

CASE SERIES & REVIEW

Use of recombinant activated factor VII in massive obstetric haemorrhage

J. Haynes, M. Laffan, F. Plaat

Obstetric Anaesthesia Department, Queen Charlotte's and Chelsea Hospital, and Department of Haematology, Hammersmith Hospital, London, UK

SUMMARY. Massive obstetric haemorrhage is a life-threatening emergency that remains a major cause of maternal mortality. Conventional management is aimed at optimising uterine tone, replacing circulating volume and blood products, and surgery to achieve haemostasis. Recently there have been numerous reports of the (unlicensed) use of recombinant activated factor VII in the management of major obstetric haemorrhage. We report our experience of using it in the treatment of major post-partum haemorrhage in four previously healthy parturients. The published reports of recombinant activated factor VII use in post-partum haemorrhage (unrelated to pre-existing coagulopathies) are compared.

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INTRODUCTION

Major haemorrhage is an obstetric emergency that occurs in every maternity unit. Most establishments have protocols for managing these emergencies, and a number conduct “drills” to rehearse and improve the management of obstetric haemorrhage. Despite these measures, haemorrhage continues to be a major cause of maternal mortality.¹ Many women who survive massive bleeding do so with significant morbidity associated with transfusion of large volumes of blood products and major surgery, including hysterectomy.

Traditional management of post-partum haemorrhage is directed at improving uterine tone, replacement of lost intravascular volume, blood and coagulation factors, and surgery. The latter includes repair of the genital tract, removal of retained products of conception and strategies to stop bleeding from the placental bed by physical

means. Arterial embolisation may be an option, but in some cases, hysterectomy is necessary to control bleeding.

Recombinant activated factor VII (rFVIIa) has begun to find a role in the management of massive haemorrhage due to trauma and major surgery. There is now increasing experience of its use in life-threatening post-partum bleeding. Recombinant activated factor VII is used in obstetrics in addition to conventional management, but according to the collected literature, the timing of the administration of rFVIIa is anywhere from early in the treatment to a last resort. The following four cases document our experience in the use of rFVIIa in major post-partum haemorrhage.

CASE 1

A 29-year-old primigravida with a posterior major placenta praevia in a fibroid uterus was admitted to our unit with bleeding per vagina at 32 weeks' gestation. She had previously undergone two myomectomies. The initial antepartum haemorrhage settled with conservative management. Spotting of blood per vagina occurred daily, and elective caesarean section was planned at 35 weeks' gestation. However, an episode of brisk haemorrhage followed by a continuous trickle of blood led to the decision to deliver her at 34 weeks' gestation by caesarean section.

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J. Haynes, Department of Anaesthesia, Barnet General Hospital,
M. Laffan, Department of Haematology, Hammersmith Hospital,
F. Plaat, Department of Anaesthesia, Queen Charlotte's and Chelsea Hospital, London, UK.

Correspondence to: Dr. F. Plaat, Department of Anaesthesia, Queen Charlotte's and Chelsea Hospital, London, W12 0HS, UK. Tel.: +0208 383 3991.

E-mail: FPlaat@hhnt.org

Significant blood loss at surgery was anticipated and multiple large-bore intravenous cannulae were sited, with four units of cross-matched blood available in theatre. The patient wished to be awake for her surgery. After discussion between the consultant anaesthetist and consultant obstetrician, a combined spinal-epidural technique was employed, the patient having been advised that conversion to general anaesthesia might become necessary. The baby was delivered in good condition, but this necessitated incising through a thickened, fibroid lower uterine segment. Immediate torrential haemorrhage followed delivery. Intravenous ergometrine 250 µg and intra-myometrial carboprost, total dose 2 mg, failed to improve the bleeding. General anaesthesia was induced, with a view to proceeding to hysterectomy. Initially haemodynamic stability was maintained with intravenous fluids and blood products. Following hysterectomy, the patient became haemodynamically compromised and developed clinical signs of a coagulopathy, with generalised oozing from the pelvis. She required intravenous epinephrine and calcium to restore cardiac output. In total, 35 units of packed red blood cells, 12 units of fresh frozen plasma, 10 units of cryoprecipitate and 5 pools of platelets (approximately 250×10^9 platelets per pool; each pool from multiple donors), were

transfused. Despite these measures, the coagulopathy persisted. A single 4.8-mg i.v. bolus of rFVIIa (70 µg/kg) was given and was followed by clinical improvement with correction of the coagulation parameters as detailed in Table 1. Within 15 min of administration of rFVIIa, haemostasis was achieved and surgical closure was performed.

Postoperatively, the patient was nursed on the intensive therapy unit. On admission to the unit her coagulation profile was within normal limits. She required no further blood products. Her trachea was extubated the following day, and she was transferred to the delivery suite high dependency unit 24 h after surgery.

CASE 2

A 27-year-old multiparous woman underwent a normal vaginal delivery on our unit. Her previous obstetric history was of a caesarean section for preeclampsia, two normal vaginal deliveries, and evacuation of retained products of conception following a miscarriage.

Immediately after delivery, there was brisk bleeding per vagina, which continued despite intramuscular administration of 10 units of oxytocin, given by the

Table 1. Perioperative blood results for cases 1-4

| | Time and event | Haemoglobin (g/dL) | Platelets ($\times 10^9/L$) | Prothrombin time (s) | APPT (s) | Thrombin time (s) | Fibrinogen (g/dL) |
|--------------|---------------------------|--------------------|-------------------------------|----------------------|-----------------|-------------------|-------------------|
| Normal range | | 13.0-18.0 | 150-450 | 9.6-11.6 | 24-32 | 10-15 | 2.2-4.3 |
| Case 1 | 13.27 caesarean section | | | | | | |
| | 16.25 | 4.0 | 38 | 21.3 | 62 | 13 | 0.61 |
| | 16.45 rFVIIa administered | | | | | | |
| | 17.00 | 6.8 | 89 | 16.7 | 72 | 14 | 0.68 |
| | 18.45 | 10.7 | 100 | 8.8 | 30 | 12 | 1.66 |
| Case 2 | 23.20 | 11.0 | 112 | 10.3 | 35 | 12 | 1.56 |
| | 18.20 vaginal delivery | | | | | | |
| | 21.40 | 10.6 | 314 | 11.5 | 33 | 12 | 3.07 |
| | 22.00 | 7.2 | 74 | 15.1 | 65 | 11 | 1.00 |
| | 23.30 | 8.2 | 28 | 16.2 | 72 | 13 | 1.11 |
| Case 3 | 23.40 rFVIIa administered | | | | | | |
| | 00.25 | 8.9 | 48 | 11.2 | 62 | 13 | 1.08 |
| | 05.00 | 9.9 | 110 | 8.7 | 39 | 13 | 2.31 |
| | 04.37 vaginal delivery | | | | | | |
| | 05.27 | 11.3 | 122 | >360 | >360 | >360 | Not available |
| Case 4 | 06.10 | 10.8 | 40 | 33.6 | >360 | 36 | Not available |
| | 08.46 | 9.6 | 8 | 12.8 | 40 | 14 | 1.53 |
| | 10.06 | 6.4 | 11 | 30.5 | >360 | 17 | 0.38 |
| | 11.10 rFVIIa administered | | | | | | |
| | 15.57 | 9.5 | 52 | 9.2 | 33 | 15 | 1.96 |
| Case 4 | 13.30 caesarean section | | | | | | |
| | 14.35 | 3.8 | 69 | 14.8 | 45.2 | 15 | 0.88 |
| | 15.29 | 10.4 | 47 | No clot visible | No clot visible | 22 | 0.35 |
| | 18.02 | 8.0 | 64 | 11.9 | 29.3 | 17 | 1.6 |
| | 19.24 | 7.7 | 109 | 11.6 | 27.0 | 17 | 2.0 |
| | 23.19 | 9.3 | 90 | 11.5 | 27.2 | 19 | 2.03 |
| | 03.01 | 6.4 | 74 | 11.2 | 26.5 | 17 | 2.03 |
| | 04.00 rFVIIa administered | | | | | | |
| | 04.36 | 8.9 | 61 | 11.2 | 28.6 | 16 | 2.00 |

APTT: activated partial thromboplastin time.

attending midwife following local guidelines, and delivery of an apparently complete placenta. Intramuscular ergometrine, (500 µg), carboprost, (2 mg given in divided doses), and suturing of an episiotomy failed to stop the bleeding and the patient rapidly became profoundly cardiovascularly unstable. She was transferred to theatre for examination under general anaesthesia during which 5 units of O-negative blood were transfused. A bleeding source could not be identified and laparotomy was performed. At surgery, extensive bleeding from the uterus and left paravaginal area was noted. A hysterectomy with ligation of the left internal iliac artery was performed. Brisk haemorrhage continued throughout and she developed the clinical signs of a coagulopathy. Despite a total transfusion of 35 units of red blood cells (in optimal additive medium; volume per unit 300-330 mL), 14 units of fresh frozen plasma, 10 units of cryoprecipitate and 1 pool of platelets, haemodynamic stability was not regained. A 7.2-mg i.v. bolus of rFVIIa (75 µg/kg) was administered. Within ten minutes the surgical team reported a decrease in oozing, allowing surgery to be completed. The prothrombin time and activated partial thromboplastin time improved from 16.2 and 72 to 8.7 and 39 s respectively over the subsequent five hours, during which time she received a further four units of fresh frozen plasma. [Table 1](#) details the changes in laboratory parameters.

The patient was transferred to the intensive therapy unit postoperatively, where she was extubated some 12 h later. Her coagulation profile normalised and she required no further rFVIIa. After returning to theatre the following day for removal of abdominal packs, she was nursed on the delivery suite and subsequently discharged home 11 days after surgery.

CASE 3

A 36-year-old multiparous woman had a precipitate labour and was delivered vaginally of a baby in poor condition, (Apgar score <7 at 1 and 5 min). Her past obstetric history consisted of a normal vaginal delivery, an emergency caesarean section for placental abruption and evacuation of retained products of conception. Immediately after delivery she developed profuse vaginal bleeding which was not stopped by intramuscular oxytocin 10 units or delivery of an apparently complete placenta. Intravenous fluids and intramuscular carboprost (1 mg in divided doses), were given. Blood loss was estimated to be 2 L (on the floor and in the bed). The patient was transferred to theatre where rapid blood transfusion was started and examination under general anaesthesia revealed an atonic uterus. Despite administration of further oxytocin infusion (12.5 units/h), ergometrine 250 µg i.v. and carboprost (1 mg in divided

doses i.m.) and the insertion of a Rusch balloon into the uterus, bleeding continued. Laparotomy revealed a partial uterine scar dehiscence. The patient developed signs of coagulopathy. Despite hysterectomy and administration of blood and clotting products, bleeding continued. At this point her coagulation parameters were grossly deranged, with a prothrombin time of 30.5 and an activated partial thromboplastin time >360 s. A 7.2-mg i.v. bolus of rFVIIa (75 µg/kg) was administered. Subsequently clinical signs of coagulopathy disappeared, the oozing stopped and haemostasis was achieved. She became haemodynamically sufficiently stable to be transferred to the radiology department where both external iliac arteries were embolised, although no discrete site of extravasation was identified on angiography. In total the patient received 42 units of red blood cells, 16 units of fresh frozen plasma, 30 units of cryoprecipitate and 3 pools of platelets.

The patient was cared for in the intensive therapy unit. Within five hours her coagulation profile had normalised ([Table 1](#)). She developed an acute lung injury and required mechanical ventilation for three days. She was transferred back to the delivery suite on day four and discharged home nine days post partum.

CASE 4

A 29-year-old woman was delivered by elective caesarean section. Her past obstetric history consisted of four miscarriages with subsequent evacuation of retained products of conception on each occasion and most recently an emergency caesarean section for antepartum haemorrhage associated with a major placenta praevia.

The patient's surgery was scheduled for 37 weeks' gestation due to a low lying placenta of abnormal ultrasound appearance and a history of recurrent abdominal pain. Due to non-clinical factors, the caesarean section took place on a weekend. In theatre, multiple large-bore venous cannulae were sited. The patient had been warned that general anaesthesia might become necessary should major blood loss occur. Regional anaesthesia was achieved using a combined spinal-epidural, needle-through-needle technique, routine in our unit. The baby was delivered easily through a thin lower uterine segment covered in venous sinuses. The adherent placenta was removed piecemeal. Subsequently there was brisk haemorrhage from the placental bed, which was initially controlled by sutures and intramyometrial carboprost, (1 mg in divided doses). A Rusch tamponade balloon was inserted in the uterus and the uterus and abdomen were closed. At this point the estimated blood loss was 4 L. Haemodynamic stability had been maintained through infusion of warmed fluids and blood

products (16 units of red blood cells, four units of fresh frozen plasma, two pools of platelets and ten units of cryoprecipitate).

A period of observation followed, during which a further 1.5 L of blood loss occurred per vagina, and the patient became haemodynamically unstable. She underwent examination and insertion of a cervical suture under epidural top-up (the patient's preference for anaesthesia). Transfusion of a further five units of red blood cells, two units of fresh frozen plasma, two pools of platelets and five units of cryoprecipitate stabilised her condition. She was transferred to the radiology department and underwent embolisation of both internal iliac arteries. She remained awake throughout.

She was transferred to the intensive therapy unit. Over the next four hours she bled 1.25 L through an abdominal drain and the haemoglobin could not be maintained above 7 g/dL despite receiving five further units of red blood cells and another pool of platelets. A single 7.2-mg i.v. bolus of rFVIIa, (85 µg/kg) was administered, and the rate of blood loss rapidly decreased. Her haemoglobin rose to 10 g/dL and remained stable (Table 1). The patient was discharged to the delivery suite 36 h later. She went home 11 days after her caesarean section.

DISCUSSION

Massive obstetric haemorrhage continues to be a major cause of maternal mortality.¹ Bleeding may occur due to placentation abnormalities, trauma to the uterus or birth canal, or uterine atony following delivery. The primary abnormality may, in fact, be a coagulopathy, whether pre-existing or as a result of peripartum events such as amniotic fluid embolism.

Haemorrhage will often persist if a coagulopathy subsequently develops. This can result from transfusion of large volumes of blood products depleted of coagulation factors. It may be due to impairment of the coagulation cascade by metabolic acidosis caused by hypoperfusion and hypothermia resulting from transfusion of cold fluids and exposure. Major obstetric haemorrhage can thus be very difficult to control once it has become established.

NovoSeven® contains genetically engineered activated recombinant clotting factor VII (rFVIIa). It was developed for use in bleeding episodes and surgical haemorrhage, for patients with acquired haemophilia or those with inherited haemophilia who had developed inhibitors to clotting factors VIII or IX. Today these remain the licensed indications for its use, although it has been approved for other coagulation disorders such as Glanzmann's thrombasthenia. There is increasing experience in the use of rFVIIa in cases of intractable haemorrhage from other causes.^{2,3} rFVIIa promotes clot

formation through its action at a number of points in the coagulation cascade. Activated factor VII binds to exposed tissue factor at the site of endothelial damage. This tissue factor-FVIIa complex activates factor X that initiates the conversion of prothrombin to thrombin on the surface of tissue factor-bearing cells. This process results in the activation of platelets. Factor VIIa also activates factor IX which complexes with factor VIIIa on the surface of activated platelets catalysing further formation of factor Xa and subsequent large-scale platelet surface thrombin generation. The result is the conversion of fibrinogen to fibrin and stabilisation of the platelet plug to form a haemostatic clot. Secondly rFVIIa can activate factor X on the surface of activated platelets in a tissue factor independent manner. It is not yet clear whether both of these mechanisms are important in vivo but both are restricted to the site of endothelial damage so that systemic activation of coagulation is not induced.⁴

Nevertheless, concerns have been raised about the potential for thrombotic complications. There have been 17 cases reported of adverse thrombotic events during a five-year period during which 480 000 doses of rFVIIa were given to haemophiliac patients. All 17 patients were high-risk, and a potential cause of thrombotic events other than rFVIIa administration could be identified.⁴

Data about use of rFVIIa in a wide variety of coagulopathic cases, including trauma, suggest that thrombosis is not usually a problem.^{2,3} Data from the recombinant factor VIIa extended-use registry support the lack of thrombotic complications in acute bleeding episodes of many aetiologies, including post-partum bleeding.³ However, the data sheet for NovoSeven® quotes a serious adverse reaction rate of 0.6%, which includes both arterial thrombotic events such as myocardial infarction or ischaemia, cerebrovascular disorders and bowel infarction, and venous thrombotic events such as pulmonary embolism and thrombophlebitis.⁵ It is recommended that rFVIIa is used with caution in the presence of sepsis, disseminated malignancy or following the use of other coagulation bypassing agents.

In the four cases presented here there was no evidence of any thrombotic complications as a result of rFVIIa administration, despite the increased risk associated with major abdominal surgery in the pregnant patient. The clinical condition and coagulation profiles, following the use of rFVIIa, did not suggest continuing disseminated intravascular coagulation and defibrination in any of our four patients. Less serious adverse effects quoted in the data sheet at a rate of 0.4% include haemorrhage, rash and fever.

The international literature now contains numerous descriptions of the successful use of rFVIIa in massive obstetric haemorrhage.⁶⁻²⁴ We are aware of 44 reported cases, which are summarised in Table 2. The case

Table 2. Cases describing the management of major obstetric haemorrhage

| Reference | Age | Diagnosis | Total blood products | Other drugs to aid haemostasis | Other treatment | Dose and no. of doses rFVIIa | Outcome | Complications related to rFVIIa use | Blood products post rFVIIa |
|--------------|-------------------------------------|---------------------------------------|--|---|--|--|------------------|--------------------------------------|---|
| 6 | 33 | DIC hepatic dysfunction renal failure | RC, Platelets, FFP, Fibrinogen ? doses | Anti-thrombin III | Hysterectomy, laparotomy | 9 × 90 µg/kg, 3 h apart | Survived | Not recorded | Yes |
| 7 | 31 | HELLP syndrome | RC 54 units FFP 50 units Platelets 7 units | Not recorded | Hysterectomy, laparotomy × 8 | Not recorded | Died of MOF | Not recorded | Not recorded |
| 8 & 9 | 31 | HELLP syndrome | RC 12 units Platelets 8 units FFP 10 units Cryoprecipitate 950 units | Not recorded | None | 90 µg/kg single dose | Survived | None | No |
| 10 (a)/11 | 29 | Uterine atony | RC 3900 mL FFP 1800 mL | Etamsylate Phytometadione Fibrinogen | Hysterectomy, laparotomy | 20 µg/kg single dose | Survived | None | Yes |
| 10 (b) | 28 | Uterine atony | RC 2100 mL FFP 1000 mL | Dinoprostone (PEG ₂) Oxytocin | Hysterectomy | 17.5 µg/kg single dose | Survived | None | Yes |
| 10 (c) | 44 | Uterine atony | RC 2100 mL FFP 400 mL | Oxytocin PEG ₂ Terlipressin | None | 20 µg/kg single dose | Survived | None | Yes |
| 10 (d) | 36 | Placenta praevia DIC | RC 5100 mL FFP 3000 mL | Not recorded | None | 30 µg/kg single dose | Survived | None (anti-thrombin III prophylaxis) | Yes |
| 10 (e) | 29 | Genital tract trauma, DIC | RC 4800 mL FFP 2200 mL | Not recorded | Hysterectomy, laparotomy | 26 µg/kg single dose | Survived | None (anti-thrombin III prophylaxis) | Yes |
| 10 (f) | 40 | Uterine atony | RC 2700 mL FFP 1000 mL | PEG ₂ Oxytocin | None | 48 µg/kg single dose | Survived | None | Yes |
| 10 (g) | 26 | Bleeding during c/section, DIC | RC 3600 mL FFP 2800 mL | Not recorded | Hysterectomy, laparotomy | 16.7 µg/kg single dose | Survived | None | Yes |
| 12 | 30 | Vaginal lacerations Uterine atony | RC 42 units FFP 34 units Platelets 6 units | Oxytocin Sulproston Tranexanic acid | Hysterectomy, bilateral internal iliac artery ligation | 1 st 60 µg/kg dose 2 nd 120 µg/kg dose | Survived | None | Yes after 1 st dose, no after 2 nd dose |
| 13 (a) | 34 | Little information (not in English) | | | | 2 ampoules | Survived | | |
| 13 (b) | 31 | Little information (not in English) | | | | 1 ampoule | Survived | | |
| 14 | 35 | Limited information (not in English) | RC, FFP, Platelets ? doses | Oxytocin PGF _{2α} Aprotinin | Hysterectomy | 2 × 60 µg/kg 4 × 15 µg/kg | Died of MOF | | |
| 15 | 37 | Preeclampsia | Limited information (not in English) | | Hysterectomy | 1.2 mg single dose | Survived | ? Brachial artery thrombosis | |
| 16 | Little information (not in English) | | | | | | | | |
| 17 (a)/18(a) | | Placenta accreta | RC 50 units FFP 30 units Platelets 60 units Cryoprecipitate 54 units | Not recorded | Hysterectomy, internal iliac artery ligation | 90 µg/kg 2 doses | Bleeding stopped | Not recorded | Yes |

| | | | | | | | | | |
|--------------|----|-------------------------|--|--|--|--------------------------------|---------------------|--------------|-----|
| 17 (b)/18(b) | | Ruptured uterus | RC 22 units FFP 20 units Platelets 60 units Cryoprecipitate 64 units | Not recorded | Hysterectomy, bilateral internal iliac artery ligation | 100 µg/kg single dose | Bleeding stopped | Not recorded | Yes |
| 17 (c)/18(c) | | HELLP syndrome | RC 22 units FFP 16 units Platelets 10 units Cryoprecipitate 13 units | Not recorded | Packing of liver lacerations | 90 µg/kg single dose | Bleeding reduced | Not recorded | Yes |
| 18 (d) | | Uterine atony | RC 12 units FFP 10 units Cryoprecipitate 8 units | Not recorded | Hysterectomy, bilateral internal iliac artery ligation | 90 µg/kg single dose | Bleeding stopped | Not recorded | No |
| 18 (e) | | Uterine rupture | RC 26 units FFP 16 units Platelets 30 units Cryoprecipitate 60 units | Not recorded | Hysterectomy, bilateral internal iliac artery ligation | 90 µg/kg single dose | Bleeding stopped | Not recorded | No |
| 18 (f) | | Placenta accreta | RC 114 units FFP 54 units Platelets 56 units Cryoprecipitate 54 units | Not recorded | Hysterectomy, arterial embolisation, laparotomy × 4 | 90 µg/kg single dose | Bleeding controlled | Not recorded | Yes |
| 18 (g) | | Uterine rupture | RC 10 units FFP 6 units Cryoprecipitate 4 units | Not recorded | Hysterectomy, bilateral internal iliac artery ligation | 90 µg/kg single dose | Bleeding reduced | Not recorded | No |
| 18 (h) | | Uterine rupture | RC 15 units FFP 6 units Platelets 15 units Cryoprecipitate 30 units | Not recorded | Hysterectomy | 90 µg/kg single dose | Bleeding stopped | Not recorded | No |
| 18 (i) | | Placenta accreta | RC 29 units FFP 30 units Platelets 10 units Cryoprecipitate 30 units | Not recorded | Hysterectomy, aortic clamp, bilateral internal iliac artery ligation | 90 µg/kg single dose | Bleeding stopped | Not recorded | Yes |
| 19 | 31 | Uterine rupture | RC 55 units FFP 27 units Platelets 10 units Cryoprecipitate 22 units | Oxytocin Misoprostol Tranexamic acid | Hysterectomy, laparotomy × 2 | 120 µg/kg 19 doses over 4 days | Survived | None | Yes |
| 20 | 26 | Amniotic fluid embolism | RC 6 units FFP 1 litre Platelets 2 units | Not recorded | None | 90 µg/kg single dose | Survived | Not recorded | No |

(continued on next page)

Table 2 (continued)

| Reference | Age | Diagnosis | Total blood products | Other drugs to aid haemostasis | Other treatment | Dose and no. of doses rFVIIa | Outcome | Complications related to rFVIIa use | Blood products post rFVIIa |
|-----------|-----------|---|---|--------------------------------|---------------------------------------|---|---------------------------------|-------------------------------------|----------------------------|
| 21 | 32 | Preeclampsia DIC | RC 22 units FFP 18 units Platelets 40 units Cryoprecipitate 20 units | Not recorded | Laparotomy | 90 µg/kg single dose | Survived | Not recorded | Yes |
| 22 (a) | Mid 30s | HELLP, eclampsia, consumptive coagulopathy, subcapsular hepatic haematoma | RC 16 units FFP 14 units Platelets 18 units Cryoprecipitate 10 units | Not recorded | Hepatic artery clamping, liver packed | 90 µg/kg, 2 doses 2 h apart | Died-severe anoxic brain damage | None | No |
| 22 (b) | Early 30s | Placenta praevia, HELLP, ruptured hepatic haematoma | RC 8 units FFP 4 units Platelets 6 units | Not recorded | Liver packed | 1 st 120 µg/kg 2 nd and 3 rd : 90 µg/kg 2h intervals | Survived | None | No |
| 22 (c) | Mid 30s | Preeclampsia, subcapsular hepatic haematoma, HELLP, consumptive coagulopathy, placental abruption | RC 2 units FFP 4 units Platelets 6 units Cryoprecipitate 10 units | Not recorded | None | 90 µg/kg 2 doses 2 h apart | Survived | None | No |
| 23 (a) | 32 | Placenta accreta | RC 54 units FFP 34 units Platelets 56 units Not recorded | Hysterectomy | 44 µg/kg ? doses | Partial response, ? outcome | Not recorded | Yes | |
| 23 (b) | 37 | Adherent placenta | RC 39 units FFP 14 units Platelets 24 units | Not recorded | Hysterectomy | 95 µg/kg ? doses | Good response, ? outcome | Not recorded | Yes |

| | | | | | | | | | |
|--------|----|----------------------------|---|------------------|---|----------------------|--------------------------------|--------------|-----|
| 23 (c) | 34 | Uterine atony, lacerations | RC 19 units FFP 8 units Platelets 16 units | Uterotonic drugs | Surgery unspecified | 78 µg/kg ? doses | Good response, ? outcome | Not recorded | Yes |
| 23 (d) | 32 | Lacerations | RC 28 units FFP 16 units Platelets 32 units | Not recorded | Surgery unspecified, arterial embolisation | 103 µg/kg ? doses | Partial response, ? outcome | Not recorded | Yes |
| 23 (e) | 34 | Lacerations | RC 32 units FFP 20 units Platelets 40 units | Not recorded | Hysterectomy | 90 µg/kg ? doses | Good response, ? outcome | Not recorded | No |
| 23 (f) | 24 | Uterine atony | RC 13 units FFP 10 units Platelets 24 units | Uterotonic drugs | Surgery unspecified, arterial embolisation | 116 µg/kg ? doses | Partial response, ? outcome | Not recorded | Yes |
| 23 (g) | 23 | Placenta accreta | RC 21 units FFP 16 units Platelets 16 units | Not recorded | Hysterectomy | 42 µg/kg ? doses | Partial response, ? outcome | Not recorded | Yes |
| 23 (h) | 32 | Lacerations | RC 20 units FFP 14 units Platelets 16 units | Not recorded | Surgery unspecified | 120 µg/kg ? doses | No response, ? outcome | Not recorded | Yes |
| 23 (i) | 36 | Placenta percreta | RC 31 units FFP 16 units Platelets 24 units | Not recorded | Hysterectomy | 77 µg/kg ? doses | Good response, ? outcome | Not recorded | Yes |
| 23 (j) | 25 | Lacerations | RC 12 units FFP 10 units Platelets 32 units | Not recorded | Surgery unspecified, arterial embolisation | 74 µg/kg ? doses | Partial response, ? outcome | Not recorded | No |
| 23 (k) | 29 | Lacerations | RC 13 units FFP 8 units Platelets 24 units | Not recorded | Surgery unspecified | 86 µg/kg ? doses | Good response, ? outcome | Not recorded | Yes |
| 23 (l) | 24 | Lacerations | RC 10 units FFP 8 units Platelets 16 units | Not recorded | Surgery unspecified, arterial embolisation | 96 µg/kg ? doses | Partial response, ? outcome | Not recorded | No |
| 24 | 28 | Uterine atony, DIC | Limited information (not in English) | Uterotonic drugs | Hysterectomy, laparotomy, packing of pelvis | 2.4 mg single dose | Bleeding controlled | | |

The literature search for this table was completed in November 2005. DIC: disseminated intravascular coagulation; RC: red cells; FFP: fresh frozen plasma; MOF: multiple organ failure.

reports make it obvious that practice relating to the use of rFVIIa in post-partum haemorrhage is far from uniform. Some authors appear to use rFVIIa early in the management of their cases when comparatively few blood products have been given. Others use it as a last resort after huge doses of blood products and major surgery. The dose of rFVIIa administered also varies, with a range from 15 to 120 µg/kg. In a minority of cases multiple doses were given, but in the majority only a single dose was administered. The mean total dose for those cases with doses quoted on a weight basis is 94 µg/kg, excluding two outlying values.^{6,19} Administration of blood products following the use of rFVIIa also varies. Due to lack of details published, it is not possible to differentiate between treatment before and after the use of rFVIIa in many reports. No complication specifically attributed to the use of rFVIIa in this situation is recorded among them. However, Michalska-Krzanowska et al. report that their patient suffered from a brachial artery thrombosis after receiving rFVIIa.¹⁵

Another recent publication relevant to the off-licence use of rFVIIa in massive haemorrhage addresses the issue of expense. Loudon and Smith estimated the major costs associated with haemorrhage management in all patients admitted over a 12-month period who required more than 5 units of red blood cells in a single transfusion episode.²⁵ The cumulative costs of standard treatment were compared to an hypothesised rFVIIa intervention for each of four groups stratified according to transfusion requirement. There was no statistically significant difference between the cost standard and hypothesised treatments. They suggest that according to their hypothetical model, the optimum time to administer rFVIIa, in terms of cost-effectiveness, follows transfusion of 14 units of red cells. Cost neutrality was maintained at this point even when two doses of rFVIIa are required. If these findings are substantiated, they need wider dissemination; cost continues to be considered a contraindication to use in many centres.

In the United Kingdom 1.2 g of NovoSeven® currently costs approximately £664.72. The cost of one unit of packed red blood cells is £150.52, one unit fresh frozen plasma £31.64, one unit cryoprecipitate £36.54 and one pool of platelets is £213.79. Table 3 gives the total transfusion costs and cost of the administered dose of rFVIIa according to these prices for each of our four cases.

Recently, the Israeli Multidisciplinary rFVIIa Task Force published suggested guidelines for the use of rFVIIa in uncontrolled bleeding.²⁶ These were based on the management of 36 trauma patients and an extensive literature search consisting of published and pre-published controlled animal trials, case reports and series. To date we are not aware of any randomised controlled trials of the use of rFVIIa in obstetric patients

Table 3. Transfusion-related costs in massive haemorrhage

| | Case 1 | Case 2 | Case 3 | Case 4 |
|------------------------------|----------|----------|----------|----------|
| Total cost of blood products | £6382.23 | £5716.91 | £7725.65 | £5200.41 |
| Cost of rFVIIa | £2658.88 | £3988.32 | £3988.32 | £3988.32 |

from which evidence-based guidelines might be developed. However given the large number of published reports of its use in obstetric case we would suggest that the development of guidelines would be timely. There are signs that the use of rFVIIa in obstetric patients continues to increase and the extended-use registry⁵ represents an important source of information for practitioners.

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