

Recombinant factor VIIa for life-threatening post-partum haemorrhage[†]

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The treatment of life-threatening post-partum haemorrhage (PPH) still remains challenging, and hysterectomy may be required to control the bleeding. We present 12 cases of severe PPH treated with recombinant factor VIIa (rFVIIa). We briefly describe the causes of the haemorrhage and the medical and surgical interventions before rFVIIa administration. In 11 women there was a partial or good response to rFVIIa administration, while in one there was no response. In the four women undergoing a subsequent selective arterial embolization, the bleeding was significantly reduced although not completely stopped. From our experience with these 12 cases, and from previously reported cases, the use of rFVIIa may be of benefit in life-threatening PPH. However, treatment with rFVIIa, in addition to standard surgical and medical interventions, may not be definitive in every patient and a selective arterial embolization may be needed.

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Although maternal mortality as a result of major haemorrhage has declined in Western nations, peri-partum haemorrhage remains a leading cause of maternal and fetal morbidity and mortality. According to the Confidential Report into Maternal Deaths in the UK 1997–1999, death from haemorrhage fell from 5.5 to 3.3 per million maternities in the UK during that period.¹ However, despite recommendations for improving the overall level of care, care was considered to be substandard in 11 of the 14 cases reviewed.¹ Various risk factors can be identified for peri-partum haemorrhage but further improvements can only be achieved with education and adoption of local protocols for the treatment of major bleeding.

The cornerstone of the treatment of major post-partum haemorrhage (PPH) consists of surgery and/or medical management with effective transfusion therapy and uterotonic drugs.^{2,3} However, additional interventions may be needed in cases with continuing bleeding. There are a number of case reports where empirical out-of-license use of recombinant factor VIIa (rFVIIa) (NovoSeven[®], Novo Nordisk A/S, Bagsvaerd, Denmark) has been effective in treating severe PPH.^{4–6} However, it seems unlikely that randomized controlled trials will ever be performed in patients with life-threatening PPH.

The Women's Clinic in Helsinki is a tertiary referral hospital for high-risk pregnancies serving the whole province of Uusimaa. There were 4718 deliveries at our institution in 2003; 1188 of these were Caesarean sections. During a 16-month period from March 2003 we used rFVIIa in the

treatment of 12 parturients with major PPH. Five of these women had to undergo angiography and four of them subsequently had selective arterial embolization. Brief case reports on these 12 women are presented in chronological order in Table 1.

Discussion

We have now treated 12 patients with major PPH using rFVIIa. In 11 cases there was a partial or good response to rFVIIa administration, but in one (case 8), there was no response and the right uterine artery had to be ligated. In the four women undergoing a subsequent selective arterial embolization, the bleeding was significantly reduced although not completely stopped. Only three of the patients required intensive care unit (ICU) treatment, each for 1–2 days. From our experience with these 12 cases, and from previously reported cases, the use of rFVIIa may be of benefit in life-threatening PPH, in addition to surgical and conservative medical interventions. However, treatment with rFVIIa may not be definitive in every patient and selective arterial embolization may be needed.

Recombinant factor VIIa is licensed for the treatment of bleeding episodes in patients with congenital haemophilia A or B and who have developed inhibitors to factors VIII or IX, and in patients with factor VII deficiency or Glanzmann's thrombasthenia with anti-GpIIb/IIIa antibodies. It induces

[†]This article is accompanied by the Editorial.

Table 1 Characteristics of the 12 parturients with major PPH treated with rFVIIa and undergoing a subsequent selective arterial embolization. *Haemoglobin just before rFVIIa administration (normal range 117–155 g litre⁻¹); †platelets just before rFVIIa administration (normal range 150–360 g litre⁻¹); ‡P-TT just before rFVIIa administration (normal range 70–130%); #D-dimer, highest intraoperative value determined (normal value <0.5 mg litre⁻¹); §units of red blood cells, fresh frozen plasma and platelets transfused before and after rFVIIa administration

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 | Case 12 |
|---|----------|----------|-------------|----------|----------|-------------|---------|---------|----------|----------|---------|---------|
| Age (yr) | 32 | 37 | 34 | 32 | 34 | 24 | 23 | 32 | 36 | 25 | 29 | 24 |
| Weight (kg) | 54 | 76 | 93 | 70 | 80 | 62 | 58 | 60 | 93 | 97 | 84 | 50 |
| Weeks of gestation | 38 | 32 | 39 | 42 | 41 | 40 | 39 | 36 | 36 | 37 | 35 | 40 |
| Type of delivery | VD | CS | VD | VD | CS | CS | VD | CS | CS | IVD | VD | VD |
| Cause of bleeding | PA | AP | At, Lac | Lac | Lac | At | PA | Lac | PP | Lac | Lac | Lac |
| Interventions | Hys | Hys | At, surgery | Surgery | Hys | Ut, surgery | Hys | Surgery | Hys | Surgery | Surgery | Surgery |
| No. of operations | 1 | 1 | 3 | 2 | 3 | 1 | 1 | 2 | 2 | 1 | 1 | 1 |
| Dose of rFVIIa (µg kg ⁻¹) | 44 | 95 | 78 | 103 | 90 | 116 | 42 | 120 | 77 | 74 | 86 | 96 |
| Response to rFVIIa administration | Partial | Good | Good | Partial | Good | Partial | Partial | None | Good | Partial | Good | Partial |
| Subsequent arterial embolization (+/-) | - | - | - | + | - | + | - | - | - | + | - | + |
| Bleeding before rFVIIa administration (litres) | 25.0 | 20.0 | 11.0 | 14.0 | 19.0 | 5.5 | 7.5 | 5.3 | 14.0 | 8.8 | 5.5 | 5.8 |
| Total bleeding (litres) | 30.0 | 22.5 | 11.5 | 15.0 | 19.5 | 7.0 | 9.5 | 10.3 | 15.0 | 9.5 | 5.8 | 6.3 |
| Haemoglobin* (g litre ⁻¹) | 117 | 87 | 98 | 96 | 108 | 97 | 104 | 88 | 85 | 103 | 78 | 83 |
| Platelets† (10 ⁹ litre ⁻¹) | 55 | 95 | 120 | 75 | 73 | 73 | 76 | 96 | 141 | 109 | 65 | 116 |
| P-TT‡ (%) | 40 | 43 | 59 | 70 | 29 | 60 | 35 | NA | 66 | 62 | 75 | 55 |
| D-dimer# (mg litre ⁻¹) | 64.1 | NA | 8.1 | 3.4 | 8.8 | 105.6 | 5.2 | 1.6 | 2.4 | 63.2 | 21.2 | 8.9 |
| RBC/FFP/platelets§ (U) | | | | | | | | | | | | |
| Before | 42/25/40 | 35/14/24 | 19/8/8 | 25/16/24 | 32/20/40 | 10/8/16 | 14/6/4 | 11/4/8 | 25/14/16 | 12/10/32 | 11/6/16 | 10/8/16 |
| After | 12/9/16 | 4/-/- | -/-/8 | 3/-/8 | -/-/- | 3/2/8 | 7/10/12 | 9/10/8 | 6/2/8 | -/-/- | 2/2/8 | -/-/- |

VD, vaginal delivery; CS, Caesarean section; IVD, instrumental vaginal delivery; Lac, uterine, vaginal or other lacerations; PA, placenta accreta; AP, adherent placenta; At, atony; PP, placenta percreta; Hys, hysterectomy; Ut, uterotonics; P-TT, thromboplastin time; NA, not available.

haemostasis at the site of vascular injury independent of the presence of factors VIII and IX by forming complexes with exposed tissue factor (TF).^{7,8} Administration of high-dose rFVIIa results in a huge increase in factor VIIa, well above that of the normal physiological levels, leading to faster and greater thrombin generation.⁹ *In vitro* studies have shown that, compared with normal clots, the fibrin clots formed in the presence of a high thrombin concentration have a different architecture that is stronger and more resistant to degradation by fibrinolytic enzymes.^{10–12} Since the first case report of the successful use of rFVIIa in a trauma patient,¹³ several case reports and some clinical studies of out-of-license use of rFVIIa have been published.^{14,15} In complex situations there is a risk of thromboembolic complications associated with the use of rFVIIa.¹⁶ However, in previously healthy patients with major haemorrhage, the risk seems to be low even in the presence of a disseminated intravascular coagulation (DIC).^{4,14}

The case reports on the use of rFVIIa in intractable PPH previously published were in severely ill patients.^{4–6} The first reported patient had uncontrollable bleeding with severe DIC despite a hysterectomy.⁴ Another patient developed haemorrhagic shock and cardiac arrest. After successful resuscitation, a hysterectomy was performed before the administration of rFVIIa.⁵ Recently, successful non-surgical treatment of major PPH with rFVIIa following Caesarean section has been reported.⁶ The patient developed a coagulopathy associated with pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) and DIC. All these patients developed severe

complications requiring ICU treatment but made a full recovery; no adverse effects of rFVIIa were noted.^{4–6}

During the last 3 years, the numbers of women undergoing hysterectomy at our institution because of life-threatening PPH were 11, 8, and 10, respectively. In five of the 12 cases discussed here, hysterectomy was performed before the administration of rFVIIa. During the same 16-month period, an additional six parturients underwent hysterectomy for life-threatening PPH but did not receive rFVIIa. At that time, we had no guidelines for the use of rFVIIa. Therefore not all women requiring hysterectomy received rFVIIa, and in two (cases 1 and 7) the dosage was too low. Clearly, hysterectomy would be avoided in normal childbirth unless there is an obvious indication such as placenta accreta. However, in severe PPH the decision-making is not straightforward. The choices are between the possibly easier option of hysterectomy and a procedure involving ligation of the uterine arteries, administration of uterotonics, compression of the bleeding, administration of rFVIIa and then waiting for the response. In a patient with intractable bleeding and no other obvious indication for a hysterectomy, the latter strategy would seem appropriate.

Uterine atony is the most common cause of PPH and one of the main reasons for performing a peri-partum hysterectomy.¹⁷ In our series, only two women were treated with rFVIIa for bleeding associated with poor uterine contraction. One (case 6) underwent a Caesarean section for arrested delivery and chorioamnionitis. In addition to repeated infusions of oxytocin and two doses of misoprostol rectally,

uterine atony was treated by intramyometrial sulprostone. Furthermore, both uterine arteries were ligated. The bleeding continued in the recovery room, and a selective arterial embolization was proposed. The patient had to wait 2 h for the procedure and, because of intractable vaginal haemorrhage, we decided to give rFVIIa. Angiography revealed an incomplete surgical ligation of the right uterine artery which was successfully embolized. In case 3, the uterine atony had been treated by repeated infusions of oxytocin, several doses of misoprostol rectally and intravenous methylergometrine. Because of ongoing life-threatening bleeding we decided to combine i.v. administration of rFVIIa and a sulprostone infusion into the uterine cavity. The bleeding stopped and hysterectomy was avoided. At our institution, we prefer not to use i.v. infusions of sulprostone because of the risk of severe adverse effects.^{18 19} Our patient receiving the intra-uterine infusion of sulprostone complained of brief visual disturbance for about 20 min, which was attributed to a cerebral vasospasm. However, we believe that although rFVIIa has no effect on uterine tone, its use simultaneously with uterotonic medications may interrupt the vicious circle of uterine atony and severe bleeding which does not respond to conservative transfusion therapy.

From our experience it is difficult to assess when to administer rFVIIa and when to proceed directly to selective arterial embolization. In cases of diffuse haemorrhage which do not respond to transfusion therapy and uterotonics, it seems appropriate to try rFVIIa. On the other hand, in cases of more localized and obvious arterial bleeding it may be reasonable to proceed with selective arterial embolization. In four of the five patients who had angiography, the haemorrhage was significantly reduced although not completely stopped before the subsequent selective arterial embolization. The remaining patient (case 9) underwent angiography twice but no arterial bleeding was found. Not all maternity hospitals have access to facilities for selective arterial embolization. In severe PPH unresponsive to standard interventions, the use of rFVIIa may give some additional time for the patient to be transferred to a hospital where a selective arterial embolization can be performed.

At our institution the embolization unit is located in a neighbouring building to which the patients have to be transferred in an ambulance, and the interventional radiologist is not always available. In some of our cases rFVIIa could have been administered earlier. However, we were cautious about using an empirical out-of-license treatment with an expensive drug. Table 1 shows that there is a learning curve in the use of rFVIIa. We now have rFVIIa available in the operating theatre and we start to consider its use when the parturient has lost about 1.5 times her blood volume. We administer a bolus dose of $\sim 90\text{--}120 \mu\text{g kg}^{-1}$ and aim for a haemoglobin level $\geq 70 \text{ g litre}^{-1}$, a platelet count $>50 \times 10^9 \text{ litre}^{-1}$ and a thromboplastin time $>40\%$ (equivalent to an INR <1.5). The plasma fibrinogen level should also be $>1.0 \text{ g litre}^{-1}$. In our experience the fibrinogen level seldom remains below this level if the parturient with

major PPH receives fresh frozen plasma to keep the thromboplastin time $>40\%$.

In summary, we have shown that, in addition to surgical and effective medical interventions, treatment with rFVIIa may be of benefit in life-threatening PPH of up to 20 l of blood in 5–8 h. At our institution, the cost of a single dose of rFVIIa is similar to that of transfusion with 50 units of red blood cells, an embolization procedure, or ICU treatment for 2 days, and thus may be cost-effective in managing massive PPH. We believe that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery. However, the indications for rFVIIa administration rather than selective arterial embolization remain to be determined.

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