

## Letter to the editor

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### Recombinant activated factor VII (NovoSeven®) stops severe intra-abdominal bleeding after liver needle biopsy without surgery

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Recombinant activated coagulation factor VII (rFVIIa) (NovoSeven®) is a coagulation factor produced by genetic engineering that was first used successfully in 1988 for therapy of haemophilia patients with allo-antibodies against exogenous factor VIII or factor IX. Later, its efficacy was demonstrated treating patients having a clotting disorder with life-threatening bleeds [1–3]. Case reports have been published on the use of rFVIIa in patients without known abnormalities of the coagulation system but with life-threatening or limb-threatening bleedings, for which all other therapeutic alternatives had been exhausted or no other treatment option was available. Recently, a study was published suggesting that treatment with rFVIIa may offer benefit for patients with liver disease undergoing laparoscopic biopsy [4].

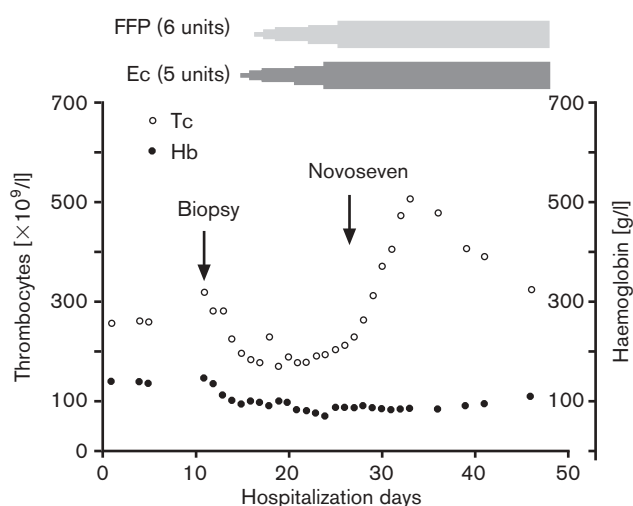
A 77-year-old man was hospitalized with jaundice of unknown origin. Biochemical analyses initially showed an elevated bilirubin of 182 µmol/l, a gammaglutamyl transpeptidase of 426 U/l and an alkaline phosphatase of 378 U/l. Apart from aspirin, which had been stopped 11 days before biopsy, the patient did not take any medication. The patient had no history of a coagulation disease, no episodes of acute bleeding or any evidence of a clotting disorder, but he had a severe chronic obstructive lung disease. Initial laboratory and image investigations did not reveal the aetiology of the jaundice and a percutaneous liver biopsy was performed. Three hours after biopsy, clinical examination revealed a rebound tenderness in the right upper abdomen. The haemoglobin level was 113 g/l, and the platelet count was  $283 \times 10^9/l$ . The International Normalized Ratio was 1.1 (normal range < 1.3), the activated partial thromboplastin time was 30 s (normal range < 40 s) and fibrinogen was 4.8 g/l (normal range,

1.5–3.5 g/l). An abdominal computerized tomography scan showed a laceration of liver tissue of a branch of the right liver vein. An initially stable abdominal haemorrhage of approximate 21 was documented. A conservative management was installed under intensive care conditions. Despite administration of 5 U packed red cell concentrates (EC) and 6 U fresh frozen plasma (FFP) (Fig. 1), the haemoglobin value dropped continuously to 65 g/l, suggesting a persistent haemorrhage. This active intra-abdominal bleeding was documented on a new computerized tomography scan. The decision to apply NovoSeven® was taken because a surgical intervention was considered too risky by the attending surgical consultant due to the patient's general conditions. Novoseven® was given as a single intravenous dose of 100 µg/kg body weight. After application of rFVIIa, the haemoglobin level was stable within 24 h reaching low-normal levels within 18 days after infusion of rVIIa, with no further EC or FFP substitution (Fig. 1). There was no need for surgery and the patient left the hospital in good condition 30 days after the liver biopsy. The obtained liver biopsy demonstrated a cholestatic injury due to senna alkaloids, which were part of a naturalist medication taken by the patient.

Although indication for NovoSeven® in acute liver bleedings has not yet been formally evaluated, the present results suggest that rFVIIa could be used effectively in acute liver bleedings. Novoseven® can induce a stable clot at the site of a local injury independent of the presence of factor VIII and factor IX. In addition, it may enhance platelet activation by generating thrombin on platelet surfaces.

Liver needle biopsy is a common procedure. Clinically significant bleeding with liver biopsy in patients with liver disease is estimated to occur in 0.35% [5]. It is believed that consumption of coagulation factors will worsen an already critical situation concerning haemostatic balance. The liver plays a major role in the maintenance and control of haemostatic balance, and liver diseases may cause an increased tendency to bleed, because it might result in substantial reduction in the synthesis of factors involved in coagulation and in factors controlling fibrinolysis [6]. Hyperbilirubinaemia has been independently correlated with platelet function; the elevated bilirubin might just be a surrogate marker for the severity of liver disease. In our patient, the bilirubin concentration was very high. However, it has to be mentioned that the degree of bleeding bears no correlation to peripheral blood coagulation parameters [7]. Novoseven® has been reported to

Fig. 1



Bars represent the cumulative dose of units of fresh frozen plasma (FFP) and packed red cells (Ec), respectively, consumed by the patient after liver biopsy. Of note, after the injection of recombinant activated factor VII (Novoseven<sup>®</sup>) no more infusion of Ec and FFP was necessary. This is reflected by the constant thickness of the two presented bars after the injection of Novoseven<sup>®</sup>. Hemoglobin (Hb), filled points; thrombocytes (Tc), open points.

induce haemostasis in patients. In addition, there is evidence supporting the role of the factor VII tissue-dependent coagulation system in the initial platelet activation for coagulation [8], which could have been the case in our patient.

In contrast to another published case report [9], our case demonstrates that with one single dose of 100 µg/kg, further bleeding in liver damage after percutaneous liver biopsy can be stopped without surgery. This case demonstrates that rFVIIa could play a role as a rescue agent for severe postprocedure bleeding.

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