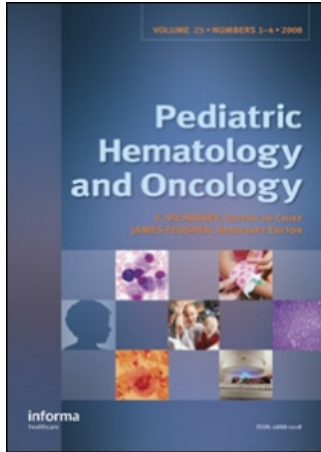


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SINGLE-CENTER EXPERIENCE: Use of Recombinant Factor VIIa for Acute Life-Threatening Bleeding in Children without Congenital Hemorrhagic Disorder

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SINGLE-CENTER EXPERIENCE: Use of Recombinant Factor VIIa for Acute Life-Threatening Bleeding in Children without Congenital Hemorrhagic Disorder

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□ *Coagulopathy is an important cause of mortality in critically ill children. Traditional therapies to correct coagulopathy lead to great time delays and cause fluid overload in patients. The authors report the effectiveness and safety of the activated recombinant factor VII (rFVIIa) administration in a series of 13 nonhemophilic children with acute, life-threatening bleeding. In this retrospective study, the records of the patients who were not diagnosed with congenital hemorrhagic disorder and were administered rFVIIa due to any other reason in Ege University Faculty of Medicine, Department of Pediatrics, between February 2002 and February 2007 were reviewed retrospectively. Thirteen nonhemophilic patients with acute life-threatening bleeding and ages ranging from 2 days to 15 years received rFVIIa over a 5-year period. Three patients were diagnosed with hemaphagocytic lymphohistiocytosis, 4 with prematurity, sepsis, and disseminated intravascular coagulation (DIC), 5 with sepsis, multiple organ dysfunction syndrome, and DIC, and 1 with acute liver failure. Severe bleeding resulted from pulmonary (n = 3), lower gastrointestinal system (n = 2), esophagus varices (n = 1), pulmonary and gastrointestinal system (n = 4), pulmonary, gastrointestinal system, and intracranial hemorrhage (n = 1), and gastrointestinal system and intracranial hemorrhage (n = 2). Median frequency of rFVIIa administration was 3 per patient (range 2{15) and median dose of rFVIIa was 90 µg/kg, ranging from 60 to 135 µg/kg each administration. All of the patients were given fresh frozen plasma and if necessary platelet transfusion (n = 10) or fibrinogen concentrate (n = 3) before administration of rFVIIa. In 6 patients, lack of success to control bleeding by conventional methods was the only cause to start rFVIIa. In 7 patients, the need for*

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volume restriction was also a significant contributing factor in deciding to start rFVIIa. Median PT was 32.9 s (range: 19{65) before rFVIIa administration and it was decreased to 11.6 s (range: 10.7{12.8), 2{3 h after rFVIIa infusion. Bleeding was stopped completely in 10 patients at least for 24 h and decreased in 3 patients 30{45 min after rFVIIa administration. Two patients had thrombotic complications attributed to rFVIIa administration. No other complication was observed in the other patients. In this retrospective study, rFVIIa was found to be effective at controlling severe hemorrhagic symptoms of different etiologies in children without congenital hemorrhagic disorder. In addition to the rapid control of bleeding, administration of this agent improved fluid balance and led to a reduction in blood product requirements in critically ill children. However, survival was still poor (23%), and 2/13 (15.4%) patients developed venous and arterial thrombosis within 3 h of treatment. The authors emphasize that in acquired, acute life-threatening bleeding, simultaneous administration of rFVIIa with conventional treatment may contribute to patient survival. However, the risk of thromboembolism should be considered before this treatment is given.

Keywords life-threatening bleeding, nonhemophilic children, pediatric intensive care unit, rFVIIa, thrombosis

Acquired hemorrhagic disorder due to multiple coagulation factor deficiencies and thrombocytopenia resulting from different etiologies is an important cause of mortality in critically ill children, especially when it causes intracranial, gastrointestinal, or pulmonary bleeding [1]. Conventional therapies consisting of fresh frozen plasma (FFP), packed red blood cell, and platelet transfusions, which correct coagulopathy, may be inadequate and time-consuming, and cause fluid overload in critically ill patients with severe bleeding. Ongoing bleeding in critically ill children may be often complicated with metabolic acidosis and shock, leading to decreased tissue perfusion in a very short time period and the clinical picture becomes worse and irreversible.

Recombinant activated factor VII (rFVIIa) was developed for the management of bleeding in hemophilic patients with inhibitors or in FVII-deficient patients. Recently it has been successfully used to correct bleeding in patients without congenital hemorrhagic disorders. Although many reports in the literature include mostly adult patients with trauma [2, 3] or liver disease [4–7] or patients undergoing surgery [8, 9], a few reports show rFVIIa is a useful agent in children and neonates with acquired severe bleeding [10–13]. Administration of rFVIIa in the treatment of acute, life-threatening bleeding in critically ill children without congenital hemorrhagic disorder may be life-saving.

The aim of this study was to evaluate the safety and effectiveness of rFVIIa in the treatment of acute, life-threatening bleeding conditions in critically ill children without congenital hemorrhagic disorder.

METHODS

The records of the patients who were not diagnosed with hemophilia and were administered rFVIIa for any reason in Ege University Faculty of

Medicine, Department of Pediatrics, were reviewed retrospectively. Multiple organ dysfunctions were scored according to the Pediatric Logistic Organ Dysfunction (PELOD) scoring system [14]. Age, gender, primary diagnosis, and PELOD scores of the patients during rFVIIa administration, bleeding site, treatment given before rFVIIa, dose, frequency, and indications of FVIIa administration, and outcome of bleeding episodes were evaluated.

Blood product requirements of the patients 24 h before and after rFVIIa treatment were determined from the patients' records. Cessation of or decreasing bleeding clinically and decrease in the requirement of blood product usage after rFVIIa treatment were defined as *efficacy* of the treatment. In this study all of the patients were followed until death or for 30 days after rFVIIa treatment was given or until they discharged from hospital, whichever happened later. Living longer than 30 days was defined as *survival*. During the first 96 h all patients were screened carefully for the symptoms and findings of thrombosis every day by an attending physician and if there was any suspicion attributed to thrombosis, patients underwent Doppler ultrasonography and D-dimer level was measured. During the first 96 h after rFVIIa treatment was completed, any thrombosis, embolism, cerebrovascular accident, or device clotting was defined as an *adverse event* related to rFVIIa treatment. Survival after rFVIIa treatment, a decreasing requirement of blood product usage, or cessation of or decreased clinical bleeding was defined as *overall benefit*.

Official procedures require the approval of a pediatric hematologist to use rFVIIa in Turkey. Therefore, all patients consulted with a pediatric hematologist before the decision to use rFVIIa was made. After the approval, informed consent was taken from the parents of the patients and they were informed about the potential toxicities and adverse effects that can be seen during rFVIIa treatment.

Statistics

In this study continuous data are reported as the median and range, and categorical data are presented as count and percentage. Statistical analyses of continuous data used paired *t* test or Wilcoxon rank sum test for parametric data and nonparametric data, respectively. A *p* value below .05 was accepted as statistically significant.

RESULTS

Patients Characteristics

Thirteen patients without congenital hemorrhagic disorder, ages ranging from 2 days to 15 years, received rFVIIa for acute life-threatening

TABLE 1 Characteristics of the Patients

Characteristics	
Age (median [range])	4 year [2 days–15 years]
Gender (female/male)	7/6
PELOD score (median [range])	51 [22–71]
Blood pH	7.2(6.9–7.41)
Primary diagnosis	
HLH [<i>n</i> (%)]	3 (23.1)
Prematurity, DIC [<i>n</i> (%)]	4 (30.8)
Sepsis, MODS, DIC [<i>n</i> (%)]	4 (30.8)
Liver failure [<i>n</i> (%)]	1 (7.7)
Bleeding site	
PH [<i>n</i> (%)]	3 (23.1)
PH + GIS-H [<i>n</i> (%)]	4 (30.8)
PH + GIS-H + ICH [<i>n</i> (%)]	1 (7.7)
GIS-H + ICH [<i>n</i> (%)]	2 (15.4)
GIS-H [<i>n</i> (%)]	2 (15.4)
Eosophageal varices [<i>n</i> (%)]	1 (7.7)

Note. DIC, disseminated intravascular coagulopathy; MODS, multiple organ dysfunction syndrome; PH, pulmonary hemorrhage; GIS-H, lower gastrointestinal system hemorrhage; ICH, intracranial hemorrhage.

bleeding between February 2002 and February 2007. Characteristics and primary diagnosis of the patients who were given rFVIIa are summarized in Table 1.

All patients were hospitalized in the Pediatric or Neonatal Intensive Care Unit before and during rFVIIa administration. The median PELOD score of the patients at the time of rFVIIa administration was 51 (ranging between 22 and 71). In 3 patients (23.1%) no organ dysfunction was detected before hemorrhage and in 10 patients hemorrhage caused an increase in the PELOD scores and the number of the organ, which demonstrated dysfunction. Seven out of 13 patients (53.8%) were admitted to the PICU with hemorrhagic shock. Central venous catheterization placement was performed in all patients for required volume replacement and medication, and to monitor central venous pressure. Blood gas analysis showed mild to severe metabolic acidosis in 9 patients, with a median blood pH of 7.2 (range 6.9–7.41) just before rFVIIa administration. Patients with metabolic acidosis were treated with NaHCO₃ to normalize blood pH.

The most commonly observed bleeding site was lower gastrointestinal system, followed by pulmonary and then intracranial areas. Eight out of 13 (61.5%) patients had more than one bleeding site. In one patient (7.7%) severe hemorrhage resulted from lower gastrointestinal, pulmonary and intracranial origin. The bleeding sites of the patients are summarized in Table 1.

TABLE 2 rFVIIa Dose and Frequency

	Median [range]
Frequency of rFVIIa administration	3 [2–5] per patient
rFVIIa dose	90 [60–135] $\mu\text{g}/\text{kg}$

Indications, Dose, Frequency, and Outcome of rFVIIa Administration

All of the patients were given FFP, packed red cell, and, if necessary (platelet count below $50 \times 10^9/\text{L}$), platelet transfusion ($n = 10$) before rFVIIa administration. Patients with a fibrinogen level below 150 mg/dL were also administered fibrinogen concentration ($n = 3$) or cryoprecipitate ($n = 1$). Octreotide treatment was given to the patient with bleeding esophageal varices.

Seven of the 13 (53.8%) patients were admitted to PICU with hemorrhagic shock and were supported with aggressive fluid administration and vasopressor agents in addition to FFP, packed red cell, and platelet transfusion. In 6 patients (46.2%), lack of success to control bleeding by conventional methods was the only reason to start rFVIIa. In 7 patients (53.8%), the need for volume restriction was also a significant contributing factor when deciding on adding rFVIIa to the conventional treatment.

Median frequency of rFVIIa administration was 3 per patient (range 2–15) and median dose of rFVIIa was 90 $\mu\text{g}/\text{kg}$, ranging from 60 to 135 $\mu\text{g}/\text{kg}$ each administration (Table 2). Intervals between two doses of rFVIIa administration were 2–3 h. All of the patients received at least two doses of rFVIIa. Five patients were given an additional 3rd dose in the first 24 h. In these patients the reason for additional doses of rFVIIa was unresolved bleeding. In the first 24 h no patient received more than 3 doses.

If rebleeding was detected 24 h after administration of first dose, additional doses were given. In all of the patients, daily 2 or 3 doses of rFVIIa caused resolution of bleeding. However, 1 patient received 4 total doses of rFVIIa (2 doses the first day and 2 doses the 2nd day) and 6 doses of rFVIIa were given in each of 2 other patients (3 doses the first day and 3 doses the 2nd day). Only 1 patient required 15 doses of rFVIIa (3 doses every day for 5 days).

Median PT was 32.9 s (range: 19–65) before rFVIIa administration and was decreased to 11.6 s (range: 10.7–12.8) 2–3 h after rFVIIa infusion. While PT was prolonged before rFVIIa administration in all patients, it falls within normal ranges 2–3 h after the first dose of rFVIIa. The difference between PT levels before and after rFVIIa treatment was found to be statistically significant (Table 3).

TABLE 3 PT Levels Before and After rFVIIa Administration

	Median [range]
PT before rFVIIa administration	32.9 [19–65] s
PT after rFVIIa administration	11.6 [10.7–14.8] s
<i>p</i>	<.05

Clinically, bleeding was stopped completely in 10 (76.9%) patients at least for 24 h and reduced in 3 (23.1%) patients, 30–45 min after rFVIIa administration. Blood product requirement was decreased significantly after rFVIIa administration (Table 4).

In this series the cost of rFVIIa therapy was between \$1070 and \$13880 with a median of \$6900 and was reimbursed by government.

Complications

Two patients had thrombotic complication after rFVIIa was given. No other complication was observed in the other patients. The first patient who experienced thrombosis was a premature newborn with a gestational age of 31 weeks. He had stage 3 RDS and DIC. A central venous catheter was implanted. He had a severe melena, hematemesis, and intracranial hemorrhage on the 6th day. Although he was given FFP regularly, gastrointestinal hemorrhage persisted for 24 h and he required transfusion twice (60 mL/kg/day) during this period. After rFVIIa was given twice at a dose of 100 μ g/kg, his bleeding stopped. However, 24 h after the last dose was given, lower gastrointestinal bleeding restarted. Administration of the same dose twice resulted in cessation of bleeding but 3 h after administration of second rFVIIa dose, he developed both arterial and venous thrombosis in brachial vessels.

The second patient who experienced a deep venous thrombosis was an 8-month-old girl. She was in the Pediatric Intensive Care Unit since she had myocarditis, decreased cardiac function, severe sepsis, septic shock, and multiple organ dysfunction with prolonged PT, aPTT, and decreased platelet count. She was critically ill and she had a central venous catheter

TABLE 4 Blood Product Consumption of the Patients Before and After rFVIIa Administration

Blood products	Before rFVIIa	After rFVIIa	<i>p</i>
	(mL/kg/day) Median [range]	(mL/kg/day) Median [range]	
FFP (<i>n</i> = 13)	40 [30–60]	10 [0–30]	<.05
Packed red cell (<i>n</i> = 13)	45 [15–60]	5 [0–20]	<.05
Platelet (<i>n</i> = 10)	15 [10–30]	5 [0–20]	<.05

placed in the femoral vein. She had gastrointestinal and intracranial hemorrhage and received FFP, packed red cell, and platelet transfusion. Since there was a necessity for volume restriction in this patient as well as a failure to control bleeding with replenishment treatment for 36 h, she was given rFVIIa twice at a dose of 135 $\mu\text{g}/\text{kg}$. Bleeding was stopped, but she developed a deep venous thrombosis in the lower extremity where the catheter was placed, 1 h after the administration of the second rFVIIa dose.

Both patients were screened for congenital risk factors for thrombosis. Mutations for factor V G1691A, factor VH1299R, prothrombin G20210A, MTHFR C677T, and MTHFR A1298C and activities of protein C, free protein S, and antithrombin were measured and found to be negative or in the normal ranges. No congenital thrombotic risk factors were detected in these patients.

Outcomes of the Patients

While 3 of the patients survived, 10 expired during the same hospitalization period. The median time for death of the patients was 3 days (1–23 days) after rFVIIa administration. In these series, none of the patients died due to bleeding.

DISCUSSION

rFVIIa was initially designed for the treatment of bleeding in hemophilic patients with inhibitors and is currently approved for the treatment of bleeding in hemophilia patients with inhibitor, and also for the treatment of patients with acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia who are refractory to platelet infusions. It initiates thrombin formation via interaction with tissue factor and activation of factor X. The results of several studies suggest that administering rFVIIa to patients with coagulopathy or hepatic insufficiency normalizes INR or PT and facilitates procedural manipulation, possibly reducing both blood loss and the use of blood products during the procedure [4–6, 14–16]. It is obvious that using this potent pro-coagulant agent in patients who are in danger of exsanguinations because of severe bleeding may be beneficial. The results of several studies suggest that administering rFVIIa to patients with life-threatening and/or intractable hemorrhage stops or slows bleeding and is associated with a reduced blood product usage [8, 17–23].

In this study, we retrospectively evaluated our experience in rFVIIa administration in nonhemophilic children and neonates with acute, life-threatening hemorrhage. Most of our patients admitted to the intensive care unit with hemorrhagic shock. Although the etiologies of coagulopathy leading to severe bleeding showed great variation, the primary approach was the same: aggressive fluid resuscitation and vasopressor agents to stabilize

hemodynamic status, vitamin K administration, FFP, and, if necessary, platelet and/or cryoprecipitate infusion to stop bleeding. All patients had a problem of longstanding peripheral vascular access and they all required central venous catheterization to receive the required volume and medication and to monitor central venous pressure. However, replenishment of depleted coagulation factors with conventional methods is time-consuming because of the need for confirmation of blood groups and thawing and administering blood products. Additionally, some difficulties may exist in the maintenance of peripheral intravenous access for a long time. Mostly they may require a central venous catheter in the setting of severe bleeding, which may be a relative contraindication to inserting a central venous catheter [24]. However, administering rFVIIa has some advantages: it is rapidly available since there is no need for blood typing or thawing, it infuses quickly via a peripheral venous access, and it is volume sparing.

Although it was originally stated that proper replacement therapy should be given before rFVIIa is considered [21], this approach is not always appropriate, especially in life-threatening bleeding, which was observed in our patients. In our series, rFVIIa was effective to stop or reduce bleeding and blood product requirement in all patients without a significant positive effect on survival. Similar experiences have also been reported by other studies [19, 20, 25]. According to our experience it seems beneficial to add rFVIIa to the standard management of the acute, severe hemorrhages in critically ill children without congenital hemorrhagic disorder at the beginning of the treatment, before organ damage related to either severe bleeding or underlying disease and shock develops. Once organ dysfunction occurs, it becomes harder to reverse the clinical situation of the patient who is suffering from severe hemorrhage even if the bleeding is under control [26]. In our series, all patients already had high PELOD scores and MOD at the time of rFVIIa administration.

In our series, 11 out of 13 (84.6%) children had pulmonary and/or intracranial hemorrhage where fluid restriction is desired. In these patients, adding rFVIIa to the conventional treatment of severe coagulopathy helped to decrease the requirement for FFP, packed red cell, and platelet transfusion and maintained fluid balance. In neonatal cases, it also has a great importance since rFVIIa can be administered immediately in small volumes without a requirement for central venous catheterization. While failure to control bleeding was the only reason to start rFVIIa treatment in 6 (46.1%) patients, the requirement for fluid restriction was an additional significant contributing factor in the decision to start rFVIIa treatment in 7 (53.9%) children.

The median dose of rFVIIa was 90 $\mu\text{g}/\text{kg}$ in this study. The rFVIIa doses used in this study are within the range of rFVIIa doses indicated in published data [2, 3, 8–10, 15–22, 27]. The optimal doses for different indications

are unknown. In the setting of thrombocytopenia, the maximal rate of thrombin generation is proportional to rFVIIa concentration, suggesting a dose-dependent effect [17, 19, 27]. Dose-ranging studies in patients with hepatic dysfunction and coagulopathy, however, indicate that INR and PT are normalized with doses of 5–120 $\mu\text{g}/\text{kg}$ but the duration of normalization is dose-dependent [7].

The hemostatic mechanisms of rFVIIa have resulted in safety concerns with its use. The most important problem is the possibility that pharmacologic doses of rFVIIa may generate an acute thrombosis. Clinical trials with rFVIIa showed that thrombotic events can be seen, especially in patients without hemophilia [28]. Two patients in our study experienced thrombosis as a possible adverse event related to rFVIIa within 6 h of administration. Both of the patients who had thrombosis were carrying a central venous catheter and suffering from sepsis. Additionally, in these patients the doses of rFVIIa administered were higher than the median dose used in our study.

It is hard to say if there were any indicators to predict which children were to develop a thrombotic complication before rFVIIa administration because of the limited number of patients in this study. However, higher dose for every administration is striking in patients developed thrombosis. Both children were given higher rFVIIa doses than usual. The first patient was given 100 $\mu\text{g}/\text{kg}$ twice in the first day and same doses were repeated at second day. A total of 400 $\mu\text{g}/\text{kg}$ rFVIIa was given to him. The second patient was given 135 $\mu\text{g}/\text{kg}$ twice (270 $\mu\text{g}/\text{kg}$) in a 2-h period. Both had a DIC and central venous catheter. It may be speculated that in patients with severe sepsis or with DIC or known thrombotic risk factors rFVIIa should be administered carefully. Lower doses of rFVIIa may be safer and helpful to lower the incidence of thrombosis in these risky patients. Larger studies in children to detect minimal effective doses might be helpful.

A recent report suggests that the degree of hemorrhagic shock at the time of admission to the hospital is the best predictor of response to rFVIIa treatment [20]. Some other series supported this suggestion: when given late in the course of the disease progression, after massive transfusion is already underway, many patients will not respond [25, 29]. It was also reported that rFVIIa activity is significantly impaired by acidosis and hypothermia [30].

It may be concluded that these are the markers that indicate how sick the patient is. In our study, most of the patients had metabolic acidosis but they were given NaHCO_3 simultaneously with replacement therapy and/or rFVIIa. Although administration of rFVIIa in our patients resulted in a good response—cessation or at least reduced bleeding—10 (76.9%) patients died. Three patients who survived in this series were already in our hospital when they got severe bleeding, so we had a chance to quickly manage them and we added rFVIIa just after the conventional treatment

failed. The biggest chances for those patients to find benefit from rFVIIa administration and to survive were experience of the intensivist to use rFVIIa and learn how effective it was to stop bleeding in critically ill patients, rapid consultation for its use with hematologists, and rapid and easy availability of rFVIIa. We do not think that rFVIIa contributed to the demise of the other patients. These patients were severely ill, with very high PELOD scores before rFVIIa treatment and we gave this treatment to most of these patients as a last-ditch therapy.

We suggest that even if rFVIIa treatment controls severe hemorrhage, organ dysfunction resulting from life-threatening bleeding determines the outcome when it is used as a last-ditch effort in severely ill patients.

CONCLUSION

In this retrospective study, rFVIIa was found to be effective at controlling severe hemorrhagic symptoms of different etiologies in children without congenital hemorrhagic disorder. In addition to the rapid control of bleeding, administration of this agent improved fluid balance and led to a reduction in the requirement of blood product in critically ill children. However, survival was still poor (23%) and 2/13 (15.4%) patients developed venous and arterial thrombosis within 24 h of treatment. We would like to emphasize that in acquired, acute, life-threatening bleeding, simultaneous administration of rFVIIa with conventional treatment may contribute to patient survival. However, the risk of thromboembolism should be considered before this treatment is given.

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