, 13.0–163.6 g/kg) and the median number of doses required was 1 (range, 1–19). The majority of patients (30/45 [66.7%]) required just one dose; 12 patients (26.7%) received two doses, 2 patients (4.4%) received three doses, and 1 patient (2.2%) required 19 doses (patient No. 26) (Table 2).

The requirement for such a high number of doses for a relatively minor injury might indicate that this patient suffered from an undiagnosed coagulation disorder; however, this cannot be confirmed.

The mean dose administered to patients with blunt trauma was 73.0g/kg, compared with 83.8g/kg in the penetrating injury group. Two or more doses were required in 14/42 (33.3%) blunt trauma patients and in 1/3 (33.3%) evaluable patients with penetrating injury. Of the 31 patients for whom data are available, 12 (38.7%) received rFVIIa within 1 hour of bleed onset; the median time to rFVIIa administration post-onset of bleed was 3.0 hours (range, 0.17 hours–52 days; n = 31) (Table 2).

Efficacy

Following administration of rFVIIa, bleeding stopped or markedly decreased in 37 patients (82.2%). Blood loss was described as "reduced" in 6 patients (13.3%; patient Nos. 14, 16, 18, 19, 40 [blunt] and 43 [penetrating]), and 2 patients (4.4%) failed to respond to rFVIIa treatment (patient Nos. 3 and 31 [blunt]).

Transfusion requirements

Data from all patients indicate median PRBC requirements of 10.0 units (90% range, 0–40.1 units) before rFVIIa treatment, and 3.0 units (90% range, 0–29.2 units) in the 24-hour period following rFVIIa dosing (P < 0.001) (Fig. 1). The median number of FFP units administered was 7.0 (90% range, 0–25 units) and 3.0 (90% range, 0–31.7 units) pre- and post-rFVIIa, respectively (P < 0.005), and median platelet requirements remained at 0 units (90% ranges, 0–13.1 and 0–9.7 units before and after rFVIIa, respectively; Fig. 1).

In patients with penetrating injuries, PRBC requirements decreased from 0–35 units before treatment to 0–7 units after treatment; FFP requirements decreased from 0–16 units to 0–3 units, whilst requirements for platelet transfusion decreased from 0–8 to 0 units.

Patient No.	Age (years)/sex (M/F)	Trauma and site/cause of bleeding	Blood pressure (mmHg)	Body temperature (°C)	pH	Haemoglobin (g/dl)
Blunt trauma						
1.	9/M	RTA polytrauma: splenic lesion; pulmonary contusion; craniofacial trauma; skull base fracture; intracerebral contusion; blow-out fracture. Blood loss from tracheal tube, nose, and ears	120/80	35.2	7.1	9.6
2.	27/M	RTA polytrauma: multiple fractures involving skull, spine, and limbs	120/70	35.0	7.3	12.4
3.	31/M	RTA polytrauma: fractures and arterial injury to limbs and pelvis. Below-knee amputation of right leg	160/80	33.0	7.3	7.1
4.	25/F	Fall (suicide attempt): fractured pelvis and thoracic injury	80/40	35.7	7.3	6.8
5.	47/M	RTA: haemopneumothorax, multiple rib fractures	90/66	ND	7.4	9.0
6.	44/M	RTA polytrauma: Right haemothorax; injuries to inferior vena cava and right kidney; pelvic fracture with arterial bleeding	60/ND	33.2	7.3	5.2
7.	41/M	RTA polytrauma: bilateral haemopneumothorax; left tension pneumothorax; multiple liver and splenic lacerations; pelvic and limb fractures.	70/38	ND	6.8	8.2
8.	81/M	RTA: pelvic fracture; bilateral haemopneumothorax; retroperitoneal haematoma; external bleeding from scalp, elbow, lower extremities	80/ND	34.6	7.2	8.2
9.	28/M	RTA polytrauma: ruptured bladder; fracture of tibia; open-book pelvic fracture	90/ND	ND	7.1	6.1
10.	27/M	RTA polytrauma: pulmonary and brain contusions; subarachnoid haemorrhage; upper gastrointestinal bleed	80/40	37.8	7.3	6.2
11.	11/F	Fall: multiple skull fractures; brain contusion; liver rupture; pelvic fracture; haematomas in pancreas and retroperitoneal space; pulmonary haemorrhage	60/40	36.0	6.9	9.7
12.	15/M	Injury while playing: severe abdominal injury including partial loss of vena cava. Massive blood loss during laparotomy	63/33	31.0	7.1	6.5
13.	8/M	RTA: pelvic injury including bladder laceration, injury to rectum and urethra; cerebral commotion. Massive bleeding during pelvic surgery	91/40	34.5	7.2	ND
14.	5/M	RTA: bleeding from mediastinum, liver, spleen	97/51	34.0	7.3	4.9
15.	12/F	RTA: femoral fracture; blood loss from liver, spleen, and both pleural cavities; coma	99/51	36.0	7.1	8.2
16.	48/M	Polytrauma: pelvic fracture with arterial injury; bladder perforation; urethral laceration; femoral fracture with arterial injury	60/40	36.0	7.1	8.5
17.	49/M	Polytrauma: lung contusion; haemorrhagic shock; fractures of pelvis, vertebrae, ribs, and femur	130/60	38.2	7.2	6.6
18.	10/M	RTA: craniofacial fractures and intracranial bleeding	81/58	36.8	7.2	6.6
19.	54/M	RTA: limb and pelvic fractures with arterial injury. Intra-operative bleeding during surgical intervention	145/70	36.0	7.3	8.4
20.	38/M	RTA: thoracic trauma: haemothorax; pericardial lacerations; multiple fractures to ribs and sternum; cardiac, pulmonary, and mediastinal contusions	100/60	36.1	7.2	4.7
21.	50/M	RTA: thoracic trauma: haemothorax; pulmonary contusion; pulmonary bleeding	110/60	37.8	7.3	7.2
22.	30/M	RTA polytrauma: open-book pelvic fracture; rupture of perineum and bladder; cardiac and pulmonary contusion. Laparotomy, suture of bladder and liver, fixation of pelvis	90/60	33.0	7.1	8.4
23.	25/M	RTA polytrauma: abdominal and pulmonary contusion; pelvic fracture with arterial injury; liver rupture; fracture of limb with arterial injury. Laparotomy, stabilisation of pelvis, osteosynthesis of the limbs	110/40	34.0	7.1	5.2
24.	8/M	Fall into outlet cesspool: head contusion, cerebral commotion, near-drowning; cardiac arrest; anoxia with reperfusion syndrome. Bleeding due to disseminated intravascular coagulation of respiratory, gastrointestinal, and urinary tracts	63/35	35.0	6.6	5.3
25.	24/F	RTA: head, thoracic, and abdominal injury (rupture of liver and spleen with haemoperitoneum)	100/60	36.2	7.2	10.7
26.	9/M	Fall onto right knee leading to continued bleeding	118/65	ND	ND	6.1

Patient No.	Age (years)/sex (M/F)	Trauma and site/cause of bleeding	Blood pressure (mmHg)	Body temperature (°C)	pH	Haemoglobin (g/dl)
Blunt trauma						
27.	25/M	RTA polytrauma: skull base fracture; intracerebral bleeding; left pneumothorax; liver rupture	123/60	35.9	7.6	ND
28.	16/M	RTA: liver rupture; right renal artery rupture; right pulmonary contusion	100/60	ND	ND	ND
29.	38/F	Attempted suicide (pedestrian collision with motor vehicle): laceration to liver; haemorrhagic shock.	ND	ND	ND	ND
30.	27/M	RTA polytrauma: fractures to ribs and pelvis; right pneumothorax	100/60	36.6	7.31	6.0
31.	64/M	RTA polytrauma: craniocerebral injury; intracranial haemorrhage; thoracic injury; retroperitoneal bleeding; multiorgan failure.	Not detectable	33.1	ND	7.4
32.	18/M	Polytrauma: rupture of diaphragm, abdominal vena cava, and liver	60/30	34.2	7.23	8.1
33.	24/M	RTA: femoral and pelvic fracture; disruption of urethra, bladder, anus, and anal sphincter	90/50	35.8	7.31	11.2
34.	19/F	RTA: injury to right kidney (Moore classification Grade III); retroperitoneal haematoma; fractures to skull and pelvis	100/50	34.0	7.29	9.7
35.	47/M	RTA: pelvic injury and right femoral fracture. Massive blood loss from liver lobe and retroperitoneal space during surgical revision of abdomen	50/0	35.2	7.29	11.6
36.	14/M	RTA polytrauma: liver rupture; cerebral contusion; right rib fracture; right pulmonary contusion; left femoral fracture. Massive blood loss from ruptured liver into abdominal cavity	60/0	36.0	7.12	9.3
37.	20/F	RTA: rupture of right liver lobe; facial skull fracture	60/20	36.0	7.3	12.2
38.	36/M	RTA: spleen laceration; rupture of kidney	50/0	34.8	7.2	10.1
39.	32/M	RTA: open-book pelvic fracture; rupture of bladder; bleeding from mesentery of the jejunum	70/40	33.0	7.2	13.2
40.	45/M	Work-related thoracic crush injury. Massive bleeding during surgery	160/115	35.7 (6h post-admission)	7.1	13.0
41.	53/M	RTA polytrauma: bilateral pneumothorax; bilateral femoral fractures; multiple rib fractures	130/80	37.0	7.1	ND
42.	30/M	Crush injury: open pelvic fracture and rectal perforation.	110/78	ND	ND	ND
Penetrating trauma						
43.	48/F	GSW to the head (suicide attempt). Blood loss from the mouth	105/50	34.8	7.2	8.9
44.	44/M	GSW to chest: haemopneumothorax	104/70	36.0	7.3	9.2
45.	17/M	GSW to abdomen; massive oozing from surgical wounds following revision of abdomen	50/ND	34.2	7.0	7.6

Table 1. Patient characteristics and status on admission to hospital

RTA – Road Traffic Accident GSW – Gunshot Wound ND – Not Documented

Among patients with blunt injuries, median PRBC transfusion was reduced from 10.0 units (90% range, 0–40.6) pre-administration to 3.0 units (90% range, 0–30.1 units; $P < 0.001$) post-administration, and median FFP requirements decreased from 7.0 (90% range, 0–25.0 units) to 3.0 units (90% range, 0–34.9 units) before and after rFVIIa, respectively ($P = 0.006$). Finally, median platelet requirements remained at 0 units among this subgroup (90% ranges, 0–13.6 units before and 0–9.9 units after rFVIIa).

Coagulation status

Coagulation parameters also showed some improvements after rFVIIa treatment (Fig. 2). Available data show that the overall median aPTT decreased from 43.0 s before rFVIIa treatment (90% range, 26.7–186 s [$n = 37$]) to 37.3 s after administration (24.9–74.0 s [$n = 36$]) ($P < 0.001$) (Fig. 2). The median PT (s) was 19.0 s (90% range, 11.5–44.7 s; [$n = 27$]) and 12.0 s (90% range, 8.4–62.1 [$n = 26$]) ($P = 0.026$) pre- and post-rFVIIa, respectively; median PT (%) increased from 52% before rFVIIa (range, 30–87% [$n = 5$]) to 70% post-treatment (90% range, 49–82% [$n = 5$]). Median fibrinogen levels increased from 153.0 mg/mL (90% range,

70–555 mg/mL [$n = 34$]) to 200.0 mg/mL (44–528 mg/mL [$n = 35$]) ($P = 0.05$) (Fig. 2).

Patients with penetrating injuries tended to show greater improvements in aPTT than those suffering from blunt injuries; however, due to the low sample size, these results did not achieve statistical significance. In the penetrating trauma subgroup, median aPTT was reduced from 68.0 s before ($n = 3$) to 44.0 s after ($n = 3$) treatment, compared with a reduction from 43.0 s ($n = 34$) to 37.0 s ($n = 33$) in patients with blunt injuries ($P = 0.001$). PT could not be compared between the two subgroups due to insufficient data among patients with penetrating trauma, although the blunt injury group demonstrated improvements from 19.5 s ($n = 26$) and 52.5% ($n = 4$) before rFVIIa treatment to 12.0 s ($n = 25$; $P = 0.033$) and 66.5% ($n = 4$) afterwards.

Improvements in median fibrinogen levels were more pronounced in the blunt trauma group, which demonstrated an increase from 156.0 mg/dL before rFVIIa ($n = 31$) to 205.5 mg/dL afterwards ($n = 32$) ($P = 0.032$). Median fibrinogen levels in the penetrating injury group showed a non-significant increase from 90 to 160 mg/dL pre- and post-rFVIIa, respectively ($n = 3$).

Patient No.	No. of doses (g/kg)	Dose interval	Time of dosing
Blunt trauma			
1.	1 (100)	NA	1 h post-onset of bleed
2.	1 (80)	NA	Not stated
3.	2 (60)	7 h 45min	1 h post-admission
4.	1 (80)	NA	30 min post-admission
5.	1 (80)	NA	Not stated
6.	1 (90)	NA	13.5 h post-onset of bleed
7.	1 (90)	NA	4 h post-onset of bleed
8.	1 (90)	NA	6.5 h post-onset of bleed
9.	2 (106.7)	4 h	Post-operative (3 h post-onset of bleed)
10.	1 (65.5)	NA	52 days post-trauma (owing to diffuse upper gastrointestinal bleeding and multiple organ failure)
11.	2 (57.1)	30 min	Not stated
12.	2 (100)	2.5 h	2 days post-operatively
13.	1 (163.6)	NA	Post-operative
14.	1 (109)	NA	1 h post-trauma
15.	1 (83.6)	NA	1 h post-trauma
16.	2 (84.7)	4 h	Post-operative (2 h post-onset of bleed)
17.	1 (120)	NA	10 days post-trauma
18.	1 (40)	NA	1 h post-onset of bleed
19.	2 (15)	20 h	Intra- and post-operatively (2 h 20 min post-onset of bleed)
20.	1 (56.5)	NA	Post-operative (29.5 h post-onset of bleed)
21.	1 (15)	NA	Post-operative (10 min post-onset of bleed)
22.	3 (73.8)	2 h	Post-operative
23.	2 (128)	2 h	Post-operative
24.	3 (48)	2 h, 3 h	3 days post-trauma
25.	2 (100)	2 h	Post-operative
26.	19 (71)	4 h	24 h post-onset of bleed
27.	2 (13 and 53)	2 h	Post-operative (4 days post-trauma)
28.	1 (64)	NA	Intra-operative (~6.5 h post-onset of bleed)
29.	1 (60)	NA	9 h post-operatively
30.	1 (38)	NA	Not stated
31.	1 (17.1)	NA	6.5 h post-operatively (18 h after ICU admission)
32.	1 (20)	NA	1 h post-operative
33.	1 (104)	NA	Intra-operative
34.	2 (47)	1 h	Intra-operative
35.	2 (90.2)	1 h	Intra-operative
36.	1 (96)	NA	1 h post-onset of bleed
37.	1 (106.7)	NA	45 min post-onset of bleed
38.	1 (53.4)	NA	15 min post-onset of bleed
39.	1 (73.9)	NA	1 h post-onset of bleed
40.	1 (60)	NA	Intra-operative (3 h post-onset of bleed)
41.	1 (72)	NA	Post-operative
42.	1 (90)	NA	3 h post-trauma Penetrating trauma
Penetrating trauma			
43.	1 (80)	NA	Within 2 h post-trauma
44.	1 (60)	NA	Not stated
45.	2 (90 and 105)	13.5 h	Post-operative (and between operations)

ICU, intensive care unit; NA, not applicable.

Table 2. Recombinant activated factor VII dosing schedules

Safety

Eight patients experienced complications; one adverse event was considered to be possibly or probably related to rFVIIa (Table 3), although the patient later recovered. No further details regarding adverse events are available.

The observed mortality for all patients was 11/45 (24.4%), and

all deaths occurred among patients with blunt injuries (Table 3). None of the deaths were considered to be directly related to rFVIIa treatment.

Discussion

Bleeding is one of the leading causes of trauma mortality,

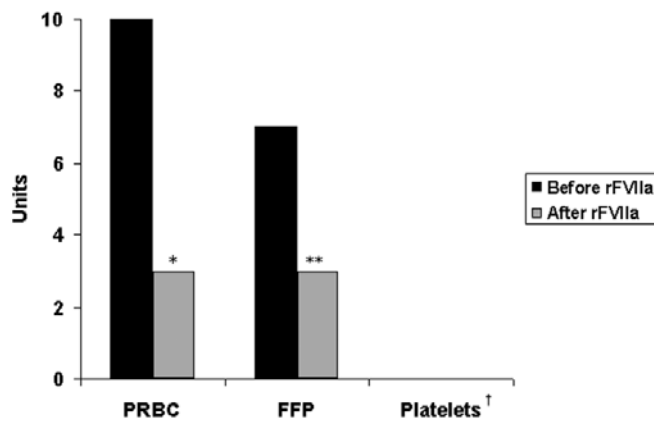


Figure 1. Median transfusion requirements before and within 24 hours after rFVIIa administration (all patients). PRBC, packed red blood cells; FFP, fresh frozen plasma; rFVIIa, recombinant activated factor VII. * $P < 0.001$; ** $P < 0.005$.

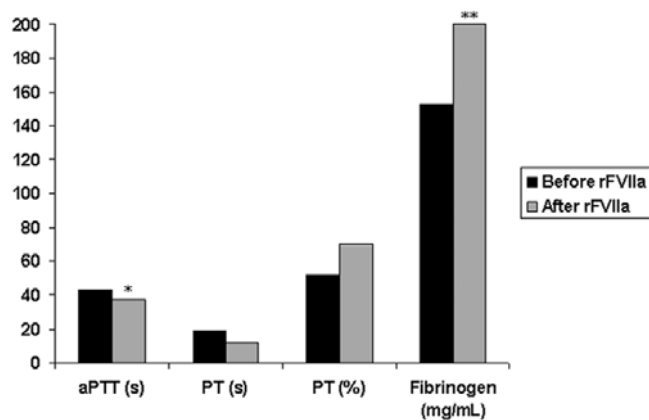


Figure 2. Coagulation parameters before and after rFVIIa administration (median values) aPTT, activated partial thromboplastin time; PT, prothrombin time; rFVIIa, recombinant activated factor VII * $P < 0.001$; ** $P = 0.026$; *** $P = 0.05$.

particularly in the early post-injury period (5–11, 13), and haemorrhage control is therefore a major priority in such patients. The killed in action (KIA) rate during a high intensity engagement is between 17–25% of all injured victims. Around the half of these patients die of haemorrhage (13). 90% of the patients killed in action are dying within 30 minutes after wounding. 70% of them died within the first 5 minutes. The cause of death is most

commonly a penetrating brain or brain stem injury, or damage to major vessels causing massive bleeding (3).

Despite the widespread use of conventional haemostatic measures, there remains a need for other therapeutic strategies, especially in the military setting, that can rapidly minimise blood loss and reduce the need for massive transfusion of blood and blood products. This is particularly important for patients with bleeds who can not be supplied with haemostatic agents or surgery or who do not respond to surgical intervention.

Recombinant FVIIa is currently licensed for the treatment and surgical prophylaxis of bleeding episodes in patients with haemophilia and other coagulopathies. At pharmacological doses, the agent is believed to exert its haemostatic effect by enhancing thrombin generation on the surface of activated platelets at the site of vessel damage, leading to the formation of a stable fibrin clot that remains resistant to premature lysis (23, 38). Over recent years, rFVIIa has demonstrated considerable haemostatic efficacy not only in coagulopathic patients, but also in surgical and trauma patients without pre-existing coagulation deficits (7, 30–37).

Based on the promising observations reported in the literature, two randomised, controlled, double-blind trials have recently investigated the efficacy and safety of rFVIIa as an adjunctive haemostatic therapy in severely bleeding patients with blunt or penetrating trauma (41). These parallel trials found that adjunctive treatment with rFVIIa (200 + 100 + 100 µg/kg) significantly reduced RBC transfusion requirements when compared with placebo in blunt trauma patients (estimated reduction of 2.6 RBC units; $P = 0.02$). The need for massive transfusion (> 20 RBC units) was also reduced in this patient population ($P = 0.03$). Trends towards similar efficacy were also found in those patients with penetrating injuries, and the incidence of adverse events was evenly distributed between the two groups. The investigators concluded that rFVIIa is a promising adjunct in haemorrhage control in trauma, with no immediate safety concerns raised by the studied dose range (41).

The current observational analysis provides further support for the use of rFVIIa in the management of trauma-related blood loss. Haemostatic efficacy (haemorrhage stopped, markedly decreased, or decreased) was achieved in 43/45 (95.6%) patients following rFVIIa administration, and the majority of patients required just one dose. The mean total dose of rFVIIa administered was 73.6 g/kg, a dosing schedule

Patient	Adverse events	Death
Blunt trauma		
11.	—	Yes (severe brain trauma)
15.	Yes (no details available)	Yes (malignant brain swelling; 3 h post-trauma)
18.	Yes (no details available)	Yes (3 h 40 min post-trauma)
19.	Sepsis; ARDS; renal insufficiency	Yes (sepsis; 23 days post-trauma)
20.	Yes (no details available)	Yes (11 days post-trauma)
22.	—	Yes (after 3 days in ICU)
23.	MOF; ARDS	Yes (after 27 days in ICU)
24.	ARDS	—
27.	—	Yes (compression of brainstem; 10 days post-trauma)
30.	Yes (septicaemia; MOD)	Yes (septicaemia; MOD)
31.	—	Yes (within 12 h of ICU admission)
36.	—	Yes (MOF; 6 days post-trauma)
Penetrating trauma		
45.	Bilateral arterial thrombosis in lower extremities – possibly related to rFVIIa use	—

Table 3. Adverse events and deaths

lower than that typically recommended for the control of bleeds in haemophilia patients with inhibitors (90–120 g/kg); only 2 patients received doses higher than 120 g/kg. These doses are also considerably lower than those administered in the recent randomised trials of rFVIIa use in trauma (200 + 100 + 100 µg/kg) (41), suggesting that higher doses may have been more beneficial in those patients with a sub-optimal response to treatment (e.g. patient Nos. 3, 14, 15–19, 31, 40, and 43). Patients with penetrating trauma received a higher mean dose than those with blunt injuries (83.8 versus 73.0 g/kg, respectively).

The early control of coagulopathy and haemorrhage is considered vital for a favourable outcome following trauma (5, 42), and it has been suggested that early use of rFVIIa may produce a more satisfactory haemostatic outcome than late administration (35). In the current study, the median time to rFVIIa dosing was 3.0 hours, with 38.7% of evaluable patients receiving the agent within 1 hour of bleed onset.

Overall, requirements for transfusion of PRBCs were significantly decreased after rFVIIa treatment (median: 10.0 units before rFVIIa, and 3.0 units within the first 24 hours post-administration; $P < 0.001$), and reductions in FFP and platelet requirements were also observed. Treatment with rFVIIa also improved coagulation parameters (aPTT, PT, fibrinogen) across the whole patient population. Investigation of the impact of trauma type (i.e. blunt versus penetrating) on rFVIIa efficacy was beyond the scope of this analysis, due to the small number of patients with penetrating trauma ($n = 3$).

The use of blood transfusions in combat casualties is associated with increased infection rate and resource utilization as well as SIRS incidence and mortality (21–24). A very early control of the haemorrhage remains the most effective treatment opportunity for combat casualties.

None of the 11 deaths that occurred in this study were considered to be related to rFVIIa use. One serious but nonfatal thrombotic adverse event was considered to be possibly or probably related to rFVIIa. This supports earlier observations that the incidence of adverse events associated with rFVIIa treatment is <1% (43, 44), though further research is clearly warranted to confirm this.

We acknowledge that our study has several obvious limitations and weaknesses that arise from the use of international registries as a mechanism for data collection and analysis. For instance, the patient population is heterogeneous, treatment practices and dosing schedules vary widely, and many of the data are subjective and/or incomplete. Logistical difficulties in collecting case information are also inherent in studies based on the analysis of registry data. Furthermore, the data available were limited to those cases for which clinician approval had been received, and by our wish to avoid dual publication of cases. We recognise that this represents an important potential source of bias, as does the fact that some rFVIIa-treated trauma patients were not reported to the registry at all; our study may therefore suffer from a bias of selection, meaning that the data cannot be generalised. Finally, our study was not controlled. These limitations mean that no definite conclusions can be drawn regarding the efficacy and safety of rFVIIa in patients with trauma-related haemorrhage. Despite the obvious limitations of our study, however, we believe that the results provide some suggestion of the favourable outcomes that might be achieved with appropriate use of rFVIIa in traumatic bleeding. Indeed, our findings are strengthened by those of two recent, randomised, clinical trials in which rFVIIa therapy reduced both transfusion requirements and incidence of critical complications in patients with blunt trauma.

In conclusion, our analysis of cases reported to an international registry suggests that rFVIIa may be of benefit to

patients suffering from traumatic haemorrhage.

Based on our findings, the early use of rFVIIa showed a benefit especially for patients who received the drug very early. These would definitely fit into a treatment regime for victims wounded in the battlefield, who cannot be moved or treated with blood products or given access to rapid surgical treatment. Additional studies are clearly needed to confirm these results, and to further delineate the efficacy, safety, and optimal treatment regimen of the agent when used in this indication.

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