

Treatment of intra-abdominal bleeding with recombinant activated factor VII in a patient with disseminated intravascular coagulation secondary to septic shock

Jesús Martínez^a, Ana Rosa Cid^b, Javier de la Rubia^a and Ricardo Gimeno^c

Although mainly indicated for treatment of bleeding in haemophilia patients with inhibitors, recombinant activated factor VII (rFVIIa) has also been successfully used in other situations. However, no data are available on its use in the treatment of disseminated intravascular coagulation (DIC) secondary to septic shock. We report a man with DIC and septic shock due to retrocaecal appendicitis and severe intra-abdominal bleeding after surgery. Despite conventional treatment, the bleeding persisted, and treatment with rFVIIa controlled the haemorrhage. No side-effects related to rFVIIa were noted. This case suggests a potential role of rFVIIa in the treatment of severe bleeding associated with DIC.

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^aDepartment of Haematology, Hospital Universitario La Fe, Valencia, ^bCongenital Coagulopathy Unit, Hospital Universitario La Fe, Valencia and ^cIntensive Care Unit, Hospital Universitario La Fe, Valencia, Spain.

Correspondence and requests for reprints to Ana Rosa Cid, Congenital Coagulopathy Unit, Hospital Universitario La Fe, Av. Campanar 21, 46009 Valencia, Spain.
Tel: +34 961 973 052; e-mail: cid_ana@gva.es

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Introduction

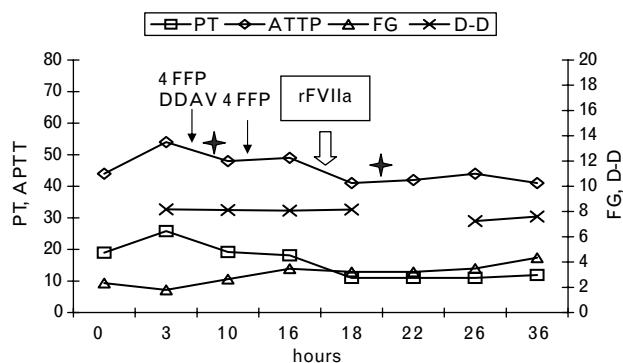
Recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) has been successfully used in patients with congenital haemophilia and inhibitors [1], in acquired haemophilia [2], and in patients with thrombocytopenia and different platelet functional defects [1,3]. Moreover, rFVIIa has also been used in patients with serious bleeding secondary to extensive surgery and severe traumas [1]. However, data regarding its application in the treatment of severe bleeding associated with disseminated intravascular coagulation (DIC) are very limited [4–6]. Furthermore, the use of rFVIIa in such cases is highly controversial. Previous clinical experience with rFVIIa suggests that it is a safe treatment, although cases of thrombotic complications have also been reported [1,7,8]. This study presents the case of a patient with DIC secondary to septic shock who developed severe intra-abdominal bleeding that was controlled using intravenous rFVIIa.

Case report

A 51-year-old man was admitted to our hospital with fever and abdominal pain. He was previously diagnosed 5 years earlier with a 'possible' mild von Willebrand's disease type 1. He responded well to treatment with desmopressin, even before surgical intervention. At admission, the patient was conscious but in a poor general state with fever, shivers, hypotension (initial blood pressure 86/61 mmHg, and subsequently 52/32 mmHg) and oliguria. He was in septic shock and displayed a volume expansion (colloids and crystalloids), and an antibiotic treatment with ceftriaxone and amikacin was initiated.

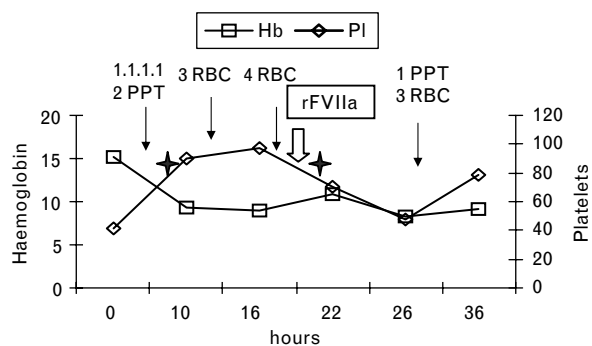
The patient remained in a state of both hypotension and oliguria, and it was for this purpose that a treatment with a dopamine perfusion of 10 µg/kg per min commenced. Serum biochemistry showed a creatinine level of 2.8 mg/dl, aspartate aminotransferase of 93 U/l, alanine aminotransferase of 91 U/l, and lactate dehydrogenase of 273 U/l (normal < 460 U/l). A complete blood count showed a white cell count of $11.9 \times 10^9/l$ (93.5% neutrophils, 2.6% lymphocytes), whereas the platelet count was $41 \times 10^9/l$, with a haemoglobin level of 15.2 g/dl. A prothrombin time of 25.8 s was recorded, with an activated partial thromboplastin time of 54 s, plasma fibrinogen levels of 1.79 g/l, and D-dimers of 8.18 mg/l. A computerized tomography scan revealed a retrocaecal appendicitis. Once the diagnosis of severe DIC secondary to septic shock was determined, 4 U fresh-frozen plasma and 2 U platelets were administered before surgery. A retrocaecal necrotizing appendix was removed with no ascites in the peritoneum. After surgery, the patient subsequently became unstable, with both hypotension and oliguria despite the use of an antibiotic treatment and vasoactive drugs (fluidotherapy, dopamine at an alpha dose, and noradrenaline at 0.4 µg/kg per min). The haemoglobin levels decreased markedly (8.9 g/dl), coagulopathy persisted (prothrombin time, 18.1 s; activated partial thromboplastin time, 49 s; and platelet count of $97 \times 10^9/l$) in spite of a transfusion of 7 U red blood cells and of 4 U fresh-frozen plasma. At this point, a new surgical procedure was planned and a single dose of 90 µg/kg rFVIIa was administered. Shortly after rFVIIa administration, a laparotomy was performed with a drainage of more than 4 l blood, but no bleeding area

Fig. 1



Laboratory test data and transfusion requirements before and after treatment with recombinant activated factor VII (rFVIIa). PT, prothrombin time (s); APTT, activated partial thromboplastin time (s); FG, fibrinogen (g/l); D-D, D-dimers (mg/l); DDAVP, desmopressin; FFP, fresh-frozen plasma. ✦, surgery.

Fig. 2



Laboratory test data and transfusion requirements before and after treatment with recombinant activated factor VII (rFVIIa). Hb, haemoglobin levels (g/dl); Pl, platelets (10⁹/l); PPT, platelet concentrates; RBC, red blood cells. ✦, surgery.

was identified. Laboratory values and transfusion requirements in the first 36 h before and after surgery are shown in Figures 1 and 2. The patient's clinical status improved and resolved following the second surgery procedure. Microbiological cultures showed *Bacteroides spp.* in blood, and both *Pseudomonas aeruginosa* and *Escherichia coli* in the peritoneal fluid. The platelet count became normal 8 days after surgery, and D-dimers normalized 5 days later. The patient was discharged uneventfully after 13 days of hospitalization.

Discussion

Only three cases of patients with DIC have been reported, one of which was secondary to the sepsis, where severe bleeding was successfully treated with rFVIIa [4–6]. Furthermore, the use of rFVIIa in such cases is

highly controversial. In this report, we present a case of severe bleeding after a surgical procedure in a patient with clinically overt DIC secondary to sepsis, which was successfully controlled with rFVIIa.

The rFVIIa action mechanism is under continuous study. Some authors suggest a factor VII-dependent coagulation pathway [activation of factor X through the activated factor VII/tissue factor (TF) complex] [9], while others suggest a platelet-dependent action of the high-dose activated factor VII (the generation of activated factor X on the surface of activated platelets) [10]. In both cases, it is believed that the activity of rFVIIa is limited to the site of injury without any systemic activation of coagulation. Few thromboembolic events have been reported, and well-known risk factors were present in most of them [1]. However, the DIC has also been described in a haemophiliac who was treated with rFVIIa for a large abscess requiring surgical management [8].

The subcommittee on DIC of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis establishes a score to diagnose an overt DIC, and to also rule out other situations, such as dilutional coagulopathy. This score is based on the existence of a disease basically related to the DIC, and of any alteration of secondary laboratory parameters in relation to the consumption of platelets and coagulation factors. Following this score, our patient could be diagnosed with overt DIC. In the DIC, the massive activation of the coagulation system may result in generation and deposition of fibrin, leading to microvascular thrombi, and also contributing to the development of multiorgan failure. A consumption of platelets and coagulation factors may also lead to an increased risk of bleeding [11]. DIC is a frequent complication of a wide variety of clinical conditions such as septicaemia. An increase in the TF expression occurs in this situation. Animal and human models of sepsis have shown that the activation of coagulation in DIC is initiated by the TF-activated factor VII-dependent pathway [12]. Moreover, the use of active-site inhibited rFVIIa attenuates the haemostatic and inflammatory effects of Gram-negative sepsis [13]. This evidences the important role that TF-activated factor VII plays in the activation of the coagulation system in DIC. Administering rFVIIa in this situation could increase thrombin generation, either due to its union at the TF or due to the generation of activated factor X on activated platelets, and this may worsen organ damage. This fact along with the existence of published cases that include the development of thromboembolic problems, even though such cases are scarce, mean that the use of rFVIIa in the DIC secondary to sepsis is particularly controversial.

Overall, data regarding the use of rFVIIa in the control of severe bleeding associated with DIC are scarce. As far as

we know, our patient is the second case of DIC secondary to septic shock treated with rFVIIa [6]. In spite of the theoretical risk involved in this case, the treatment was chosen because of the lack of response to previous treatments, and of the necessity to perform a second surgical procedure. Although we cannot ensure that rFVIIa was the only factor responsible for stopping the bleeding as other treatments had already been administered, it actually permitted the patient to become stable, thus enabling a second surgical procedure to be performed.

Therapeutic doses of rFVIIa are not established in this type of patient. A dose similar to that used for patients with haemophilia and inhibitors was administered to our patient, although we know that both clinical situations are quite different. However, response to the treatment was very good with no adverse events.

Although the ultimate mechanism by which the bleeding was stopped remains elusive, and the effective dosage remains unclear, our case suggests that rFVIIa may be an option when other treatments have failed in the management of severe refractory bleeding associated with DIC. However, a special caution in this type of patients is required, and well-designed controlled trials with a control group are clearly needed to assess the role of rFVIIa in the haemorrhage management in a patient without pre-existing bleeding disorders, and particularly in patients with DIC.

References

- Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002; **42**:114–124.
- Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost* 1997; **78**:1463–1467.
- Poon MC, d'Orion R, and the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. Recombinant activated factor VII (NovoSeven[®]) treatment of platelet-related bleeding disorders. *Blood Coagul Fibrinolysis* 2000; **11**:S55–S68.
- Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teerararkul S, Hogeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2000; **11**:S101–S105.
- Moscardó F, Pérez F, De La Rubia J, Balerdi B, Lorenzo JI, Senent ML, *et al.* Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001; **113**:174–176.
- Holcomb JB, Neville HL, Fischer CF, Hoots K. Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding in a septic patient. *Curr Surg* 2003; **60**:423–427.
- Schulman S. Safety, efficacy and lessons from continuous infusion with rFVIIa. *Haemophilia* 1998; **4**:564–567.
- Stein SF, Duncan A, Cutler D, Glazer S. Disseminated intravascular coagulation (DIC) in a hemophiliac treated with recombinant factor VIIa [Abstract]. *Blood* 1990; **76**:438a.
- Buteras S, Brumemel KE, Branda RF, Paradis SG, Mann KG. Mechanism of factor VIIa-dependent coagulation in hemophilia blood. *Blood* 2002; **99**:923–930.
- Hoffman M, Monroe DM, Roberts HR. Platelet-dependent action of high-dose factor VIIa. *Blood* 2002; **100**:364–365.
- Levi M, de Jonge E, van der Poll T, ten Cate H. Advances in the understanding of the pathogenetic pathways of disseminated intravascular coagulation result in more insight in the clinical picture and better management strategies. *Semin Thromb Hemost* 2001; **27**:569–575.
- Levi M. Current understanding of disseminated intravascular coagulation. *Br J Haematol* 2004; **124**:567–576.
- Taylor FB, Chang AC, Peer G, Li A, Ezban M, Hedner U. Active site inhibited factor VIIa (DEGR VIIa) attenuates the coagulant and interleukin-6 and -8, but not tumor necrosis factor, responses of the baboon to LD100 *Escherichia coli*. *Blood* 1998; **91**:1609–1615.