

Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII

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Summary. Recombinant activated factor VII (rFVIIa) is indicated mainly for the treatment of patients with haemophilia and inhibitors. However, little information is available on the use of rFVIIa in the treatment of the severe bleeding associated with disseminated intravascular coagulation (DIC). We report a pregnant woman with DIC, who developed severe intra-abdominal bleeding after caesarean section. Despite treatment with fresh-frozen plasma, fibrinogen, platelet transfusions and surgery, the abdominal

bleeding persisted and intravenous treatment with rFVIIa was initiated. The response to treatment was rapid, with control of the bleeding and resolution of the coagulopathy. No side-effects related to rFVIIa were noted. This case suggests a potential role for rFVIIa in the treatment of severe and refractory bleeding associated with DIC.

Keywords: recombinant activated factor VII, disseminated intravascular coagulation, intra-abdominal bleeding.

Recombinant activated factor VII (rFVIIa, NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) was developed primarily for the treatment of bleeding episodes in haemophilic patients with inhibitors (Hedner, 1990; Negrier & Lienhart, 2000). However, it has been used successfully in other disorders, including acquired haemophilia and Glanzmann thrombasthenia (Hay *et al.*, 1997; Shafi *et al.*, 1997; Poon *et al.*, 1999). Nevertheless, little information is available about other possible applications of the treatment, such as intractable post-surgery bleeding or severe bleeding associated with disseminated intravascular coagulation (DIC) (Kenet *et al.*, 1999; White *et al.*, 1999; Chuansumrit *et al.* 2000; Vlot *et al.* 2000). The potential thrombogenicity of this treatment (Negrier & Lienhart, 2000) has made its application in cases of severe bleeding associated with DIC very controversial. Because of the difficulty in performing randomized therapeutic trials in a subset of these patients, information based on case reports should be useful.

We present here the case of a pregnant woman with DIC who developed severe and refractory intra-abdominal bleeding after caesarean section. The bleeding was successfully controlled using intravenous rFVIIa.

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CASE REPORT

A 33-year-old woman was admitted to our hospital with severe DIC, liver dysfunction and renal failure. She presented at 31 weeks of a twin pregnancy that was effected by intracytoplasmic sperm injection. Two weeks previously, the patient had presented with elevated serum transaminase levels [416 U/l aspartate aminotransferase (AST) and 406 U/l alanine aminotransferase (ALT)] and she was serologically negative for viral hepatitis B and C. At the time of admission, the patient had jaundice, and oedema in her ankles. Serum biochemistry showed a creatinine level of 203.2 µmol/l, AST 145 U/l, ALT 146 U/l, bilirubin 65 µmol/l and lactate dehydrogenase 390 U/l. A complete blood count showed a white cell count of $14.3 \times 10^9/l$ (82% neutrophils and 12% lymphocytes), a platelet count of $122 \times 10^9/l$ and a haemoglobin level of 12.2 g/dl, with normal blood cell morphologies. A prothrombin time (PT) of 27 s was recorded, with an activated prothrombin time of longer than 60 s, plasma fibrinogen (FG) levels of 5.6 g/l and D-dimers at 6.78 mg/l. With the diagnosis of severe DIC, a caesarean section was performed after transfusion with fresh-frozen plasma (FFP) and FG. The patient subsequently became haemodynamically unstable, with hypotension and oliguria. Haemoglobin levels decreased markedly, coagulopathy persisted in spite of the transfusion of FFP and FG, and

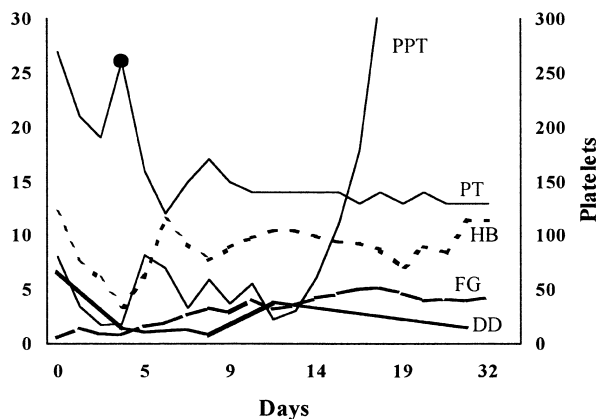


Fig 1. The condition of the patient before and after treatment with rFVIIa, according to haemoglobin levels (HB; g/dl), platelet count (PPT; $\times 10^9/l$), prothrombin time (PT; s), plasma fibrinogen levels (FG; g/l) and D-dimers (DD; mg/l). The rebound point indicates the start of rFVIIa treatment.

abdominal echography revealed the presence of significant intra-abdominal bleeding. A further surgical procedure was performed, with drainage of 3 l of intra-abdominal blood, although no clear bleeding point was evident. A hysterectomy was then performed. Despite this intervention, the patient remained haemodynamically unstable, with coagulopathy and decreasing haemoglobin levels and platelet counts, although intensive transfusions with red blood cells (RBCs), platelets (PPTs), FFP and FG were maintained. Another laparotomy was carried out on the third day, with drainage of a large amount of intra-abdominal blood; a small bleeding point in the left parametrium was identified, which was ligated. However, massive intra-abdominal bleeding persisted, together with severe DIC and decreasing haemoglobin levels that reached 3.5 g/dl. At this point, new surgical procedures were eschewed and treatment with rFVIIa was begun, with the administration of two single doses of 90 $\mu\text{g}/\text{kg}$ at 3-hourly intervals. A response was clearly observed after the first two doses. The patient became haemodynamically stable with adequate diuresis and a good response to transfusions. After the first hours of treatment, haemoglobin levels increased significantly. Treatment with rFVIIa was continued at the same dose every 3 h, for a total of nine doses. Supportive treatment with FFP, RBCs and PPTs was maintained. The outcome was favourable, with resolution of DIC, liver dysfunction and renal failure. Figure 1 shows the condition of the patient before and after treatment with rFVIIa, in terms of haemoglobin levels, PPT count, PT, FG levels and D-dimers respectively.

DISCUSSION

In this report, we present a case of severe bleeding after caesarean section in a pregnant woman with DIC that was successfully controlled using rFVIIa.

DIC is a disorder characterized by the systemic activation of coagulation, which can result in organ failure as a result

of thrombosis in the small vessels. It can also produce severe bleeding by the depletion of coagulation factors (Levi & ten Cate, 1999). DIC is associated with many conditions including obstetric complications, such as pre-eclampsia, and the acute fatty liver of pregnancy (McCrae & Cines, 1997; Levi & ten Cate, 1999). Although prophylaxis of bleeding episodes in patients with DIC in the absence of high-risk bleeding remains controversial, it seems clear that patients with severe haemorrhagic events can benefit from the replacement of PPTs and FFP (Levi & ten Cate, 1999). In spite of the theoretical risk involved in the administration of rFVIIa in DIC because of its potential thrombogenicity (Negrier & Lienhart, 2000), the treatment was chosen in this case because of the decline in the patient's condition, the extreme seriousness of the situation and the lack of response to previous treatments.

Recombinant FVIIa has proved a successful treatment, not only in patients with haemophilia and inhibitors, but also in other disorders, such as acquired haemophilia and Glanzmann thrombasthenia (Hedner, 1990; Hay *et al.*, 1997; Shafi *et al.*, 1997; Poon *et al.*, 1999; Negrier & Lienhart, 2000). However, data are very limited regarding its application to address the severe bleeding associated with DIC. In fact, there are only two reports of patients with DIC and associated acute bleeding who have been treated with rFVIIa (Kenet *et al.*, 1999; Chuansumrit *et al.*, 2000). In both these reports, the response to the treatment was very good with no consequent side-effects, in agreement with our observations.

The ultimate mechanism by which the bleeding was stopped remains unknown. Unfortunately, previous plasma levels of factor VII were not available in this case. However, we discounted the possible presence of acquired haemophilia, which might have explained the observed response. FFP, PPTs, FG and anti-thrombin III (ATIII) were also administered, together with rFVIIa, and this could be a possible confounding factor in determining the efficacy of rFVIIa. Nevertheless, by the time rFVIIa was given, the patient had already failed to respond to treatments with FFP, PPTs and FG. On the other hand, ATIII was administered in a continuous infusion and, when the patient had received the first five doses of rFVIIa and clear improvement was noted, less than one dose of ATIII had been administered. Therefore, we believe that the positive outcome for the patient was related to treatment with rFVIIa.

In summary, this case suggests that rFVIIa may be an option for the treatment of the severe refractory bleeding associated with DIC. However, the theoretical potential risk of its administration in DIC necessitates further investigations in this field.

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