



Successful Treatment of Gastrointestinal Bleeding With Recombinant Factor VIIa After Kidney Transplantation in Patients With Pancytopenia

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ABSTRACT

Hemostatic disorders can often complicate transplantation procedures. Moreover, anti-hemorrhagic drugs may not efficiently control bleeding that occurs in such cases. We report on a patient who underwent kidney transplantation complicated by bone marrow aplasia and gastric bleeding who was successfully treated with recombinant activated FVII (Novoseven). In May 2005, a 53-year-old man affected by chronic renal insufficiency underwent kidney transplantation. At the beginning of June, laboratory tests showed progressive reduction in the blood cell count with anemia, granulocytopenia, and thrombocytopenia related to the development of marrow insufficiency. We commenced transfusion therapy and administered hematologic growth factors. On June 3, 2005, the patient underwent surgical procedure to repair the abdominal wall. Two days thereafter, the postsurgical period was complicated by an episode of melena. The patient received additional treatment with packed red cells, platelets, and fresh-frozen plasma. The gastrointestinal bleeding continued until June 9, 2005, when therapy with recombinant activated FVII (Novoseven) was commenced at an initial dose of 90 $\mu\text{gr}/\text{kg}$. The first bolus did not significantly reduce the blood loss; it was therefore administered as a successive bolus at the same dosage that was able to stop bleeding. Endoscopic examination performed the day after showed the absence of the hemorrhagic lesion in the gastric mucosa. In the subsequent days, the need for transfusion was dramatically reduced with no episode of bleeding. At the same time, the laboratory and clinical findings of marrow insufficiency disappeared. Our case report showed that the use of a global antihemorrhagic factor, such as Novoseven, can successfully control gastrointestinal bleeding even in complicated patients despite failure of traditional antihemostatic therapy.

HEMOSTATIC DISORDERS are common among patients undergoing kidney transplantation. When they occur, the management of posttransplant bleeding can be difficult. Traditional hemostatic measures based on antifibrinolytic or transfusion therapy may not always be successful. In this situation, a new antihemorrhagic recombinant activated drugs may be more appropriate since high hemostatic activity is achieved with a small volume of drug.¹ Little evidence supports the use of activated FVII (Novoseven) in patients who underwent kidney transplantation.^{2,3} Herein we have reported a patient who developed massive gastric hemorrhage after kidney transplantation with marrow insufficiency due to immunosuppressive therapy. The hemorrhage was successfully treated with recombinant acti-

ated FVII after the inability of transfusion therapy to control the bleeding.

CASE REPORT

In May 2005, a 53-year-old man underwent kidney transplantation because of chronic renal insufficiency. The patient was

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Table 1. Transfusion Request According to Laboratory Findings

	Kidney Transplantation (05/17/05)	Day 14 Posttransplant	Second Surgery (06/3/05)	Day 1 po	Day 2 po	Day 3 po	Discharge (06/20/05)
RBC	8820	9450	1740	410	440	1100	22,400
Hg	14.2	8.5	7.9	7.8	8.2	8.1	8.7
PLT	244,000	82,000	34,000	51,000	42,000	58,000	114,000
PT (%)	80	65	62	77	74	86	80
aPTT (s)	22	24	30	23	28	22	23
FBG (mg/dL)	250	350	430	338	278	320	298
D-d (mg/dL)	1123	2348	1200	1560	1648	800	430
PRC	0	1	0	8	2	0	1
PLTt	0	0	6	6	0	0	0
FFP	0	0	6	6	0	0	0
Note			Repair of the abdominal wall	Melena, beginning of G-CSF	rFVIIa (90 µg/Kg, b.i.d.)	Dialysis	

RBC, red blood cells; Hg, hemoglobin; PLT, platelets count; PT, prothrombin time; FBG, fibrinogen; D-d, D-dimer; PRC, packed red cell; PLTt, platelet transfusion; FFP, fresh-frozen plasma; G-CSF, granulocyte colony stimulating factor; po, postoperative.

positive for hepatitis C virus. In the recent past he had an episode of gastric hemorrhage; he also was on antihypertensive drugs because of primary arterial hypertension. The preoperative laboratory blood tests were normal (Table 1). In the postsurgical period, the patient was treated with antibiotic, antimycotic, and immunosuppressive therapy (ceftazidime 1.5 g/d, mycophenolate mofetil 2 g/d, Solumedrol 1 g/d, then progressively reduced to 20 mg/d and erythropoietin 4000 IU three times/week). Immediately after surgery we commenced antithrombotic therapy (subcutaneous calcium nadroparine 0.3 mL/d). About 1 week after transplantation, blood routine tests showed laboratory findings suggestive of marrow insufficiency, with progressive reduction of hemoglobin, white blood cells, and platelets (Table 1). Immunosuppressive therapy was therefore withdrawn. In the beginning of June, the patient underwent surgery for repair of the abdominal wall. During this period, he stopped antithrombotic prophylaxis and received supportive transfusion therapy with packed red cells and platelets. He also commenced therapy with granulocyte growth factor (subcutaneous G-CSF 1 fl/d). On June 3, 2005, he suffered dramatic episodes of melena that lasted about 2 days. Supportive therapy was therefore increased and we started additional infusions of fresh-frozen plasma. Endoscopy of the stomach and duodenum showed diffuse hemorrhagic lesions of the entire gastric mucosa; however, signs of uremic gastritis were not present. Because of the inability of supportive therapy to control the gastric bleeding, we decided to start a novel global antihemostatic agent. Recombinant activated FVII (rFVIIa, Novoseven) was started at the dosage of 90 µg/kg. The first bolus did not resolve the bleeding significantly; a second bolus, at the same dosage delivered after 6 hours dramatically reducing the volume of blood loss. This clinical finding was successively confirmed by gastric endoscopy, which showed the absence of the previously reported diffuse gastric hemorrhagic lesion of the mucosa. A few days thereafter, the hematological findings progressively returned to normal (Table 1); antibiotics, steroids, and immunosuppressive therapy were started again. About 10 days after the resolution of gastric haemorrhage, the laboratory findings became normal and the patient was discharged for clinic follow-up.

DISCUSSION

rFVIIa is currently authorized for the treatment of hemophilic patients who developed inhibitors against FVIII or in patients with congenital Glanzmann thrombasthenia.⁴ Recent randomized clinical trials have highlighted the potential benefit of administering rFVIIa during critical bleeding among patients with posttraumatic intracranial hemorrhage and in other clinical settings. Many case reports have described successful treatment of Novoseven in off-label situations of critical bleeding, usually after the inefficacy of standard therapy with fresh-frozen plasma, antifibrinolytic agents, and supportive therapy.⁵ Notwithstanding the limits of case reports, usually published in cases of a positive result, it is quite evident that in clinical practice the use of a global hemostatic agent¹ used in a small volume of infusion permits physicians to actively control massive bleeding. It is still unclear whether this drug can be safely used as first treatment or after failure of traditional antihemostatic approaches.

Our case is interesting because of the some of the issues that arose: first, standard doses of rFVIIa were able to control the critical episode of gastric bleeding after failure of supportive therapy. The temporal sequence of novel therapy with rFVIIa and the cessation of bleeding makes it likely that the effect was mainly related to the second bolus of Novoseven. Then, rFVIIa was efficacious even in our patient who, at the time of hemostatic therapy, had a low platelet count (40,000 mmc³). Finally, even in the absence of antithrombotic prophylaxis during dialysis after posttransplantation procedure, Novoseven did not produce a thrombotic complication. This aspect is interesting since our patient can be considered at high risk of venous thrombosis, because of a recent surgical procedure, bed rest, and supportive therapy with fresh-frozen plasma.

In conclusion, our case report highlighted the role of Novoseven to control an episode of critical bleeding in

a complicated patient who had recent surgery for renal transplantation and repair of the abdominal wall, along with marrow insufficiency due to immunosuppressive therapy.

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