

CASE REPORT

## Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature

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### Case report

A 31 year old woman was admitted to a regional hospital at 41 weeks of gestation for cervical ripening with prostaglandin E<sub>2</sub> gel. She was gravida III (caesarean delivery seven years before for an acute fetal distress, one abortion). During the present pregnancy she had received prophylactic anticoagulation with low molecular weight heparin (enoxaparin 40 mg per day) due to the presence of varicose veins. This was stopped three days before the delivery. She laboured and was delivered vaginally with forceps for fetal distress with a fetus in the left occipital posterior position. A mediolateral episiotomy complicated by a fourth degree perineal tear was repaired. Two hours after delivery she presented with heavy vaginal haemorrhage with shock and was given oxytocin 5 U intravenously and misoprostol 800 mg intrarectally.

An emergency laparotomy revealed uterine rupture, which was sutured. A uterine atony without any retained placental fragments was observed. A bladder injury was identified and repaired in two layers using 3-0 polyglycolic acid suture. Because of persistent bleeding and shock without any response to a second intrarectal dose of misoprostol 800 mg, a hysterectomy was performed. The internal iliac arteries were not ligated. Despite the transfusion of 10 red blood cell concentrates, 5 fresh frozen plasma, 10 units of platelets and 1200 IU of prothrombin

complex concentrate, she remained haemodynamically unstable and was transferred to our tertiary care hospital.

On arrival, the blood pressure was 80/50 mmHg, pulse 130 per minute and temperature 32°C. Haematocrit was 15.8%, haemoglobin 51 g/dL, platelets 158 G/L, prothrombin time 34%, activated partial thromboplastin time > 200 seconds (normal range 25–32 seconds) and fibrinogen 1.6 g/L (normal range 2.0–4.0 g/L). A few minutes after admission, she suffered a cardiac arrest for 7 minutes which attributed to a hyperkalemia at 8.5 mmol/L, and needed resuscitation. She received 16 red blood cell concentrates and 6 fresh frozen plasma in 2 hours. A second haemostatic laparotomy was planned and, due to the persistent bleeding and life-threatening condition, the decision to administer recombinant activated factor VII (rFVIIa, NovoSeven) was taken. At the beginning of the laparotomy, a first dose of rFVIIa 120 µg/kg was given, and repeated after 1 and 3 hours. This surgical procedure, not complicated by bleeding, allowed the drainage of 4 L of intra-abdominal blood. A pelvic pressure pack constructed with gauze rolls tied end to end was used to fill the pelvis. After 1 hour the packing was removed and no bleeding source was obvious. During this surgical procedure, she received a further six units of red blood cell concentrates and six of fresh frozen plasma.

She was transferred to the intensive care unit where a new onset of bleeding was observed at all puncture and drainage sites (1250 mL in 3 hours). Coagulation tests confirmed the presence of disseminated intravascular coagulation: platelet count 65 G/L, activated partial thromboplastin time 53 seconds, fibrinogen 1.2 g/L and D-dimers >10,000 ng/mL. Blood volume was restored with crystalloids as well as blood transfusions and three further doses of rFVIIa 120 µg/kg were administered during the second day. The situation improved during the night but a sudden new increase of bleeding (1350 mL in 1 hour) occurred the next morning. Due to the previous satisfactory responses to rFVIIa, it was decided to increase the doses of rFVIIa (two doses at 1 hour intervals followed by further doses every 3 hours). Tranexamic acid was also given. A third

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**Table 1.** Clinical details of the 13 reported cases of severe postpartum haemorrhage treated with rFVIIa.

Patient and delivery details	Bleeding complication	Treatment before rFVIIa	rFVIIa and evolution	Ref.
31 year old nulliparous triplet pregnancy, CS at 34 weeks of gestation (beginning of HELLP syndrome)	Haemorrhagic shock 8 hours postpartum related to atonic uterine bleeding	Hysterectomy 8 laparotomies 54 RBCC 50 FFP 7 platelet concentrates	Introduced at day 2 Dose not recorded Favourable effect on bleeding Death at day 9 (MOF)	4
33 year old twins, CS at 31 weeks of gestation for severe DIC	Intra-abdominal bleeding with haemodynamic instability, related to DIC	Surgical drainage Hysterectomy Second laparotomy RBCC FFP Fibrinogen Platelets	90 µg/kg repeated 3 hours later (total of nine doses) Haemodynamic stabilisation	5
31 year old second pregnancy, Emergency CS at 38 weeks of gestation (HELLP syndrome and fetal distress)	Massive vaginal bleeding and from the wound with haemorrhagic shock and DIC 2 hours post CS	12 RBCC 8 FFP 950 IU of cryoprecipitate 8 units of platelets	90 µg/kg, one dose Significant reduction of the rate of bleeding with normalisation of coagulation tests Discharged at day 12	8
29 year old Grav II triplets, CS at 39 weeks of gestation	Massive bleeding shortly after CS related to uterine atony and subhepatic haematoma; hypovolaemic shock	Hysterectomy Relaparotomy 3000 mL of RBCC 1600 mL of FFP	20 µg/kg, one dose during relaparotomy Rapid normalisation of haemostasis	7
28 year old Grav III twins, CS at 37 weeks of gestation	Post-delivery uterine atony bleeding one hour after CS; hypovolaemic shock, intra-operative (hysterectomy) bleeding	Hysterectomy 1500 mL of RBCC 800 mL of FFP	17.5 µg/kg, one dose during hysterectomy Cessation of bleeding in the following minutes	7
44 year old Grav VI, CS at 39 weeks of gestation (cardiologic indication)	Post-delivery uterine atony bleeding with hypovolaemic shock; sudden haemorrhage 10 hours after CS	1200 mL of RBCC 400 mL of FFP	20 µg/kg, one dose 10 hours after CS Stop of the bleeding No hysterectomy needed	7
36 year old Grav VI (4 CS and 2 abortions), CS with hysterectomy at 35 weeks of gestation (serologic incompatibility, placenta praevia)	Intra-operative bleeding and DIC with hypovolaemic shock	3600 mL of RBCC 2000 mL of FFP	30 µg/kg, one dose 5 hours after hysterectomy Decrease of bleeding within 30 minutes and stop	7
29 year old Grav I, Spontaneous delivery at 40 weeks of gestation	Bleeding from genital tract with DIC and hypovolaemic shock; intra-operative bleeding (hysterectomy; retroperitoneal haematoma)	Hysterectomy Relaparotomy 3900 mL of RBCC 1800 mL of FFP	26 µg/kg, one dose during relaparotomy Cessation of bleeding within 15 minutes	7
40 year old Grav II (abortion), CS at 37 weeks of gestation (pre-eclampsia)	Post-delivery uterine atony bleeding and DIC with hypovolaemic shock	1200 mL of RBCC 600 mL of FFP	48 µg/kg, one dose Stop of bleeding and stabilisation of coagulation parameters No hysterectomy needed Prolonged mechanical ventilation due to 'shock lung'	7
26 year old Grav II, CS at 41 weeks of gestation	Intra-operative bleeding and DIC with hypovolaemic shock	Hysterectomy Relaparotomy 1500 mL of RBCC 1400 mL of FFP	16.7 µg/kg, one dose after hysterectomy Lack of haemostatic effect; increasing peritoneal effusion due to poor surgical ligation of parametrium blood vessels Second dose of rFVIIa during surgical correction?	7

**Table 1.** (continued)

Patient and delivery details	Bleeding complication	Treatment before rFVIIa	rFVIIa and evolution	Ref.
38 year old Grav II, CS at 37 weeks of gestation, UFH treatment for artificial mitral heart valve with resistance to heparin and administration of antithrombin	Preventive (excessive bleeding according to the surgeon, related to heparin treatment)	400 mL of FFP	17.5 µg/kg, first dose during CS (in alternative to protamine sulphate) repeated 2 hours later Good peri-operative haemostasis	7
29 year old, CS	Intra-operative bleeding with hypovolaemic shock	Hysterectomy 3 abdominal cavity revision	Administration during the 3rd abdominal cavity revision Rapid intra-operative control of haemorrhage	9
30 year old nullipara, Vacuum extraction	Postpartum haemorrhage 1 hour after delivery; neither placenta retention nor cervical rupture but vaginal lacerations; atonic uterus	Laparotomy Bilateral ligation of the internal iliac arteries Subtotal hysterectomy 42 RBCC 34 FFP 7 U of pooled platelet concentrates	60 µg/kg 12 hours postpartum Stop of bleeding 120 µg/kg 2 hours later for consolidation Pulmonary oedema, bilateral pneumothorax, ARDS Discharged at day 10	10

rFVIIa = recombinant factor VIIa; CS = caesarean section; UFH = unfractionated heparin; DIC = disseminated intravascular coagulation; IU = international units; RBCC = red blood cell concentrates; FFP = fresh frozen plasma; MOF = multiple organ failure; ARDS = acute respiratory distress syndrome.

exploratory laparotomy was performed and small arteries were ligated in the broad ligaments. No other active source of haemorrhage was seen.

However, bleeding resumed rapidly post-operatively. Arteriography confirmed the absence of any obvious bleeding source so embolisation of internal iliac arteries was not performed. During the night, the bleeding began to decrease. rFVIIa was progressively diminished and stopped the fifth day, a total of 19 doses being administered. She received a total of 55 red blood cell concentrates, 27 fresh frozen plasma, 10 units of platelets and 22 plateletpheresis.

During the first three days, the patient had developed a multiple organ failure with liver and renal failure associated with an acute respiratory distress syndrome. No haemodialysis or haemofiltration was necessary and she was extubated at day four. Thrombotic prophylaxis with unfractionated heparin was introduced at day four and she was transferred to the obstetric unit at day eight. She was discharged from the hospital at day 21. A bladder–vaginal fistula was repaired three months later without any complications.

## Discussion

Severe postpartum haemorrhage remains an important cause of maternal mortality.<sup>1</sup> Such bleeding is most often due to uterine atony but other causes exist. The initial management of a massive postpartum haemorrhage consists in the evaluation of the primary cause and is managed by the restoration of blood volume, the administration of blood products and the use of different other treatments

such as uterotonic drugs. When the medical therapy is unsuccessful, surgical procedures may be necessary.

Recombinant factor VIIa is currently used to treat haemophilic patients with inhibitors<sup>2</sup> but has also been successfully administered for other bleeding disorders<sup>3</sup> and in heavy blood loss due to trauma.<sup>4</sup> The use of rFVIIa in postpartum massive haemorrhage has been reported in 13 cases (Table 1), with good success in most of the cases.<sup>5–10</sup> Few data are available about its use in cases of disseminated intravascular coagulation.<sup>5,11</sup>

Despite a hysterectomy, two subsequent laparotomies and a constant support of fluids, red blood cells, plasma and platelets, the bleeding persisted. This critical situation led us to consider the administration of rFVIIa. The drug was first administered during the second laparotomy with a partial success. Due to a new bleeding and the desperate clinical condition, rFVIIa was readministered the second day with a good success. A new major bleeding the third day prompted us to increase the dosage of rFVIIa. On the fourth day the bleeding had notably decreased and stopped on the fifth day. No adverse events related to the administration of rFVIIa were observed.

In the present case, even if it is difficult to appreciate the exact relationship, it was obvious to the team that the administration of rFVIIa was related to cessation of bleeding and finally led to the positive outcome. In most of the case reports (Table 1), only one or two doses of rFVIIa were administered and small doses were often sufficient (around 20 to 40 µg/kg). Only one case report mentions the use of nine doses of rFVIIa of 90 µg/kg.<sup>5</sup> In our case, although the coagulation parameters were improved after the first day and the haemoglobin maintained at more than 100 g/L, recurrent bleeding was observed. This is the reason

why we decided to repeat the administration of rFVIIa. The persistence of a platelet consumption, which required many transfusions of platelets, could have also played a role. Our patient was transfused to maintain a platelet count above 50 G/L. It might be that rFVIIa could help platelet function because its efficacy has been shown even in case of severe thrombocytopenia.<sup>12</sup>

The success of repeated doses as high as 120 µg/kg has not been described in postpartum haemorrhage before. Although we do not advocate for a systematic use of high and prolonged doses of rFVIIa in postpartum haemorrhage, we would like to indicate a possible use of this haemostatic agent in case of a particular life-threatening condition unresponsive to conventional therapy. This new therapeutics may allow not only to decrease the number of blood products administered,<sup>13</sup> but also to avoid a hysterectomy if used more rapidly. Ideally, appropriate trials should be conducted to determine the indications of rFVIIa in case of massive postpartum haemorrhage but such trials will not be easy to perform due to the difficulty to randomise such particular cases.

## References

1. Bonnar J. Massive obstetric haemorrhage. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;**14**:1–18.
2. Negrier C, Hay CR. The treatment of bleeding in hemophilic patients with inhibitors with recombinant factor VIIa. *Semin Thromb Hemost* 2000;**26**:407–412.
3. Hedner U. Recombinant factor VIIa (NovoSeven) as a hemostatic agent. *Semin Hematol* 2001;**38**(Suppl 12):43–47.
4. Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001;**51**:431–438.
5. Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intra-vascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001;**114**:174–176.
6. Brueckner S, Sedemund-Adib B, Malik E, et al. Treatment of a postpartum bleeding complication with recombinant factor VIIa [abstract 3945]. American Society of Hematology Congress. Orlando, Florida, USA, 2001.
7. Breborowicz GH, Sobieszczyk S, Szymankiewicz M. Efficacy of recombinant activated factor VII (rFVIIa, NovoSeven) in prenatal medicine. *Arch Perinat Med* 2002;**8**:21–27.
8. Zupancic Salek S, Sokolic V, Viskovic T, Sanjug J, Simic M, Kastelan M. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. *Acta Haematol* 2002;**108**:162–163.
9. Sobieszczyk S, Breborowicz GH, Markwitz W, Mallinger S, Adamski D, Kruszynski Z. Effect of recombinant activated factor VII (RFVIIa; NovoSeven) in a patient in haemorrhagic shock after obstetrical hysterectomy. *Ginekol Pol* 2002;**73**:230–233.
10. Bouwmeester FW, Jonkhoff AR, Verheijen RH, van Geijn HP. Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII. *Obstet Gynecol* 2003;**101**:1174–1176.
11. Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teeraratkul S, Hongeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2000;**11**(Suppl 1):S101–S105.
12. Laurian Y. Treatment of bleeding in patients with platelet disorders: is there a place for recombinant factor VIIa? *Pathophysiol Haemost Thromb* 2002;**32**(Suppl 1):37–40.
13. Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002;**42**:114–124.

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