

Letter to the Editor

Recombinant factor VIIa treatment of bleeding associated with acute renal failure

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Acute renal failure (ARF) is commonly associated with uremic platelet dysfunction, a bleeding disorder similar in nature to von Willebrand disease [1,2]. Primary hemostasis is deficient as a result of the acquired platelet dysfunction and this leads to prolongation of the bleeding time [3]. The bleeding tendency and the degree of anemia are usually correctable by treating the underlying cause of the ARF. If this approach is not appropriate, short-term, symptomatic therapy must be employed. Transfusion of platelet concentrates is standard first-line therapy; the use of desmopressin, although it has a favorable effect on platelet dysfunction, is limited because of the intravascular volume overload, which frequently complicates the ARF.

A 49-year-old man was admitted with ARF, and pancytopenia. The onset was sudden, with hemorrhagic syndrome and anuria. Of these, the bleeding syndrome was the most urgent, presenting as hematuria, hematemesis, and hemorrhage at the sites of venous puncture, catheter insertion and of the gingiva. The patient had no medical history of renal disease, or of any medication for other (chronic) diseases, but declared the ingestion of an alcoholic drink of unknown origin, 24 h before hospitalization.

Hematological readings and normal ranges are shown in Table 1. The evolution of the main laboratory parameters during hospitalization are shown in Table 2.

We also considered a hemolytic uremic syndrome, but there were no indicators of hemolysis (normal

Table 1. Hematological values in a 49-year-old male admitted with acute renal failure, nephrotoxic syndrome and pancytopenia

Parameter	Value at admission	Normal range
Platelet count ($\times 10^3/\mu\text{l}$)	11	150–350
Prothrombin time (s)	15.8	1–13
APTT (s)	49.9	20–32
Urea (mg/dl)	300.3	15–43
Bleeding time (min)	14	2–4

APTT, Activated partial thromboplastin time.

bilirubin, reticulocytes absent, normal red blood cells with moderate anisocytosis, without microangiopathy, normal fibrinogen and D-dimers absent). Therefore, the clinical context suggested an ARF associated with hemorrhagic syndrome of unknown etiology (probable toxic), and excluded a hemolytic uremic syndrome with microangiopathy and disseminated intra-vascular coagulation (DIC).

The bleeding tendency was thought to stem from the marked thrombocytopenia and acquired platelet dysfunction arising from ARF with uremic syndrome [4,5]. The ongoing bleeding that excluded the immediate initiation of the hemodialysis (i.e. the insertion of a central venous catheter for venous-venous dialysis) was life-threatening, and necessitated transfusions of fresh frozen plasma, red blood cells and platelet concentrates. Although these trans-

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Table 2. Main laboratory parameters during hospitalization

Main laboratory parameters	Laboratory range	Days of hospitalization				
		1	2	3	4	5
Urea (mg/dl)	15.00–43.00	300.3	415	511.1	460	420
Creatinine (mg/dl)	0.60–1.20	22.4		19.8		18.5
HBG (g/dl)	11.0–16.5	6.9	6.8	7.9	7.5	8.3
HCT (%)	34.0–54.0	21.9	21.2	24.7	23.3	26.5
PLT ($\times 10^3/\mu\text{l}$)	150–350	11.0	12.0	9.0	16.0	31.0
WBC ($\times 10^3/\mu\text{l}$)	4.0–9.0	8.0	4.6	2.7	3.1	400.4
RBC ($\times 10^6/\mu\text{l}$)	3.60–5.50	2.2	2.21	2.65	2.46	2.84
PT	11–13 s	15.8		14.2		17.1
	93–116%	58.6%		52.8%		51.9%
	0.96–1.14 (INR)	1.31		1.4		1.48
APTT (s)	20–32	49.9		28.2		53.6
BT (min)	2–4	14	16	7	9	13
Diuresis (ml)		100	100	1000	1300	1500

HBG, hemoglobin; HCT, hematocrit; PLT, platelets; WBC, white blood cells; RBC, red blood cells; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; BT, bleeding time.

fusions did not correct the bleeding tendency, they maintained the hematocrit and hemoglobin levels within acceptable limits.

Coagulation parameters were unchanged by the third day of hospitalization and, consequently, the patient was given a single intravenous dose (90 $\mu\text{g}/\text{kg}$) of activated recombinant factor VII (rFVIIa) (NovoSeven[®]; Novo Nordisk A/S, Bagsvaerd, Denmark). The effect was spectacular: there was a prompt cessation of bleeding and the bleeding time decreased from 16 to 7 min within 30 min of administration. Four hours after rFVIIa administration and complete cessation of the aforementioned hemorrhagic syndrome, the central venous catheter for dialysis could be inserted. The first dialysis was initiated 6 h after the rFVIIa administration, while the shortening of the bleeding time was still present.

After 24 h, the bleeding time increased to 9 min and, by 48 h, it was 13 min. No bleeding tendency was observed after this single injection of rFVIIa, despite extremely low platelet levels. No significant change was noted in the prothrombin time. However, the activated partial thromboplastin time (APTT) decreased by approximately 43%, which meant that hemodialysis could be initiated.

We did not correlate the shortening of bleeding time with the dialysis. The elevated values of prothrombin time and APTT were not improved by the administration of fresh frozen plasma. However, those values could not explain the diffuse and important bleedings observed with the patient.

The mechanism by which rFVIIa brings about hemostasis is not fully understood. The suggested mechanism in thrombocytopathia is enhancement of platelet activation and thrombin generation on the surface of the vessel wall, even in the absence of tissue factor [6].

In conclusion, a single 90 $\mu\text{g}/\text{kg}$ bolus dose of rFVIIa may be an efficient therapy in controlling the bleeding syndrome occasionally observed in ARF with accompanying uremic platelet dysfunction and/or thrombocytopenia. Administration of rFVIIa provides several days of stabilization, allowing the initiation of hemodialysis under safer conditions, and, as a recombinant product, rFVIIa may reduce the use of plasma-derived products, thereby reducing the risk of viral transmission.

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