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Administration of Recombinant Activated Factor VII (NovoSeven) in Three Cases of Uncontrolled Bleeding Caused by Disseminated Intravascular Coagulopathy

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Summary: Recombinant activated factor VII has been used successfully in many cases of traumatic and surgical bleeding complications that were unresponsive to standard treatment. However, because disseminated intravascular coagulation can develop from a thrombin burst as a side effect of recombinant activated factor VII, it is not yet established for bleeding complications induced by disseminated intravascular coagulation. This article presents 3 patients with severe sepsis and fulminant disseminated intravascular coagulation. Excessive microvascular bleeding persisted despite conventional therapy, and surgical

intervention and radiologic embolization did not control bleeding. After administration of recombinant activated factor VII, bleeding ceased in all patients, and no overt thromboembolic events occurred. One patient survived to be discharged from the hospital. The other 2 patients died from refractory multiorgan failure and overall poor prognosis. Recombinant factor VIIa might be an option for the treatment of severe bleeding complications in the case of DIC refractory to the conventional therapy.

Key Words: rFVIIa—Disseminated intravascular coagulopathy—Disseminated intravascular coagulation—Bleeding.

Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic intravascular activation of coagulation in the context of a variety of disorders. This causes fibrin deposition, followed by microvascular thrombosis in various organs, which contributes to the development of multiorgan failure (1, 2). The consequence of this derangement of the hemostatic system is consumption and exhaustion of coagulation factors and platelets, which can induce severe bleeding complications and thrombotic problems (3). Despite activation of the coagulation system, which results in consumption of clotting factors and platelets, coagulation therapy is mandatory for severe bleeding complications (4). Nevertheless, the

administration of platelet concentrates, fresh frozen plasma, antifibrinolytic agents, or clotting factor concentrates might “add fuel to the fire,” so these compounds should be used with caution.

Recombinant activated factor VII (rFVIIa, NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) is approved for the treatment of bleeding episodes in patients with congenital hemophilia and inhibitors of factor VIII or IX, as well as for patients with acquired hemophilia, and Glanzmann thrombasthenia. However, there are several reports about the successful use of rFVIIa for traumatic and surgical bleeding episodes that did not respond to standard treatment (5-7). Recombinant activated FVII enhances thrombin generation at sites of vascular injury by forming tissue factor VIIa complex and thereby activating factor X to Xa, as well as by providing Xa on the surface of already activated platelets (8). As a possible side effect of rFVIIa, DIC can develop from a thrombin burst, thereby activating the coagulation system. In this context, the administration of rFVIIa for DIC induced bleeding is discussed very controversially (9, 10).

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TABLE 1. Definition of the Scoring System for Disseminated Intravascular Coagulation as Suggested by the International Society of Thrombosis and Haemostasis^a

Points	0	1	2	3
Platelet count ($10^3/\mu\text{L}$)	>100	>50	<50	
D-dimer ($\mu\text{g/mL}$)	<1.0	—	1.0-5.0	>5.0
Fibrinogen (mg/dL)	>100	<100	—	—
Prothrombin index (%)	>70	40-70	<40	—

a. The score ranges from 0 to 8 points. A scoring system for >5 points is compatible with overt disseminated intravascular coagulation (2).

We here present 3 patients with expected overt DIC resulting from severe sepsis. These patients presented with severe microvascular bleeding complications and needed massive transfusion, including red blood cell (RBC) concentrates, fresh frozen plasma, and platelet concentrates. In addition to coagulation therapy, all patients were treated with antibiotics according to clinical criteria and microbiologic findings. Further, they were treated with fluids and catecholamines, guided by a Swan Ganz catheter, as well as with hydrocortisone and insulin. Bleeding was successfully controlled with the use of rFVIIa, without occurrence of any thromboembolic complication or enhancement of DIC.

METHODS

For standard coagulation analysis, arterial blood samples were obtained. The red blood cell count was obtained as well as the prothrombin index (PT; Thromborel S, Dade Behring, Marburg, Germany), activated partial thromboplastin time (aPTT; Pathrombin SL, Dade Behring), fibrinogen antigen (immunoturbidimetric method, Turbiquant TM Fibrinogen, Dade Behring), and antithrombin (AT; Antithrom Stago, Boehringer Mannheim, Germany). Normal reference ranges for these variables are PT, 70% to 130%; aPTT, 23 to 40 seconds; fibrinogen, 190 to 380 mg/dL; and AT, 80% to 120%.

CASE REPORTS

Patient 1

A 27-year-old woman was admitted to our intensive care unit (ICU) because of septic shock 1 day after a cesarean section. She initially presented with symptoms of an acute abdomen. An intraoperative examination showed severe cellulitis and necrotizing fasciitis of the abdominal region and diffuse

peritonitis. Fasciotomy and débridement were performed. On arrival at the ICU, she became anuric, hemodynamically unstable, and needed maximum catecholamine supply with epinephrine, norepinephrine, and vasopressin.

Massive abdominal wall bleeding associated with severe DIC developed after the first surgical intervention. The worst results of the coagulation analysis were found at about 5 hours before administration of rFVIIa. The platelet count was $21 \times 10^3/\mu\text{L}$, PT was 22%, aPTT exceeded 78 seconds, plasma fibrinogen level was 170 mg/dL, AT was 22%, and D-dimer level was 2939 $\mu\text{g/L}$. These values were comparable with an overt DIC (Tables 1 and 2). Serum biochemistry showed lactate concentration at 250 mg/dL combined with severe metabolic acidosis.

Transfusion of about 4 units of RBC concentrates every hour became necessary for the next 22 hours. Coagulation therapy included administration of platelet apheresis concentrates (PLT), 60 μg desmopressin (Octostim, Ferring, Vienna, Austria), fresh-frozen plasma (FFP), 1.500 IU antithrombin (AT), 2 million IU aprotinin (Pantanol, Gerot Parmazeutika, Vienna, Austria), 12 000 IU prothrombin complex concentrate (Beriplex, Aventis Behring, Marburg, Germany), and 14 grams of fibrinogen (Hemocompletan, Aventis Behring) was guided by modified thrombelastography (ROTEM, Pentapharm Munich, Germany).

Several surgical interventions failed to stop bleeding from the abdominal wall. Bleeding persisted despite transfusion of 86 units of RBCs, 19 units of PLTs, 147 units of FFP, substitution of coagulation factor concentrates, and several surgical interventions (Table 3). In this futile situation, recombinant activated factor VII (rFVIIa) was administered in 3 doses of 100 $\mu\text{g/kg}$ each. In combination with local application of fibrin glue and tranexamic acid, bleeding stopped. The patient was finally discharged from the hospital after 4 months.

Patient 2

A 68-year-old woman was transferred to the ICU because of purulent tissue infection caused by *Staphylococcus aureus* infection of the right thigh after an intramuscular nonsteroidal antiinflammatory drug injection because of low back pain due to rheumatism. Fasciotomy and debridement were initiated.

The patient's clinical course was complicated by severe sepsis and acute respiratory distress syndrome.

TABLE 2. Standard Coagulation Tests Before and After Administration of Recombinant Activated Factor VII (NovoSeven)^a

Test	Patient 1		Patient 2		Patient 3	
	Before	After	Before	After	Before	After
aPTT (sec)	78	42	51	38	45	39
Prothrombin index (%)	22	78	77	92	76	84
Fibrinogen (mg/dL)	170	223	132	228	225	285
AT (%)	21	64	52	73	79	82
Platelet count ($10^3/\mu\text{L}$)	21	98	60	112	42	108
Hemoglobin (G/L)	7.8	9.2	9.5	9.4	8.8	9.8

aPTT = activated partial thromboplastin time; AT = antithrombin.

a. The coagulation tests before recombinant activated FVII (rFVIIa) administration include the worst results within 5 hours before rFVIIa administration. More precisely, the first analysis was performed 5 hours before rFVIIa administration in patient 1, within 2 hours before rFVIIa administration in patient 2, and within 3 hours in patient 3. The second analysis was made immediately after rFVIIa administration in all 3 patients.

TABLE 3. Transfusion Requirements Within 24 Hours Before and 24 Hours After Administration of Recombinant Activated Factor VII Ia (NovoSeven)

	Patient 1		Patient 2		Patient 3	
	Before	After	Before	After	Before	After
RBC (units)	86	6	12	2	16	2
FFP (units)	147	6	5	4	23	0
PLT (units)	19	1	2	0	2	1

RBC = red blood cell concentrates; FFP = fresh frozen plasma; PLT = platelet apheresis concentrates.

Catecholamine supply became essential. After a surgical procedure, severe and diffuse bleeding resulted from the wound area. In this context, the patient again became hemodynamically unstable. Despite transfusion of 12 units of RBC, 2 units of PLT, 5 units of FFP, and substitution of coagulation factor concentrates, including 1000 IU factor XIII concentrate (Fibrogamin, Aventis Behring), bleeding continued profusely even though coagulation parameters improved to PT, 77%; aPTT, 51 seconds; AT, 52%; plasma fibrinogen level, 132 mg/dL; platelet count, $60 \times 10^3/\mu\text{L}$ (Tables 1 and 2). Two hours later, a single dose of rFVIIa (120 $\mu\text{g}/\text{kg}$) was administered. The patient responded rapidly to treatment, bleeding stopped, and DIC resolved.

On postoperative day 42, intensive care was withdrawn on account of overall poor prognosis because of multiorgan system failure and sepsis.

Patient 3

A 77-year-old man with an aneurysm of the common iliac artery was transferred to our ICU after implantation of a bifurcated endoprosthesis. On postoperative day 1, a fasciotomy was initiated because of a compartment syndrome of the right leg. The clinical course was complicated by multiple

organ failure, *Klebsiella* sepsis, and profuse bleeding from the wound and retroperitoneum.

The sepsis was treated with carbapenem and ciprofloxacin according to clinical and microbiologic findings. After administration of 16 units of RBC, 23 units of FFP, 2 packages of apheresis PLT, aprotinin, and coagulation factor concentrates, bleeding persisted in the face of improvement of all coagulation parameters (PT, 76%; aPTT, 45 seconds; AT, 79%; plasma fibrinogen levels, 225 mg/dL; platelet count, $42 \times 10^3/\mu\text{L}$; Tables 1 and 2). Three hours later, after unsuccessful surgical interventions, a dose of rFVIIa (120 $\mu\text{g}/\text{kg}$) was administered. Bleeding ceased rapidly and DIC resolved. The patient's condition improved over the following days.

On postoperative day 35, the patient began to bleed again. Angiographic coiling of the internal iliac artery was successfully performed. However, acute deterioration followed, with refractory multiorgan system failure resulting in fatal liver dysfunction after a stay of 42 days at our ICU.

DISCUSSION

This report includes 3 patients with sepsis and severe DIC. All patients showed excessive

microvascular bleeding that persisted despite conventional therapy with platelet concentrates, FFP, and clotting factor concentrates, including fibrinogen concentrate and prothrombin complex concentrate. The criteria for DIC as suggested by the International Society of Thrombosis and Haemostasis (ISTH) were not achieved in patients 2 and 3, but they were still treated with FFP, platelet concentrates, and clotting factors to decrease microvascular bleeding. Nevertheless, clinical conditions appeared futile, because neither surgical procedure nor interventional radiologic therapy was able to control the bleeding. After administration of rFVIIa, bleeding ceased in all patients without any overt thromboembolic events.

Disseminated intravascular coagulation is characterized as an ongoing activation of coagulation, leading to microvascular fibrin deposition and thrombosis, thereby compromising adequate blood supply to various organs, which finally contributes to multiorgan system failure (11). Ongoing activation of coagulation, impaired synthesis, and increased consumption of clotting factors and platelets as well as systemic hyperfibrinolysis may result in serious bleeding situations, especially in patients at risk for a major blood loss, such as perioperative patients or those with multiple traumas (12, 13).

The main features of DIC are theoretically well understood. Nevertheless, the clinical situation of simultaneously occurring thrombosis and microvascular bleeding remains an unsolved problem. Replacement of clotting factors and platelets is indicated in patients with active bleeding and in those requiring invasive procedures or otherwise at risk for bleeding complications (14). The efficacy of FFP, platelet concentrates or clotting factor concentrates is not based on randomized controlled trials but appears to be the only rational therapy in the case of bleeding or when a patient is at high risk for a bleeding complication caused by depletion of hemostatic factors.

However, replacement of clotting factors and platelets in this situation is not the only area where investigation has been inadequate (15, 16): scant information is available on the administration of rFVIIa in bleeding patients with DIC. It is important to realize that administration of rFVIIa is not a substitute for missing hemostatic factors but is an effective pharmacologic therapy. The literature contains only few reports on the administration of rFVIIa for DIC, whereas most cases that presented as DIC appeared not to be true DIC, but rather, coagulopathy resulting from liver failure or a combination of consumption and exhaustion of

hemostatic factors caused by huge blood loss and dilutional coagulopathy.

The number of patients treated successfully with rFVIIa in case of severe bleeding related to DIC is very small, but first observations are promising. Our approach of administering rFVIIa to counteract massive bleeding related to DIC is confirmed by a series of 18 nonsurgical patients with advanced or metastatic cancers, and bleeding secondary to DIC. Fifteen responded with cessation of bleeding, and no thromboembolic complications were observed (17). In addition, 2 other case reports confirm our results. Moscardo et al (18) report a woman with DIC who developed severe intraabdominal bleeding after a cesarean section. This persisted despite conventional treatment with FFP, fibrinogen, platelet concentrates, and surgery. Bleeding was controlled by administering rFVIIa, and no side effects developed (18). A further report describes a patient with intra-abdominal bleeding related to DIC caused by septic shock, and this patient was also unresponsive to conventional therapy with FFP. Bleeding stopped rapidly after rFVIIa administration, without evidence of thrombosis or other adverse effects (19).

Nevertheless, the use of rFVIIa in the case of sepsis and DIC remains controversial because of the increased risk for the development of thrombosis or thromboembolic complications and exacerbation of DIC as a result of circulating tissue factor. During sepsis, tissue factor is rapidly induced on blood mononuclear cells and endothelium cells. Among others, rFVIIa enhances thrombin generation by forming a tissue factor-rFVIIa complex, thereby activating factor X to factor Xa as well as providing factor Xa on the surface of already activated platelets. Binding of rFVIIa to tissue factor and activated platelets circulating systemically in the case of DIC and sepsis may result in a systemic activation of hemostasis and the risk of thromboembolic complications and further exacerbation of DIC.

CONCLUSION

Recombinant activated FVII might be an option for the treatment of severe life-threatening bleeding complications in the case of DIC refractory to the conventional replacement of clotting factors and platelets. The theoretic risk associated with the administration of rFVIIa demands that the risks and benefits be objectively weighed on a case-by-case-basis.

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