

Recombinant Factor VII (Activated) for Haemorrhagic Complications of Severe Sepsis Treated with Recombinant Protein C (Activated)

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Key Words

Activated protein C · Recombinant factor VIIa · Septic shock · Sepsis

Abstract

We report on 2 cases of severe sepsis treated with drotrecogin-alpha (Xigris, Eli Lilly), where massive perioperative haemorrhage required administration of recombinant factor VIIa. The first patient developed severe sepsis after surgery (laparoscopic cholecystectomy, laparotomy due to peritonitis). After 18 h of treatment with Xigris, the patient developed massive, refractory gastrointestinal and abdominal bleeding. Effective haemostasis was achieved after 2 doses of NovoSeven (Novo Nordisk, Denmark). The patient died due to a cerebral bleed. The second patient developed septic shock in the course of pyelonephritis and right hydronephrosis. She was treated with Xigris and nephrectomy. Uncontrollable perioperative bleeding was effectively treated with 2 doses of NovoSeven. The patient survived.

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Sepsis and its sequelae are currently a significant cause of death in the population of hospitalized patients. Despite the application of standard treatment protocols for severe sepsis, which include targeted antimicrobial treatment, surgery and supportive measures (administration of fluids, vasopressors, low-dose steroids, as well as provision of normoglycaemia and mechanical ventilation), mortality in severe sepsis still falls within a range between 30 and 50% [1]. Severe sepsis involves major impairment of synthesis and activation of protein C, which acts as an antithrombotic, profibrinolytic, anti-inflammatory and antiapoptotic agent. It plays an important role in maintaining normal haemostasis and limiting cell death [2, 3].

Human activated protein C (drotrecogin-alpha activated, Xigris, Eli Lilly, USA) is a new, promising drug indicated for the treatment of severe sepsis. Its efficacy has been assessed by PROWESS, a multicentre randomized trial that found a 19.4% reduction in 28-day mortality in treated patients versus controls [4, 5]. The most dangerous of the drug's adverse effects is an increased risk of serious haemorrhage including intracranial bleeds [6, 7].

The present paper reports on cases of severe sepsis treated with Xigris that developed uncontrollable peri-

operative bleeding. In the face of failure of routine management, which included traditional anti-haemorrhagic measures as well as transfusion of red blood cell (RBC) concentrate, fresh frozen plasma (FFP), platelet concentrate and cryoprecipitate, we elected to administer recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk, Denmark).

The attempt to treat with rFVIIa was based on reports by many authors who successfully applied the drug for refractory bleeds occurring in a number of specialties, including gynaecology, transplantation, cardiac surgery, neurosurgery, vascular and abdominal surgery as well as traumatology. It should be stressed that in the majority of cases, the drug was applied as an emergency measure following the failure of other treatment modes and that such an application constituted off-label use.

Case Reports

Case 1

A 52-year-old female patient was admitted to the Intensive Care Department (ICD) in serious condition, displaying signs of multi-organ failure. Fifteen months earlier she had undergone renal transplantation and since then was treated with immunosuppressive agents (cyclosporine, steroids). About 2 weeks prior to admittance to the ICD, she had undergone laparoscopic cholecystectomy followed on the 7th post-operative day by laparotomy for ileus and empyema of the cholecystectomy site. On the following days, the patient's condition had deteriorated and on admittance to the ICD, she was found to have altered consciousness (8 points on the Glasgow Scale). On admission her APACHE II score was 25. Heart rate was regular with a sinus rhythm of 108 beats per minute. Blood pressure was 100/70 mm Hg and central venous pressure was 14 cm H₂O. We intubated the patient and started mechanical ventilation. Abdominal ultrasound revealed a hypoechoic fluid collection. Laboratory test abnormalities included: C-reactive protein (CRP) 149 mg/l; white blood cells (WBC) $15.5 \times 10^9/l$; Hb 8.87 g/dl; Ht 0.24; RBC $3.35 \times 10^{12}/l$; platelets $75 \times 10^9/l$; BUN 25.56 mmol/l; creatinine 193.8 $\mu\text{mol}/l$; albumin 20 g/l; total protein 36.1 g/l. Coagulation tests: prothrombin time (PT) 18.90 s; INR 1.61; activated partial thromboplastin time (APTT) 40.80 s; D dimers 2,737 ng/ml; fibrinogen 2.67 g/l; anti-thrombin III 76%.

The overall clinical picture was suggestive of developing septic shock. We instituted standard supportive measures including the administration of antibiotics selected according to previous culture and susceptibility results. The patient's condition deteriorated. Despite adequate hydration, her systolic arterial pressure fell to 90 mm Hg, therefore we added catecholamines at rates sufficient to maintain mean arterial pressure at 90 mm Hg. We applied diuretics at gradually increasing doses. Following the advice of a consulting neurologist, we performed a cranial CAT scan, which demonstrated no focal intracranial lesions. After a follow-up ultrasound study of the abdomen, the patient was taken for yet another laparotomy, during which pus collections were evacuated from the subphrenic

region and the recto-uterine fossa, and drainage tubes were placed. The abdomen was left open.

Since the patient's condition failed to improve with conventional management, we elected to administer human activated protein C (Xigris, Eli Lilly, USA). Twelve hours post-operatively, we started a continuous infusion of the drug at a rate of 24 $\mu\text{g}/\text{kg}/\text{h}$. During the infusion, cardiovascular function improved, allowing for a reduction of catecholamine infusion rate and after 8 h catecholamines were withdrawn. However, the patient's general condition still failed to improve, low-grade fever persisted, while the CRP level grew to 189.8 mg/l and the platelet count dropped to $35 \times 10^9/l$. The infusion of Xigris was discontinued. Another laparotomy was performed and new pus collections were evacuated. Xigris infusion was reinstated 12 h post-operatively. This time, the patient's condition improved. She regained consciousness and was able to answer logically to simple questions. Her diuresis and respiratory parameters improved. Her CRP levels fell to 142.9 and 79.8 mg/l after 7 and 12 h, respectively.

Eighteen hours after the start of the second Xigris infusion, the patient developed a gastrointestinal bleed. In response, we administered omeprazole (Losec, AstraZeneca, Sweden) infused at 8 mg/h and blood products, including platelet concentrate to address a platelet count drop to $30 \times 10^9/l$; however, we did not withdraw Xigris. Over the following hours, the patient's condition deteriorated. She developed haemorrhagic shock caused by massive bleeding from the abdomen and upper gastrointestinal tract. At that stage, her blood count was as follows: Hb 8.06 g/dl; Ht 0.24; RBC $2.78 \times 10^{12}/l$; WBC $20.3 \times 10^9/l$; platelet count $30 \times 10^9/l$. We determined the following coagulation parameters: PT 19.60 s; INR 1.68; APTT 34.50 s; fibrinogen 3.76 g/l; D dimers 14,313.56 ng/ml. The patient received 8 units of RBC concentrate, 6 units of FFP, 12 units of cryoprecipitate and 6 units of platelet concentrate. In response to a deterioration of her general condition related to a bleeding that was refractory to conventional treatment, we resorted to an emergency administration of 2.4 mg of human rFVIIA (NovoSeven). The blood count parameters improved within several hours of NovoSeven administration: Hb 10.48 g/dl; Ht 0.30; RBC $3.49 \times 10^{12}/l$; WBC $13.7 \times 10^9/l$; platelets $66.0 \times 10^9/l$. At that stage, her coagulation parameters were as follows: PT 17.90 s; INR 1.52; APTT 63.70 s; fibrinogen 2.31 g/l; D dimers 2,300.16 ng/ml. The patient regained consciousness and was capable of basic logical contact.

Another massive bleed from the abdomen and gastrointestinal tract occurred 20 h following the administration NovoSeven, at the end of Xigris therapy. We decided to administer another bolus of 2.4 mg of NovoSeven. The patient was taken for emergency surgery, and received 12 units of RBC concentrate and 8 units of cryoprecipitate. The application of these measures restored good haemostasis. The laboratory parameters of coagulation are presented in tables 1 and 2.

At this stage, Xigris was withdrawn. Unfortunately, the patient's neurological condition deteriorated. The patient died due to a massive cerebral bleed with a marked mass effect.

Case 2

This 32-year-old female patient had been admitted to the Department of Obstetrics and Gynaecology in the 27th week of her 4th pregnancy with a history of 3 deliveries following transfer from a community hospital with the diagnosis of pyelonephritis and hydronephrosis of the right kidney. On the basis of clinical examina-

Table 1. Coagulation parameters before and after administration of rFVIIa (NovoSeven)

Parameters	Before rFVIIa	After rFVIIa
APTT, s	>200 (25–37)	43.7
PT, s	58.20 (11.1–14.1)	30
INR	5.33 (0.9–1.16)	2.44
Fibrinogen, g/l	2.00 (1.5–4.0)	1.90
Thrombin time, s	>100 (11.0–17.8)	21.4
D dimers, ng/ml	2,858.4 (0–500)	2,418.4

Figures in parentheses are normal ranges.

Table 2. Blood count parameters

Parameters	Before rFVIIa	After rFVIIa
WBC, $\times 10^9/l$	7.80	5.83
RBC, $\times 10^{12}/l$	2.12	4.42
Hb, g/dl	6.13	12.58
Ht	0.17	0.38
Platelets, $\times 10^9/l$	43	72

Table 3. Blood count and coagulation parameters in relation to rFVIIa administration

Parameters	Before rFVIIa	After rFVIIa
WBC, $\times 10^9/l$	20.0	18.8
RBC, $\times 10^{12}/l$	2.29	3.32
Hb, g/dl	7.30	10.17
Ht	0.20	0.29
Platelets, $\times 10^9/l$	34.1 (150–400)	37.0
Fibrinogen, g/l	1.47	1.59
APTT, s	52.60 (25–37)	50.60
D dimers, ng/ml	9,694.5	7,072.43
PT, s	27.1 (11.0–17.8)	18.6

Figures in parentheses are normal ranges.

tion and diagnostic work-up, the patient underwent a nephrostomy of the right kidney, which initially yielded 500 ml of purulent discharge. The patient was left with an indwelling nephrostomy tube. She remained febrile, with body temperatures up to 40°C. Within 10 h from admission, her condition continued to deteriorate. Her blood pressure dropped to 80/50 mm Hg. Her heart sounds were dull, with regular rhythm and a rate of 120 beats per minute. The nephrostomy yielded 2,000 ml of bloody purulent discharge. The contralateral kidney ceased to produce urine. The patient complained of dyspnoea and her awareness became impaired. She was transferred to the ICD.

The patient was intubated and ventilated mechanically. She received fluids and catecholamines on the basis of haemodynamic monitoring. We found the following laboratory test abnormalities: WBC $18.6 \times 10^9/l$; Hb 6.93 g/dl; Ht 0.21; RBC $2.37 \times 10^{12}/l$; platelets $13 \times 10^9/l$; BUN 78.30 mmol/l; creatinine 271.25 $\mu\text{mol}/l$; CRP 104.9 mg/l. Coagulation test results were as follows: PT 18.30 s; INR 1.86; APTT 53.10 s; D dimers 6,300 ng/ml; fibrinogen 1.35 g/l. The overall clinical picture was suggestive of developing septic shock. We elected to supplement the treatment protocol with activated protein C (Xigris) infused at 24 $\mu\text{g}/\text{kg}/\text{h}$. During 9 h of treatment at the ICD, the nephrostomy yielded increasing volumes of bloody discharge, which amounted to a total of 5,000 ml. The patient's anaemia progressed despite massive transfusions of RBC concentrate, FFP and cryoprecipitate.

In the face of urinary tract infection, significant blood loss through the nephrostomy tube, and a rapidly progressing multi-organ failure that was life-threatening to the fetus, we elected to deliver the child by caesarean section and perform an emergency nephrectomy of the right kidney. The infusion of Xigris was discontinued 2 h prior to surgery. To address her coagulation impairment, we decided to employ emergency therapy with NovoSeven at a dose of 2.4 mg (40 $\mu\text{g}/\text{kg}$) at the end of the surgical procedure, obtaining a satisfactory reduction of bleeding in the surgical sites as well as an improvement of coagulation parameters (table 3).

Within 12 h following the administration of NovoSeven, the patient received 4 units of RBC concentrate, 10 units of platelet concentrate and 6 units of FFP. After that, we resumed the infusion of Xigris. However, 10 h after NovoSeven was injected, the patient's anaemic state worsened and the abdominal drainage tubes started to produce increasing amounts of bloody discharge, again destabilizing the patient's condition. After 30 h, we decided to inject another dose (2.4 mg) of NovoSeven. Due to progressing instability and persistent bleeding, the patient was reoperated on twice with satisfactory haemostasis (table 4). At the second reoperation, she was hysterectomized. In the post-nephrectomy site, which was previously mottled with numerous copiously bleeding points, no haemorrhage was noted. The infusion of Xigris was interrupted and resumed according to previously defined procedures.

Within 12 h of injecting the second NovoSeven dose, the patient received 14 units of RBC concentrate, 9 units of FFP, 9 units of platelet concentrate and 12 units of cryoprecipitate. On the second day following the second NovoSeven dose, her coagulation parameters improved and showed a tendency to normalize. Gradually, the patient's condition stabilized and she was extubated on the 6th day of her stay at the ICD. After 16 days of treatment, she was transferred to the Urology Department in good general condition.

Table 4. Blood count and coagulation parameters in relation to second rFVIIa administration

Parameters	Before rFVIIa	After rFVIIa
WBC, $\times 10^9/l$	22.1	23.0
RBC, $\times 10^{12}/l$	2.41	2.93
Hb, g/dl	7.09	8.87
Ht	0.21	0.26
Platelets, $\times 10^9/l$	17 (150–400)	28
Fibrinogen, g/l	2.53	2.67
APTT, s	79.03 (25–37)	60.30
D dimers, ng/ml	2,283.60	2,068.35
PT, s	14.4 (11–17.8)	10.3

Figures in parentheses are normal ranges.

Discussion

In our paper, we have attempted to present our own limited experience gathered from combined treatment with activated protein C and rFVIIa. The short history of the latter drug's use in controlling perioperative haemorrhage has generated numerous reports on its beneficial effects [8–10]. Although rFVIIa cannot solve all bleeding problems related to surgery, we found it to be highly effective. The presented case reports reflect the special benefits obtained from rFVIIa therapy in the unusual situation where major surgery is performed in the setting of failing coagulation. We feel the drug should be used only in cases of acute, life-threatening bleeds [11–13].

The size of the dose and the dosing frequency should be tailored to the clinical situation. The cited reports suggest a dosing regimen that differs from ours. Some authors propose a dose of 60 $\mu\text{g}/\text{kg}$ [14], or even 260 $\mu\text{g}/\text{kg}$ [15]. Most authors recommend the application of a similar or larger dose, several hours after the first, regardless of the result achieved. In both cases discussed in our report, rFVIIa was applied twice, with each dose causing a significant improvement. The monitoring of the effects of treatment is based on clinical visibility of improved bleeding control and the improvement of laboratory parameters of the coagulation system (shorted PT and APTT). For Case 1, PT did improve, although it remained above the upper limit of normal. One could argue that this justified the application of a higher dose; however, surgical haemostasis was satisfactory, the initial bleeding was controlled and the recurring bleed was not

as massive. Low dosage is sufficient to control the majority of surgical bleeds, which are not complicated by a severe fibrinolytic haemorrhagic diathesis [10–13]. However, the literature argues convincingly that in cases of severe bleeding, which requires prolonged treatment and involves major laboratory test disturbances, a higher dose should definitely be considered with a view to controlling the haemorrhage.

Both of our cases exemplify an unusual application of rFVIIa. Both situations were dramatic and life-threatening. The administration of the drug yielded rapid and spectacular results. These were, however, short-lived in Case 1, while Case 2 suggests that sometimes a small dose can help to control a seemingly lethal bleeding. As a rule, we adhere to a judicious and balanced classical approach to haemostasis management that applies the principles of the physiology of coagulation and meticulous surgical haemostasis, although exceptions to the rule should be acknowledged and recognized. Our modest experience contributes to a hypothesis that rFVIIa might improve treatment results in a selected population of patients and become a valuable addition to our armamentarium applied in the treatment of severe, life-threatening haemorrhages.

At present, we have found no reports in the world literature on combined treatment with Xigris and Novo Seven, hence we cannot compare our experience to that of other authors.

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