

## Case Report

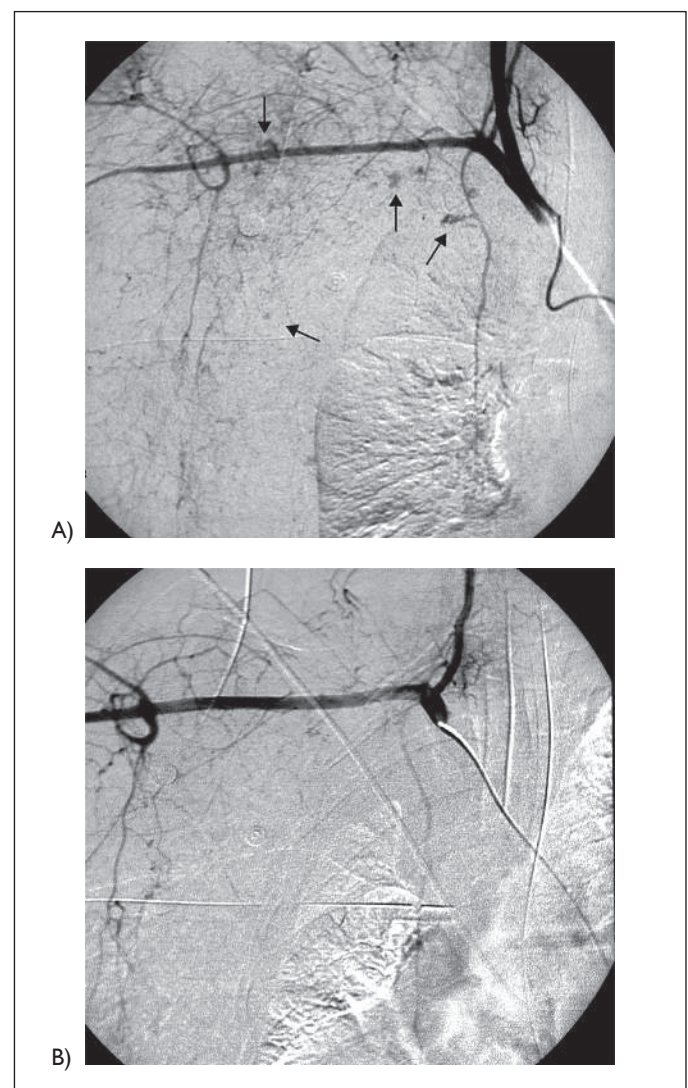
### Angiographic documentation of the efficacy of recombinant activated factor VII (NovoSeven) to control diffuse bleeding in major trauma

A 54-year-old female was admitted to the emergency department, following a fall of approximately 18 meters. On arrival, the patient was shocked with a blood pressure of 80/10 cm Hg, a heart rate of >100. She was sedated and mechanically ventilated. The arterial pH was 7.14 with a base deficit of 16 mEq/L. Radiological investigations revealed a pneumothorax, multiple costal fractures as well as a displaced fracture of the right forearm and open fractures of the left and right tibia.

The patient's condition continued to deteriorate, with persistent haemorrhage and was referred for urgent angiographic assessment. The angiogram demonstrated diffuse oozing from the branches of the right internal iliac artery, the right deep femoral artery and the right subclavian artery. An arterial embolization with gelfoam and microspheres (Embogold™) was successfully performed in the vascular network arising from the right internal iliac artery, the right deep femoral artery and the right hepatic artery. During and after the procedure the patient remained haemodynamically unstable and required rapid infusions of crystalloid and colloid solutions as well as 12 units of red cells, 8 units of platelets, 5 units of fresh frozen plasma and 2 grams of fibrinogen. In spite of this, the hemoglobin level dropped to 3.9 g/dl, corresponding to a blood loss of approximately 13 units red cell concentrates/hour. The platelet count fell to  $45 \times 10^9/L$  and coagulation parameters became severely disrupted with an activated partial thromboplastin time (APTT) of >180 seconds (reference range: 23–35) and an international normalized ratio (INR) at 2.24 (reference range : 0.9–1.3). The fibrinogen level fell to 32 mg/dl and D-dimers were significantly elevated at 5448 ng/ml (normal <500).

In an attempt to control the bleeding, 90 µg/kg of recombinant activated factor VII (rVIIa) was given intravenously. As demonstrated on the angiogram, the oozing from the branches of the right subclavian artery diminished within 15 minutes (Fig. 1) and coagulation tests improved. The APTT fell from >180 seconds to 68, the INR normalized at 1.02 and the fibrinogen level rose from 96 to 175 mg/dl. The patient became haemodynamically stable allowing further radiographic assessment of internal

organ damage. This showed a large pre- and retrosternal haematoma, as well as a diffuse haemoperitoneum with active bleeding from the Couinaud segments IV, V and VI of the liver. Surgical stabilization of the multiple fractures and an exploratory laparotomy were then performed. The latter confirmed the presence of the haemoperitoneum, but no clear bleeding sites were visualized. During these surgical interventions further transfusion with



**Figure 1: Selective digital subtracted angiogram of the right subclavian artery.** An equal amount (10 ml) of Iodixanol 320 mg I/ml (Visipaque, Amersham) has been injected at a rate of 4 ml/sec: (A) First angiogram acquired just before the intravenous injection of NovoSeven®, showing multiple small spots of contrast medium extravasation (arrows). (B) Second angiogram obtained 15 minutes later, demonstrating marked reduction of oozing from subclavian and axillary branches.

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Cedric Hermans has worked as a consultant for Novo Nordisk and has lectured at symposia organized by Novo Nordisk.

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15 units of red cells, 16 units of platelets and 13 units of fresh frozen plasma was required. Since reimbursement of rVIIa in trauma patients is not supported by the national health insurance scheme, administration of rVIIa could unfortunately not be repeated.

The patient was admitted to the intensive care unit where she again became haemodynamically unstable requiring further administration of 6 units of red cells, 16 units of platelets and 3 units of fresh frozen plasma. A second angiographic study performed on day two showed massive bleeding from the right internal mammary artery that was successfully controlled by arterial embolisation securing permanent haemostasis. No haemorrhagic or thrombotic complications were later observed.

Since the initial spectacular case report in a young Israeli soldier (1), a large number of case reports of successful use of rVIIa in patients with uncontrolled bleeding secondary to trauma have been published (2–5). More recently, Boffard et al. conducted a randomized, placebo-controlled, double blind trial of the efficacy and safety of rVIIa as an adjunctive therapy for control of bleeding in 301 patients with severe blunt or penetrating trauma requiring transfusion of 8 units of red cells. In blunt trauma red cell transfusions and the incidence of acute respiratory distress syndrome were reduced and the incidence of multiple-organ failure tended to be reduced in patients with penetrating trauma. Mortality was equal in the two groups (6). As suggested by a recent systematic review on the efficacy and safety of rVIIa for the treatment of severe bleeding, off-label use of rVIIa may be considered in patients with life-threatening bleeding although additional randomized controlled trials are required (7).

The efficacy of rVIIa to control bleeding in trauma patients has been evaluated on the basis of transfusion requirements, changes in laboratory tests and the clinical outcome. Although the use of rVIIa as an adjunct to selective arterial embolisation has been shown to control life-threatening post-partum haemorrhage (8), the present report is the first to our knowledge in which angiographic imaging was performed concomitantly with the administration of rVIIa. The haemostatic efficacy of this haemostatic agent was demonstrated not only by a dramatic im-

provement of the coagulation parameters and the haemodynamic status of the patient, but also by the *in vivo* radiographic visualization of the arrest of diffuse bleeding (Fig. 1).

We used an empirical dose of 90 µg/kg of rVIIa in an attempt to stop profuse bleeding. The experience of rVIIa use in trauma with excessive bleeding indicates a haemostatic effect in doses of 20–120 µg/kg. Initial dosage has been recommended to be a 4.8 mg vial, which for an adult patient is a dose in the range of 50–100 µg/kg for a body weight range of 50–100 kg (9). As rVIIa acts on the patient's own clotting mechanism, it is important to correct any underlying coagulopathy wherever possible. Ideally fibrinogen levels should be kept above ≥50 mg/dL (preferably 100 mg/dl) and platelet counts ≥50 × 10<sup>9</sup>/L (10). Although the optimal timing of rVIIa administration has not been clearly defined, early use appears to be more effective than 'last-ditch' or rescue therapy.

Preliminary data from the recently completed rVIIa in trauma trial suggests that the incidence of thromboembolic complications is no higher amongst patients treated with rVIIa than in the placebo group. However, rVIIa should be used with caution in trauma patients at risk of thrombotic complications e.g. after cardiac surgery, in patients with a history of coronary artery disease, venous or arterial thrombosis, DIC, or those undergoing ECMO or in whom a ventricular assist device is being used and lastly in patients with a history of cerebral vascular disease (9).

In conclusion, the angiographic visualization of the effectiveness of rVIIa to achieve haemostasis provided in this case report represents an illustration of the beneficial role rVIIa may play as an adjunctive treatment to control massive bleeding in severe trauma.

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