

## CASE REPORT

# Successful use of recombinant factor VIIa for severe surgical liver bleeding in a 5 month-old baby

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**Summary.** A 5 month-old baby developed non-ceasing intra-peritoneal bleeding after extensive surgical biopsy for an hepatoblastoma. A single recombinant

activated factor VII injection following enlarged hepatectomy helped to resolve quickly this life-threatening haemorrhagic syndrome.

Recombinant activated factor VII (rFVIIa) (Novoseven<sup>®</sup>; Novo Nordisk, Denmark), represents an efficient therapeutic mean for severe bleeding episodes in haemophilia patients who develop inhibitors [1] or in acquired haemophilia [2,3]. Several case reports describe rFVIIa use in serious bleeding episodes of Glanzmann's thrombasthenia [4–6] or Bernard-Soulier syndrome [7] as well as in acquired thrombopenia [8]. Recombinant FVIIa activation of the coagulation system is localized to sites of injury; therefore its peculiar and efficient mechanism of action has prompted its use in severe and intractable haemorrhages occurring with liver failure [9] or in post-surgical [10–13] or traumatic situations [14,15]. We report the use of rFVIIa to control a life-threatening haemorrhage in a 5 month-old baby undergoing liver surgery who did not respond to intensive transfusion support.

### Case report

The patient was a 5 month-old male baby weighing 7.2 kg. He presented with normocytic anemia and a recent increase in abdominal volume: a huge intra-hepatic multicystic tumoral mass measuring 10 by 7.5 cm was diagnosed. An extended surgical biopsy

of the intra-hepatic mass was carried out, showing its tumoral nature and excavation. Surgical liver biopsy was followed by collapse of the cyst. Pathologic analysis ascertained diagnosis of an hepatoblastoma. Three drainage tubes were installed: one intra-cystic, one in the Douglas and the third sub-hepatic. During surgery, haemostasis became defective: prothrombin time (PT) increased up to 18.3 s (Table 1). Haemorrhage initially developed from the tumour cystic compartment. Blood loss was deemed 300 mL. The baby received transfusion support represented by 120 mL albumin, 320 mL packed red blood cells (PRBC) and 370 mL fresh frozen plasma (FFP) without efficiency on bleeding. Blood loss went on at 20 mL h<sup>-1</sup> in the drainage tube from the cystic mass. Mechanical haemostasis by clamping of the drain was attempted in vain 24 h later.

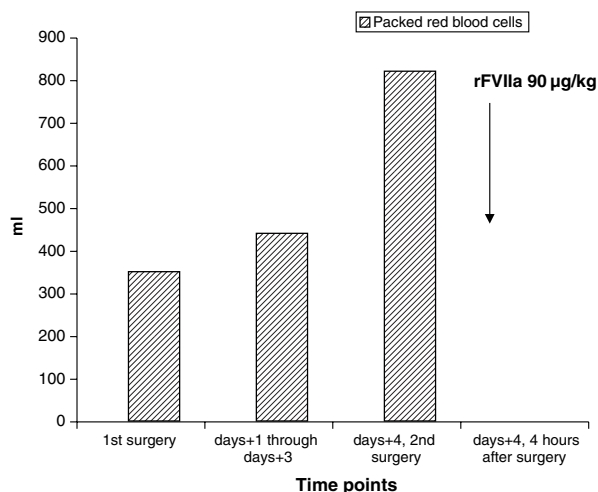
Four days after surgical biopsy, the baby had received twice his blood mass. Abdominal echography revealed a huge haematoma in place of the cystic mass, which was covering right liver and was compressive for nearby vascular structures. Because of non-ceasing haemorrhage a second surgical intervention was compulsory. Surgeons effected a right hepatectomy combined with liver segment IV removal because of a doubtful nodule. During surgery, vasoactive amines were used because of a dramatic drop in blood pressure. Transfusion support via a central venous line was accomplished with approximately three blood masses of the baby, i.e. 820 mL PRBC (Fig. 1), 230 mL FFP, 70 mL platelet transfusion, 100 mL albumin, 200 mL ionic perfusion and 100 mL hydroxyethyl amidon. Back from

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	Before biopsy	After biopsy	Before hepatectomy	Shortly after hepatectomy	12 h after rFVIIa injection
Platelets (g L <sup>-1</sup> )	473	131	198	189	147
PTs (control = 12.5 s)	14.2	18.3	16.8	32.4	20.5
Fibrinogen (g L <sup>-1</sup> )	2.1	1.4	1.6	0.7	3.0
APTTs (control = 33 s)	49	42	50	>120	48

**Table 1.** Haemostatic parameters before and after biopsy and hepatectomy.



**Fig. 1.** Transfusion needs reduction after rFVIIa use for liver surgery.

the operating room, PT was increased to 32.4 s, APTT was longer than 120 s, fibrinogen was down to 0.7 g L<sup>-1</sup>, while platelet number remained normal (189 g L<sup>-1</sup>). The magnitude of bleeding despite intensive filling and resuscitating care led to consider recombinant factor VIIa use: a single bolus dose of 90 µg kg<sup>-1</sup> Novoseven<sup>®</sup> was effected. Shortly after, an intravenous perfusion of 1.5 g (100 mL) fibrinogen concentrate (Clottagen<sup>®</sup>, LFB, Les Ulis, France) was initiated. Bleeding ceased very shortly after rFVIIa injection. The baby did not need any more transfusion nor haemostatic treatment. The following day, he suffered from overhydration, as undesirable effect of massive transfusions. No evidence of thrombosis was observed even in the six following months, as he received chemotherapy for his cancer.

## Discussion

Recombinant FVIIa has been already used in children with acute bleeding resulting from liver failure [9], as well as in fulminant liver failure during hepatic transplantation [11] and also to control surgical bleeding in non-haemophiliac patients [10]. Chuansumrit *et al.* [16] have recently reported safe recombinant activated factor VII use to control bleeding in a preterm baby undergoing

exploratory laparotomy: there was no adverse event and no thrombosis. In the case we report, one single dose of rFVIIa (90 µg kg<sup>-1</sup>) was efficient enough to help stop haemorrhage. Surgery certainly played the essential role to achieve haemostasis and fibrinogen helped restore an adequate coagulation; however, fibrinogen alone may hardly explain the dramatic and quick reversal of clinical situation, which improved before the end of fibrinogen infusion. Although it is impossible to say with certainty whether fibrinogen replacement or rFVIIa stopped the bleeding, the answer may well be that they did work in synergy to restore an adequate haemostasis. As haemorrhage went on for a long time, the lack of a potent haemostatic trigger like rFVIIa, may have resulted in further transfusion needs. Blood-borne infectious risk was avoided with rFVIIa use but we have to stress that safety considerations for rFVIIa may be a matter of concern if we consider thrombotic risk [17,18] although as reported by Roberts [19], the incidence of thrombotic events is very low, allowing to consider that rFVIIa treatment is safe. Efficacy of rFVIIa in resolving life-threatening haemorrhage in this young baby and in other cases reported in young children should give incentives to discuss rFVIIa use in severe bleeding situations such as surgical ones in babies. As recombinant factor VIIa is a costly medicine preventing its broader use, we need planned studies to further consider both clinical use and cost-effectiveness in children.

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## References

- Ingerslev J, Snekken O, Hvid I, Fredberg U, Kristensen HL, Sindet-Petersen S. Treatment of acute bleeding episodes with rFVIIa. *Vox Sanguinis* 1999; 77 (Suppl. 1): 42–6.

- 2 Hay CRM, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost* 1997; **78**: 1463–7.
- 3 Michiels JJ. Acquired haemophilia A in women postpartum: clinical manifestations, diagnosis, and treatment. *Clin Appl Thromb/Hemost* 2000; **6**: 82–6.
- 4 Chuansumrit A, Sangkapreecha C, Hathirat P. Successful epistaxis control in a patient with Glanzmann thrombasthenia by increased bolus injection dose of recombinant factor VIIa. *Thromb Haemost* 1999; **82**: 1778.
- 5 D'Oiron R, Ménart C, Trzeciak MC *et al.* Use of recombinant factor VIIa in 3 patients with inherited type I Glanzmann's thrombasthenia undergoing invasive procedures. *Thromb Haemost* 2000; **83**: 644–7.
- 6 Poon M-C, Demers C, Jobin F, Wu JWY. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood* 1999; **94**: 3951–3.
- 7 Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa. *Thromb Haemost* 1998; **80**: 352.
- 8 Meijer K, Sieders E, Slooff MJH, de Wolf J Th M, van der Meer J. Effective treatment of severe bleeding due to acquired thrombocytopenia by single dose administration of activated recombinant factor VII. *Thromb Haemost* 1998; **80**: 204–5.
- 9 Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teeraratkul S, Hongeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coag Fibrinol* 2000; **11**: S101–5.
- 10 Aldouri M. The use of recombinant factor VIIa in controlling surgical bleeding in non-haemophiliac patients. *Pathophysiol Haemost Thromb* 2002; **32** (Suppl. 1): 41–6.
- 11 Kalicinski P, Kaminski A, Drewniak T *et al.* Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. *Transpl Proc* 1999; **31**: 378–9.
- 12 Laffan MA, Cummins M. Recombinant factor VIIa for intractable surgical bleeding. *Blood* 2000; **96** (Abs 4048): 85b.
- 13 White B, McHale J, Ravi N *et al.* Successful use of recombinant FVIIa (NOVOSEVEN<sup>®</sup>) in the management of intractable post-surgical intra-abdominal haemorrhage. *Br J Haematol* 1999; **107**: 677–8.
- 14 Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; **354**: 1879.
- 15 Martinowitz U, Kenet G, Segal E *et al.* Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001; **51**: 431–9.
- 16 Chuansumrit A, Nuntnarumit P, Okascharoen C, Teeratkul S, Suwansingh S, Supannachart S. The use of recombinant activated factor VII to control bleeding in a preterm infant undergoing exploratory laparotomy. *Pediatrics* 2002; **107**: 169–71.
- 17 Aledort LM. rFVIIa – its thrombogenicity. *Thromb Haemost* 2000; **84**: 522–3.
- 18 Van der Planken MG, Schroyens W, Vertessen F, Michiels JJ, Berneman ZN. Distal deep venous thrombosis in a hemophilia A patient with inhibito and severe infectious disease, 18 days after recombinant activated factor VII transfusion. *Blood Coagul Fibrinolysis* 2002; **13**: 367–70.
- 19 Roberts HR. Recombinant factor VIIa (Novoseven) and the safety of treatment. *Semin Hematol* 2001; **38** (4 Suppl. 12): 48–50.