

Correspondence

SUCCESSFUL USE OF RECOMBINANT FVIIa (NOVOSEVEN®) IN THE MANAGEMENT OF INTRACTABLE POST-SURGICAL INTRA-ABDOMINAL HAEMORRHAGE

Massive gastrointestinal haemorrhage is a rare but well-recognized complication of Crohn's disease and bowel lymphoma (Gheorghe *et al*, 1997; Cirocco *et al*, 1995). The treatment of choice involves localization of the site of bleeding with endoscopy or angiography followed by surgical resection (Roberts *et al*, 1991). Clinical management may be complicated by failure to identify the site of bleeding, multiple bleeding points and persistent haemorrhage despite surgical resection which is associated with significant mortality (Cirocco *et al*, 1995; Roberts *et al*, 1991). We report the successful use of recombinant factor VIIa (rh-FVIIa, Novoseven®) in two patients with intractable intra-abdominal bleeding associated with bowel resection for Crohn's disease and large bowel lymphoma.

Case 1. A 22-year-old female with a prior history of terminal ileal Crohn's disease presented with a massive lower gastrointestinal haemorrhage requiring emergency right hemicolectomy with terminal ileal resection. She had no personal or family history suggestive of a bleeding disorder. The patient had a normal pre-operative platelet count ($350 \times 10^9/l$) and coagulation screen (prothrombin time (PT) 14 s (normal range 12–16), activated prothrombin time (APTT) 25 s (normal range 24–36)). Her post-operative course was complicated by persistent intra-abdominal haemorrhage from the posterior abdominal wall requiring transfusion with red cell concentrate (32 units), fresh frozen plasma (38 units), cryoprecipitate (6 units) and platelets (22 units). Despite a platelet count of $100 \times 10^9/l$, PT of 16 s, APTT of 28.9 s and a normal von Willebrand screen she continued to bleed heavily and failed to respond to either tranexamic acid (1 g intravenously 6-hourly) or desmopressin (0.4 µg/kg intravenously). The following day the patient received two doses of Novoseven at 90 µg/kg with immediate resolution of bleeding. The administration of Novoseven resulted in a reduction in the prothrombin time 30 min post infusion from 16 s to a mean (\pm SD) of 7.5 ± 0.5 . The patient made a full and uneventful recovery and no further blood product support was required.

Case 2. A 62-year-old male was initially diagnosed with Crohn's colitis by colonoscopy and biopsy and was successfully treated with prednisolone (1 mg/kg). He had no personal or family history suggestive of a bleeding disorder and had a normal PT and APTT at the time of endoscopy. Two months later he was readmitted with a massive lower gastrointestinal haemorrhage and an abnormal coagulation profile (PT 21 s (reference range 12–16), APTT 30.6 s (reference range 23–35)), platelet count of $45 \times 10^9/l$, D-dimers <500 ng/ml and fibrinogen of 1.6 g/l. After correction of his coagulation parameters he underwent

emergency colectomy. His postoperative course was complicated by continued heavy bleeding from intra-abdominal drains and per rectum. A further laparotomy demonstrated multiple bleeding sites in the posterior abdominal wall. Over the following 24 h the patient continued to bleed and developed multiorgan failure requiring ventilation and inotropic support. He received 60 units of red cell concentrate, 60 units of fresh frozen plasma (FFP), 100 units of platelets and 60 units of cryoprecipitate. Despite a platelet count of $100 \times 10^9/l$, PT of 18 s and APTT of 36 s he continued to bleed heavily. He received two doses of Novoseven 90 µg/kg 2 h apart which resulted in immediate resolution of bleeding. The cessation of bleeding was clearly demonstrated at repeat laparotomy, which was undertaken immediately after the second dose of Novoseven. The administration of Novoseven resulted in a reduction in prothrombin time 30 min post infusion from 18 s to a mean (\pm SD) of 11.3 ± 0.7 s. No further red cell transfusion support was required. Three days later the patient died from multiorgan failure affecting the lungs, liver, kidneys and cardiovascular system. At time of death his haemoglobin was normal and there was no evidence of active bleeding. Histological assessment of the resected bowel demonstrated multi-focal high-grade T-cell lymphoma that macroscopically mimicked Crohn's disease with patchy ulceration and apparent pseudopolyps. Biopsies adjacent to areas of lymphoma revealed a reactive cellular infiltrate that in the absence of lymphoma was mistaken for Crohn's disease in the initial biopsy samples. Post-mortem examination revealed that there had been no further bleeding and in addition demonstrated lymphomatous involvement of the lungs and liver. There was no evidence of venous or arterial thromboses.

Novoseven was selected to achieve haemostasis because it provides site-specific thrombin generation by enhancing tissue factor (TF):FVIIa assembly at the site of vessel injury. Endothelial damage at the site of bleeding is associated with an increased tissue factor expression which in turn binds to circulating FVII resulting in its activation and the formation of the TF:FVIIa complex. The tissue factor:FVIIa complex has now been recognized as the pivotal activator of the of the coagulation cascade and results in localized thrombin generation (Hedner, 1998). Thus, it is likely that infused Novoseven will act in a similar way to the natural protein and bind to TF expressed at sites of vascular injury resulting in site-specific haemostasis. Although recombinant FVIIa was initially developed for the treatment of bleeding associated with inhibitors to factor VIII and IX (Hedner *et al*, 1988), more recently it has been used effectively in the management of inherited and acquired deficiencies of factor

VII and platelet function defects (Hedner, 1998; White *et al*, 1999). As far as we can ascertain, this is the first report of the use of Novoseven in the management of intractable intra-abdominal haemorrhage. In both patients bleeding ceased within a very short time following infusion of Novoseven and in the patient who died there was no evidence of disseminated thromboses on post-mortem examination, emphasizing the site-directed nature of FVIIa.

In conclusion, we believe that Novoseven has the potential to act as a universal haemostatic agent and therefore it should be further evaluated in situations where there is intractable intra-abdominal haemorrhage which has failed to respond to conventional therapy.

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