Recombinant Activated Factor VII in Controlling Bleeding in Non-Hemophiliac Patients

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Objective: To evaluate the use of recombinant factor VIIa (rFVIIa) in non-hemophiliac patients who had severe blood loss due to major trauma associated with extensive organ damage and received multiple blood transfusions.

Design: Retrospective study.

Setting: Alnoor Specialist Hospital, Makkah, Saudi Arabia.

Method: Medical records of patients who received rFVIIa from November 2007 to May 2011 were reviewed. Data collection included personal characteristics, diagnosis, indications, comorbidities, amount of blood products used with rFVIIa, dose of rFVIIa, mortality and adverse events.

Result: Forty-four patients were reviewed, 30 (68.18%) males and 14 (31.81%) females. The median age was 34.7 years. The median dose of rFVIIa was 5.2 mg (range, 2.4-8.2 mg). Seven (15.9%) patients needed a second dose of rFVIIa (range, 6-7 mg).

There was a marked and significant reduction in transfusion requirements for packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate. Twenty-two patients (50%) died and the median APACHE score was 46 (range, 18-69).

Eleven units (U) of packed RBCs (R), 9.2 U of platelets (P), 15.4 U of fresh frozen plasma (F) and 5.8 U of cryoprecipitate (C) were required as a pre-treatment compared to post treatment of an average of 3 U R, 5.1 U P, 4.7 U F and 2.4 U of C.

Conclusion: Our study showed that the early use of rFVIIa was associated with decreased 50-day mortality in non-hemophiliac patients who have experienced heavy blood loss and who have received multiple blood transfusions with haemostatic changes without success. The early use of rFVIIa was associated with marked reduction in the transfusion requirements.

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Recombinant activated factor VII (rFVIIa) is a pro-hemostatic agent used to control bleeding in patients with hemophilia with inhibitors to factor VIII concentrate or factor IX[1,2]. Factor VII (rFVIIa) was used for non-hemophiliac patients with active bleeding and as a prophylactic agent for high-risk patients with obstetrical bleeding, hemorrhage associated with warfarin toxicity, intracerebral hemorrhage, upper gastrointestinal bleeding, intractable bleeding after cardiopulmonary bypass in children and adults and Glanzmann's thrombocytopenia[3-6].

Coagulation abnormalities could be due to multiple factors: disseminated intravascular coagulation (DIC), excessive fibrinolysis due to release of tissue plasminogen activator (tPA), fluid replacement and massive blood product transfusion, dysfunctional platelets, acidosis and hypothermia[7].

The mechanism of action of rFVIIa remains unclear, it might bind to the surface of activated platelets and directly activates Factor X, thus bypassing the early steps of the coagulation cascade. Activated Factor X (Xa) combines with activated Factor V (Va) on the platelet surface, leading to rapid conversion of prothrombin to thrombin[7]. Thrombin generated near activated platelets at the site of vascular injury would promote hemostasis. rFVIIa may be effective in controlling hemorrhage due to trauma, surgery and other causes.

The aim of this study is to evaluate the use of recombinant factor VIIa (rFVIIa) in non-hemophiliac patients who had severe blood loss due to trauma associated with extensive organ damage and received multiple blood transfusions with haemostatic changes without success.

METHOD

Non-hemophiliac patients who received rFVIIa to control their bleeding from November 2007 to May 2011 were reviewed and followed up for 50 days after the infusion. The patients had bleeding that could not be controlled by conventional transfusion therapy. Data collection included personal characteristics (age, sex, weight), diagnosis, comorbidities, cause of bleeding, mortality, cause of death, dose of rFVIIa, medication (anticoagulation or anti-platelets before bleeding), transfusion data (amount of RBCs, fresh-frozen plasma [FFP], platelets, cryoprecipitate before and up to 48 hours after infusion of rFVIIa).

Data were analyzed by SPSS version 19.

RESULT

Forty-four patients were reviewed from November 2007 to May 2011, 30 (68.18%) were men and 14 (31.81%) were women. The mean age was 34.7 years ((SE) 2.27, range 9-72). The mean period of staying in ICU was 10 days (range 0.5-50). The causes of bleeding were major trauma, gastrointestinal tract, post-partum, central nervous system and other surgical procedures. The median APACHE score was 46 (range, 18-69). The median dose of rFVIIa administered was 5.2 mg (range, 2.4 – 8.2 mg); seven patients needed a second dose of rFVIIa (median dose, 6), see table 1.

Table 1: Characteristics of Patients

		Number of Patients (44)
Sex	Male	30 (68.18%)
	Female	14 (31.81%)
Age (years)	Mean ± SE	34.7 ± 2.27
	Range	9 - 72
ICU Length of Stay (days)	Mean ± SE	10 ± 1.7
	Range	0.5 - 50
APACHE II Score	Mean ± SE	46 ± 2.19
	Range	18 – 69
Dose (mg)	Mean ± SE	5.2 ± 0.23
	Range	2.4 – 8.2

Transfusion requirements before and after the administration of rFVIIa are shown in table 2 (in the first 48 hours). Before the administration of rFVIIa, the patients received on average 10.52 U of packed RBCs (range 2-26), 9.25 U of platelets (range 0-34), 15.43 U of fresh frozen plasma (range 0-41) and 5.86 U of cryoprecipitate (range 0-32). Post rFVIIa treatment, an average of 2.68 U of packed RBCs (range 0-10), 5.11 U of platelets (range 0-46), 4.72 U of fresh frozen plasma (range 0-55) and 2.40 U of cryoprecipitate (0-37) were transfused.

Pre rFVIIa administration, hemoglobin was 8.9 (range 5.2-15.1) and post rFVIIa administration became 9.7 (range 3.9-14.7), no significant difference was found. The difference between the pre- and post-transfusion requirement was significantly lower for all blood products: packed RBCs (p=0.0000), platelets (p=0.0307), fresh frozen plasma (p=0.0000) and cryoprecipitate (p=0.0360).

Table 2: Transfusion Requirements before and after Infusion of rFVIIa

Transfusion		Before rFVIIa	After rFVIIa	Mean Difference	P value
Hemoglobin (HB)	Mean ± SE	8.9 ± 0.36	9.7 ± 0.3	0.8	0.1055
	Range	5.2 – 15.1	3.9 – 14.7		
No of units packed RBCs	Mean ± SE	11 ± 0.8	3 ± 0.3	8	0.0000
	Range	2 – 26	0 – 10		
No of units platelets	Mean ± SE	9.2 ± 1. 2	5.1 ± 1.3	4.1	0.0307
	Range	0 – 34	0 – 46		
No of units fresh frozen plasma	Mean ± SE	15.4 ± 1.5	4.7 ± 1.3	10.7	0.0000
	Range	0 – 41	0 – 55		
No of units of cryoprecipitate	Mean ± SE	5.8 ± 1.2	2.4 ± 1.0	3.4	0.0360
	Range	0 – 32	0 – 37		

Twenty-two patients (50%) died, 17 (38.6%) were males and 5 (11.4%) were females. The median age of these patients was 35 years (range, 12-59 years) and the median APACHE score was 51 (range, 29-69).

The median dose of rFVIIa administered to patients who died was 5.26 mg (range 2.4-7.2). The patients who died had received Pre rFVIIa treatment on average 11.63 U of packed RBCs (range 2-26), 9.18 U of platelets (range 0-34), 15 U of fresh frozen plasma (range 0-41) and 7.95 U of

cryoprecipitate (range 0-32). Post rFVIIa treatment, an average of 2.77 U of packed RBCs (range 0-10), 6.18 U of platelets (range 0-46), 6.72 U of fresh frozen plasma (range 0-55) and 4.31 U of cryoprecipitate (range 0-37) were transfused. Hemoglobin was measured pre rFVIIa administration was 9 (range 3.9-13) and post rFVIIa administration became 8 (range 5.2-14.6). The causes of death were acute heart failure, multi-organ failure, septic shock and disseminated intravascular coagulation, see table 3.

The median dose of rFVIIa administered to patients who survived was 5.77 mg (range 2.4-8.2). The patients who survived had received Pre rFVIIa treatment on average 9.40 U of packed RBCs (range 2-19), 9.31 U of platelets (range 0-25), 15.86 U of fresh frozen plasma (range 4-41) and 3.77 U of cryoprecipitate (range 0-12). Post rFVIIa treatment, an average of 2.5 U of packed RBCs (range 0-6), 4 U of platelets (range 0-28), 2.72 U of fresh frozen plasma (range 0-8) and 0.5 U of cryoprecipitate (range 0-6) were transfused. Hemoglobin was measured pre rFVIIa administration was 9 (range 5.7-15.1) and post rFVIIa administration became 11 (range 9.1-14.7).

Table 3: Outcome of Bleeding

Patients		**Survived Patients**	**Died Patients**
44 patients		22 (50%)	22 (50%)
Sex	Male	13 (29.5%)	17 (38.6%)
	Female	9 (20.5%)	5 (11.4%)
Age (years)	Mean $\pm$ SE	33.7 $\pm$ 3.43	35.6 $\pm$ 3.04
	Range	9 - 72	12 – 59
ICU length of stay (days)	Mean $\pm$ SE	9 $\pm$ 1.6	11 $\pm$ 3.1
	Range	2 - 40	0.5 – 50
APACHE II score	Mean $\pm$ SE	42 $\pm$ 0.03	51 $\pm$ 0.03
	Range	18 - 67	29 – 69
Dose (mg)	Mean $\pm$ SE	5.7 $\pm$ 0.33	5.26 $\pm$ 0.31
	Range	2.4 - 8.2	2.4 - 7.2

DISCUSSION

In this study, the mortality rate in the patients who used rFVIIa among non-hemophiliacs was 50%, which is higher than that reported in other studies[8,9]. Use of rFVIIa reduces the need for blood transfusion and reduces mortality, especially if the dose of rFVIIa is limited to therapeutic doses of 90 μg/kg. The higher mortality rate in our study could be due to several factors, higher APACHE score, the patient's condition, time of infusion of rFVIIa, age, the presence of comorbid conditions and electrolyte disorders.

Our study showed that the early use of rFVIIa was associated with decreased mortality in non-hemophiliac patients who have experienced heavy blood loss and who have received multiple blood transfusions. The early use of rFVIIa was associated with marked reduction in the transfusion requirements.

A study showed that the benefits and risks of rFVIIa in cardiac surgery are unclear, but its benefits may outweigh its risks in selected patients[10-13]. The adverse events and mortality are due to the several factors and combination of various pathologies.

The timing, the interval of administration and the underlying cause of bleeding have influenced the efficacy of rFVIIa in controlling bleeding in 22 patients and the observed mortality in 22 patients.

Several other factors such as low APACHE score, age, and comorbid conditions could have an effect on reduction in transfusion requirements and the survival of these patients.

A study suggests that the use of the rFVIIa mega dose protocol is safe and effective in young patients. It might provide a faster rate of response[14]. The effect of rFVIIa may be enhanced if it is given early in the course of blood loss[14].

There was an obvious decrease in transfusion requirements in patients after rFVIIa infusion; the average became 2.7 and 2.5 respectively. There was a decreased mortality when rFVIIa was given. Therefore, in severely injured patients, who received the drug sooner, the mortality had decreased. The timing of rFVIIa use might be essential regarding its efficacy.

The small sample size in our study does not allow for adequate comparisons of adverse events. Eight randomized controlled trials (RCT) in surgical patients did not reveal an increased of thrombotic complication rate with rFVIIa[15-17]. The optimal dose of rFVIIa for these patients is unknown.

It would appear that earlier treatment with rFVIIa might improve the outcome and prevent the rapid clinical deterioration in patients. A study showed that rFVIIa is effective and well tolerated when used in the home setting to treat mild to moderate bleeding episodes in patients with hemophilia A or B with inhibitors[18]. Another study showed that high levels of recombinant activated factor VII have been found to be effective in providing hemostasis in hemophiliacs and in normal individuals with acquired inhibitors to factor VIII (FVIII) or FIX[19].

Extension of life for critical care patients is important to improve the overall mortality in these patients. Recombinant FVIIa may not improve survival if used too late in the resuscitation when the patient is in a state of irreversible shock[20].

CONCLUSION

Early use of rFVIIa was associated with decreased mortality and marked reduction in the transfusion requirements in non-hemophiliac patients who had heavy blood loss and who had received multiple blood transfusions with haemostatic changes without success.

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