

Use of recombinant factor VIIa to treat persistent bleeding following dental extractions in two cirrhotic patients

A.-M. Berthier¹, A. Guillygomarc'h², M. Messner², M. Pommereuil¹, G. Bader³ & G. De Mello³

Departments of ¹Haematology, ²Hepatology and ³Oral Surgery, University Hospital, Rennes, France

Vox Sanguinis

Background and Objectives A single dose of recombinant factor VIIa (rFVIIa) has been shown to be effective and safe in correcting the prothrombin time (PT) in cirrhotic patients, but no clinical data exists demonstrating its efficacy in arresting active bleeding.

Materials and Methods rFVIIa was used in two cirrhotic patients for persistent bleeding following dental extractions despite repeated treatment at the wound site and, in one case, repeated administrations of fresh-frozen plasma (FFP).

Results Bleeding stopped promptly in both patients after administration of rFVIIa. However, bleeding recurred in the patient who had not received concomitant treatment at the extraction sites. No recurrence of bleeding was observed in the second patient, who underwent local treatment 15 min after rFVIIa.

Conclusions Recombinant factor VIIa arrested bleeding after dental extractions in two cirrhotic patients who had been unsuccessfully treated with FFP. However, additional local treatment is needed to limit the risk of recurrence as a result of the short half-life of rFVIIa.

Key words: bleeding, coagulopathy, dental extraction, liver cirrhosis, recombinant factor VIIa.

Received: 20 April 2001,
revised 12 November 2001,
accepted 23 December 2001

Introduction

A single dose of recombinant factor VIIa (rFVIIa) has been shown to be effective and safe in correcting prothrombin time (PT) in patients with coagulopathy related to liver cirrhosis [1]. However, the clinical efficacy of rFVIIa to really stop bleeding has been questioned as liver coagulopathy results in dysfunction in many areas [2], including a reduced production of coagulation factors, low platelet count and, in some instances, hyperfibrinolysis and acquired thrombocytopenia. To date, the haemostatic efficacy of rFVIIa in cirrhotic patients remains to be demonstrated as its only reported use in hepatology has been for decreasing bleeding during liver transplantation in two children with fulminant liver failure [3] and in six adults with end-stage chronic liver disease [4], and for prevention of bleeding complications in

a cirrhotic patient undergoing therapeutic alcohol injections for hepatocellular cancer [5]. Bleeding was reported as minimal [3] or decreased [4] in liver transplantations and no bleeding complication was observed after the alcohol injections. Fresh-frozen plasma (FFP) and/or platelet concentrates are used to prevent or treat bleeding in cases of severe liver coagulopathy, but treatment may not be optimal and some safety concerns persist (i.e. the risk of transmission of human viruses and of plasma volume overload). Recombinant FVIIa (NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) is produced using biotechnology without any human derivatives, thereby eliminating the risk of contamination with human viruses. After obtaining informed consent, rFVIIa was used to treat bleeding after dental extractions in two patients with coagulopathy arising from end-stage liver cirrhosis.

Patients and methods

Haemostasis parameters were performed using local standard methods. The PT was determined using STA Neoplastine® CI (Diagnostica Stago, Asnières, France) and the Activated

Correspondence: Anne-Marie Berthier, Haematology Laboratory, University Hospital Pontchaillou, Rue Henri Le Guilloux, F-35033 Rennes, France
E-mail: Anne-Marie.Berthier@chu-rennes.fr

Partial Thromboplastin Time (APTT) determined using STA®-PTTA (Diagnostica Stago). The normal PT value is 12.3 seconds (range: 11.5–14.4 seconds). The normal APTT value is 36 seconds (range: 27–44 seconds). The normal factor V level is > 80%, and for factors VII + X the level is > 70%. The normal platelet range is 150–400 × 10⁹/l.

Case reports

Case 1

A 60-year-old male with abnormal haemostatic parameters (PT = 29.4/12.3 seconds; APTT = 66/36 seconds; factor V = 19%; factors VII + X = 52%; platelet count = 63 × 10⁹/l) underwent extraction of four teeth (nos 14, 17, 44, 48) after administration of FFP (6 ml/kg). Local haemostasis measures included use of intra-alveolar gauze (oxidized cellulose), fibrin glue and sutures. There was no abnormal bleeding during the procedure, but bleeding was observed 18 h later at three of the four extraction sites. Bleeding continued despite repeated local treatment, including gauze, fibrin glue, new sutures and use of FFP on two occasions (3 ml/kg, then 6 ml/kg). Compression was performed without success using gauze soaked in tranexamic. The general use of antifibrinolytic drugs was not considered because this is thought to convey a potential risk of intravascular coagulation in cirrhotic patients. The haemoglobin level dropped from 111 to 66 g/l in 28 h, requiring transfusion of 5 units of red blood cells (RBC). A single dose of rFVIIa (68 µg/kg) was administered without further local treatment. Bleeding stopped within 10–15 min but recurred at the same three extraction sites 6 h later. The PT (15.2/12.3 seconds at 30 min; 15.4 seconds at 90 min; and 17.8 seconds at 210 min) and APTT (50/36 seconds at 30 min and 52 seconds at 90 min) were partially corrected following treatment with rFVIIa. A second dose of rFVIIa (68 µg/kg) produced a similar result, i.e. rapid cessation of bleeding but recurrence 8 h later. FFP was administered twice at 9 ml/kg without success and two more units of RBC were transfused. Signs of encephalopathy developed that were probably related to the amount of blood swallowed. Recombinant FVIIa (68 µg/kg) was again administered and bleeding ceased promptly after this injection. No local procedure was performed, but rFVIIa was continued for five additional doses at 3–4-h intervals at 34 µg/kg, then 17 µg/kg, without any bleeding. Fibrin-soluble monomer complexes and/or an increase in fibrin degradation products were detected transiently in some instances after administration of rFVIIa, but without any decrease in factor V (19–33%), fibrinogen (1.1–1.8 g/l) or platelets (43–86 × 10⁹/l). However, bleeding recurred 9 h after the last injection of rFVIIa (PT = 23.6/12.3 seconds; APTT = 60/36 seconds; fibrinogen = 1.45 g/l; platelets = 72 × 10⁹/l). A further local procedure was performed 2 days later, including

extensive cleaning, intra-alveolar oxidized cellulose, fibrin glue and new sutures on prolonged general sedation (6 h) to avoid any contact of the tongue on the operated sites; the bleeding stopped without any further recurrence. This patient, with end-stage cirrhosis, died more than 2 weeks later from liver insufficiency.

Case 2

A 40-year-old female with abnormal haemostatic parameters (PT = 19.8/12.3 seconds; APTT = 48/36 seconds; factor V = 25%; factors VII + X = 40%; platelet count = 72 × 10⁹/l) underwent extraction of three teeth (nos 26, 37, 45) after administration of FFP at 5 ml/kg. Local haemostasis included intra-alveolar gauze and sutures. No abnormal bleeding occurred during the procedure, but bleeding was observed 90 min later at the three extraction sites. Two additional local procedures with cyanoacrylate glue temporarily arrested the bleeding; but bleeding recurred 12 h after each procedure. Haemoglobin levels dropped from 117 to 97 g/l over 48 h. Taking into account the previous experience where rFVIIa had been used after administration of FFP and RBC transfusions with no additional local procedure, it was decided to use rFVIIa 15 min before further local treatment. Bleeding stopped promptly after a single dose of rFVIIa (91 µg/kg) allowing the local procedure to be carried out more easily, although suturing was difficult owing to gingival inflammation. There was no recurrence of bleeding and the patient was discharged from hospital 5 days later. No RBC transfusion was required.

Discussion

In a previous study [1], it was demonstrated that a single dose of rFVIIa was efficacious and safe in correcting PT and partially correcting aPTT. Previous use of rFVIIa in nine patients with liver coagulopathy showed its efficacy to prevent bleeding after an invasive procedure [5] and to decrease bleeding and transfusion requirements during liver transplantation in eight patients [3,4].

In this report, rFVIIa was shown to stop excessive bleeding at the site of dental extractions in two patients with severe coagulopathy related to cirrhosis. However, in one patient, the cessation of bleeding was transient (6–9 h), demonstrating that, although rFVIIa stopped bleeding, its short half-life, of 2–3 h [1], meant that local haemostasis could not be maintained in the absence of local or general measures. A similar situation has recently been reported for a major peptic ulcer bleed in a patient without pre-existing coagulopathy [6]. Taking into account our preliminary experiences, rFVIIa stopped bleeding in patients with severe liver coagulopathy, at least temporarily, thereby reducing blood loss and facilitating easier local treatment by providing a drier surgical

field. Double-blind randomized clinical studies are needed to better define the efficacy : safety ratio and optimal treatment regimen of rFVIIa to treat bleeds or prevent bleeding during invasive procedures in cirrhotic patients with coagulopathy.

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