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SHORT REPORT

Recombinant Factor VIIa in the Treatment of Intractable Bleeding in Vascular Surgery

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Intractable bleeding unresponsive to conventional haemostatic measures is an uncommon but potentially life threatening surgical complication. Several studies have suggested that recombinant factor VIIa (rVIIa), a genetically engineered substitute for endogenous factor VIIa may have therapeutic application in patients with uncontrollable haemorrhage not previously diagnosed with coagulopathy. We report our experience of rVIIa use in eight such vascular surgery patients who developed life-threatening non-surgical haemorrhage either intra-operative or post-operatively. In all but one patient a marked clinical improvement was noted following treatment with rVIIa with significantly less transfusion, and obvious haemostasis associated with haemodynamic stability without adverse thrombotic complications.

Keywords: Recomdinant factor VIIa; Haemorrhage; Haemostasis.

Introduction

A recombinant form of activated factor VII (rVIIa) has become standard treatment of bleeding in patients with factor VIII of factor XI deficiency (haemophiliacs) or inhibitors to these factors.[1] There is a growing body of evidence which shows rVIIa to be of benefit and potentially life-saving in patients with bleeding not related to previous coagulation abnormalities.[2] This intractable 'non-surgical' bleeding cannot usually be attributable to a single or a small number of bleeding vessels. We report our experience of the use of rVIIa in vascular surgery patients who develop intra-operative or post-operative life threatening haemorrhage unresponsive to conventional haemostatic measures.

Report

Between July 2003 and June 2004 vascular surgery patients who developed major haemorrhagic complications were considered for treatment with rVIIa. This off label use was agreed on a individual basis on compassionate grounds similar to its use in previous studies.[2,3] Informed consent was obtained from all patients presenting for major vascular procedures for the possible use of rVIIa. The decision to administer rVIIa at the time of surgery was made in cases where hypotension and anaemia were associated with generalised ooze in the operative field, in the absence of a major arterial bleed. A dose of 40 μg/kg was administered as a bolus injection over 2 min, repeated once depending on the clinical response. Full blood count and coagulation profile were measured prior to and after rVIIa administration. Blood product administration, haemodynamic profile, peri-operative course and outcome were all recorded retrospectively (Table 1).

Of 310 patients who underwent major vascular reconstruction in the study period, eight developed life threatening haemorrhage unresponsive to conventional haemostatic measures either intra-operatively (six patients) or post-operatively (two patients), and met with our criteria for treatment with rVIIa. Clinical improvement was reported following treatment in seven of eight patients in the study. Bleeding was

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Table 1. Patients details

Patient	Age	Sex	Surgery	Emergency	rVIIa dose/kg (μg)	Improvement
1	80	F	Juxtarenal AAA repair	Yes	40	Yes
2	77	M	Suprarenal AAA repair	Yes	80	Yes
3	79	F	Juxtarenal AAA repair	No	80	Yes
4	77	F	Suprarenal AAA repair	No	80	No
5	56	M	Excision of infected aortic graft	No	80	Yes
6	75	M	Juxtarenal AAA repair retroperitoneal bleed*	No	40	Yes
7	82	M	EVAR internal iliac aneurysm ligation. Retroperitoneal bleed†	No	40	Yes
8	66	F	Pelvic fracture with major vascular trauma‡	Yes	40	Yes

AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.
* Developed a retroperitoneal haematoma 12 day post-operatively.
† Developed a retroperitoneal haematoma several hours post-operatively which was explored with insertion of a suction drain in the area of non-surgical haemorrhage.
‡ Unstable pelvic fracture treated with external fixation. External iliac artery and common illiac vein and superficial femoral vein trauma treated with covered stent insertion and groin exploration.

successfully controlled as evidenced by improved haemodynamic parameters and decreased inotrope and transfusion requirement (Table 2). There was one intra-operative death (patient 4), where rVIIa did not have any visible effect on non-surgical haemorrhage. A further patient (patient 3) remained inotrope-dependent post-operatively despite haemodynamic stability, and died on the first post-operative day. Post-mortem examination did not report any evidence of acute thrombotic events in either case.

Discussion

The absence of a prospective randomised trial of the use of rVIIa in patients with life threatening haemorrhage is perhaps not surprising given the difficulty in identifying objective outcome parameters which would be independent of the many other variables in the treatment of bleeding and the ethical considerations implicit in withholding a potentially life-saving treatment with a low adverse side effect profile. The successful arrest of haemorrhage in seven of the eight patients treated with rVIIa cannot be attributed solely to this product with certainty as its administration coincided with blood product transfusion, as well as surgical cauterisation and aggressive measures to correct hypothermia and metabolic acidosis. However, in patients 1, 2, 3 and 5 an obvious reduction in the generalized ooze in the operative field was noted within minutes of rVIIa administration. Patient 6 developed a retroperitoneal haematoma following dialysis treatment 12 days post-operatively with associated haemodynamic instability. Systolic blood pressure increased from 85 to 130 mmHg within minutes of rVIIa administration, without the need for continued blood transfusion. Patient 7 underwent endovascular stenting of an infra-renal aortic aneurysm with open ligation of an aneurysmal internal iliac artery. A post-operative retroperitoneal haematoma was evacuated and a suction drain inserted which yielded 780 ml of blood over the subsequent 10 h. rVIIa was administered to good effect with drainage decreasing to 208 ml over a subsequent 10 h period.

The low risk of thrombotic complications of rVIIa is borne out by experience in haemophiliacs and the limited reports from non-coagulopathic patients where the risk is estimated at less than 1%. We found

Table 2. Blood production transfusion and coagulation parameters

	Pre-rVIIa	Post-rVIIa	*P*-value
PRBCs	8.13±2.0*	3.2±1.1*	0.05
FFP	4 (0–15)†	0 (0–2)†	0.003
INR	1.2 (1–1.5)†	1.2 (0.8–3.1)†	0.33
APTT	38.3 (30–205)†	38.7 (29–190)†	0.65

PRBCs, packed red blood cells; FFP, fresh frozen plasma; INR, international normalizing ratio; APTT, activated partial thromboplastin time.
* Values are mean±s.e.m., (Student *t*-test).
† Values are median (range), (Mann–Whitney test).

a dose or 40–80 μg to be effective for most patients, lower than the dose recommended for those with haemophilia-associated inhibitors.[4] Dosage was based on clinical response, rather than on measured coagulation parameters, which we did not differ significantly before and after rVIIa administration.

Only three patients received more than 8 units of RCC in total. Similar to the experience of others[5] we observed that rVIIa is more likely to be therapeutic if given as soon as an uncontrollable non-surgical bleeding is encountered and least effective in patients who had already received massive transfusion volumes prior to its administration.

Although the high cost of the treatment, as well as the small but real association with thrombotic complications, necessitates a highly selective use of rVIIa, our experience of its use in vascular surgery patients with life threatening non-surgical haemorrhage is that it can produce a marked improvement in haemostasis, with obvious clinical improvement, haemodynamic stability, and reduced blood product requirement.

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