

Management of Life-Threatening Hemorrhages and Unsafe Interventions in Nonhemophiliac Children by Recombinant Factor VIIa

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The literature on the use of recombinant factor VIIa (rFVIIa), which was initially used in hemophiliac patients with inhibitors, for hemorrhages that cannot be managed with conventional methods or operations that cannot be performed safely is increasingly growing. This study presents a group of nonhemophiliac patients with hemorrhagic problems or hemorrhage risk for some interventions that were successfully resolved with the use of rFVIIa. The patient group was composed of 20 patients with different disorders resulting in similar results as hemorrhage or hemorrhage risk. Most of the patients were diagnosed with liver disorders primary or secondary to other diseases. The remaining cases were patients with leukemia, sepsis, intracranial hemorrhage, and burn. Some of the

patients had multiple problems like a patient with liver disorder and intracranial hemorrhage or a leukemia patient with sepsis and disseminated intravascular coagulation. rFVIIa had been administered to the patients at dosages between 70 and 150 $\mu\text{g}/\text{kg}$ up to 6 doses with 2-hour to 3-hour intervals. All the patients had benefited from the use of rFVIIa even though some of them died because of primary disease. This study shows that rFVIIa can be safely used in high-risk patients with a history of recurrent hemorrhage, for whom no improvement can be achieved in the hemostasis tests.

Keywords: NovoSeven; recombinant activated factor VII; bleeding; children

Recombinant factor VIIa (rFVIIa, NovoSeven, Novo Nordisk, Denmark) originally came on the market for use in hemophilia patients with inhibitors, generally in cases of bleeding. The literature on the use of rFVIIa for hemorrhages that cannot be managed with conventional methods or operations that cannot be done safely is increasingly growing. Its success has increased the usage in many nonhemophiliac conditions because of incapability of other treatment modalities. These conditions include surgeries (liver and other abdominal or cardiac), factor VII deficiency, some invasive procedures,

gastrointestinal bleeding, sepsis, and other causes of coagulopathies, thrombocytopenia, or thrombocyte function impairments.¹⁻⁵

In this study, we present retrospective analysis of patient characteristics, rFVIIa dosages, and success of the usages of rFVIIa for the off-label indications in our patients with serious bleeding.

Patients and Methods

This was a retrospective analysis of 20 non-hemophiliac patients between 2 months and 17 years of age who were administered rFVIIa for their different clinical hemorrhagic conditions that could not be resolved with other measures between January 2003 and March 2006. Their demographic profiles and diseases with the complications causing rFVIIa usage are summarized in Table 1 as the hemorrhage

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Table 1. Hemorrhage Group Patients' Characteristics With the Results of rFVIIa Use

Patient No.	Age/Gender	Disease	Condition Used	Result
1. AND	2 months/female	Pancytopenia, sepsis	GIS hemorrhage	Hemorrhage ceased
2. MY	15 years/male	Kala-Azar, sepsis, DIC	Epistaxis	Hemorrhage ceased
3. BO	8 years/female	Chronic liver disease	GIS hemorrhage	Hemorrhage ceased
4. MB	4 years/female	ALL-L1, sepsis, DIC	Toxic hepatitis, GIS hemorrhage	Hemorrhage ceased
5. RB	17 years/male	Myelofibrosis, thrombocytopenia	Postsplenectomy, intra-abdominal hemorrhage	Hemorrhage ceased
6. ŞC	2 years/female	Tuberculosis, meningitis, sepsis	GIS hemorrhage	Hemorrhage ceased
7. YK	2 years/male	Acute fulminant hepatitis	Pulmonary hemorrhage	Hemorrhage ceased
8. HA	14 years/female	ALL-L1, pulmonary mycosis	Pulmonary hemorrhage	Hemorrhage ceased
9. AD	4 years/male	Klippel Weber syndrome	Pulmonary hemorrhage	Hemorrhage ceased
10. HII	13 months/male	AML	Epistaxis	Hemorrhage ceased

NOTES: GIS = gastrointestinal system; DIC = disseminated intravascular coagulation; ALL-L1 = acute lymphatic leukemia-L1; AML = acute myeloid leukemia.

Table 2. Prophylaxis Group Patients' Characteristics With the Results of rFVIIa Use

Patient No.	Age/Gender	Disease	Condition Used	Result
11. HB	3 months/female	Hepatosplenomegaly etiology	Liver biopsy	No complication
12. AA	9 years/male	Chronic hepatitis B	Scrotal operation	No complication
13. EÇ	9 years/female	Wilson disease	Liver biopsy	No complication
14. ZY	7 years/male	Chronic liver disease	Liver biopsy	No complication
15. RI	16 months/male	Sepsis + MODS, DIC	Operation for ileal perforation	No complication
16. EH	2 months/male	Hepatosplenomegaly etiology	Liver biopsy	No complication
17. MO	3 years/female	ICH	Operation	No complication
18. YY	7 months/female	Gaucher disease, chronic liver disease	Operation for ICH	No complication, hemorrhage ceased
19. BA	4 months/male	Liver disease	Liver biopsy	No complication
20. SM	5 years/male	Burn	Grafting and debridement	No complication

NOTES: MODS = multiple organ dysfunction syndrome; DIC = disseminated intravascular coagulation; ICH = intracerebral hemorrhage.

group and in Table 2 as the prophylaxis group. Most of the patients (11/20) had primary liver disorders or diseases resulting in secondary liver effects hemorrhages (patients 2, 3, 4, 7, 11-14, 16, 18, and 19). All the patients were receiving daily approximately 20 to 30 cm³/kg fresh frozen plasma before rFVIIa administration, but enough improvement was not achieved. Hematological parameters of the patients are summarized in Tables 3 and 4. These patients' rFVIIa dosages ranged between 70 and 150 µg/kg with 1 to 4 doses.

Of the 20 cases, 14 patients were thrombocytopenic (patients 1, 2, 4-8, 12-15, 17, 18, and 19), who were administered rFVIIa because of thrombocytopenia and desperate clinical conditions even after conventional preventive measures such as platelet transfusions. The dosages of drug were again between again 70 and 150 µg/kg.

One of the patients (patient number 2) is a 15-year-old male diagnosed with kala-azar, *Escherichia coli* septicemia, and disseminated intravascular coagulation (DIC). Clinical examination revealed distended abdomen, indistinctive navel, palpable liver, and spleen extending down to the inguinal area. The laboratory investigations revealed pancytopenia and coagulopathy. During the follow-up, the patient developed epistaxis. After insertion of an anterior nose tampon, during his treatment the patient was administered with 5 units platelets, 4 units packed red cells, 8 units fresh frozen plasma, 3 mg vitamin K and 2 g fibrinogen for management of thrombocytopenia, anemia, and acquired coagulopathy. Because coagulopathy showed no improvement and epistaxis continued actively, 3 doses (120 µg/dL each dose) of rFVIIa were administered intravenously for 5 minutes at 2-hour intervals. After 3 doses of rFVIIa administration, the

Table 3. Hematological Parameters of the Hemorrhage Group Patients Before and After rFVIIa Use and the Dosing Schedule

Patient No.	Before/After					
	PT (s)	PTT (s)	Fibrinogen (mg/dL)	Bleeding Time (min)	Platelet count(/mm ³)	Dosage (µg/kg)
1. AND	24/17	48/36	96/104	13/10	9000	120 × 1
2. MY	20/13	44/39	110/90	>15/12	13 000	92 × 3
3. BO	16/18	75/33	171/209	5/5	607 000	70 × 2
4. MB	28/18	56/43	136/128	14/12	25 000	133 × 2
5. RB	15/11	33/29	610/645	11/9	64 000	120 × 2
6. ŞÇ	23/12	40/34	129/174	8/3	132 000	120 × 1
7. YK	19/15	42/58	158/196	9/7	70 000	109 × 4
8. HA	16/14	44/34	198/156	12/9	33 000	70 × 1
9. AD	17/12	37/26	415/476	5/6	431 000	92 × 2
10. HII	16/15	69/37	400/900	8/7	50 000	92 × 1

NOTES: PT = prothrombin time; PTT = partial thromboplastin time.

Table 4. Hematological Parameters of the Hemorrhage Group Patients Before and After rFVIIa Use and the Dosing Schedule

Patient No.	Before/After					
	PT (s)	PTT (s)	Fibrinogen (mg/dL)	Bleeding Time (min)	Platelet count(/mm ³)	Dosage (µg/kg)
11. HB	20/14	40/34	173/165	7/5	267 000	120 × 3
12. AA	24/16	41/32	160/167	9/8	57 000	96 × 4
13. EÇ	26/14	52/39	152/144	8/6	67 000	150 × 3
14. ZK	20/18	45/44	310/241	5.5/4	60 000	104 × 3
15. RI	27/16	56/44	86/110	>15/11	17 000	120 × 6
16. EH	19/14	34/33	398/375	6/5	164 000	120 × 2
17. MD	36/12	72/43	287/226	8/5	435 000	70 × 1
18. YY	18/12	43/40	117/145	8/6	53 000	120 × 3
19. BA	22/16	44/38	156/142	6/6	168 000	120 × 1
20. SM	18/13	22/28	322/309	7/4	106 000	96 × 2

NOTES: PT = prothrombin time; PTT = partial thromboplastin time.

patient's bleeding ceased completely although coagulopathy and thrombocytopenia continued due to primary disease. The laboratory tests showed a stable hemoglobin concentration post-rFVIIa use.

There were 4 patients (patients 2, 4, 6, 15) with sepsis and DIC causing gastrointestinal hemorrhage in 2 of them, ileal perforation in 1, and epistaxis in the other. These hemorrhages were unresponsive to platelet and fresh frozen plasma replacements. Hemorrhages terminated with the use of rFVIIa and ileal perforation was safely operated.

A leukemia patient (patient 4) with toxic hepatitis secondary to high-dose intravenous methotrexate treatment received 2 doses of 90 µg/kg rFVIIa, and her gastrointestinal bleeding was successfully terminated. Another leukemia patient (patient 8) with pulmonary mucormycosis was a 14-year-old girl hospitalized

after long-term dexametasone treatment. She was admitted with febrile neutropenia and septic shock clinic. During the improvement in her condition, she developed secondary pulmonary lobar pneumonia. It was microscopically shown that it was caused by mucormycosis pulmonary opportunistic infection. While on antifungal treatment, she had massive hemoptysis secondary to thrombocytopenia, coagulopathy and fungal intrapulmonary vascular invasion with tissue necrosis resulting in obstructive apnea. Despite intensive replacement of thrombocyte apheresis and fresh frozen plasma, her condition worsened. Just before intubation, rFVIIa 2.4 mg was administered and after 15 minutes hemoptysis had stopped. She was not intubated later.

Other patient (patient 18) was a 7-month-old female infant with Gaucher disease. Her medical

history revealed repeated intracranial hemorrhages and 3 operations for them. Just before hematology consultation, a new focus of hemorrhage was detected. The patient, for whom an operation was planned, was twice supplemented with platelet suspension at a dose of 10 cm³/kg (53 000/mm³) for her thrombocytopenia. Despite the administration of frozen plasma supplement, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen level were found to be 18 seconds, 42.8 seconds, and 117 mg/dL, respectively. A dose of 1.2 mg of rFVIIa was administered to the patient once preoperatively and twice postoperatively at a 2-hour interval due to her history of postoperative hemorrhage. On the preoperative observation of PT, PTT, and fibrinogen as 12.1 seconds, 43.1 seconds, and 145 mg/dL, respectively, and bleeding and clotting times as 6 and 5 minutes, respectively, the patient was operated on. No new postoperative hemorrhages or other complications were observed and the relevant treatment was planned.

After the application of rFVIIa we observed no mortality in our patients because of the serious bleedings. All bleedings stopped and no thromboembolic complication was seen. Nevertheless, 4 patients (patients 1, 2, 4, 7) died because of the progression of primary diseases in the hemorrhage group. Patients 1 and 2 died because of with sepsis and septic shock. Other 2 patients (patients 4 and 7) died because of hepatic failure and brain edema.

Discussion

In this report, we present 20 patients with different conditions, who were administered rFVIIa for resolving their problems. The most common conditions were bleedings secondary to liver disorders and interventions as liver biopsies in the same situation. They account for 11 of the 20 cases where rFVIIa was administered. Coagulopathy in acute or chronic liver disease occurs mainly due to the decrease in the hepatic synthesis of clotting factors and the condition is further deteriorated by the presence of other factors, including DIC, hyperfibrinolysis, dysfibrinogenemia, hemolysis, and decreased platelet counts.¹ The fact that factor VII is detected at a lower level compared with other factors due to its short half-life, particularly in patients with cirrhosis, has made it a significant prognostic finding in the course of the disease.⁶ Recombinant FVIIa was shown to correct the prolonged PT in hepatic insufficiency and demonstrated

successful outcomes when used for hemorrhagic complications that cannot be managed with conventional methods.⁷ In a previous study, rFVIIa was used as intravenous bolus doses of 34 to 163 µg/kg (median 66 µg/kg) in children with liver disease. In our cases, dosages of rFVIIa ranged between 70 and 150 µg/kg from 1 up to 4 doses. In addition, some studies have reported the successful usage of rFVIIa at dosages between 60 and 120 µg/kg from 1 up to 10 doses.⁸

In patients with leukemia and myelofibrosis, bone marrow platelet production was decreased. In a patient with kala-azar, hypersplenism also contributed to the thrombocytopenia. Kristensen et al⁹ in their study with 105 patients—majority having immune thrombocytopenia—have reported the use of rFVIIa at dosages of 50-100 µg/kg. Duration of bleeding was noted to decrease by more than 2 minutes in 52% of the patients. Moreover, the bleeding episodes were terminated in 6 out of 8 patients with thrombocytopenia (platelet count 5 × 10⁹ to 33 × 10⁹/L) and in the remaining 2 patients, bleeding episodes were reduced. However, the results did not correlate with the bleeding time.⁹ In another study reported by Poon,¹⁰ rFVIIa has been reported to be effective in controlling the bleeding of a patient whose spleen had been removed due to allo-immune thrombocytopenia and who developed bleeding during the postoperative period, in spite of the fact that he had been administered supportive therapies for thrombocytopenia and coagulopathy.

After the use of rFVIIa in 18 patients with hemorrhagic DIC, Schmid et al¹¹ reported that no thromboembolic complications were observed besides clinical positive response to stop bleeding (15/18 patients). It is known that DIC is the result of a variety of disorders, for example, systemic intravascular activation of coagulation. It causes fibrin deposition resulting in microvascular thrombosis and multiorgan failure. Although the coagulation system is activated, platelet and coagulation therapy is necessary because of consumption of clotting factors. The possible effect of rFVIIa is that it enhances thrombin generation at the injured vascular site by forming tissue factor VIIa complex and then activates factor X to Xa as well as by providing Xa on the surface of the already activated platelets. It is concluded that rFVIIa may be used successfully in DIC.¹¹ This result correlates with the conditions of 4 patients in our study and their responses to rFVIIa. After the administration of rFVIIa, bleedings stopped without evidence of thrombosis or other adverse effects in all patients.

rFVIIa has revealed successful results when used within the first 4 hours following hemorrhage to reduce the dimensions of hematoma in intracerebral hemorrhages, and there are also studies of rFVIIa use in neurosurgical interventions.¹²⁻¹⁵ The neurosurgical intervention, similar to that performed in one of our patients with chronic liver disease, is the placement of intracranial pressure monitor. Although there is actually no consensus on the requirement for the limits of coagulation indices, rFVIIa administered at a dose of 40 µg/kg (due to the fact that preoperative administration of plasma may increase the intracranial pressure) was reported to correct the PT values of the patients whereas no correction was achieved in the PT values of the control group, which was given plasma.⁷ Normalization of the PT value with rFVIIa, which we used at higher doses due to the patient's history of recurrent hemorrhage, is consistent with this study. In addition, our patient (patient 16) who underwent repeated operations due to recurrent intracranial hemorrhages occurring secondary to liver disease represents one of the rare cases where rFVIIa is used.

The most interesting cases of our patients are bleedings because of infectious complications and their management. One of them was a kala-azar patient and the other had pulmonary mycormycosis with thrombocytopenia and coagulopathy. This is the first report of rFVIIa use in controlling the overt resistant bleeding in these conditions. These results show that rFVIIa can be used effectively for some selective nonhematological diseases with bleeding due to coagulopathy and thrombocytopenia.

There is no reimbursement for the off-label indications of all drugs in Turkey. It is necessary to get permission from the health authorities. We think that off-label use could be limited for all countries, but some drugs could be useful in the life-threatening conditions like in our cases. The use of rFVIIa in such cases of hemorrhages may be a life-saving application.

rFVIIa induces hemostasis by binding activated platelets and causes thrombin generation in non-hemophilic patients as well. Therefore under many clinical conditions, including intractable/recurrent bleedings or troubled interventions, it has been used widely and successfully even in conditions that were not related to hemophilia. Consequently, hemorrhages of the patients, which we found attributable to the absence of a complete correction of coagulopathy,

could be prevented using rFVIIa, which provides effective management of hemorrhage. Therefore, rFVIIa can be used safely in urgent surgical interventions performed in high-risk patients or in patients with a history of recurrent hemorrhage, for whom no improvement can be achieved in the hemostasis tests. Thus patients' exposure to new surgical traumas can be prevented.

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