

“Low-Dose” Recombinant Activated Factor VII Results in Less Blood and Blood Product Use in Traumatic Hemorrhage

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Background: This study was designed to compare mortality and blood product use in patients who received recombinant activated factor VII (rFVIIa) for traumatic hemorrhage to a matched historic control.

Methods: Trauma registry data of bleeding trauma patients who received rFVIIa (40 $\mu\text{g}/\text{kg}$, repeated once if needed) included 28-day mortality; pre- and post-rFVIIa international normalized ratio; and packed red blood cell (PRBC), fresh frozen plasma, platelet, and cryoprecipitate requirements. A

control group was created of bleeding patients who did not receive rFVIIa by matching for Injury Severity Score and age. The χ^2 and Student's *t* tests were used to test for significance.

Results: Twenty-nine patients, well matched to 72 control patients, made up the rFVIIa group. rFVIIa corrected international normalized ratio within 4 hours (from 4.4 to 1.2; $p < 0.0001$). There was no difference in mortality (control, 40.3%; rFVIIa, 41.4%). The rFVIIa group required significantly fewer PRBC transfusions than the control group (18.3 ± 7.5

vs. 22.0 ± 9.7 ; $p = 0.036$). Compared with the control group, the rFVIIa group required fewer platelet transfusions (1.4 ± 1.2 vs. 2.3 ± 2.1 ; $p = 0.01$) and less cryoprecipitate (0.59 ± 0.54 vs. 1.5 ± 1.8 ; $p = 0.006$).

Conclusion: rFVIIa resulted in significantly less PRBC, platelet, and cryoprecipitate use and equivalent mortality when compared with the matched control group, with no increase in complications.

Key Words: Recombinant activated factor VII, Blunt trauma, Traumatic hemorrhage, Blood product use.

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Exsanguination is second only to head injuries as the leading cause of death after trauma.¹ Hemorrhage is often complicated by coagulopathy, acidosis, and hypothermia. Treatment of this condition involves control of bleeding, damage control techniques, prevention of hypothermia, and blood product transfusion. Despite aggressive control of surgical bleeding, the diffuse hemorrhage from coagulopathy plays a significant role in mortality from trauma.²

Recombinant activated factor VII (rFVIIa) was approved in 1999 in the United States for use in hemophiliacs with inhibitors and patients with congenital factor VII deficiency. Significant off-label use of this product has been reported, specifically in patients undergoing retropubic prostatectomy as well as in the setting of intractable hemorrhage associated with cirrhosis, cardiac surgery, aortic aneurysm repair, postpartum bleeding, and trauma.^{3–6} The first reported use of rFVIIa in trauma was from an Israeli group in 1999.⁷ Since then, several case studies have been published describing anecdotal reports of success with rFVIIa in trauma-associated hemorrhage.^{8–10} A randomized, controlled trial comparing rFVIIa to placebo in traumatic hemorrhage has been per-

formed outside the United States. However, the results of this trial have not yet been published.

Our institution has been using rFVIIa in severe traumatic hemorrhage since February 2003 as part of a massive transfusion protocol. The purpose of this study was to compare blood product use and mortality in trauma patients who received a “low dose” (40 $\mu\text{g}/\text{kg}$) of rFVIIa versus a matched control group. Secondary outcomes examined included venous thromboembolism (VTE) rates, infections, intensive care unit (ICU) length of stay (LOS), total LOS, and ventilator days.

PATIENTS AND METHODS

Institutional review board approval was obtained to retrospectively review prospectively collected trauma registry data of patients receiving rFVIIa. Demographic information, as well as 28-day mortality, Injury Severity Score (ISS), blood product usage, international normalized ratio (INR) before and after rFVIIa, initial pH, VTE rates, infections, ICU LOS, total LOS, and ventilator days were collected. Blood product use was broken down into packed red blood cells (PRBCs) given before and after administration of rFVIIa, up to 72 hours after admission, and fresh frozen plasma (FFP), platelets, and cryoprecipitate transfusions in the first 72 hours.

We then created a cohort of matched historic controls by screening our trauma database. Patients receiving rFVIIa (study group) were matched to their control group by age ± 5 years, ISS ± 5 , and PRBC use before receiving rFVIIa. The matched control patient had to have received at least as many units of PRBCs as the study group patient received before the

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Table 1 Demographics

| | Control | rFVIIa | <i>p</i> Value |
|---------------------|-----------------|-----------------|----------------|
| n | 72 | 29 | |
| Age (y) | 41.8 ± 21.6 | 40.9 ± 20.8 | NS |
| ISS | 31.9 ± 10.2 | 31.4 ± 10.3 | NS |
| Mortality (%) | 40.3 (29 of 72) | 41.4 (12 of 29) | NS |
| Blunt mechanism (%) | 86 | 86 | NS |

NS, not significant; rFVIIa, recombinant activated factor VII; ISS, Injury Severity Score.

administration of rFVIIa. This allowed us to create a control group of bleeding patients to compare with our study group. We attempted to find three match patients for every study group patient. In instances where more than three matches were found, the closest ISS match was prioritized. As with the study group, we collected total PRBC, FFP, platelets, and cryoprecipitate transfusions in the first 72 hours of hospital admission in the control group. VTE rates, infections, ICU LOS, total LOS, and ventilator days were also recorded. The χ^2 and Student's *t* tests were used for statistical analysis, with *p* < 0.05 considered significant.

RESULTS

Between February 2003 and December 2003, 34 patients with traumatic hemorrhage at our institution received rFVIIa. We excluded five patients for the following reasons: One patient had no matched controls, three patients had isolated severe closed head injuries with no active hemorrhage, and one patient was a Jehovah's Witness and declined all transfusions. This left 29 patients in our study group. A blunt mechanism of injury accounted for 25 (86%) of the 29 patients. Each patient received a dose of 40 $\mu\text{g}/\text{kg}$ rFVIIa initially, with the option of repeating the dose once. Fifteen patients received a repeat dose, and the average dose for all patients was 60 $\mu\text{g}/\text{kg}$.

A matched historic control group of 72 patients was used as a comparison. These patients were admitted between 1995 and 2003. In seven patients, only two matches could be found, and in four patients, only one match could be found, accounting for the less than 3:1 ratio of control group to study group. Blunt trauma again accounted for 86% of the mechanism in these patients (62 of 72).

Demographics of the study group and control group are represented in Table 1. The 28-day mortality rates were similar between both groups (41.4% in the study group and 40.3% in the control group).

In the study group, we compared the highest INR before rFVIIa administration to the first recorded value after dosing (all within 4 hours). The value decreased from an average of 4.4 to an average of 1.2 (*p* < 0.0001). Total PRBC transfusion in the first 72 hours was 18.3 ± 7.5 in the rFVIIa group and 22.0 ± 9.7 in the control group. This difference was statistically significant (*p* = 0.036). We also evaluated PRBC use after rFVIIa was administered. Each study group patient

Table 2 Blood Product Use

| | Control | rFVIIa | <i>p</i> Value |
|---|-------------|-------------|----------------|
| Total PRBCs | 22.0 ± 9.7 | 18.3 ± 7.5 | 0.036 |
| Total PRBCs after rFVIIa or equivalent blood loss in controls | 8.5 ± 9.6 | 2.4 ± 6.2 | 0.001 |
| Total FFP | 14.1 ± 11.4 | 14.2 ± 7.2 | NS |
| Total platelets (in 5-packs) | 2.3 ± 2.1 | 1.4 ± 1.2 | 0.01 |
| Total cryoprecipitate (in 5-packs) | 1.5 ± 1.8 | 0.59 ± 0.54 | 0.006 |

FFP, fresh frozen plasma; NS, not significant; PRBC, packed red blood cell; rFVIIa, recombinant activated factor VIII.

had a number of PRBCs received before administration of rFVIIa. We used this number to represent a point of similar blood loss in his or her control group of patients. All PRBCs given after this number were compared with the study group PRBCs given after rFVIIa. An average of 2.4 ± 6.2 units of PRBCs were given after administration of rFVIIa in the study group. After similar blood loss in the control group, an additional 8.5 ± 9.6 units were transfused. This difference was strongly statistically significant (*p* = 0.001). These results are summarized in Table 2.

Interestingly, there was no difference in FFP use in the first 72 hours (14.2 ± 7.2 in the study group and 14.1 ± 11.4 in the control group). Platelet and cryoprecipitate transfusions are given as packs at our institution (1 pack = 5 units). The rFVIIa group received a mean of 1.4 ± 1.2 packs of platelets in the first 72 hours, compared with 2.3 ± 2.1 packs in the control group, a difference that was statistically significant (*p* = 0.01). Similarly, significantly less cryoprecipitate was used in the rFVIIa group. The rFVIIa group received a mean of

Table 3 Temperature and pH

| | Survivors | Nonsurvivors | <i>p</i> Value |
|--------------------------------|-----------------------|-----------------------|----------------|
| rFVIIa group | | | |
| pH | 7.19 ± 0.03 n = 16 | 7.07 ± 0.05 n = 12 | 0.02 |
| Temperature | 95.5 ± 0.55 n = 17 | 95.0 ± 0.95 n = 12 | NS |
| Control group | | | |
| pH | 7.27 ± 0.02 n = 41 | 7.08 ± 0.04 n = 27 | 0.00002 |
| Temperature | 95.5 ± 0.3 n = 40 | 95.3 ± 0.51 n = 24 | NS |
| rFVIIa group vs. control group | | | |
| Total pH | 7.19 ± 0.02 n = 68 | 7.13 ± 0.03 n = 28 | NS |
| pH survivors | 7.27 ± 0.02 n = 41 | 7.19 ± 0.03 n = 16 | 0.02 |
| Total temperature | 95.6 ± 0.3 n = 64 | 95.3 ± 0.5 n = 29 | NS |
| Temperature survivors | 95.5 ± 0.3 n = 40 | 95.5 ± 0.55 n = 17 | NS |

NS, not significant; rFVIIa, recombinant activated factor VII.

Table 4 Complications

| | Control | rFVIIa | p Value |
|----------------|-----------------|-----------------|---------|
| VTE rate (%) | 19.7 (14 of 71) | 6.9 (2 of 29) | 0.2 |
| Infections (%) | 40.8 (29 of 71) | 34.5 (10 of 29) | NS |

NS, not significant; rFVIIa, recombinant activated factor VII; VTE, venous thromboembolism.

0.59 ± 0.54 packs versus 1.5 ± 1.8 packs in the control group ($p = 0.006$).

Within the rFVIIa group, there was no difference in admission temperature between survivors and nonsurvivors: (95.5 ± 0.55 vs. 95.0 ± 0.95°, respectively). Not surprisingly, the admission pH in the rFVIIa group survivors was 7.19 ± 0.03 as compared with 7.07 ± 0.05 in the nonsurvivors, which was statistically significant ($p =$

0.02). A significant difference was also seen in the control group between the pH of survivors and nonsurvivors (7.27 ± 0.02 and 7.08 ± 0.04, respectively; $p = 0.00002$). We also compared admission pH between study group survivors and control group survivors. Interestingly, the patients who received rFVIIa survived at a lower pH, 7.19 ± 0.03, than the control group, 7.27 ± 0.02 ($p = 0.02$). Results are summarized in Table 3.

A total of 6.9% (2 of 29) of rFVIIa group patients had VTE complications, 1 pulmonary embolus and 1 deep vein thrombosis. The control group had a VTE rate of 19.7% (14 of 71), with 1 pulmonary embolus and 13 deep vein thromboses. In one control group patient, we were unable to accurately assess his VTE or infectious complications, so the patient was excluded from that part of the analysis.

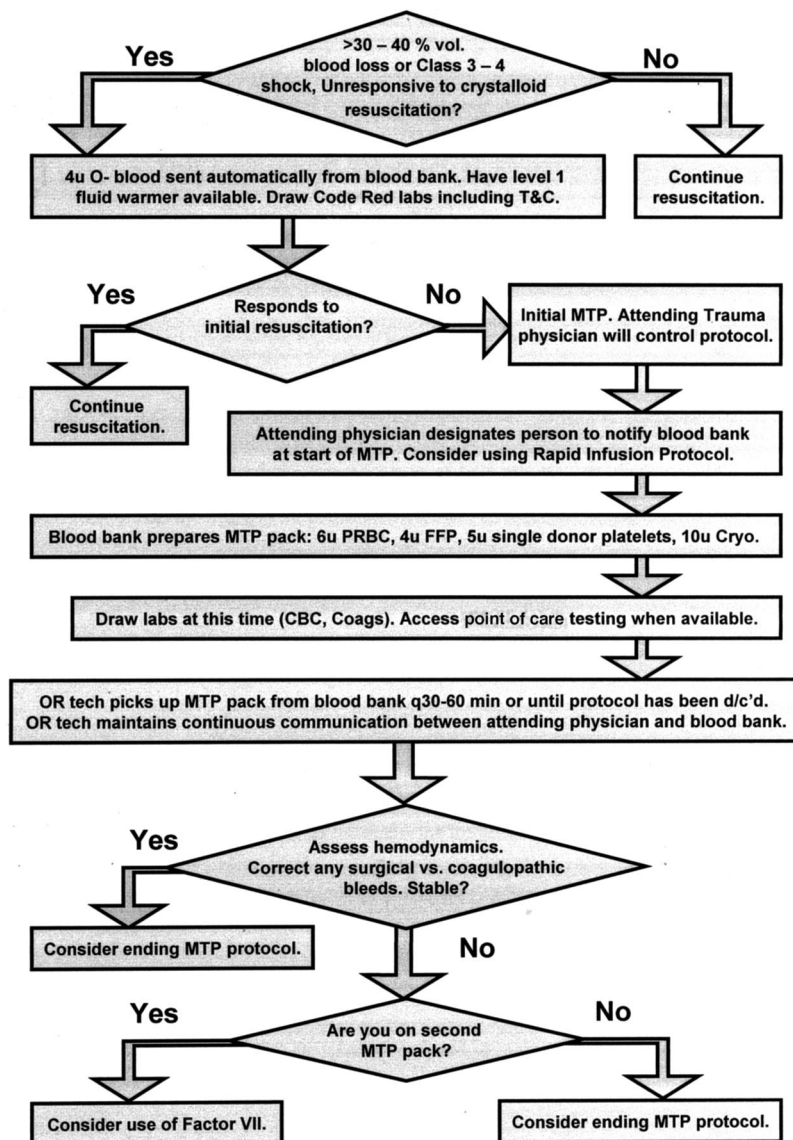


Fig. 1. Massive transfusion protocol (MTP). CBC, complete blood count.

In recording infectious complications, we included pneumonia, line infections, urinary tract infections, wound infections, sinusitis, and cellulitis. The rFVIIa group had a 34.5% (10 of 29) infection rate, whereas the control group's rate was 40.8% (29 of 71). No statistical significance was noted in comparing infection rates between the groups (Table 4).

There was no significant difference between the rFVIIa group and the control group with respect to ICU LOS (15.0 ± 3.3 and 14.0 ± 2.3 , respectively), total LOS (20.9 ± 4.0 and 19.7 ± 2.9 , respectively), or total ventilator days (13.0 ± 2.9 and 11.8 ± 2.3 , respectively).

We were able to calculate the Trauma Injury Severity Score for 21 of 29 rFVIIa patients and 58 of 71 control group patients. The average Trauma Injury Severity Score between groups was the same, 0.59 for the rFVIIa group and 0.57 for the control group ($p =$ not significant). The rFVIIa group had 3 of 21 unexpected survivors compared with 8 of 58 in the control group. This was not significantly different using χ^2 analysis.

DISCUSSION

Naturally occurring factor VII initiates hemostasis via the extrinsic pathway with its cofactor, tissue factor (TF). This leads to activation of factor VII, subsequent activation of factor X, and ultimately to production of thrombin. Although this pathway is surely important in the efficacy of rFVIIa, an alternate mechanism has been described in the setting of supraphysiologic levels of factor VIIa, as is seen with exogenous administration of rFVIIa. There is a TF-independent activation of factor X that occurs on the surface of activated platelets that has been shown to be an important contributor to hemostasis with rFVIIa.¹¹ Recent *in vitro* data suggest diminished impact of rFVIIa in acidotic patients but preserved function in hypothermic patients as a result of the TF-independent mechanism.¹²

Our data indicate that the use of rFVIIa in hemorrhaging trauma patients decreases PRBC transfusion requirements when compared with a matched control group. The detrimental effect of blood transfusions has been well documented in large, multicenter trials.^{13,14} A rapid normalization of the patient's INR after administration of rFVIIa translated to decreased blood loss during the first 72 hours of admission. However, we did not observe a decrease in FFP transfusion requirements. The effect of rFVIIa on the INR, the laboratory value that provokes FFP transfusion, is transient. Often, the INR tends to increase after its initial normalization by rFVIIa. In reviewing the charts of the study group patients, the increasing INR often prompted the treating physician to order FFP transfusions despite the cessation of clinically significant bleeding as evidenced by a stable hemoglobin level. This phenomenon of "treating a number" probably accounts for the similar FFP transfusions between groups. Platelet and cryoprecipitate transfusions were also significantly decreased in the rFVIIa group as compared with controls. Cessation of ongoing diffuse hemorrhage with the administration of

rFVIIa resulted in less consumption of platelets and fibrinogen, thus accounting for the diminished transfusion requirements of these products.

Acidosis in the setting of severe hemorrhage, whether measured as pH or base deficit, has been correlated with mortality.^{15,16} Our data support this, with both the control and rFVIIa group nonsurvivors having a significantly lower pH than the survivors. However, the rFVIIa survivors had a significantly lower pH than the control group survivors, i.e., the rFVIIa group survived at a lower pH. This is somewhat contrary to the *in vitro* data suggesting that rFVIIa is less effective in acidotic patients.¹² Therefore, acidosis by itself should not preclude the use of rFVIIa in an exsanguinating trauma patient.

There has been inadequate evaluation of complications attributable to rFVIIa in the trauma population. Because its use in this setting is considered off-label, there are significant patient safety and medicolegal implications. A relative contraindication for rFVIIa use is disseminated intravascular coagulation. The coagulopathy associated with traumatic hemorrhage is often called disseminated intravascular coagulation, although this rarely represents true intravascular coagulation but rather consumptive and dilutional coagulopathy. The administration of rFVIIa in a patient with multiple injuries could in theory result in diffuse coagulation secondary to significant tissue factor exposure. We found no reference to this complication in the published literature, and this did not occur in our population.

Venous thromboembolism is a major cause of morbidity after trauma. The theoretical concerns involving the use of the procoagulant rFVIIa in the already hypercoagulable setting of trauma have not been evaluated previously. We saw no increased risk of VTE disease in patients who received rFVIIa when compared with a cohort of matched controls. The VTE protocol used in this population has been previously published in this journal in 2002.¹⁷ All trauma patients receive compression boots. Low-molecular-weight heparin is added to all high-risk patients when their bleeding risk is acceptable. Screening lower extremity duplex examinations are performed for high-risk patients who cannot receive low-molecular-weight heparin in the first 48 hours. Until 1998, duplex screening was performed for all high-risk patients, regardless of prophylaxis. This may account for the higher VTE rate seen in the control group.

There were also no significant differences in infection rates between groups, despite a decrease in transfusion requirements. Convincing evidence in recent publications has linked PRBC transfusions and nosocomial infections, and this seems to be dose related. In a cohort of mixed ICU patients, Taylor et al.¹⁸ reported that the chance of development of a nosocomial infection increased by 1.5 for every unit of PRBC transfused. These data did not demonstrate a decrease in infections; therefore, future studies with larger sample size or specifically addressing infectious complications are needed to establish this theoretical link.

There is substantial variability in the dosing of rFVIIa in the reported literature, in part because of its off-label use. Doses range from as low as 10 $\mu\text{g}/\text{kg}$ to as high as 320 $\mu\text{g}/\text{kg}$, with some sources recommending repeating the dose.¹⁹ The current cost of the drug, approximately \$1,700 per 1,200- μg vial, may limit its use. Although there would be many variables in any future cost analysis involving rFVIIa, maintained efficacy at a lower dose could tip the scales in its favor. After reviewing the literature available at the time, we decided on a 40- $\mu\text{g}/\text{kg}$ dose, with the option to repeat the dose once (average, 60 $\mu\text{g}/\text{kg}$). Therefore, we decreased PRBC, platelet, and cryoprecipitate transfusions at a much lower dose than is generally used.

Although we have substantial experience with the use of rFVIIa in traumatic hemorrhage, our study is limited by its retrospective nature. The use of historic controls is never optimal; nonetheless, we believed that this method assessed the efficacy of rFVIIa with respect to transfusion requirements and mortality. This also allowed us to compare complication rates. The use of rFVIIa is regulated to some degree by the massive transfusion protocol; however, its administration is still largely at the discretion of the attending trauma surgeon. There was variability as to the timing and setting of delivery. This imparts a selection bias on our rFVIIa group that cannot be overlooked. Since the evaluation of these data, a more stringent protocol has been instituted to assure a more uniform administration policy (Fig. 1). A prospective, randomized trial conducted in the United States is warranted to more completely assess the impact of rFVIIa in the trauma population.

We have demonstrated that rFVIIa reduces PRBC, platelet, and cryoprecipitate requirements in hemorrhagic trauma patients. Its use should be considered in critically injured patients who require massive transfusions after surgical bleeding has been controlled. Despite theoretical concerns, there is no increased risk of VTE complications associated with the use of rFVIIa.

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