The Effect of Recombinant Activated Factor VII on Mortality in Combat-Related Casualties With Severe Trauma and Massive Transfusion

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Background: **The majority of patients with potentially survivable combat-related injuries die from hemorrhage. Our objective was to determine whether the use of recombinant activated factor VII (rFVIIa) decreased mortality in combat casualties with severe trauma who received massive transfusions and if its use was associated with increased severe thrombotic events.**

Methods: **We retrospectively reviewed a database of combat casualty patients with severe trauma (Injury Severity Score [ISS] >15) and massive transfusion (red blood cell [RBCs] ≥10 units/24 hours) admitted to one combat support hospital in Baghdad, Iraq, between December 2003 and October 2005. Admission vital signs and laboratory data, blood products, ISS, 24-hour and 30-day mortality, and severe thrombotic events were compared between patients who received rFVIIa (rFVIIa$^+$) and did not receive rFVIIa (rFVIIa$^-$).**

Results: **Of 124 patients in this study, 49 patients received rFVIIa and 75 did not. ISS, laboratory values, and admission vitals did not differ between rFVIIa$^+$ and rFVIIa$^-$ groups, except for systolic blood pressure (mm Hg) 105 ± 33 and 92 ± 28, $p = 0.02$ and temperature (°F) 96.3 ± 2.1 and 95.2 ± 2.4, $p = 0.03$, respectively. Interactions between all vital signs and laboratory values measured upon admission, to include systolic blood pressure and temperature, were not significant when measured between rFVIIa use and 30-day mortality. Twenty-four-hour mortality was 7 of 49 (14%) in rFVIIa$^+$ and 26 of 75 (35%) in rFVIIa$^-$, ($p = 0.01$); 30-day mortality was 15 of 49 (31%) and 38 of 75 (51%), ($p = 0.03$). Death from hemorrhage was 8 of 14 (57%) for rFVIIa$^+$ patients compared with 29 of 37 (78%) for rFVIIa$^-$ patients, ($p = 0.12$). The incidence of severe thrombotic events was similar in both groups.**

Conclusions: **The early use of rFVIIa was associated with decreased 30-day mortality in severely injured combat casualties requiring massive transfusion, but was not associated with increased risk of severe thrombotic events.**

Key Words: **Recombinant FVIIa, Trauma, Mortality, Hemorrhage, Coagulopathy, War.**

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Upon autopsy review, 80% to 85% of combat deaths are classified as nonsurvivable as the result of massive and devastating injury.[1,2] In the 15% to 20% of potentially survivable deaths, 66% to 80% of patients died from hemorrhage.[1,2] Severe trauma, defined as an injury severity score (ISS) of greater than 15,[3] is common during combat, (20% of trauma admissions at one combat support hospital in Baghdad in 2004). Recently, the early coagulopathy of trauma present at admission has been described in civilian and military patients.[4–6] The severity of trauma and shock correlates with the degree of coagulopathy, which has also been associated with mortality.[5–8] Patients with severe trauma are at risk for requiring massive transfusion, defined as 10 or more units of red blood cells (RBCs) in a 24-hour period.[9] Massive transfusions are relatively infrequent, occurring in 5% of all military and 1.2% of all civilian admissions, but in 25% of those who receive at least 1 unit of blood.[4,10] Massive transfusion is independently associated with increased mortality.[10] Methods that successfully address the coagulopathy of trauma early in the resuscitation process may prevent uncontrollable bleeding and the need for massive transfusions, potentially decreasing mortality.

The concept of damage control resuscitation and the coagulopathy of trauma have been reviewed previously.[11–16] Hemostatic or damage control resuscitation can be described as the early diagnosis and aggressive treatment of the early coagulopathy of trauma. This approach includes: rapid control of bleeding, prevention and treatment of hypothermia and metabolic acidosis, minimizing dilutional coagulopathy by

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decreasing crystalloid and RBC transfusions, the empiric transfusion of plasma:RBC:platelets in a ratio of 1:1:1, and the early transfusion of fibrinogen and other pro-hemostatic agents in patients with life-threatening hemorrhage.

Recombinant activated factor VII (rFVIIa) (Novo Nordisk, Denmark) is a pro-hemostatic agent that is licensed in the United States for control of bleeding in patients with hemophilia with inhibitors to factor VIII concentrate. Additionally, it is licensed in Europe for patients with Glanzmann thrombasthenia who are refractory to platelet transfusions. In the only published randomized controlled trial evaluating rFVIIa in trauma patients, its use in patients with blunt traumatic injury was associated with reduced RBC usage and acute respiratory distress syndrome (ARDS) without an increase in adverse thrombotic events.[17] In addition, a retrospective study indicated that the early use of rFVIIa in patients with combat-related traumatic injury decreased RBC transfusions when compared with similarly injured patients receiving rFVIIa later in the resuscitation.[18]

Our objective was to determine whether the use of rFVIIa was associated with decreased 24-hour and 30-day mortality in combat-related severe trauma patients receiving massive transfusions, and if its use was associated with increased severe thrombotic events.

PATIENTS AND METHODS

Data for this retrospective analysis were obtained from the Joint Theater Trauma Registry (JTTR), maintained at the US Army Institute of Surgical Research, Ft. Sam Houston, Texas, under a human use protocol that received Institutional Review Board approval at Brooke Army Medical Center. The JTTR was queried for all trauma patients admitted to one combat support hospital (CSH) in Iraq between December 2003 and October 2005.

Patients with severe trauma were included if they received a massive transfusion within 24 hours of admission to the CSH. Severe trauma was defined as an ISS greater than 15.[3] Injuries were coded using the 1998 version of the Abbreviated Injury Scale (AIS). ISS and AIS were calculated according to the methods described by the Association for the Advancement of Automotive Medicine AIS, 1998 Revision.[19]

Massive transfusion was defined as receiving $\geq$10 units of RBCs in 24 hours.[9] When identifying massive transfusion, each unit of fresh whole blood (FWB) was counted as a unit of RBCs. The primary outcome in this study was 30-day mortality. Foreign national patients (civilians and Iraqi military) transferred to Iraqi hospitals before 30 days and without subsequent follow up by day 30 were excluded. Patients were also excluded if they were treated at another medical facility before transport to the CSH.

Data retrieved from the JTTR included: admission vital signs and laboratory values, time from admission to administration of rFVIIa, amount of crystalloid and blood products transfused in the first 24 hours, and ISS. Mortality was measured at 12 hours, 24 hours, and 30 days. Primary cause, mechanism, and location of injury were analyzed from clinical records. Adverse events were determined from documentation in clinical notes, computerized reports, or discharge summaries. The adverse events included bacteremia, ARDS, Multi-Organ Failure (MOF), deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke. Similar to the Boffard study,[17] the effect of rFVIIa on 24-hour blood product administration was only determined for patients who lived for at least 24 hours.

Clinical practice guidelines for the transfusion of blood products[20] and administration of rFVIIa were established during the time period of this study. The rFVIIa guideline suggested its use at 120 μg/kg for patients with life-threatening hemorrhage after 4 to 6 units of RBCs were transfused. In addition, it suggests the rapid treatment of hypothermia and acidemia, and the use of FWB as a source of plasma and platelets with rFVIIa.

Data are presented as median (interquartile-range [IQR]) or mean ($\pm$standard deviation) according to the distribution of the data. Comparison of continuous data was performed with Wilcoxon rank sum test and Student's t test as appropriate. Comparison of binomial data was performed with χ^2 or Fisher's exact test, as appropriate. Interaction effects of rFVIIa, with vital signs and laboratory values recorded upon admission, 24-hour total amount of blood products transfused for patients who survived at least 24 hours, and ISS for the outcome of 30-day mortality, were tested using logistic regression models. Each model contained effects for rFVIIa, a single independent variable of interest, and an interaction between this independent variable and rFVIIa. The logistic regression model evaluated 30-day survival by a single independent variable of interest versus the variables' interaction with rFVIIa. The p values recorded in Tables 7 and 8 are for testing the hypotheses that these interaction terms are zero. Statistical analysis was performed with SPSS 14.0 (SPSS, Inc, Chicago, IL) and SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

There were 5,293 patients with combat-related traumatic injuries admitted to the CSH between December 2003 and September 2005. Two hundred and forty-six patients received a massive transfusion within the first 24 hours of admission. Forty-seven patients were treated at another facility before transfer to the CSH and were excluded from analysis. Of the remaining 199 patients who received a massive transfusion, 157 of 199 (79%) had an ISS $>$15. Of these, 33 patients were excluded who did not have 30-day mortality rates because of transfer to Iraqi hospitals before 30-day follow up. Thus, data for 124 of 157 (79%) patients were available for analysis.

Forty-nine of 124 (40%) patients received rFVIIa. Ninety-two percent of patients had a penetrating mechanism of injury, with similar rates in both study groups (Table 1). No differences were noted for mechanism or location of injury (Tables 1 and 2).

Table 1 Mechanism and Cause of Injury for Each Study Group

Mechanism and Cause of Injury	rFVIIa$^-$ (n = 75)	rFVIIa$^+$ (N = 49)	*p* Value
Penetrating (%)	70/75 (95%)	44/49 (89%)	0.52
Gunshot wound	27/75 (36%)	16/49 (33%)	0.5
Explosions	42/75 (56%)	31/49 (63%)	0.42
Motor vehicle crash	6/75 (8%)	2/49 (4%)	0.39

p value for comparison between patients who did and did not receive rFVIIa.

Table 2 Comparison of Injury Location for Each Study Group

Injury Location	rFVIIa$^-$ (n = 75)	rFVIIa$^+$ (n = 49)	*p* Value
Abdomen	33/75 (44%)	24/49 (49%)	0.59
Extremity	25/75 (33%)	23/49 (47%)	0.13
Thorax	24/75 (32%)	19/49 (39%)	0.44
Pelvis	15/75 (20%)	12/49 (24%)	0.35
Head	13/75 (17%)	8/49 (16%)	0.88
Face	2/75 (3%)	2/49 (4%)	0.66

The sum of the total percentage of injury location is greater than 100% as a result of the inclusion of each significant injury for patients with multiple injuries.

Table 3 Comparison of Admission Vital Signs, Laboratory Values, and Mortality Outcomes Between Study Groups

Variable	rFVIIa$^-$ (n = 75)	rFVIIa$^+$ (n = 49)	*p* Value
Heart rate (bpm)	115 ± 30	111 ± 27	0.46
SBP (mm Hg)	92 ± 28	105 ± 33	0.02
Temperature (°F)	95.2 ± 2.4	96.3 ± 2.1	0.03
Hemoglobin (g/dL)	10.3 ± 2.8	11.1 ± 2.9	0.14
PLT ($\times 10^3$/mm^3)	205 ± 100	215 ± 83	0.60
INR	2.2 ± 1.6	2.0 ± 1.3	0.47
Base deficit	11 ± 7.8	10 ± 6.3	0.59
pH	7.14 ± 0.19	7.19 ± 0.14	0.20
ISS	25 ± 9	26 ± 10	0.60

Data presented as mean ± SD.

SBP, systolic blood pressure; HR, heart rate; Hb, hemoglobin; PLT, platelet concentration; INR, international normalized ratio.

Admission systolic blood pressure (SBP) and temperature were higher in the patients who received rFVIIa (Table 3). ISS was 25 ± 9 versus 26 ± 10, for rFVIIa$^+$ and rFVIIa$^-$ patients, respectively ($p = 0.6$) (Table 3). For patients who survived more than 24 hours, the rFVIIa$^+$ group received a larger 24-hour total amount of RBCs, cryoprecipitate, and FWB compared with the rFVIIa- patient group (Table 4). The time to administration of rFVIIa from hospital admission was available for 35 of 49 (71%) patients. The median (IQR) time to administration of rFVIIa in these patients from hospital admission was 120 (84–192) minutes.

Admission vital signs and laboratory values associated with mortality included heart rate, hemoglobin, international normalized ratio, and base deficit (Table 5). No 24-hour transfusions (crystalloid or blood products) were associated with survival (Table 6). Interactions were not significant between rFVIIa use and each of the following variables: admission vital signs and laboratory values, ISS, and 24-hour

Table 4 Comparison of the 24 h Total Amount of Crystalloid and Blood Products Transfused Patients who Survived for 24 h in Both Study Groups

Variable	rFVIIa$^-$ (n = 49)	rFVIIa$^+$ (n = 41)	*p* Value
Crystalloid (L)	10.8 (8–13.5)	11.6 (8.2–17.3)	0.38
RBC (U)	14 (11–19)	16 (13–27)	0.02
FFP (U)	8 (5.5–12)	10 (7–18)	0.06
aPLT (U)	0 (0–0)	0 (0–1)	0.11
Cryo (U)	0 (0–10)	10 (7–20)	0.001
FWB (U)	0 (0–2)	4 (0–9)	<0.001
ISS	24.8 (±9)	26.4 (±10)	0.38

Data presented as median (IQR) or mean (±SD).

rFVIIa, recombinant activated factor VII; RBC, red blood cell; FFP, fresh frozen plasma; FWB, fresh whole blood; Cryo, cryoprecipitate; aPLT, apheresis platelet; LR, lactated ringers solution; ISS, injury severity score.

Table 5 Comparison of 30-d Mortality and Variables Measured Upon Admission

Variable	Survived (n = 71)	Died (n = 53)	*p* Value
Temperature (°F)	95.6 (2.1)	95.7 (2.6)	0.96
SBP (mm Hg)	96 (78–120)	90 (74–114)	0.31
HR (bpm)	108 (28)	120 (28)	0.024
Hb (g/dL)	11.4 (2.7)	9.6 (2.7)	0.001
PLT ($\times 10^3$/mm^3)	222 (90)	189 (93)	0.065
INR	1.4 (1.2–1.7)	2.1 (1.5–3.1)	<0.001
Base deficit	7 (3.3–12.8)	14 (8.5–17.5)	0.005

Data presented as mean (SD) or median (IQR).

SBP, systolic blood pressure; HR, heart rate; Hb, hemoglobin; PLT, platelet concentration; INR, international normalized ratio.

Table 6 For Patients Who Survived 24 h, a Comparison of 24 h Totals of Crystalloid and Blood Products Transfused Between Patients who Survived and Died

Variable	Survived (n = 71)	Died (n = 19)	*p* Value
Crystalloid (L)	11.6 (8.3–14)	9.8 (7.6–12.1)	0.23
RBC (U)	16 (12–21)	14 (11–20)	0.5
FFP (U)	10 (7–13)	8 (5–11)	0.12
aPLT (U)	0 (0–1)	0 (0–1)	0.59
Cryo (U)	9 (0–17)	9 (0–10)	0.51
FWB (U)	0 (0–6)	2 (0–4)	0.9
rFVIIa	34/71 (47%)	15/53 (28%)	0.03
ISS	25 (±10)	27 (±9)	0.4

Data presented as mean (SD) or median (IQR).

rFVIIa, recombinant activated factor VII; RBC, red blood cell; FFP, fresh frozen plasma; FWB, fresh whole blood; Cryo, cryoprecipitate; aPLT, apheresis platelet; LR, lactated ringers solution; ISS, injury severity score.

Table 7 **Interactions Calculated Between Admission Vitals or Laboratory Values and rFVIIa to Determine 30-d Survival**

	Survived at Least 30 Days		Died Within 30 Days		Interaction *p* Value*
	rFVIIa$^-$ (n = 35)	rFVIIa$^+$ (n = 34)	rFVIIa$^-$ (n = 40)	rFVIIa$^+$ (n = 15)	
Temperature (°F)	95.1 (89–99)	96 (94–100)	94.9 (89–99.7)	97 (92–100.5)	0.83
SBP (mm Hg)	93.5 (51–171)	95.5 (48–196)	83 (40–144)	114 (61–175)	0.08
HR (bpm)	107 (58–167)	111 (60–163)	124 (38–160)	121 (63–172)	0.48
Hb (g/dL)	11 (4–16)	11.6 (6–17.9)	9.6 (3–15.2)	10.2 (6–14.5)	0.81
PLT ($\times 10^3$/mm3)	232 (44–469)	214 (35–427)	157 (29–406)	187 (88–377)	0.44
INR	1.5 (1–7)	1.4 (1–6.3)	2.1 (1–10)	1.6 (1–5.9)	0.42
Base deficit	7 (0–25)	8 (0–22)	14 (0–30)	10 (0–21)	0.29

Data presented as median (range).

* Interaction with rFVIIa ($^-$, $^+$) per variable for the outcome of 30-day survival determined by logistic regression model.

rFVIIa, recombinant activated factor VII; SBP, systolic blood pressure; HR heart rate; Hb, hemoglobin; PLT, platelet concentration, INR, international normalized ratio.

Table 8 **Interactions Calculated Between Blood Products or Crystalloid and rFVIIa to Determine 30 d Survival***

	Survived at Least 30 Days		Died Within 30 Days		Interaction *p* Value†
	rFVIIa$^-$ (n = 35)	rFVIIa$^+$ (n = 34)	rFVIIa$^-$ (n = 11)	rFVIIa$^+$ (n = 8)	
RBC (U)	14 (7–30)	16 (6–69)	16 (9–24)	23 (12–33)	0.98
FFP (U)	9 (2–30)	10 (1–44)	6 (1–21)	13 (7–28)	0.09
FWB (U)	0 (0–7)	4 (0–22)	0 (0–11)	3 (0–20)	0.14
Cryo (U)	0 (0–20)	10 (0–59)	0 (0–18)	9.5 (8–40)	0.37
aPLT (U)	0 (0–3)	0 (0–7)	0 (0–1)	0.5 (0–4)	0.24
LR (L)	10.8 (4.4–20.7)	11.8 (3.6–21.1)	11.4 (8–17.9)	9.9 (4.2–17.8)	0.24
ISS	22 (16–54)	24 (16–59)	25 (16–38)	25 (16–43)	0.56

Data presented as median (range).

* Crystalloid and blood product amounts reported are 24 h totals for patients who survived for at least 24 h only.

† Interaction with rFVIIa ($^-$, $^+$) per variable for the outcome of 30-day survival determined by logistic regression model.

rFVIIa, recombinant activated Factor VII; RBC, red blood cell; FFP, fresh frozen plasma; FWB, fresh whole blood; Cryo, cryoprecipitate; aPLT, apheresis platelet; LR, lactated ringers solution; ISS, injury severity score.

amount of crystalloid and blood product transfused to patients surviving >24 hours for the outcome of 30-day mortality (Tables 7 and 8).

Mortality was lower in the rFVIIa$^+$ patients at 12 hours, 24 hours, and 30 days compared with the rFVIIa$^-$ patients. Twelve-hour mortality was 6 of 49 (12%) for the rFVIIa$^+$ group and 25 of 75 (33%) for the rFVIIa$^-$ group ($p = 0.008$). Twenty-four hour mortality was 7 of 49 (14%) for rFVIIa$^+$ and 26 of 75 (35%) for rFVIIa$^-$ patients ($p = 0.01$) (Fig. 1). Thirty day mortality was 15 of 49 (31%) for rFVIIa$^+$ and 38 of 75 (51%) for rFVIIa$^-$patients ($p = 0.03$) (Fig. 1). Hemorrhage as the cause of death was numerically decreased for rFVIIa$^+$ patients compared with rFVIIa$^-$ patients, although this decrease was not statistically significant ($p = 0.12$) (Table 9).

In the 53 patients in this study who died, the median time of death was 4 (2–45) hours. Patients who did not receive rFVIIa died at a median of 3.7 (1.7–24) hours compared with those who received rFVIIa who died at a median of 43 (2.7–155) hours, respectively ($p = 0.035$). Alternatively, 31 of 53 (58%) patients died within 12 hours of admission. The percentage of patients who died within 12 hours was 6 of 15 (40%) for rFVIIa$^+$ compared with 25 of 38 (63%) for rFVIIa$^-$ patients ($p = 0.035$). The incidence of severe thrombotic events (DVT, PE, and stroke), bacteremia, ARDS, and MOF were similar in both groups studied, despite the difference in survival time in those patients who ultimately died (Table 10).

DISCUSSION

Our results indicate that the use of rFVIIa was associated with decreased 24-hour and 30-day mortality in combat-related casualties with severe traumatic injuries who received massive transfusions, without a significant increase in thrombotic complications. Our approach to the administration of rFVIIa is supported by consensus statements and review articles which describe the optimal use rFVIIa.[11,21] These guidelines recommend rFVIIa for patients with life-threatening hemorrhage who are in a hypocoaguable state from severe trauma after metabolic acidosis and hypocalcemia are corrected. In addition, these guidelines recommend rFVIIa for patients with adequate concentrations of platelets, fibrinogen and coagulation factors.

Our findings differ from those of a randomized controlled trial by Boffard et al. that reported that rFVIIa usage

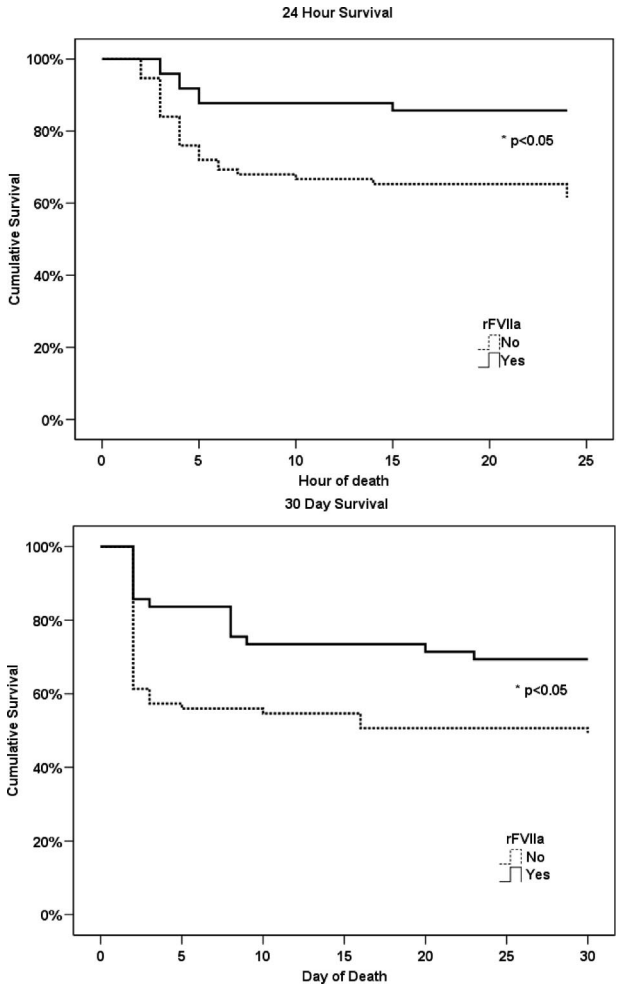

Fig. 1. *Kaplan–Meier Curve of 24-hour and 30-day mortality for patients who received rFVIIa compared with patients who did not receive rFVIIa. Log rank test determined a* p *value of 0.004 for 24-hour and 0.002 for 30-day mortality, respectively.*

Table 9 Comparison of Cause of Death Between Study Groups

Physiologic Cause of Death (n = 51)	rFVIIa$^-$ (n = 37)	rFVIIa$^+$ (n = 14)	*p* Value
Hemorrhage n = 37	29/37 (78%)	8/14 (57%)	0.12
Pulmonary failure n = 3	1/37 (3%)	2/14 (14%)	0.18
CNS injury n = 7	4/37 (11%)	3/14 (21%)	0.37
Sepsis n = 3	2/37 (5%)	1/14 (7%)	0.6
MOF n = 2	2/37 (5%)	0/14 (0%)	1.00

Data on physiologic cause of death available for 51 of 53 deaths recorded.

rFVIIa, recombinant activated factor VII; CNS, central nervous system; MOF, multi-organ failure.

did not significantly improve survival in patients with penetrating or blunt injuries.[17] Increased injury severity and indicators of admission hypoperfusion may account for these differences. Despite similar ISS in the RCT by Boffard et al. and the patients we studied, the ISS underestimates the severity of injury in combat-related casualties with penetrating injuries.[22] The mortality reported in the Boffard trial was 26% compared with 43% in this report, which may also indicate more severe injuries in our patient population of combat-related trauma. Admission SBP, and pH were lower, and transfusion requirement in the first 24 hours was higher in the patients we studied, possibly indicating a greater state of hypoperfusion upon admission. Hypoperfusion has been associated with increased coagulopathy and mortality in trauma patients.[7] Improvement in mortality may only occur when rFVIIa is given to patients who are significantly coagulopathic or severely injured.

Table 10 Comparison of Adverse Events Between Study Groups

Variable	rFVIIa$^-$ N = 75	rFVIIa$^+$ N = 49	*p* Value
Bacteremia	12/75 (16%)	3/49 (6%)	0.1
Thrombotic events	0/75	2/49 (4%)	0.15
ARDS	3/75 (4%)	1/49 (2%)	1.00
MOF	4/75 (5%)	1/49 (2%)	0.65

rFVIIa, recombinant activated factor VII; ARDS, acute respiratory distress syndrome; MOF, multi-organ failure.

The physiology of hemostasis in patients with traumatic injuries is a dynamic process. Most patients with mild to moderate traumatic injuries are hypercoaguable, but those with severe trauma are frequently hypocoagulable at admission.[5,23,24] Our report indicates that in patients with severe trauma (ISS >15) and requiring massive transfusion, who are at higher risk of presenting in a hypocoaguable state, use of rFVIIa may improve survival. Both groups had high comparable international normalized ratio values upon admission. The ISS cannot be used to indicate use of rFVIIa since it is not able to be determined upon admission. Alternative methods are needed to rapidly identify who is at risk for massive transfusion, which would indicate the need for plasma, platelets, fibrinogen, and potentially, rFVIIa.[16] Recent reports have described methods that can quickly determine who is at risk of requiring massive transfusion.[25,26] These methods can be completed within 5 minutes of admission and can predict the need for massive transfusion with a sensitivity of approximately 80%. Prompt recognition of the risk of massive transfusion is important since death as a result of severe trauma occurs quickly, typically 1 to 6 hours from admission.[25,27–30] This is similar to the 58% of deaths that occurred within 12 hours in our study. The rapid use (<2 hours from admission) of rFVIIa in our study was associated with a lower mortality rate at 12 hours from admission for rFVIIa$^+$ (12%) compared with rFVIIa$^-$ patients (33%). Conversely, the time to death from admission also increased dramatically in rFVIIa$^+$ (43 hours) compared with rFVIIa$^-$ patients (4 hours). Extension of life for patients who eventually died is important since this may allow the critical care team additional time to intervene and support the critically ill patient, improving the overall mortality in these patients.

Recombinant FVIIa may not improve survival, however, if used too late in the resuscitation when the patient is in a state of irreversible shock.[11,31] A retrospective report, based upon a similar cohort in combat-related trauma patients requiring massive transfusion, revealed that early administration of rFVIIa decreased RBC use by 23%.[18] This concept of timing of rFVIIa administration and effect on outcome may be illustrated in a comparison of the two previously published randomized controlled trials.[17,32] In the Mayer intracerebral hemorrhagic stroke trial, when rFVIIa was administered at a mean of 2 hours from the onset of symptoms, there was a mortality benefit compared with those who did not receive rFVIIa, 18% versus 29%, respectively. This trial included patients with hemorrhagic stroke and not traumatic brain injury, which limits the application of its results to patients with traumatic injury. In the Boffard trauma trial, when rFVIIa was given at a median of 4 hours from admission, mortality was unchanged. The differences in mortality outcomes between our retrospective review and the Boffard trial may be affected by the time to administration of rFVIIa. In our study, there was an association with decreased mortality when rFVIIa was given at a median of 2 hours from admission. Thus, in a group of more severely injured patients who received the drug sooner, a mortality benefit was seen. The timing of rFVIIa use may be essential regarding its efficacy. There is currently an ongoing phase III trauma trial of rFVIIa, which will address the question whether earlier administration of rFVIIa improves the outcome of severely injured civilian trauma patients.

Since the majority of potentially preventable deaths that occur in combat are caused by truncal hemorrhage, it is likely that the decreased mortality rate in our population was a result of the pro-hemostatic effect of rFVIIa decreasing life-threatening bleeding. The main effect of rFVIIa on mortality was within 12 hours of injury, corresponding to data suggesting that most patients who receive a massive transfusion stop bleeding or die within 12 hours.[25,27–30] The decrease in mortality at each time measured was approximately 20% lower in the $rFVIIa^+$ compared with the $rFVIIa^-$ group. The incidence of hemorrhage as a cause of death was not statistically significant between both groups studied, but interestingly was approximately 20% lower in the $rFVIIa^+$ group. The lack of significance of hemorrhage as a cause of death may be a function of inadequate sample size of patients that died.

Animal models of hemorrhage have demonstrated increased clot strength with rFVIIa use[33] and increased survival when combined with hypotensive resuscitation.[34] For rFVIIa to be able to promote thrombosis it requires adequate concentrations of fibrinogen, clotting factors, and platelets for clot formation. Generally, our practice was to use rFVIIa, cryoprecipitate, fresh frozen plasma, and, when available, FWB and apheresis platelets, early in the resuscitation for patients with severe traumatic injuries. Subsequently, calcium replacement has received considerable attention. FWB has been demonstrated to have superior coagulation function compared with component therapy,[35,36] and independently associated with increased 48-hour and 30-day survival in combat-related casualties (Unpublished data, Perkins JG). The increased amount of cryoprecipitate and FWB, used in patients who received rFVIIa in our study may have also contributed to the decreased mortality in these patients. These results support the concept of hemostatic or damage control resuscitation, which emphasizes the early and increased use of multiple hemostatic agents to aggressively treat the coagulopathy of trauma in patients with life-threatening traumatic injuries.[9,11,12,15,16,37]

Similar to the randomized controlled trial in penetrating trauma patients by Boffard et al.,[17] in our study there was no statistical difference in the incidence of MOF, ARDS, and severe thrombotic events (DVT, PE, and stroke) between study groups. We did not prospectively assess patients for any of these conditions, though, and as a result they were likely equally under-reported in both groups. In addition, the small sample size in our analysis does not allow for adequate power to make adequate comparisons of adverse events. There are now eight randomized controlled trials (RCT) in surgical patients, none of which show an increased thrombotic complication rate with rFVIIa.[17,32,38–43] Because of the recent concern of increased thrombotic events in trauma patients receiving rFVIIa,[44] additional trials are needed to confirm the findings in the Boffard trial that the use of rFVIIa is not associated with these complications in trauma patients. No study using rFVIIa that has a blinded control group has shown evidence of an increased thrombotic rate.

The interpretation of our results is limited by the retrospective nature of this study, which includes lack of randomization and the potential for selection bias. It is possible that the increased SBP or temperature upon admission in the patients given rFVIIa affected the survival rates measured in our study, although the differences noted may not be clinically significant and these variables were not associated with mortality at 30 days. It is important to note that if these variables are not associated with 30-day mortality on univariate analysis, they cannot affect the relationship between rFVIIa use and 30-day mortality. The patients in our study had a mean ISS of 25 and SBP was 105 and 92 mm Hg for $rFVIIa^+$ and $rFVIIa^-$ patients, respectively. In an attempt to analyze whether this difference in SBP was clinically significant we queried the National Trauma Database, version 5.0. In patients with an ISS of 25, mortality was not different in the National Trauma Database for patients with an admission SBP of 105 ($n = 74$) compared with 92 mm Hg ($n = 109$), 31.1% versus 34.9%, respectively ($p = 0.6$). Multivariate logistic regression was not able to be performed to simultaneously adjust for all confounders that were associated with 30-day mortality because of inadequate sample size in the analysis. Attempts were made to fit logistic regression and Cox proportional hazards models to the data. Preliminary models as well as univariate analyses shown in Tables 6 and 7 showed many important factors associated with 30-day

mortality. Unfortunately, scattered missing data among several of these important variables limited the sample size. There were not enough data to produce stable regression models without biasing results by leaving out important predictors of 30-day mortality. An alternative method to account for the effect of variables measured on the relationship of rFVIIa use and 30-day mortality, using logistic regression models, was to calculate interactions between each of these variables and rFVIIa use and 30-day mortality. Interactions between all vital signs and laboratory values measured upon admission, including SBP and admission temperature, were not significant when measured between rFVIIa use and 30-day mortality (Table 7). Additionally, interactions between blood product administration and the relationship between rFVIIa use and 30-day mortality were not significant (Table 8). Despite these results, this retrospective analysis can only report an association between rFVIIa use and decreased mortality in severe trauma patients requiring massive transfusions.

CONCLUSIONS

The use of rFVIIa was associated with decreased 24-hour and 30-day mortality in patients requiring massive transfusions with severe traumatic injuries, but not with an increased incidence of severe thrombotic events, ARDS, or MOF. The ability of rFVIIa to improve outcomes in patients with traumatic injuries, without increasing adverse effects, likely depends upon it being administered within 2 hours to patients with life-threatening traumatic injuries who are in a hypocoaguable state. Our results support the concept of hemostatic or damage control resuscitation, which emphasizes the early and increased use of hemostatic agents to aggressively treat the coagulopathy of trauma in patients with life-threatening traumatic injuries.[9,11,12,15,16,37]

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DISCUSSION

Dr. Thomas M. Scalea (Baltimore, MD): This was the hardest manuscript that I have ever discussed. This morning, you have seen a fraction of the data in this paper. It represents a huge amount of work.

The authors have retrospectively reviewed 124 combat casualty patients who were severely injured and massively transfused. All patients were admitted to a single combat hospital over nearly a two-year period of time. Rather than reiterate any more of the presentation, let me instead provide you with some perspective and comments.

Any discussion of this work has to begin with congratulating the authors on obtaining the data out of a war zone. Last year we said that this was needed and this year they have done it. Something as simple as 30-day mortality can be enormously complicated in patients that may receive treatment in five different hospitals on three different continents. Those of us working in civilian trauma centers think we have trouble collecting data. We have just seen, in fact, that we have it awfully easy. Let me pose some questions to the authors.

I am concerned that the non-factor VII group was sicker at the time of admission. There were no differences in ISS, perhaps not surprising given the numbers of patients with penetrating trauma. They were, in fact, more hypotensive and more hypothermic. The authors question whether this is clinically significant. I would argue that it might be. The authors attempted to address this by controlling for these factors in their mortality analysis but were unable to do regression due to the inadequate sample size.

This raises the possibility of selection bias. Did the doctors chose to give factor VII when they thought that the patients had a better chance to survive? I would appreciate the authors' comments.

I'm also intrigued by a population that seems to have vanished. What happened to the patients that got VIIa that then did not require massive transfusion? How many patients were there? How did they fare? This is particularly interesting as the patients who got factor VIIa and died had a higher blood pressure than the other patients. What does this mean?

It would also be interesting to note whether patients later in the study got the drug earlier than those during the first year. The data would be interesting to present as it could yield more evidence that giving the drug early would make a difference.

The authors state that there were no differences in the incidence of thrombotic events when patients that received factor VIIa were compared to those who did not.

How hard did you look for thrombotic complications? Did you have an active surveillance for deep vein thrombosis? Did you review CT scans late looking for cerebral ischemia?

While I recognize that this data may be hard to come by, knowing that there was a standardized surveillance system in place will go a long way to being sure that the statement on complications is in fact correct.

Coming from the institution in North America that has the largest experience in the use of factor VIIa I believe that

the association that the authors have identified is both real and valid.

I congratulate the authors on having the tenacity to see this project through and look forward to further work from them.

Dr. Donald H. Jenkins (Lackland Air Force Base, TX): Yes, Dr. Spinella, thank you very much for that outstanding presentation. Just one simple question for you. How am I going to know who to give Factor VII to? Exactly how do I make that determination?

Dr. Charles E. Lucas (Detroit, MI): Nice presentation. Two questions. How many micro units of un-activated factor VII are present in a unit of fresh frozen plasma? And, secondly, once administered, how long does it take for that un-activated factor VII to become activated?

Dr. Carlos V.R. Brown (Austin, TX): I was, you focused on the timing of your factor VII. When was the earliest dose given after arrival? And when was the latest dose given? And was there a difference based on when it was given based on your mean intermediate?

Dr. Andrew Berson (Colorado Springs, CO): Andrew Berson, Colorado Springs. I had one question. You had someone touch on the fact that this was done in multiple trauma centers throughout the military command.

Did all the patients that received factor VII receive a uniform dose? And if so what was that dose and was it a single dose or a stacked dose as is being currently investigated in an ongoing study? Thank you.

Dr. Juan Carlos Puyana (Pittsburgh, PA): I don't know if I understood correctly your slide where you breakdown the population. Did you have a group of patients who had a massive transfusion with an ISS less than 15?

If that is so, can you tell us what was the pattern of injury and why did they get a massive transfusion? Is it the ISS doesn't correlate to the magnitude of injury?

Dr. Philip C. Spinella (San Antonio, TX): I want to thank Dr. Scalea and all of the other discussants for their insightful comments and questions. I also appreciate the kind words of Dr. Scalea regarding our effort to complete this study.

All the coauthors deserve credit for this study but I want to give special credit to Dr. Jeremy Perkins who singlehandedly has developed our massive transfusion database and without his work we wouldn't be able to do any of these projects that we've presented.

Dr. Scalea, regarding your concern that patients who received factor VII had increased systolic blood pressure and temperature upon admission, these variables were not associated with survival on univariate analysis and did not affect the association of improved survival with factor VII use upon regression analysis. Therefore it appears that these differences in the factor VII patients were not statistically meaningful and could not be potential confounders for the association measured between rFVIIa use and 30 day survival.

Regarding the possibility of selection bias, it's possible and this limitation is inherent in all retrospective studies. But all measured indicators of severity of illness were equal between groups and those that were, were not associated with survival.

Regarding adverse events, they were retrieved by chart review to include gastrointestinal events. They were not prospectively screened for. The resultant underestimation, then, of thrombotic events should then be equal for both study groups that we report.

Lastly, I don't have any information on the incidence or outcomes for patients who received factor VII who did not receive a massive transfusion, nor have I analyzed the outcome for those who received factor VII prior to two hours or to those after two hours.

Those are excellent questions and I would be honored to present the results of those at the conference next year in Maui. Truly honored. Honestly.

Now, Dr. Jenkins, regarding your question how can we determine who is hypocoagulable enough to require factor VII or that it may help and who is hypercoagulable and it may not help, I think thromboelastography has the potential to give us those answers.

It is a rapid test that with new methods can rapidly, within 10 minutes, allow us to determine who is hypocoagulable but still have enough fibrinogen and platelet effect available that the use of rFVIIa would have the potential to improve hemostasis. There is also potential to use TEG to determine appropriate dosing and efficacy of rFVIIa based upon newly generated thrombus generation times and amounts. TEG would also be useful to determine who has become hypercoagulable and still bleeding due to the development of DIC over time and prevent the use of rFVIIa and the potential for adverse thrombotic complications in these cases. Hopefully future studies with factor VII in the trauma population will incorporate thromboelastography so we can try to answer some of these questions.

Regarding the question, of the relationship between ISS and massive transfusion, it appears that the ISS for patients with penetrating injury underestimates the severity of injury. I think that's probably the reason why some patients who received massive transfusions also had an ISS of less than 15.

I don't know the answer to how much factor VII is in fresh frozen plasma, nor the timing of when it becomes activated.

The dose that was used during the study period ranged between 90 to 120 mcg/kg per kilogram. The standard dose was 7.2 milligrams.

Most patients in this study received one dose. Few patients, probably between 10 to 15 percent, did receive multiple doses. If they were dosed again it was at the same dose, generally, 90 to 120mics per kilo.