

Recombinant Factor VIIa is an Effective Therapy for Abdominal Surgery and Severe Thrombocytopenia: A Case ReportVenancio Conesa,^a Andrés Navarro-Ruiz,^b Joaquín Borrás-Blasco,^b Angela Mompel,^a
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Abstract

A 50-year-old woman was admitted to the emergency room. An appendectomy was done. On the sixth day the patient's general state deteriorated and she became somnolent with jaundice due to distal obstructive cholelithiasis. The results of laboratory tests were platelets $12 \times 10^9/L$, prothrombin time 13 seconds, international normalized ratio 1.19, activated partial thromboplastin time 31.8 seconds, and fibrinogen 8.78 g/L. There was no evidence of disseminated intravascular coagulation. In view of the patient's clinical condition, surgery was considered to be indicated. Because it was a life-threatening situation and at the time there was no platelet concentrate available for immediate transfusion, she was treated with a single dose of recombinant factor VIIa (rFVIIa) (60 $\mu g/kg$). The dose of 60 $\mu g/kg$ was selected on the basis of experience with rFVIIa in the treatment of hemophilic patients. In this case, use of rFVIIa was a valid alternative to control the bleeding in a patient with thrombocytopenia. However, despite the efficacy of the treatment, it should not be forgotten that it was used because of the unavailability of platelets and that we were dealing with a life-threatening situation. Clinical trials should be carried out to verify the safety, effectiveness, and efficiency of rFVIIa in these cases.

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Key words: Recombinant factor VIIa; Thrombocytopenia; Hemorrhage; Surgery; Platelets**1. Introduction**

Recombinant factor VIIa (rFVIIa) is indicated for the treatment of hemorrhages in patients with hemophilia A or B with inhibitors of factor VIII or factor IX. rFVIIa is useful in the treatment of factor VII deficiency and in patients with congenital or acquired thrombocytopenia. We report a case of a patient who was treated with a single dose of rFVIIa because she had severe thrombocytopenia and had to undergo life-threatening surgery.

2. Case Report

A 50-year-old woman who had had a cholecystectomy 11 years previously was admitted to the emergency room. She complained of vomiting and abdominal pain in the epigastrium, and she had a temperature of 38.5°C and also leuko-

cytosis. Hematological and biochemical findings were normal. An appendectomy was done and she made good postoperative progress. On the sixth day the patient's general state deteriorated, and she became somnolent with jaundice due to distal obstructive cholelithiasis. The results of laboratory tests were leukocyte count $14.2 \times 10^9/L$, platelets $12 \times 10^9/L$, prothrombin time 13 seconds (normal range, 12-14 seconds), international normalized ratio 1.19, activated partial thromboplastin time 31.8 seconds (normal range, 25-40 seconds), fibrinogen 8.78 g/L, total bilirubin 1.75 mg/L, aspartate aminotransferase 103 U/L, and alkaline phosphatase 478 U/L. Other laboratory findings were normal. There was no evidence of disseminated intravascular coagulation. In view of her clinical condition, surgery was considered to be indicated. Because it was a life-threatening situation and there was no platelet concentrate available for immediate transfusion, the patient was treated with a single dose of rFVIIa (60 $\mu g/kg$).

There were no complications due to hemorrhage during surgery or during the postoperative period in the intensive care unit and hospital ward. No adverse effects were observed. Bile cultures yielded *Escherichia coli* and *Klebsiella oxytoca*. Twenty days later the patient had fully recovered and was discharged from the hospital.

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3. Discussion

In surgery, patient bleeding secondary to thrombocytopenia is a major cause of morbidity and mortality. Consequently, major bleeding can have devastating consequences, because no good therapeutic options have been available. A Medline search was performed (1966-March 2004) and several reports of treatment of severe thrombocytopenic bleeding with rFVIIa were found. Vidarsson and Óunundarson reported a case of persistent thrombocytopenia refractory to platelet transfusions in a female patient who underwent treatment for acute myelogenous leukemia [1-4]. rFVIIa therapy was started, with a schedule of 100 µg/kg every 2 hours (5 doses) then every 4 hours (6 doses), and resulted in the stopping of bleeding. The optimal dosage of rFVIIa in thrombocytopenia has not been established because of lack of experience in these patients. Neither is the dosage well established in cases of acquired or congenital thrombocytopenia. The reported dose range varied from 50 µg/kg [5] given once to more than 40 doses of 110 µg/kg [6]. Kristensen et al demonstrated that rFVIIa reduced the bleeding time in 55 of 105 patients with thrombocytopenia of various causes. The decrease was significantly more marked when the platelet count exceeded $20 \times 10^9/L$ [5]. In our case the bleeding time was more than 20 minutes in spite of rFVIIa therapy. Gerotziakas et al reported 2 cases with severe thrombocytopenia and bleeding that were successfully treated with a single dose of rFVIIa (90 µg/kg) [7]. The dose of 60 µg/kg in our patient was selected on the basis of experience in the treatment of hemophilic patients with rFVIIa.

The fact that administration of high doses of rFVIIa does not cause generalized activation of the coagulation system implies that its activity is localized to the site of the lesion. rFVIIa does not cause systemic thrombin generation. The usefulness of rFVIIa may be explained by a local generation of thrombin on the exposed endothelial surface and on the activated platelets adhering to the damaged vascular wall. When generation of thrombin is increased, more fibrin is formed in the lesion, thereby facilitating platelet aggregation with the result that the thrombus grows more rapidly, and

this growth favors platelet interaction [8,9]. In our case, use of rFVIIa was a valid alternative to control the bleeding in patients with thrombocytopenia. However, despite the efficacy of the treatment, it should not be forgotten that it was used because of the unavailability of platelets and the fact that we were dealing with a life-threatening situation. Clinical trials should be carried out to verify the safety, effectiveness, and efficiency of rFVIIa in cases of hemorrhage in patients with severe thrombocytopenia.

References

1. Vidarsson B, Óunundarson FT. Recombinant factor VIIa for bleeding in refractory thrombocytopenia. *Thromb Haemost.* 2000;83:634-635.
2. Erhardtson E. To general haemostasis—the evidence-based route. *Pathophysiol Haemost Thromb.* 2002;32(suppl 1):47-52.
3. Laurian Y. Treatment of bleeding in patients with platelet disorders: is there a place for recombinant factor VIIa? *Pathophysiol Haemost Thromb.* 2002;32(suppl 1):37-40.
4. Slappendel R, Huvers FC, Benraad B, Novakova I, van Hellemondt GG. Use of recombinant factor VIIa (NovoSeven) to reduce postoperative bleeding after total hip arthroplasty in a patient with cirrhosis and thrombocytopenia. *Anesthesiology.* 2002;96:1525-1527.
5. Kristensen J, Kjällander A, Hippe E, et al. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. *Haemostasis.* 1996;26(suppl 1):159-164.
6. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost.* 1996;75:981-982.
7. Gerotziakas GT, Zervas C, Gavrelidis G, et al. Effective hemostasis with rFVIIa treatment in two patients with severe thrombocytopenia and life-threatening hemorrhage. *Am J Hematol.* 2002;69:219-222.
8. Monroe DM, Hoffman M, Oliver IA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. *Br J Haematol.* 1997;99:542-547.
9. Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. *Br J Haematol.* 2001;114:114-120.