



Rapid Correction of Prothrombin Time After Low-Dose Recombinant Factor VIIa in Patients Undergoing Orthotopic Liver Transplantation

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ABSTRACT

Orthotopic liver transplantation (OLTx) is associated with a major risk of blood loss resulting from portal hypertension, collateral circulation, and clotting disturbances. Application of a recombinant factor VIIa (rFVIIa) has been reported to promptly correct clotting abnormalities reducing the risk of intraoperative bleeding. This study included 8 patients who underwent OLTx for end-stage liver cirrhosis, with prothrombin times (PT) exceeding the upper limit of normal by more than 4 seconds before surgery. All subjects were administered a small single intravenous dose of rFVIIa [mean 68.37 $\mu\text{g}/\text{kg}$ body mass (range, 32.88–71.64)] 10 minutes prior to the skin incision. The PT was then measured 15 minutes later, following graft reperfusion, and 12 hours since drug application. All patients showed rapid correction of PT within 15 minutes after injection (median PT before injection 20.25 seconds vs 11.5 seconds after injection, $P < .0001$). Following the reperfusion PT was found to be prolonged again. These values are not significantly different from those before surgery and are comparable to PT values after reperfusion in patients who did not receive rFVIIa. None of the patients developed thromboembolic complications. In conclusion, lower than recommended dose of rFVIIa caused rapid improvement in the PT shortly after injection. After reperfusion PT became prolonged again, which may account for the lack of thromboembolic complications observed in this group of patients.

CLOTING DISTURBANCES resulting from compromised hepatic function are often responsible for a complicated perioperative course due to increased blood loss in patients undergoing liver transplantation. The risk is obviously higher among cases of portal hypertension, collateral circulation, vascularized adhesions and a history of upper abdominal surgery. Usually prior to surgery the treatment of clotting abnormalities begins with administration of fresh frozen plasma (FFP), platelets, and fibrinogen. Antifibrinolytic medications including aprotinin are also used in some centers to prevent hyperfibrinolysis during liver transplantation. Rapid clotting corrections may decrease blood loss, reducing morbidity and mortality, following the major surgical procedures.^{1,2}

Recombinant factor VIIa (rFVIIa) has been reported to improve or quickly normalize clotting parameters. It binds to a tissue factor and activates thrombin generation both in plasma and on the surface of platelets.³ The requirements for transfusion of blood products following rFVIIa application may thus be substantially lower among patients undergoing emergent or elective liver transplantation.^{4–6} How-

ever, the available data on use of rFVIIa in hepatology are scant including only a small group of patients. Optimal dose of rFVIIa required for liver transplantation must be estimated; since rFVIIa is an expensive substance, in eight consecutive adult liver transplant recipients presenting with clotting abnormalities we employed lower doses than those previously recommended in order to assess their effectiveness.

MATERIAL AND METHODS

Eighteen primary adult orthotopic liver transplantations were performed for different indications in the Department of General and Transplantation Surgery, M. Curie Hospital, Szczecin, Poland, between January 2002 and May 2003. The indication for rFVIIa

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Table 1. Demographic and Clinical Data of Patients Included Into This Study

No.	Gender	Age (years)	Diagnosis	Child-Pugh score	Previous abdominal operations	Blood loss (mL)
1	F	55	HCV cirrhosis	11	Yes	1750
2	F	51	Cryptogenic cirrhosis	10	No	2450
3	F	37	ALD	9	No	2100
4	M	54	HCV cirrhosis	10	Yes	2800
5	M	54	HCV cirrhosis	12	No	3150
6	F	51	Autoimmune cirrhosis	14	Yes	2800
7	M	48	HCV cirrhosis	11	No	700
8	F	33	Wilson's disease	14	No	1750

administration was prolongation of prothrombin time (PT) by more than 4 seconds above the upper limit of normal. Overall, eight recipients suffering from end-stage liver cirrhosis, including two scored as Child-Pugh B and six as Child-Pugh C (Table 1) were administered rFVIIa (NovoSeven, Novo Nordisk, Copenhagen, Denmark) as a single bolus injection at a median dose of 68.37 $\mu\text{g}/\text{kg}$ body mass (range, 32.88–71.84), 10 minutes prior to the skin incision. All patients were transplanted using the piggyback technique without a venovenous bypass. PT was measured 15 minutes after rFVIIa injection, following graft reperfusion, and 12 hours after drug administration. The indication for FFP application was a 1.5-fold prolonged activated partial thromboplastin time (APTT) and a fibrinogen level below 100 mg/dL. Platelet concentrate (PC) was given whenever the platelet count was below $70 \times 10^9/\text{L}$. Aprotinin was administered to all patients prior to the end of surgery. All values are expressed as means with statistical analysis performed using paired-Student *t* tests. *P* values less than .05 were considered statistically significant.

RESULTS

The demographic and clinical data on analyzed patients shown in Table 1 reveal good early function of all transplanted grafts. Median cold ischemia time, warm ischemia time, and anhepatic phase were 8 hours, 45 minutes (range, 7 hours, 15 minutes to 10 hours, 30 minutes), 43 minutes (range, 37–58), and 78 minutes (range, 60–100), respectively. The median blood loss during surgery expressed as an amount of red blood cells transfused was 7 units (range, 2–9). The patients were administered a mean of 12.5 units of FFP (range, 11–15) during surgery. Four subjects also received 6 units of platelet concentrate transfusions. Statistically significant and prompt correction of PT was observed in all patients within 15 minutes after injection of rFVIIa ($P < .0001$) (Fig 1). The laboratory results showed signs of PT hypercorrection in four patients with values decreasing to 8.5, 10.2, 8.9, and 9.8 seconds. In the postreperfusion phase the PT value was observed again to be prolonged to a mean of 18.05 seconds (range, 14.2–32 seconds) (Fig 2). These values were not significantly different from those before surgery; they were comparable to PT values after reperfusion in patients who did not receive rFVIIa (data not presented). All the patients underwent bedside Doppler ultrasound examinations each day for the first 4 days and again on day 7 following surgery. No thromboembolic complications were observed.

DISCUSSION

Blood loss has traditionally been regarded as an unavoidable risk factor of liver transplant surgery. Owing to improvements in surgical and anesthetic techniques, in better graft preservation, and in clotting monitoring with correction of clotting factors and platelets, the requirements for transfusion of blood products at the time of OLT is decreasing; the transplant procedure is becoming less hazardous in most centers. In order to maintain hemodynamic stability during surgery, it is often necessary to transfuse large amounts of blood products, crystalloids, and colloids during a rather limited period of time.^{7,8} This maneuver may increase portal pressure, aggravate bleeding, and lead to volume overload, thereby requiring prolonged artificial ventilatory support and intensive care unit stay as well as increasing the rate of infectious complications. Therefore, there is an urgent need to reduce blood loss during surgery.

Recombinant factor VIIa initiates the coagulation process when tissue factor has been exposed at the site of

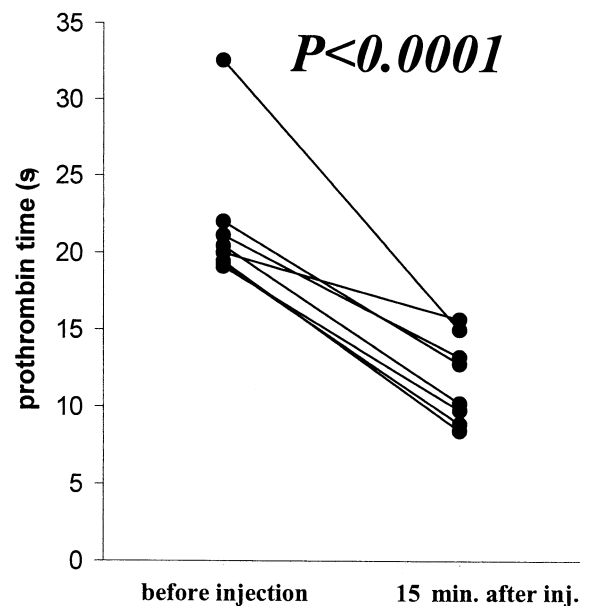


Fig 1. Prothrombin time before injection of rFVIIa and 15 minutes later in all analyzed patients.

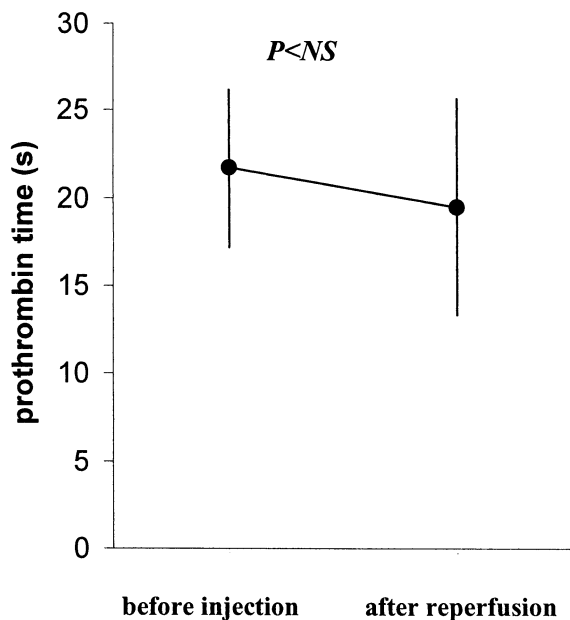


Fig 2. Prothrombin time before injection of rFVIIa and after reperfusion in all analyzed patients.

injury. Its administration quickly, corrects clotting abnormalities, thereby improving hemostasis in the operating field. However, the half-life of rFVIIa is short.⁹ In some studies 80 $\mu\text{g}/\text{kg}$ doses returned plasma levels of rFVIIa to almost baseline levels before the end of the transplant procedure; however, although the levels of the compound, are not detectable, it seems to remain active and effective.^{1,4}

Despite the above observations, the risk of thromboembolic complications seems to be low. Because rFVIIa is expensive, we have used it in low dose, seeking to effectively correct clotting abnormalities. In all subjects we observed rapid normalization of the PT after injection of rFVIIa. After reperfusion the PT was again prolonged and did not differ from that observed in our patients who did not fulfill the criteria of drug administration. We did not observe any thromboembolic complications among our patients. In the era of financial constraints in the health care system, attempts to use the lowest effective dose of an expensive compound are justified. This pilot study, which supports the effectiveness of low dose rFVIIa, should encourage larger, preferably multicenter studies that compare transfusion requirements, effectiveness, and possible complications of various doses in a randomized design.

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