

Successful Treatment of Life-Threatening Postpartum Hemorrhage With Recombinant Activated Factor VII

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BACKGROUND: Postpartum hemorrhage is one of the most common causes of maternal mortality and morbidity worldwide. The aims of treatment are to maintain the circulation and to stop the bleeding. The latter is achieved by either medical or surgical management. In intractable bleeding, emergency hysterectomy is usually required.

CASE: A 30-year-old nullipara presented with major postpartum hemorrhage due to uterine atony and vaginal lacerations. The patient developed hemorrhagic shock, resulting in prolonged prothrombin time, prolonged activated partial thromboplastin time, and low levels of factor VIII and fibrinogen. Treatments with uterotonic drugs, suturing, ligation of internal iliac arteries, subtotal hysterectomy, packing of the pelvis, and blood transfusion failed to control diffuse pelvic and vaginal bleeding. Recombinant activated factor VIIa (60- μ g/kg intravenous bolus injection) was given as a final attempt to control the bleeding. The bleeding was successfully controlled within 10 minutes after administration. No side effects were noted.

CONCLUSION: Recombinant factor VIIa may be an alternative hemostatic agent in a patient with life-threatening postpartum hemorrhage unresponsive to conventional therapy. (Obstet Gynecol 2003;101:1174-6. © 2003 by The American College of Obstetricians and Gynecologists.)

Postpartum hemorrhage is one of the most common causes of maternal mortality and morbidity worldwide. Primary postpartum hemorrhage is defined as bleeding from the genital tract of 500 mL or more in the first 24 hours after the delivery of the newborn.¹ Blood loss of more than 1000 mL after delivery is used as a clinical diagnosis of major postpartum hemorrhage, which occurs in 1-6% of deliveries in developed countries.^{2,3} The most common cause of postpartum hemorrhage is uter-

ine atony. Other causes include retained placental fragments, abnormal adhesion of the placenta, lower genital tract lacerations, uterine rupture, uterine inversion, and coagulopathy.

Acute management of postpartum hemorrhage involves restoration of blood volume and control of bleeding. Several therapies have been used to control the bleeding: Medical therapies include oxytocin, ergot alkaloids and prostaglandins, and surgical procedures include suturing, uterine packing, uterine artery or internal iliac artery ligation, and selective arterial embolization.⁴ In cases of intractable bleeding unresponsive to treatments, hysterectomy is usually required as a final measure to control the bleeding. This is often associated with high morbidity.

Recombinant activated factor VIIa (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) was originally developed for the treatment of bleeding in patients with hemophilia A or B with inhibitors to factor VIII or IX. Recently, it has been successfully used to prevent or control bleeding in several other conditions, including thrombocytopenia, platelet function disorders, impaired liver functions, and extensive surgery and severe trauma with profuse bleeding.⁵ Little information is available on the use of recombinant activated factor VIIa in obstetrics and gynecology. We report a case of life-threatening postpartum hemorrhage due to uterine atony and vaginal lacerations, in which uterotonic drugs, suturing, ligation of internal iliac arteries, subtotal hysterectomy, and blood transfusions failed to control the bleeding. As a final attempt, recombinant activated factor VIIa was given, resulting in successful control of the bleeding.

CASE

A 30-year-old nullipara delivered a 3670-g boy at 40 weeks' gestation in a local hospital, by means of vacuum extraction because of maternal exhaustion and prolonged second stage of labor. She developed postpartum hemorrhage 1 hour after delivery. Examination under anesthesia did not reveal any retained placental fragments or cervical rupture. There were several vaginal lacerations with profuse bleeding. Suturing failed to control the bleeding. The patient was transfused with 12 U of packed red blood cells and 8 U of fresh frozen plasma. Because of the uncontrollable bleeding, the patient was referred to our academic hospital 6 hours after delivery.

At presentation, she was in hemorrhagic shock. Blood oozing from the intravenous cannula insertion site was noted. The laboratory results were as follows (normal range): hemoglobin 7.7 g/dL (12.1-16.1), hematocrit 22% (37-47%), platelet count $225 \times 10^9/L$ (150-450), prothrombin time (PT) international normalized ratio

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Table 1. Summary of Clinical Course, Laboratory Results, and Treatments

	0-6	7	8	9	10	11	12	13
Blood transfusion (U)								
RBCs	12	4	4	6	8	8	-	-
FFP	8	4	4	6	6	3	3	-
Platelets	-	2	-	2	-	-	2	-
Clinical manifestation	PPH started 1 h after delivery	Hemorrhagic shock, cardiac arrest, distended abdomen	Uterine atony, pulmonary edema, pneumothorax	Subtotal hysterectomy	Oozing from operative wound	Bleeding stopped	ARDS	
Treatments	Oxytocin, ergot alkaloids, examination under anesthesia	Resuscitation, high-pressure ventilation, laparotomy, desmopressin	Sulprosten, bimanual compression, bilateral iliac artery ligation	Subtotal hysterectomy	Packing of pelvis	rFVIIa 60 µg/kg		rFVIIa 120 µg/kg
PT (INR)		1.99	1.78	1.96	2.39	2.11	1.39	0.91
APTT (s)		56	58	107	133	92	118	51
Hct (%)/Hb (g/dL)		22/7.7	32/11.0				43/15.3	33/12.6
Platelet count ($\times 10^9/L$)		225	135		22		19	85

RBCs = red blood cells; FFP = fresh frozen plasma; PPH = postpartum hemorrhage; ARDS = adult respiratory distress syndrome; rFVIIa = recombinant activated factor VIIa; PT = prothrombin time; INR = international normalized ratio; APTT = activated partial thromboplastin time; Hct = hematocrit; Hb = hemoglobin.
 * Patient was transferred from a local hospital to our academic hospital 6 hours after delivery.

1.99 (0–1.20), and activated partial thromboplastin time (PTT) 56 seconds (0–40). During stabilization the patient went into cardiac arrest. Resuscitation was successful. Furthermore, the patient’s abdomen rapidly distended, and it became progressively difficult to maintain adequate artificial ventilation because of high intraabdominal pressure. Emergency exploratory laparotomy revealed a massive amount of ascites and a large atonic uterus. Despite bimanual compression, oxytocin intravenous infusion, and sulproston (250 mg \times 2) injection into the myometrium, the uterus remained atonic with profuse vaginal bleeding. A bilateral ligation of the internal iliac arteries also could not stop the bleeding. Consequently, a subtotal hysterectomy was done. After hysterectomy, blood oozing continued from the operative and vaginal wounds despite packing of the pelvis. In total, the patient received 42 U of red blood cells, 34 U of fresh frozen plasma, and 6 U of pooled-platelet concentrates over the period of 12 hours. The laboratory results showed prolonged PT (international normalized ratio 2.39) and activated PTT (133 seconds), with low levels of factor VIII (22% [normal range 60–120%]) and fibrinogen (0.9 g/L [normal range 2.0–4.0]) and a low platelet count ($22 \times 10^9/L$). Because all attempts to control the life-threatening bleeding had failed, an intravenous bolus injection of 60-µg/kg NovoSeven was given as a last attempt to control the bleeding. Within 10 minutes after administration of recombinant activated factor VII, the bleeding from the operative and vaginal wounds nearly stopped. Besides fresh frozen plasma and tranexamic acid, no other hemostatic agents were given at that time. Two hours after the first dose, a second dose of 120-µg/kg bolus intravenous injection was given for consolidation. There were no further hemorrhagic episodes, and no further blood transfusions were required. Table 1 shows the clinical course of the patient and the treatments received. The patient developed pulmonary edema, bilateral pneumothorax, and adult respiratory distress syndrome, requiring high-pressure ventilation. Her clinical condition improved 3 days after the operation. Ten days after delivery, the patient was discharged from the hospital in good clinical condition. No adverse effects from recombinant activated factor VII were noted.

COMMENT

Postpartum hemorrhage remains a major cause of maternal morbidity and mortality worldwide. The World Health Organization estimated 585,000 maternal deaths yearly worldwide, of which 25% were due to severe bleeding. The World Health Organization also estimated 20 million annual maternal morbidities due to

bleeding.⁶ When medical therapies and conservative surgical procedures fail to control the bleeding, hysterectomy is usually needed. Emergency postpartum hysterectomy is associated with significant blood loss, need for blood transfusion, and more postoperative complications.⁷ An emergency hysterectomy will also have a major psychological impact on the mother.

Recombinant activated factor VII has been successfully used to prevent and control bleeding in both hemophilic and nonhemophilic patients.⁵ The hemostatic effect of recombinant activated factor VII is thought to be mediated by enhancing the rate of thrombin generation, leading to a full thrombin burst necessary for providing a fully stabilized fibrin plug with a tight fibrin structure, making it resistant to premature lysis.^{5,8}

There is limited literature on the use of recombinant activated factor VII in obstetrics and gynecology. Recombinant activated factor VII was successfully used to control bleeding in the following cases: intractable postoperative bleeding after pelvic exenteration for recurrent cervical cancer, endometrial ablation in a patient with intractable menorrhagia due to hereditary factor VII deficiency,⁹ and pregnant women with hereditary factor VII deficiency who underwent normal delivery as well as cesarean delivery.^{10,11} Regarding postpartum hemorrhage, a case report¹² showed that recombinant activated factor VII successfully controlled life-threatening postpartum hemorrhage in a woman who developed severe disseminated intravascular coagulation, liver dysfunction, and renal failure.

In our reported case, the hemostatic effectiveness of recombinant activated factor VII was immediate and dramatic. The bleeding was successfully controlled within 10 minutes after the administration of the first dose of recombinant activated factor VII. The patient did not need any further red blood cell transfusion. It is not possible to judge whether the second increased dose given 2 hours after the first dose was required. It is plausible that if recombinant activated factor VII had been given at an earlier stage, the amount of blood loss would have been less. Further studies on the optimal dose and timing of recombinant activated factor VII administration in postpartum hemorrhage are needed.

In conclusion, this case suggests a potential role of recombinant activated factor VII in the treatment of

major postpartum hemorrhage unresponsive to conventional treatments.

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