

CASE REPORT

The use of recombinant activated Factor VII in the control of haemorrhage following blunt pelvic trauma

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Summary

This article reports two cases of severe blunt pelvic trauma associated with road traffic accidents, where the patients developed significant bleeding and haemodynamic instability, poorly responsive to conventional management. Both patients required massive transfusion of blood products with a resultant dilutional coagulopathy. In each case, a single dose of recombinant activated factor VII (rFVIIa) was used to achieve haemostatic control, with a subsequent decrease in blood product requirements and improvement in haemoglobin concentration and clotting profile.

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Accepted: 13 January 2005

Case reports

Case 1

A 17-year-old male was involved in a high speed road traffic accident where he was the passenger in a car that lost control and collided with a wall. Ambulance services found him conscious although confused and he was taken to our accident and emergency department at 0430 h.

Primary survey revealed a clear airway with a central trachea, a respiratory rate of 20, and a pulse oximetry reading of 95% on high flow oxygen. Cervical spine immobilisation was *in situ*, and he had evidence of facial injuries. His heart rate was 120 beats per minute, arterial blood pressure (BP) 120/80 mmHg, and he was peripherally vasoconstricted. His Glasgow Coma Scale (GCS) was 10/15 (E4, V2, M4) and he had symmetrical reactive pupils. His abdomen was soft, and there was no evidence of pelvic instability, although he did have a significant scrotal haematoma. He had an obvious compound fracture of the shaft of his right femur.

Blood was taken for urgent cross match and 2 litres of crystalloid was administered rapidly. A urinary catheter was inserted that drained blood-stained urine. A trauma series of X-rays did not demonstrate any abnormality of the cervical spine or thorax; however, the antero-posterior (AP) film of his pelvis showed an open book

type pelvic fracture with widening of the pubic symphysis and the sacroiliac joints.

Within 20 min of arrival he became haemodynamically unstable with marked hypotension (BP 50/30) and a fall in haemoglobin (Hb) concentration from 11 g.dl⁻¹ to 5 g.dl⁻¹ (arterial blood gas samples). Four units of packed red blood cells were administered, which produced a transient improvement. His trachea was intubated with in-line immobilisation and a rapid sequence induction was performed. An arterial line was sited and a right subclavian central venous line was inserted. Fluid resuscitation continued with ongoing blood products. Given his cardiovascular instability, a Hoffman pelvic external fixator was applied in the accident and emergency department and his pelvic fracture was reduced.

Computerised tomography (CT) imaging of his brain demonstrated evidence of possible diffuse axonal injury, whilst his cervical spine was normal. Imaging of his abdomen revealed a large amount of free fluid with an extensive retroperitoneal haematoma. He continued to be haemodynamically unstable and therefore proceeded to an emergency laparotomy at 0730 h. At this point he had already received 20 units of packed red blood cells, 4 units of fresh frozen plasma and 2 units of platelets.

Laparotomy revealed a large pelvic haematoma which was evacuated and the pelvis tightly packed, with no

Table 1 Coagulation profile and haemoglobin concentration in Case 1.

Time	Hb; g. dl ⁻¹	Platelet count; × 10 ⁹	APTT; s	PT; s	INR	Fibrinogen; g.l ⁻¹
Intra-operatively						
0751 hours	9.7					
0942 hours	9.0					
1147 hours	6.3	103	57	20	1.5	1.8
14.00 hours rFVIIa given						
1441 hours	13.7					
1626 hours	11.4	145	40	9	0.7	2.8
Post-operatively						
1943 hours	10.4					
2047 hours	11.0	176	36	12	0.9	3.1
2259 hours	11.0					
0146 hours	10.1					
0910 hours	10.0	184	38	16	1.2	4.7

evidence of any other significant intra-abdominal injury. Post laparotomy, his facial injuries were treated by the ear, nose and throat (ENT) surgeons, and the compound fracture of his right femur was internally fixed using an intramedullary nail.

Throughout the surgery he continued to require the administration of blood products to maintain an adequate arterial blood pressure and subsequently an aprotinin infusion was started. His clotting profile in theatre is shown in Table 1.

He continued to bleed despite attempts at correcting his coagulation, and his total blood product requirement throughout the day reached 46 units of packed red blood cells, 12 units of FFP, 6 units of platelets, and 20 units of cryoprecipitate. Given the ongoing dependence on blood products, despite a relatively normal coagulation profile, 4.8 mg of activated Factor VIIa (Novoseven, Novo Nordisk, Hillerød, Denmark) was administered intra-operatively at 1400 h. Following this, he became more cardiovascularly stable, and his blood product requirement decreased dramatically. His total time in the operating theatre approached 10 h and he was admitted to the Intensive Therapy Unit (ITU) at 1730 h later that day.

Following theatre, no further blood products were required in the subsequent 36 h on ITU and his clotting profile and Hb concentration remained stable (Table 1). Despite postoperative complications including renal impairment and acute respiratory distress syndrome, this patient went on to be discharged from the ITU after 3 weeks of treatment and has made a complete recovery.

Case 2

The following week, a 43-year-old male motorcyclist was brought by ambulance to the Accident and Emergency department after being involved in a collision with a car, at a speed of approximately 30 mph.

Primary Survey revealed a clear airway with the trachea in the midline, a respiratory rate of 26 with pulse oximetry reading of 96% on air, a tender left clavicle and right chest wall. His heart rate was 110 beats per minute, arterial blood pressure (BP) 69–104/38–64 mmHg and he was peripherally vasoconstricted. His abdomen was tense and his pelvis was tender on palpation. His Glasgow Coma Score was 15. The chest radiograph revealed left clavicular fracture and multiple right sided rib fractures with a small apical pneumothorax. The pelvic radiograph suggested a left 'vertical shear' fracture of the pelvis with vertically displaced left sacro-iliac joints and fractures of the upper and lower pubic rami. He remained tachycardic, his haemoglobin (Hb) was 8.5 g.dl⁻¹ and he was resuscitated with 2500 ml colloid, 1000 ml crystalloid and one unit of packed red cells. A urethral catheter was passed which showed frank haematuria.

A CT scan demonstrated a right-sided haemopneumothorax and ipsilateral multiple fractured ribs, a fractured left clavicle and confirmed the nature of the pelvic injury. There was no clear evidence of any intra-abdominal abnormality. He continued to be tachycardic and his arterial BP remained around 90/50 mmHg. A further two units of packed red cells and 1000 ml of colloid were given during the CT scan. He was transferred directly to the Intensive Therapy Unit (ITU) where further resuscitation continued. Application of skeletal traction for the pelvic fracture was planned to take place once he was haemodynamically stable.

On the ITU his heart rate increased to 140 beats per minute and he remained hypotensive; however, his urine output was > 100 ml.h⁻¹ and his GCS remained 15. Fluid resuscitation continued, guided by arterial blood gas, Hb and coagulation analysis (Table 2).

Table 2 Coagulation profile and haemoglobin concentration in Case 2.

Time	Hb; g. dl ⁻¹	Platelet count; × 10 ⁹	APTT; s	PT; s	INR	Fibrinogen; g.l ⁻¹
Preoperatively						
1308 hours	8.5					
1730 hours	5.2	106				
1840 hours	9.2	77	Off scale	33	2.7	0.4
Postoperatively						
2130 hours	8.7					
2340 hours	10.5	32	46	22	1.7	1.8
0040 hours	8.7					
0125 hours	8.0					
02.00 hours rFVIIa given						
03.00 hours	9.1					
04.00 hours	10.1					
05.00 hours	9.3		36	11	0.7	2.7
06.00 hours	8.1	78	31	11	0.8	2.8

He received a further 7 units of packed red cells, 1 000 ml of crystalloid and 1500 ml of colloid. His deranged clotting was treated with 4 units of fresh frozen plasma and 10 units of cryoprecipitate. Despite these measures he remained unstable and his urine output fell to 15 ml.h^{-1} . In order to reduce his bleeding he was taken to theatre to reduce his pelvic fracture.

A thoracostomy tube was sited in the right pleural space and he was anaesthetised uneventfully using a rapid sequence induction. The thoracostomy drained approximately 2000 ml of serosanguinous fluid. A left tibial Steinman traction pin was inserted. Further resuscitation continued with infusion of a further 6 units of blood, 500 ml of colloid and 1000 ml of crystalloid.

Within an hour the patient was returned to ITU, and received intermittent positive pressure ventilation. He remained cardiovascularly unstable and repeat coagulation studies revealed further abnormalities (Table 2). There was continuing blood loss as shown by an increasing abdominal girth and decreasing Hb. Over the 14 h since admission, he had already received 18 units of packed red cells, 8 units of fresh frozen plasma, 10 units of cryoprecipitate, 2 pools of platelets, 6000 ml of colloid and 2000 ml of crystalloid. Based on our previous experience with Case 1, we decided to administer a single dose of 4.8 mg ($68 \mu\text{g.kg}^{-1}$) recombinant Factor VIIa (rFVIIa). Haemodynamic stability was achieved within an hour and his urine output improved to more than 50 ml.h^{-1} . His Hb increased over the subsequent 2 h with no blood given during that time and there was an improvement in his clotting profile (Table 2).

He remained stable after this and needed a further 2 units of packed red cells over the next 36 h. He was extubated successfully within this time and was discharged to the ward (day 6). He was transferred to a specialist orthopaedic unit for definitive management of his pelvic fracture.

Discussion

These two cases represent a scenario where despite maximal conventional management we were unable to achieve adequate control of ongoing blood loss. We administered a dose of recombinant activated factor VIIa and, in each case, we saw a fairly dramatic response in terms of haemorrhage control, blood product requirement and clotting profile.

Naturally occurring activated factor VII combines with tissue factor (TF) at the site of vascular injury to initiate the coagulation cascade leading to production of a fibrin clot. This involves the activation of factors IX and X, with subsequent conversion of prothrombin to thrombin [1]. Administration of recombinant factor VIIa (rFVIIa)

has been shown to increase significantly the rate and amount of thrombin generated, resulting in the formation of a rigid, secure fibrin clot that is resistant to fibrinolytic degradation [2]. In addition, rFVIIa adhering to the surface of activated platelets can activate factor X independently of being bound to TF [3]. This novel haemostatic agent has been traditionally used to treat haemophilia patients with or without inhibitors undergoing major surgery [4], but is now increasingly being employed in a variety of peri-operative settings for the treatment of massive uncontrolled haemorrhage [5].

A number of reports have been published regarding the role rFVIIa in obstetric haemorrhagic emergencies [6–8], and in each the authors have documented a clear reduction in the amount of bleeding post administration. A single dose of rFVIIa has also been successfully employed in the treatment of significant non-surgical bleeding in a patient undergoing suprarenal abdominal aortic aneurysm repair [9]. A further series reports its successful use in four patients with intractable bleeding during spinal surgery, with a direct improvement in clotting profile and cessation of bleeding [10]. In eight cases of active haemorrhage from oesophageal varices, rFVIIa was used to achieve haemostasis where standard measures (pharmacotherapy and endoscopic techniques) were unsuccessful [11].

Friederich *et al.* published a randomised double-blind placebo controlled trial of the use of prophylactic rFVIIa in reducing peri-operative blood loss in elective retropubic prostatectomy [12]. They were able to demonstrate a statistically significant reduction in peri-operative blood loss and transfusion requirements in the treatment arm. Recombinant factor VIIa has also been successfully used in life-threatening bleeding in pelvic surgery [13].

With respect to trauma, Martinowitz *et al.* [14] have published a series of seven patients with severe blunt and penetrating trauma, all of whom had significant haemorrhage and massive transfusion requirements and were treated with rFVIIa after failure of conventional measures to achieve haemostasis. Administration of rFVIIa in this setting resulted in a decrease in the amount of bleeding and blood product requirements, and an improvement in clotting profile. Similarly, Boffard *et al.* [15] have recently reported the results of a multicentre, double-blind, randomised prospective placebo controlled trial into the use of rFVIIa in patients with blunt or penetrating trauma and significant blood loss. Their findings suggested a statistically significant reduction in the number of red cell transfusions in the treatment group with blunt trauma, as well as a non-statistically significant trend towards reduced multiorgan failure and acute respiratory distress syndrome.

The incidence of adverse effects associated with the use of rFVIIa has been reported as being < 1%, and this underlies its accepted safety in a variety of clinical settings [16]. This is predictable given the localised effects of rFVIIa in binding to TF and activated platelets at the site of endothelial injury, therefore avoiding universal activation of the coagulation cascade. While the risks of using rFVIIa in practice seem rare, there does remain a theoretical risk of inducing thrombosis, and its use should be carefully reviewed in elderly patients or those with pre-existing cardiovascular disease [17]. However, rFVIIa has recently been used successfully in a patient with severe coronary artery disease and intra-abdominal bleeding post kidney transplantation [18].

In conclusion, these pelvic trauma cases have further emphasised the potential role for recombinant activated factor VII as a novel haemostatic agent in the control of life threatening bleeding where conventional measures have failed. There is a growing body of anecdotal and scientific evidence that suggests it is both effective and safe in controlling non-surgical haemorrhage, improving clotting profile and reducing the need for further blood products. Further definitive work is required on the safety profile and dose regimen for this drug.

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