HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2011 September 01.

Published in final edited form as:

J Perinatol. 2011 March ; 31(3): 188–192. doi:10.1038/jp.2010.85.

Recombinant Activated Factor VIIa Treatment for Refractory Hemorrhage in Infants

Chi N Dang, PharmD[1], **Lakshmi I Katakam, MD**[2,3], **P Brian Smith, MD, MHS**[2,3,4], **C Michael Cotten, MD, MHS**[2,3], **Ronald N Goldberg, MD**[2,3], **Nicole Chandler, MD**[2], **Courtney D Thornburg, MD, MS**[2], and **Margarita Bidegain, MD, MHS-CL**[2,3]

[1] Department of Pharmacy, Duke University Medical Center, Durham, North Carolina, United States

[2] Department of Pediatrics, Duke University Medical Center, Durham, North Carolina, United States

[3] Jean and George W. Brumley Jr. Neonatal-Perinatal Research Institute

[4] Duke Clinical Research Institute, Durham, North Carolina, United States

Abstract

Objective—Report clinical response to recombinant factor VIIa in a cohort of critically ill infants.

Study Design—We identified all infants who received factor VIIa in the Duke Neonatal Intensive Care Unit between January 2005 and July 2008. Hematologic data and volume of blood transfusions before and after factor VIIa treatment were compared. The precipitating diagnosis for each factor VIIa use and the ensuing clinical outcomes of bleeding, thrombosis, and mortality were noted.

Result—We identified 18 infants with median birth weight of 880 g and median gestational age of 26 weeks. One to six doses of factor VIIa (90 mcg/kg/dose) were administered, with 13 (72%) infants receiving a single dose. Hemostasis was achieved in 13 (72%) of the infants. Prothrombin time and activated partial thromboplastin time significantly decreased following treatment with factor VIIa. Volume of plasma transfusions significantly decreased following treatment with factor VIIa (p=0.02). Thrombosis occurred in 1 (11%) infant. Six (33%) infants died within 72 hours of treatment, and overall mortality was 10/18 (56%).

Conclusion—Treatment with factor VIIa at doses of 90 mcg/kg improved coagulation studies and decreased the need for plasma transfusions in a group of critically ill infants without significant risk. Factor VIIa may be an effective addition to current treatment modalities for refractory hemorrhage in infants.

Corresponding author: Margarita Bidegain, MD, MHS-CL, Assistant Professor of Pediatrics, Duke University Medical Center, Box 2739, Durham, NC 27710, Phone: 919-681-4844, Fax: 919-681-6065, margarita.bidegain@duke.edu.

Conflicts of Interest

The authors declare no conflict of interest

Keywords

infants; blood products; transfusion; coagulation factors

INTRODUCTION

Recombinant activated Factor VIIa (rFVIIa; NovoSeven® Novo Nordisk, Princeton, NJ) is approved by the US Food and Drug Administration to treat hemophilia patients with inhibitors to factor VIII or IX. rFVIIa acts locally, at the site of endothelial damage, by binding to tissue factor. This complex leads to the development of a fibrin clot by promoting thrombin formation and activating platelets1.

rFVIIa is commonly used off-label to stop life threatening bleeding refractory to conventional treatment with fresh frozen plasma (FFP) and cryoprecipitate in adults, children, and infants. However, reports on the use of rFVIIa in infants and particularly premature infants are scarce.

Since 2005, rFVIIa has been used off-label as rescue treatment for critical bleeding refractory to conventional replacement therapy in infants admitted to the Duke Neonatal Intensive Care Unit (NICU). We report a series of patients who received rFVIIa, their treatment indications, dosage, and clinical outcomes.

METHODS

We conducted a retrospective cohort study of all infants receiving at least one dose of rFVIIa at Duke NICU between January 2005 and July 2008. Clinical data and demographic information were collected by review of medical and pharmacy records. Age at treatment, number of rFVIIa doses, and precipitating diagnosis warranting treatment were recorded. Coagulation studies, complete blood counts, blood product transfusions, and blood culture results in the 72 hours prior to and 72 hours following administration of each rFVIIa dose were recorded. Hemostasis was clinically defined by the cessation of hemorrhage. The sampling technique for coagulation studies was per our NICU practice guidelines that require peripheral blood draws as the primary mode of sampling.

Adverse outcomes such as necrotizing enterocolitis (NEC), sepsis, thrombosis, and mortality were noted. The diagnosis of NEC was made if the infant met stage IIA or greater of the modified Bell's criteria, which includes the radiographic finding of pneumatosis intestinalis2. Sepsis was defined by a positive blood culture.

All of the patients received blood products and vitamin K prior to the administration of rFVIIa. rFVIIa was administered at a dose of 90 mcg/kg, as a rapid IV push, at 2 hour intervals and repeated until hemostasis was achieved.

During the study period, it was standard practice in the unit to use rFVIIa, in consultation with hematology-oncology service, for patients with refractory bleeding. No parental consent was obtained prior to rFVIIa administration. " Data were analyzed using logistic regression, Fisher's exact and t-tests where appropriate. STATA 10 (College Station, TX)

was used for statistical analysis. This study was approved by the Duke University Institutional Review Board.

RESULTS

Demographic Data

We identified 18 infants who received at least one dose of rFVIIa during the study period. Sixteen infants (88%) were born prematurely. The median gestational age was 26 weeks (interquartile range [IQR], 24–32) and the median birth weight was 880 g (IQR, 694–2241). One to six doses of rFVIIa were administered at a median postnatal age of 9 days (IQR, 1–18). For the 18 infants included in the study, the clinical diagnoses that precipitated administration of rFVIIa included pulmonary hemorrhage (5), post surgical hemorrhage (6), gastrointestinal hemorrhage (1), intracranial hemorrhage (2), superficial skin hemorrhage (1), and disseminated intravascular coagulopathy (DIC) (3) (Table 1).

Effectiveness

Hemostasis was achieved in 13 of 18 infants (72%) within 72 hours of rFVIIa administration. 9 of the 13 patients who achieved hemostasis did so after only one dose of FVIIa. The rate of hemostasis among preterm infants was similar, 69% (11/16). There were statistically significant differences in the following coagulation studies less than or equal to 72 hours before and less than or equal to 72 hours after rFVIIa administration: prothrombin time (PT) (24 seconds vs. 14 seconds; p=0.001) and activated partial thromboplastin time (aPTT) (144 seconds vs. 70 seconds; p=0.01) (Table 2).

The median volume of FFP infusions decreased significantly from 30 mL/kg to 8 mL/kg in the 72 hours before and after rFVIIa administration (p=0.02). Median transfusion volumes of packed red blood cells decreased from 30 mL/kg to 10 mL/kg (p=0.35), platelets from 28 mL/kg to 10 mL/kg (p=0.26), and cryoprecipitate decreased from 9 mL/kg to 0 mL/kg (p=0.06). The total volume of blood products transfused before and after rFVIIa administration did not differ significantly (Table 3). Analysis with exclusion of the 6 early deaths (deaths within 72 hours of rFVIIa administration), did not significantly alter the volume of PRBC, platelet, and FFP transfusions before and after rFVIIa administration (Table 3).

Hematocrit increased from median of 25 to 27% (p=0.11) and fibrinogen levels increased from 120 mg/dL to 184 mg/dL (p=0.16) after rFVIIa therapy.

Safety

One infant in this cohort was found to have a non-occlusive aortic thrombus diagnosed by ultrasound 64 days after rFVIIa administration. The infant also had history of umbilical arterial line placement during the first week of life. The patient did not require medical or surgical intervention for thrombosis but died at 73 days of life secondary to respiratory failure and persistent chylothorax. Six (33%) infants died early, within 3 days of rFVIIa treatment. Causes of death included fulminant DIC (n=4), and intracranial hemorrhage (n=2). Four additional infants died later of non-bleeding complications: one of NEC 6 days

after rFVIIa therapy, one of *Escherichia coli* sepsis 8 days after rFVIIa therapy, and two of respiratory failure (73 days and 197 days after rFVIIa therapy) (Table 4). Overall hospital mortality was 10/18 (56%).

DISCUSSION

There are a number of reports describing the off-label use of rFVIIa in older infants and children for the treatment of refractory bleeding and prophylaxis for surgical procedures3–15. However, the experience in premature infants is scarce. Here, we report a large case series of premature infants treated with rFVIIa in the NICU.

The indications for use of rFVIIa in this cohort are similar to the ones previously reported: pulmonary hemorrhage, gastrointestinal hemorrhage, NEC, subgaleal hemorrhage, subdural hematoma and post-surgical hemorrhage16–26. The overall rate of hemostasis in our cohort (72%) is comparable to that of these published reports for infants of varying age groups. A similar rate (69%) was noted among preterm infants in our study. Hemostasis was achieved in all of the infants with pulmonary hemorrhage (5/5), ranging in gestational age from 24 to 32 weeks, after 1–3 doses of 90 mcg/kg of rFVIIa. Two case reports have described the successful use of rFVIIa for treatment of preterm infants with pulmonary hemorrhage, Cetin et al. reported on a single case and Olomu on 2 infants, using doses of 50–120 mcg/kg16,17.

One infant in our cohort achieved hemostasis after receiving two doses of rFVIIa for gastrointestinal hemorrhage refractory to vitamin K and blood product transfusions, including FFP, cryoprecipitate, platelet, and packed red blood cells. Similarly, Hunseler et al treated one 27 week infant with a large gastrointestinal tract hemorrhage unresponsive to vitamin K, FFP and platelet transfusions. In that case, effective hemostasis was achieved after a single 110 mcg/kg dose of rFVIIa18.

Overall, in our cohort, clinical hemostasis was not achieved in five of eighteen infants (28%). The non responders included 2 premature infants with intracranial hemorrhage, 2 infants with DIC and 1 infant with a large, hemorrhagic, sacrococcygeal teratoma (Table 4, patients #7, 8, 10, 12 and 14). It is important to note that 88% (16/18) of the infants in our study were premature with a median gestational age of 26 weeks and median age at treatment of 9 days. Young and investigators found that in their 17 infants less than 1 month, there was a 47% response rate compared to 61–72% response rates in the 122 older children that were studied.28 Lack of response to rFVIIa may be related to on-going co-morbidities, bleeding from sites of invasive procedures, bleeding that is unresponsive to increased thrombin generation, or more severe impairments in the hemostatic system (i.e. thrombocytopenia, DIC, or immature vasculature) which reduce effectiveness of rFVIIa. Correcting thrombocytopenia and hypofibrinogenemia and treating underlying illnesses may improve the response rate. 28

Additional studies are specifically required in premature neonates to fully assess thrombin generation potential and thrombin generation in response to rFVIIa. Levels of most procoagulant and anticoagulant proteins are lower in preterm infants than term infants and older children. However, these levels may not predict risk of bleeding or thrombosis. Global

assays of coagulation such as thrombin generation assays may be more predictive29. Tripodi et al found that despite preterm infants having lower levels of procoagulant proteins than term infants, their thrombin generation potential was significantly higher30. No studies to date have measured thrombin generation in neonates in response to rFVIIa.

The need for blood product requirements before and after treatment with rFVIIa has not been examined closely. We noted statistical significant decreases in PT and aPTT as well as a reduction in plasma transfusion requirements following rFVIIa administration. Although not statistically significant, our findings showed an overall trend toward an increase in fibrinogen level and a decrease in requirements of total volume of blood product transfusions.

In 2006, a review of all adverse events reported to the FDA in the first five years of rFVIIa licensure was published. Seventeen of the events occurred in patients with hemophilia while 151 occurred during unlabelled use. The adverse events included cerebrovascular accidents (n=39), acute myocardial infarction (n=34), other arterial thrombosis (n=26), pulmonary embolism (n=32), other venous thrombosis including deep venous thromboses (n=42) and clotted devices (n=10) 27. Puetz et al compared the rate of thromboses in 134 neonates who received 30–300mcg/kg of rFVIIa for refractory bleeding versus 100 neonates who received FFP transfusions alone to treat coagulopathy. They reported no statistical significant difference in the incidence of thrombotic events between the 2 groups (7.5% vs 7%).

One thrombotic event was noted in our study. The non-occlusive aortic thrombus was found incidentally, 64 days after treatment with rFVIIa. It is unlikely that this thrombus is related to rFVIIa treatment considering the lag between treatment and discovery of the clot and the history of umbilical arterial line in this patient during the first week of life.

rFVIIa doses of 40 mcg/kg to 300 mcg/kg have been used for varying indications and severity of bleeding in infants. Our strategy of using repeat doses of 90 mcg/kg of rFVIIa, at a minimum of 2 hour intervals despite prolonged coagulation studies, rather than less frequent and larger doses, may be responsible for the low incidence of thrombotic adverse events in our study. Nonetheless, when rFVIIa is given, close attention should be paid to signs of thrombosis.

Our overall mortality of 56% is reflective of the critically ill population. Almost 30% of the infants treated, died due to bleeding complications. Further advancements in the use of hemostatic agents to prevent or stop bleeding may significantly reduce this mortality rate.

While limited by small sample size and retrospective nature, this is the largest case series of rFVIIa use among premature infants, showing successful hemostasis and reduction of blood product requirements following rFVIIa administration.

CONCLUSIONS

rFVIIa at doses of 90 mcg/kg effectively contributed to achieving hemostasis in majority of the infants in our study with severe acute hemorrhage. In extremely premature infants, for whom bleeding complications such as pulmonary hemorrhage are relatively common, the

use of rFVIIa offers an alternative to large volume replacement with plasma or cryoprecipitate. Larger studies are needed to assess safety, pharmacokinetics, efficacy, and long-term outcome in this population.

Acknowledgments

We thank Kimberley A. Fisher, RN, PhD and Sandra Grimes, RN for their expert technical contributions.

Support: The Jean and George W. Brumley, Jr. Neonatal Perinatal Research Institute provided financial support for this study. Dr. Smith received support from NIH-1K23HD060040-01.

References

1. Lindley CM, et al. Pharmacokinetics and pharmacodynamics of recombinant Factor VIIa. Clinical Pharmacology & Therapeutics. 1994; 55 (6):638–648. [PubMed: 8004880]
2. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986; 33(1):179–201. [PubMed: 3081865]
3. Agarwal HS, Bennett JE, Churchwell KB, Christian KG, Drinkwater DC Jr, He Y, Taylor MB. Recombinant factor seven therapy for postoperative bleeding in neonatal and pediatric cardiac surgery. Ann Thorac Surg. 2007 Jul; 84(1):168–9. [PubMed: 17588405]
4. Alten JA, Benner K, Green K, Toole B, Tofil NM, Winkler MK. Pediatric off-label use of recombinant factor VIIa. Pediatrics. 2009 Mar; 123(3):1066–72. [PubMed: 19255041]
5. Veldman A, Neuhaeuser C, Akintuerk H, Thul J, Gehron J, Schranz D, Michel-Behnke I. rFVIIa in the treatment of persistent hemorrhage in pediatric patients on ECMO following surgery for congenital heart disease. Paediatr Anaesth. 2007 Dec; 17(12):1123–5. [PubMed: 17986029]
6. Heller M, Lau W, Pazmino-Canizares J, Brandao LR, Carcao M. A comprehensive review of rFVIIa use in a tertiary care pediatric center. Pediatr Blood Cancer. 2008 May; 50(5):1013–7. [PubMed: 17960639]
7. Guzzetta NA, Huch S, Fernandez JD, Tosone SR, Miller BE. Use of recombinant factor VIIa for uncontrolled bleeding in neonates after cardiopulmonary bypass. Paediatr Anaesth. 2008 Dec 23.
8. Yilmaz D, Karapinar B, Balkan C, Akisu M, Kavakli K. Single-center experience: use of recombinant factor VIIa for acute life-threatening bleeding in children without congenital hemorrhagic disorder. Pediatr Hematol Oncol. 2008 Jun; 25(4):301–11. [PubMed: 18484474]
9. Grizelj R, Vukovic J, Filipovic-Grcic B, Saric D, Luetic T. Successful use of recombinant activated FVIIa and aminocaproic acid in four neonates with life-threatening hemorrhage. Blood Coagul Fibrinolysis. 2006 Jul; 17(5):413–5. [PubMed: 16788319]
10. Jen H, Shew S. Recombinant activated factor VII use in critically ill infants with active hemorrhage. J Pediatr Surg. 2008 Dec; 43(12):2235–8. [PubMed: 19040942]
11. Tancabelic J, Haun SE. Management of coagulopathy with recombinant factor VIIa in a neonate with echovirus type 7. Pediatr Blood Cancer. 2004 Aug; 43(2):170–6. [PubMed: 15236286]
12. Ekert H, Brizard C, Eyers R, Cochrane A, Henning R. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard hemostatic replacement therapy. Blood Coagul Fibrinolysis. 2006 Jul; 17(5):389–95. [PubMed: 16788315]
13. Razon Y, Erez E, Vidne B, Birk E, Katz J, Tamari H, et al. Recombinant factor VIIa (Novoseven®) as a hemostatic agent after surgery for congenital heart disease. Pediatric Anesth. 2005; 15:235–240.
14. Velik-Salchner C, Sergi C, Fries D, Moser P, Streif W, Kolbitsch C. Use of recombinant factor VIIa (Novoseven) in combination with other products led to a thrombotic occlusion of the truncus brachiocephalicus in a neonate supported by extracorporal membrane oxygenation. Anesth Analg. 2005; 101:924. [PubMed: 16116021]

15. Wittenstein B, Ng C, Ravn H, Goldmann A. Recombinant factor VII for severe bleeding during extracorporeal membrane oxygenation following open heart surgery. Pediatr Crit Care Med. 2005; 6:473–476. [PubMed: 15982438]
16. Cetin H, Yalaz M, Akisu M, Karapinar DY, Kavakli K, Kultursay N. The use of recombinant activated factor VII in the treatment of massive pulmonary hemorrhage in a preterm infant. Blood Coagul Fibrinolysis. 2006 Apr; 17(3):213–6. [PubMed: 16575260]
17. Olomu N, Kulkarni R, Manco-Johnson M. Treatment of Severe Pulmonary Hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. J Perinatol. 2002; 22:672–674. [PubMed: 12478454]
18. Hunseler C, Kribs A, Eifinger F, Roth B. Recombinant activated factor VII in acute life-threatening bleeding neonates: report on three cases and review of the literature. J Perinatol. 2006; 26:706–713. [PubMed: 17066067]
19. Filan PM, Mills JF, Clarnette TD, Ekert H, Ekert P. Spontaneous liver hemorrhage during laparotomy for necrotizing enterocolitis: a potential role for recombinant factor VIIa. J Pediatr. 2005; 147:857–859. [PubMed: 16356448]
20. Brady KM, Easley RB, Tobias JD. Recombinant activated factor VII treatment in infants with hemorrhage. Ped Anesthesia. 2006; 16:1042–1046.
21. Girisch M, Rauch R, Carbon R, Habash T, Hofbeck M. Refractory bleeding following major surgery of a giant sacrococcygeal teratoma in a premature infant: successful use of recombinant factor VIIa. Eur J Pediatr. 2004 Feb; 163(2):118–9. [PubMed: 14716558]
22. Fischer D, Schloesser R, Buxmann H, Veldman A. Recombinant activated factor VII as a hemostatic agent in very low birth weight preterms with gastrointestinal hemorrhage and disseminated intravascular coagulation. J Pediatr Hematol Oncol. 2008; 5:337–342. [PubMed: 18458565]
23. Mitsiakos G, Papaioannou G, Giougi E, Karagianni P, Garipidou V, Nikolaidis N. Is the use of rFVIIa safe and effective in bleeding neonates? A retrospective series of 8 cases. J Pediatr Hematol Oncol. 2007 Mar; 29(3):145–50. [PubMed: 17356391]
24. Yilmaz D, Karapinar B, Balkan C, Akisu M, Kavakli K. Single-center experience: use of recombinant factor VIIa for acute life-threatening bleeding in children without congenital hemorrhagic disorder. Pediatr Hematol Oncol. 2008 Jun; 25(4):301–11. [PubMed: 18484474]
25. Altuncu E, Berrak S, Bilgen H, Yurdakul Z, Canpolat C, Ozek E. Use of recombinant factor VIIa in a preterm infant with coagulopathy and subdural hematoma. J Matern Fetal Neonatal Med. 2007 Aug; 20(8):627–9. [PubMed: 17674281]
26. Abdullah F, Hunter C, Hargrove C, Arnold M, Stein J. Recombinant factor VIIa for treatment of massive liver fracture in a premature infant. J Pediatr Surg. 2006 Oct; 41(10):1764–7. [PubMed: 17011285]
27. O'Connell KA, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA. 2006; 295:293–298. [PubMed: 16418464]
28. Young, et al. Off-label use of rFVIIa in children with excessive bleeding: a consecutive study of 153 off-label uses in 139 children. Pediatr Blood Cancer. 2009; 53:178–183.
29. Manco-Johnson M, Nuss R. Hemostasis in neonates. Neoreviews. 2000; 1:e191–e195.
30. Tripodi A, Ramenghi LA, Chantarangkul V, De Carli A, Clerici M, Groppo M, Mosca F, Mannucci PM. Normal thrombin generation in neonates in spite of prolonged conventional coagulation tests. Haematologica. 2008; 93:1256–1259. [PubMed: 18403390]
31. Puetz J, Darling G, Brabec P, Blatny J, Mathew P. Thrombotic Events in Neonates Receiving Recombinant Factor VIIa or Fresh Frozen Plasma. Pediatr Blood Cancer. 2009; 53:1074–1078. [PubMed: 19621430]

Table 1

Characteristics of Infants receiving rFVIIa

Characteristic	**n=18**
Gender - male (%)	56
Gestational age - weeks (median, IQR)	26 (24, 32)
Weight - g (median, IQR)	880 (694, 2241)
Outborn (%)	61
Postnatal age at rFVIIa administration - days (median, IQR)	9 (1, 18)
Doses of rFVIIa administered - n (%)	
One dose	13 (72)
Two doses	1 (5.6)
Three doses	2 (11)
Five doses	1 (5.6)
Six doses	1 (5.6)
Precipitating diagnosis - n (%)	
Pulmonary hemorrhage	5 (28)
Gastrointestinal hemorrhage	1 (5.5)
Intracranial hemorrhage	2 (11)
Superficial skin hemorrhage	1 (5.5)
Disseminated intravascular coagulopathy	3 (17)
Post surgical hemorrhage	6 (33)

Table 2

Coagulation studies before and after rFVIIa administration

	Prior to rFVIIa Median (IQR)	After rFVIIa Median (IQR)	P-value
Platelets (n)[1]	60 (39, 81)	59 (33, 97)	0.84
Prothrombin time (sec)	24 (18, 30)	14 (12, 16)	0.001
Partial thromboplastin time (sec)	144 (79, 150)	70 (35, 77)	0.01
Fibrinogen (mg/dL)	120 (102, 140)	184 (132, 228)	0.16

[1] Platelet count – $\times 10^3$/mm3

Table 3

Transfusions administered before and after rFVIIa treatment

	Prior to rFVIIa Median (IQR)	After rFVIIa Median (IQR)	P-value
Packed red blood cells (mL/kg)	30 (18, 52) 51 (18, 60)*	10 (5, 54) 9 (7.5, 29)*	0.35 0.37*
Platelet (mL/kg)	28 (5, 78) 40.5 (4.5, 96)*	10 (5, 22) 10 (6, 21.5)*	0.26 0.44*
Fresh frozen plasma (mL/kg)	30 (5, 116) 30 (14.5, 123.5)*	8 (0, 26) 7.5 (0,13)*	0.02 0.03*
Cryoprecipitate (mL/kg)	9 (0, 26) 7.5 (0, 26)*	0 (0, 10) 0 (0,0)*	0.07 0.26*

*Analysis with exclusion of the 6 early deaths in the cohort

Table 4

Clinical Outcomes of Infants treated with recombinant factor VIIa

Infant	Weight (grams)	GA (weeks)	Diagnosis	Doses of rFVIIa[1]	Outcome (cause of death)
1	580	25	Pulmonary hemorrhage	1	Late death[2]
2	3217	32	Pulmonary hemorrhage	3	Survived
3	930	26	Pulmonary hemorrhage	1	Survived
4	605	24	Pulmonary hemorrhage	1	Survived
5	830	25	Pulmonary hemorrhage	1	Survived
6	2880	38	Gastrointestinal hemorrhage	2	Survived
7	697	24	Intracranial hemorrhage	1	Early death[3]
8	450	24	Intracranial hemorrhage	3	Early death
9	518	23	Superficial skin hemorrhage	1	Early death
10	2622	39	DIC	1	Early death
11	2241	34	DIC	5	Survived
12	1750	29	DIC	1	Early death
13	1770	31	Post surgical hemorrhage	1	Survived
14	3960	33	Post surgical hemorrhage	6	Early death
15	730	25	Post surgical hemorrhage	1	Late death
16	1083	28	Post surgical hemorrhage	1	Late death
17	740	24	Post surgical hemorrhage	1	Late death
18	735	26	Post surgical hemorrhage	1	Survived

[1] Recombinant activated Factor VII at dose of 90 mcg/kg

[2] Death occurring 72 hours after treatment

[3] Death occurring within 72 hours of treatment