



Administration of a Recombinant Factor VIIa in Patients Undergoing Liver Transplantation for Fulminant Hepatic Failure

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ABSTRACT

Background. Fulminant hepatic failure (FHF) is associated with profound clotting disturbances leading to the risk of a major blood loss during orthotopic liver transplantation (OLT). Application of a recombinant factor VIIa (rVIIa) that promptly corrects clotting abnormalities remains controversial in the OLT setting. We conducted a retrospective analysis of the effect of rVIIa on the prothrombin time (PT) and other perioperative parameters in patients transplanted for FHF in our center.

Materials and Methods. Nineteen consecutive patients (9 males/10 females) of overall mean age of 33 ± 13 years underwent the procedure due to: Wilson's ($n = 8$), non-A–non-B hepatitis ($n = 6$) or *Amanita phalloides* toxicity ($n = 5$). All subjects received rVIIa at a mean dose of $54 \pm 16 \mu\text{g/kg}$ body weight at 10 minutes before the skin incision. The PT was measured at 15 minutes and 12 hours after injection. Data were analyzed with StatView program with $P < .05$ considered significant.

Results. Rapid correction of PT was observed in all patients: the mean PT before injection was 37 ± 14 versus 14 ± 3 after 15 minutes ($P < .0001$). Twelve hours after the injection the PT was 19 ± 5 ($P < .0001$ vs before injection and $P < .0007$ vs 15 minutes after injection). Two patients died at 1 and 4 days after OLT. Mean red blood cell requirement was 5 ± 4 U and fresh frozen plasma was 11 ± 5 U. The mean operative time was 527 ± 126 minutes and intensive care unit stay 8 ± 9 days. None of the patients developed thromboembolic complications.

Conclusion. Administration of rVIIa caused a rapid improvement in the PT shortly after injection. It was safe and not associated with any thromboembolic events in our series.

ACCORDING TO THE definition proposed by American Association for the Study of Liver Diseases (AASLD), fulminant hepatic failure (FHF) is defined as a rapid deterioration of previously normal synthetic liver function with coexisting encephalopathy.¹ One of the most important prognostic parameters is the degree of coagulation disturbances and their dynamic changes in time reflecting impairment of hepatic synthesis functions.

The liver produces clotting factors involved in the hemostatic cascade, most importantly factors II, V, VII, and IX. In FHF, their deficiency can lead to massive bleeding and patient death.² In such patients, the use of genetically recombinant active coagulation factor VIIa (recombinant factor VIIa [rVIIa]; NovoSeven, Novo Nordisk, Denmark) has been proposed to correct clotting abnormalities and possibly also reduce the need for transfusions of blood

products.³ This factor has been originally used to hemorrhage among patients with hemophilia A. The indications for its use have been gradually extended to include patients undergoing orthotopic liver transplantation (OLT); however, this application remains controversial.⁴

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Because prompt correction of profound coagulopathy is paramount in cases of major surgery, we use rVIIa routinely for patients with severe clotting abnormalities, undergoing OLT for FHF. The aim of this study was to analyze our experience with the use of rVIIa in these patients.

MATERIALS AND METHODS

We performed 202 OLT among 191 adult recipients between February 2002 and March 2009. In 19 patients, FHF was the indication for emergency OLT due to Wilson's disease ($n = 8$) non-A–non-B hepatitis ($n = 6$), and *Amanita phalloides* toxicity ($n = 5$). The mean recipients age was 33 ± 13 years. Patients were accepted for emergency OLT based on the King's College criteria, and Nazer's criteria for patients with Wilson's disease. The mean model for End-Stage Liver Disease score was 36 (range, 28–46). All patients were treated in the intensive care unit (ICU) preoperatively. rVIIa factor was administered 10 minutes before skin incision at a mean dose of $54 \pm 16 \mu\text{g}/\text{kg}$ of body weight. The prothrombin time (PT) was measured at 3 time points: just before drug administration and 15 minutes and 12 hours thereafter. We recorded the amount of blood products—red blood cells (RBC) and fresh frozen plasma (FFP)—transfused, as well as the duration of surgery from skin incision to skin suture as well as the ICU and the hospital stay. We also assessed the incidence of thromboembolic events in the perioperative period. Data are presented as mean values \pm SD. Statistical analysis was performed using the Stat-View program: a P value $< .05$ was considered significant.

RESULTS

Two (11%) patients died in the postoperative period. The first succumbed on the first day after OLT due to severe cardiovascular failure, which was present at the beginning of surgery and required major inotropic support. The second patient expired at day 4 after OLT as a consequence of a severe surgical complication with massive aortic hemorrhage during the transplantation with subsequent multi-organ failure.

A significant correction of PT was observed at 15 minutes after drug administration. Within the next 12 hours, the PT increased again to 19 ± 5 seconds ($P < .0001$) versus before injection and versus 15 minutes after injection ($P < .0007$). These data are shown in Figure 1. No patient developed a thromboembolic complication in the postoperative period. An average of 5 ± 4 U RBC and 11 ± 5 U FFP were transfused during transplantation. The average duration of surgery was 527 ± 126 minutes and the average ICU stay 8 ± 9 days.

DISCUSSION

Supplementation of coagulation factors is often necessary when the synthesis of proteins progressively fails in patients with FHF. The intravenous administration of fluids including large amounts of plasma preparations may pose a problem due to the risk of serious adverse events, including brain edema.⁵ These events have been repeatedly addressed in the literature in terms of the outcome of extensive surgical procedures for patients with coexistent chronic liver diseases or multiorgan injuries.⁶

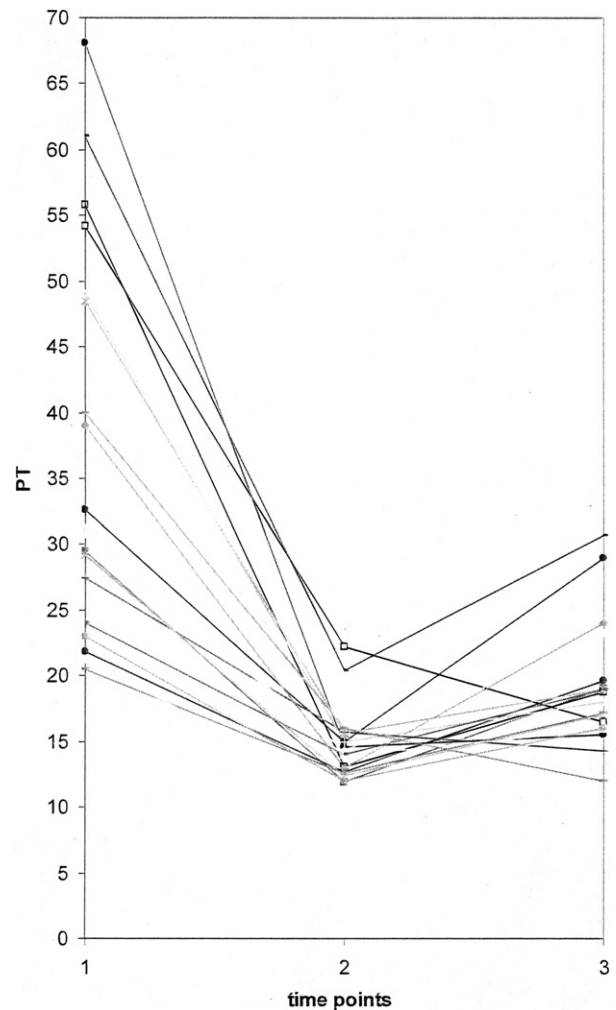


Fig 1. Individual results of prothrombin time (PT) before injection of rVIIa (time point 1), 15 minutes (time point 2), and 12 hours (time point 3) after injection. PT at 12 hours versus before injection ($P < .0001$) and versus 15 minutes after injection ($P < .0007$).

In the light of these considerations intravenous fluid administration should often be limited, which can be achieved by using rVIIa instead of large volumes of plasma. In this study we have confirmed that rapid correction of coagulopathy may be possible with the use of rVIIa in patient undergoing OLT for FHF. This therapy may result in reduced transfusion requirements for blood products.^{3,7} There is still the need for blood products administration; however, the amounts of RBC and FFP transfusions in our patients were relatively low. Some reports have indicated the possibility of thromboembolic complications with the use of rVIIa,⁴ but we did not observe such events.

In conclusion, the administration of rVIIa enabled rapid correction of the prolonged prothrombin time among patients with FHF undergoing OLT. This therapy may con-

tribute to increased patient safety and a reduced incidence of complications in the perioperative period.

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