SUCCESSFUL USE OF RECOMBINANT FACTOR VIIa FOR TREATMENT OF SEVERE POSTPARTUM HEMORRHAGE

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Primary postpartum hemorrhage, defined as bleeding from the genital tract of 500 mL or more in the first 24 hours after childbirth, is one of the most common causes of maternal death worldwide. Although the maternal mortality of primary postpartum hemorrhage is lower in European countries (1 in 100,000 deliveries) than in developing countries (1 in 1000 deliveries), 1 postpartum blood loss still results in severe maternal morbidity,2 such as hypovolemic shock, adult respiratory distress syndrome, hepatic failure, and disseminated intravascular coagulopathy.3 Early, effective, and preferably noninvasive treatment is therefore essential.

Primary postpartum hemorrhage is initially managed by restoration of blood volume, administration of oxytocin and prostaglandins, and the correction of coagulation.2 If these initial conservative therapeutic measures do not control the bleeding, more drastic and invasive interventions such as bilateral artery ligation, angiography with selective embolization, or, as a last resort, hysterectomy can be performed.

Recombinant factor VIIa (rFVIIa; NovoSeven) is a safe and effective drug for the treatment of bleeding episodes in patients with inherited or acquired hemophilia A or B and antibodies to the relevant coagulation factor (VIII or IX, respectively). Recently rFVIIa has been used successfully in patients with congenital or acquired platelet disorders, thrombocytopenia, and severe von Willebrand’s disease (type 3). The use of rFVIIa in patients with severe bleeding without known coagulation factor deficiencies or (preexisting) bleeding disorders has been reported in several case reports.4-7

We describe a case of severe postpartum hemorrhage due to uterine atony resistant to conservative treatment in which use of a single dose of rFVIIa successfully controlled the bleeding and thereby obviated invasive procedures.

Case Report

A 33-year-old nulliparous woman was delivered of a healthy boy (weight 3540 g) at 41 weeks’ gestation at home under the supervision of a midwife. The delivery was uncomplicated, and 10 minutes after childbirth an intact placenta was delivered spontaneously. Because of excessive and persistent vaginal bleeding, the mother was referred to our hospital.

At arrival, approximately 40 minutes after childbirth, the estimated blood loss was about 1 L. On physical examination, the mother’s hemodynamic condition was stable, with an arterial blood pressure of 120/70 mm Hg and a regular heart rate of 84/min. The uterus was hypotonic and had several small vaginal lacerations for which suturing was not necessary. The hemoglobin level was 106 g/L, and hematocrit was 0.31. The mother’s coagulation status was not determined.

Initial management consisted of routine monitoring of vital signs, placement of a urinary catheter, fluid replacement with 1 L of crystalloids, and intravenous infusion of oxytocin at 6.5 µg/min. During the next few hours, the bleeding persisted, and the patient’s hemodynamic condition became unstable; she had an arterial blood pressure of 84/38 mm Hg and a pulse rate of 124/min. She was transferred to the operating room for inspection of the genital tract.

In the operating room, initial management consisted of rapid replacement of blood volume with 1 L of colloids and 3 units of packed cells during a period of 30 minutes, which resulted in stabilization of the hemodynamic parameters. Examination did not reveal...
any retained placental fragments or major rupture of the birth canal, but profuse bleeding originating from the uterus was noted. Despite an infusion of oxytocin, the uterus remained hypotonic; an intravenous infusion of sulprostone (60-120 µg/h) was started, and bimanual massage of the uterus was performed. The patient was transferred to the postanesthesia care unit for continuous hemodynamic monitoring and correction of coagulation status.

The laboratory results were as follows: hemoglobin 76 g/L, hematocrit 0.22, platelet count 36 x 10^9/L, and activated partial thromboplastin time 49 seconds. Desmopressin 0.3 µg/kg was administered intravenously. Six hours after arrival in the postanesthesia care unit, the patient had received 13 units packed red blood cells, 6 units of fresh-frozen plasma, and 2 units of 5-donor concentration platelets for transfusion. The hemoglobin level was 79 g/L and the platelet count was 79 x 10^9/L. Despite nearly normal in vitro coagulation parameters, vaginal bleeding persisted at 600 mL/h. The estimated total blood loss at this point was almost 6 L. In a last attempt to control the bleeding noninvasively, an intravenous bolus injection of 90 µg/kg rFVIIa was administered.

The response to rFVIIa was rapid; the bleeding was controlled within 15 minutes. The oxytocin and sulprostone infusions were continued for another 6 hours. Because no further hemorrhaging occurred, we did not administer a second dose of rFVIIa. The blood loss in the 24 hours after rFVIIa administration was less than 250 mL. No side effects were noted. Four days after delivery, the patient was discharged from the hospital in good clinical condition. Further evaluation by a hematologist did not reveal evidence of any inherited or acquired bleeding disorder.

**Discussion**

The mechanism of action of FVIIa involves increased thrombin generation at sites of vascular damage, changes in fibrin structure, and enhanced platelet deposition and platelet aggregation at the site of vascular injury.4 Recombinant FVIIa is well established as an effective hemostatic agent for the treatment of spontaneous and surgical hemorrhaging in patients with hemophilia A or B and antibodies to factor VIII or factor IX, respectively. More recently, reports have indicated that the clinical usefulness of rFVIIa is not confined to patients with coagulation abnormalities. In experiments in animals, use of rFVIIa resulted in a dramatic reduction in trauma-related blood loss and mortality.7 In a double-blind randomized trial,8 rFVIIa reduced perioperative blood loss and the need for transfusion in patients undergoing retropubic prostatectomy. Although rFVIIa is increasingly being used to achieve hemostasis in hemorrhaging in a variety of clinical situations,11,12 only a few cases13,14 have been reported in which rFVIIa was used to treat obstetric hemorrhage in patients without preexisting coagulopathy. In these cases, rFVIIa was used successfully in a last attempt to control life-threatening bleeding after conservative and surgical measures had been unsuccessful.

In our case, rFVIIa was given at an earlier stage, and invasive interventions could be avoided. The early use of rFVIIa as presented here could potentially reduce the need for invasive interventions such as bilateral artery ligation, angiographic selective embolization, or hysterectomy, thereby avoiding the inherent risks and costs of these interventions and the enormous consequences of a possibly preventable hysterectomy in young women.

We found no indication of systemic activation of coagulation in our patient. Extended clinical experience in patients with hemophilia suggests that administration of rFVIIa is relatively safe; the incidence of thrombotic events has been low.

**Conclusion**

Diagnosis of the underlying cause of postpartum bleeding, fluid replacement, uterotonics, and therapy with specific coagulation factors, plasma, or platelets remain the initial treatment for patients with postpartum hemorrhage. However, when these measures are not successful, administration of rFVIIa should be considered before invasive therapy. However, further studies on the optimal timing of rFVIIa administration and on its cost-effectiveness and safety in obstetric patients are necessary.

**REFERENCES**


Successful Use of Recombinant Factor VIIIa for Treatment of Severe Postpartum Hemorrhage
Ankie E.W. Hamaekers, Walther N.K.A. van Mook, J.P.M. Offermans and Marco A.E. Marcus

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