Recombinant Factor VIIa in Management of Spontaneous Subcapsular Liver Hematoma Associated With Pregnancy

Shakil H. Merchant, MD, Prasad Mathew, MD, Timothy J. Vanderjagt, MD, Thomas R. Howdieshell, MD, and Kendall P. Crookston, MD, PhD

Departments of Pathology, Pediatrics, and Surgery, University of New Mexico, Albuquerque, New Mexico

BACKGROUND: Spontaneous subcapsular liver hemorrhage is a rare but life-threatening complication of pregnancy. Optimal management of an expanding hematoma or ruptured capsule has not been established.

CASES: We report 3 patients with preeclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome with spontaneous subcapsular liver hematomas. The first 2 patients with ruptured liver hematomas experienced life-threatening hemorrhage. The third patient experienced uncontrollable vaginal bleeding, liver hemorrhage, and was in imminent danger of capsule rupture. Despite aggressive surgical intervention and traditional blood component therapy, adequate hemostasis could not be achieved in any of these patients. Recombinant factor VIIa was used to achieve hemostasis in all three patients.

CONCLUSION: Recombinant factor VIIa is an effective adjunct in the treatment of preeclamptic patients with expanding or ruptured subcapsular liver hematoma. (Obstet Gynecol 2004;103:1055–8. © 2004 by The American College of Obstetricians and Gynecologists.)

Spontaneous subcapsular liver hemorrhage with or without rupture is a rare but potentially life-threatening complication of pregnancy that is almost exclusively associated with severe preeclampsia or with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. It occurs in approximately 1% to 2% of patients with preeclampsia, with a quoted incidence of approximately 1 per 45,000 live births.[1] The optimal management of spontaneous liver hematoma with capsule rupture has not been established. Conservative management with hemodynamic support results in high maternal and fetal mortality, whereas aggressive surgical intervention (hepatic artery ligation or embolization, hepatorrhaphy, liver packing), though often successful at hemorrhage control, carries the risk of hepatic ischemia and further dysfunction. This added surgical insult to a liver already compromised because of toxemia might result in liver failure and death.[2]

Recombinant factor VIIa (NovoSeven, Novo Nordisk, Princeton, NJ) is a hemostatic agent approved by the U.S. Food and Drug Administration for use in hemophilia patients with factor inhibitors. It has also been shown to be effective in nonhemophiliac patients with extensive organ damage, hemorrhage, and coagulopathy who do not respond to blood component therapy.[3] However, there are no prior reports of the use of recombinant factor VIIa in the management of patients with subcapsular liver hematomas. Here we report three cases wherein recombinant factor VIIa was successfully used in the management of such patients.

CASE 1

Case 1 was a woman in her mid-30s, gravida 3, para 2, with a history of preeclampsia who presented at 23 weeks of gestation with severe right upper quadrant pain. She was transferred by life flight from an outlying hospital to a tertiary care center. Upon arrival, she suffered seizures and cardiac arrest and was successfully resuscitated. Results of initial laboratory studies are shown in Table 1. The patient was clinically diagnosed with eclampsia, HELLP syndrome, consumptive coagulopathy, and fetal demise. A computed tomography scan revealed a subcapsular liver hematoma with capsule rupture. A stillborn fetus was delivered by cesarean. Exploratory laparotomy revealed a ruptured subcapsular hematoma of the liver and lacerations involving predominantly the right lobe. Approximately 2.5 L of clotted blood was evacuated from the hematoma. The hepatic artery was clamped for 20 minutes, and the liver was packed to achieve hemostasis. During surgery and in the immediate postoperative period the patient received 16 U of packed red cells, 18 U of platelets, 10 U of cryoprecipitate, and 14 U of fresh frozen plasma. However, the liver continued to bleed, and the patient remained hemodynamically unstable. As a last resort, a dose of intravenous recombinant factor VIIa (90 μg/kg) was administered and repeated 2 hours later. Within a few hours of beginning treatment there was dramatic control of bleeding, and so a third dose was withheld. Hemodynamic stability was achieved over the next 24 hours; the hematocrit stabilized at 33%, with an activated partial thromboplastin time (PTT) of 31 seconds and prothrombin time (PT) of 10.7 seconds (international normalized ratio 0.95). However, the patient developed anuric renal failure. Despite continued hemodynamic and ventilatory support, her condition did not improve.

Address reprint requests to: Kendall P. Crookston, MD, PhD, University of New Mexico Health Sciences Center, Department of Pathology, MSCO8-4640, One University of New Mexico, Albuquerque, NM 87131; e-mail: kcrookston@bigfoot.com.

0029-7844/04/$30.00

doi:10.1097/01.AOG.0000127943.68645.96

Table 1. Hematology, Coagulation, and Liver Profile Test Results From the Three Patients Discussed

Laboratory test	Case 1	Case 2	Case 3	Reference range
White blood count	6.4×10^9/L	19.6×10^9/L*	11.2×10^9/L*	4–10.6×10^9/L
Hemoglobin	3.2 g/dL*	10.9 g/dL*	9.6 g/dL*	12–16 g/dL
Hematocrit	11%*	33%*	29%*	36–48%
Platelet count	34×10^9/L*	66×10^9/L*	102×10^9/L*	150–400×10^9/L
Schistocytes on blood smear	None	None	None	< 1/high power field
Prothrombin time	35.5 s*	14.1 s*	17.5 s*	9–14 s
International normalized ratio	3.2*	1.26*	1.57*	0.88–1.24
Activated partial thromoboplastin time	88 s*	33 s	31 s	24–37 s
Fibrinogen	40 mg/dL	197 mg/dL	81 mg/dL*	150–400 mg/dL
D-dimer (qualitative)	Increased			Normal
D-dimer (quantitative)		14.1 μg/mL*	> 20 μg/mL*	< 0.5 μg/mL
Total protein (serum)	3.4 mg/dL*	2.0 mg/dL*	4.4 mg/dL*	5.9–8.3 mg/dL
Albumin (serum)	1.4 mg/dL*	1.0 mg/dL*	1.7 mg/dL*	3.1–4.7 mg/dL
Bilirubin (total)	1.4 mg/dL	0.1 mg/dL	0.5 mg/dL	0–1.4 mg/dL
Aspartate aminotransferase	3400 U/L*	547 U/L*	96 U/L*	3–70 U/L
Alanine aminotransferase	2843 U/L*	484 U/L*	7 U/L	3–78 U/L
Alkaline phosphatase	66 U/L	71 U/L	250 U/L*	20–145 U/L

* Abnormal result.

It was determined that the patient had suffered severe anoxic brain damage as a result of the cardiac arrest. Ventilatory support was withdrawn by family request on the fourth day after admission.

Autopsy revealed a large subcapsular liver hematoma dissecting Glisson's capsule from the surface of the entire right lobe, with laceration of the hepatic parenchyma and capsule rupture. There was no evidence of systemic thrombosis identified.

CASE 2

Case 2 was a woman in her early 30s, gravida 1, para 0, who presented at 32 weeks of gestation with severe right upper quadrant pain. She was initially evaluated at a local hospital, where an ultrasound examination was performed and revealed placenta previa, intrauterine fetal death, and a liver mass. The patient was immediately transferred to a tertiary care center. Results of laboratory studies upon her arrival are shown in Table 1. The patient was clinically diagnosed with preeclampsia and HELLP syndrome and was taken to the operating room, where a stillborn fetus was delivered by cesarean. Exploratory laparotomy revealed a ruptured liver hematoma with active hemorrhage and lacerations involving both lobes of the liver. Approximately 3 L of blood was evacuated from the abdominal cavity and hematoma; the liver was packed to achieve hemostasis. During the course of surgery, the patient received 6 U of packed red cells, 6 U of platelets, and 4 U of fresh frozen plasma. The hemorrhage was controlled only partially. She continued to bleed, and the hematocrit could not be stabilized despite an additional 2 U of packed red cells given postoperatively. In an attempt to achieve hemostasis, 3 doses of recombinant factor VIIa were administered at 2-hour intervals (120 μg/kg initially, then 90 μg/kg × 2). Over the course of treatment there was dramatic control of bleeding, with no further transfusion requirement. The hematocrit and coagulation profile stabilized, with a hematocrit of 32%, an activated PTT of 35 seconds, and a PT of 9.3 seconds (international normalized ratio 0.83). Over the next few days, the packs were removed and the abdominal wall closed with absorbable mesh in preparation for skin grafting. Her postoperative complications included a pleural effusion requiring tube thoracostomy and infection of a subphrenic fluid collection requiring open drainage. The patient recovered and was discharged 20 days later from the intensive care unit.

CASE 3

Case 3 was a woman in her mid-30s, gravida 1, para 0, presented at 33 weeks' gestation who complained of headache. Her blood pressure was 170/100 mm Hg but normalized with bed rest and magnesium sulfate administration. She was hospitalized for observation, with a working diagnosis of preeclampsia. Laboratory studies on admission revealed a white blood cell count of 8.8×10^9/L with normal differential count, hemoglobin of 13.5 g/dL, hematocrit of 39%, and a platelet count of 239×10^9/L. Urine analysis revealed trace proteinuria, whereas her coagulation profile, liver profile, serum creatinine, uric acid, and lactate dehydrogenase levels were essentially within normal limits. Over the next several days, the patient reported positive fetal movement and denied headache, right upper quadrant pain, and visual changes. Regular biophysical profiles remained reassuring.

Three days after admission, the patient acutely developed severe vaginal bleeding and uterine cramping. Her blood pressure was 136/68 mm Hg. An ultrasound examination revealed no overt signs of placental abruption; however, there was no fetal heart movement, and a 16-cm subcapsular liver hematoma was discovered that was confirmed by computed tomography scan of the abdomen. Laboratory results are shown in Table 1. The patient was clinically diagnosed as having preeclampsia, HELLP syndrome, and consumptive coagulopathy secondary to suspected placental abruption. Over the next 2 hours she continued to bleed; blood pressure dropped to 70/40 mm Hg, hematocrit and platelet count decreased to 19% and 60 $\times$ 10^9/L, respectively, and her PT increased to 24 seconds (international normalized ratio 2.17). Lactate dehydrogenase was 2786 U/L (reference 300–650).

A cesarean delivery was performed; a stillborn fetus was delivered, and the suspected abruption of the placenta was confirmed. Estimated blood loss during surgery was approximately 1,300 mL. Postoperatively, the patient continued to bleed from the surgical site. Her coagulation studies remained abnormal despite transfusion of 2 U of packed red cells, 6 U of platelets, 4 U of fresh frozen plasma, and 10 U of cryoprecipitate. Two doses of recombinant factor VIIa (approximately 90 μg/kg) were administered 2 hours apart. Within a few hours after the first dose, the bleeding was controlled, and her hematologic parameters began to stabilize, with a hematocrit of 25%, an activated PTT of 26 seconds, and a PT of 9 seconds (international normalized ratio 0.8). There were no signs suggestive of thromboembolism or other adverse effects. She recovered quickly, and no further blood products were needed. She was discharged 6 days later from the intensive care unit.

COMMENT

This report describes 3 cases of pregnancy-associated spontaneous subcapsular liver hematoma in which recombinant factor VIIa was used to achieve hemostatic control. The pathogenesis of subcapsular liver hematoma and subsequent rupture is unclear. More than 80% of cases occur in patients with preeclampsia or eclampsia; HELLP syndrome is commonly present.[1] Fibrin deposition in the hepatic sinusoids is speculated to be the initiating event.[2] Fibrin deposition might lead to platelet activation, thrombus formation, occlusion of capillaries, and subsequent hepatic hemorrhage and necrosis. Coalescence of these hemorrhagic areas leads to dissection of Glisson's capsule from the liver surface. Concurrent consumptive coagulopathy occurring in preeclamptic patients often aggravates the condition. A tense subcapsular hematoma might rupture spontaneously or secondary to trivial trauma during labor or convulsions, leading to catastrophic, life-threatening hemorrhage. It is reasonable to conclude that achieving adequate hemostasis would not only control blood loss in the event of a rupture, but might prevent the formation or expansion of the subcapsular hematoma.

Recombinant factor VIIa is an effective drug that induces hemostasis via 2 potential mechanisms: through the tissue factor pathway, and also by acting on activated platelets independently of tissue factor.[3,4] Both mechanisms lead to generation of thrombin and formation of a hemostatic plug through cleavage of fibrinogen to form fibrin. Because recombinant factor VIIa–mediated thrombin generation is predominantly localized to the surface of activated platelets, it is assumed to produce a local effect without systemic activation of coagulation.[3,4] However, the efficacy and safety of its use in pregnant patients has not been established. Although there are anecdotal reports citing successful use of recombinant factor VIIa in pregnant patients with factor VII deficiency and in other obstetric bleeding emergencies, there are no prior reports of the use of recombinant factor VIIa in the management of subcapsular liver hematoma or subsequent rupture.[5,6] The decision to use this agent in our patients was based on an individual risk-and-benefit assessment. In the first patient, recombinant factor VIIa was administered after conventional therapies had failed and as a last resort to stop life-threatening hemorrhage. The results clearly demonstrated effective hemostasis; however, the beneficial effects were realized too late, as the patient had already suffered postarrest anoxic damage to vital organs. The use in the other 2 patients was influenced by the initial hemostatic success from the first case and also by the decision to be more proactive in the management of patients with subcapsular liver hematoma. Although the use of recombinant factor VIIa in the third patient was directed to control refractory vaginal bleeding, in retrospect achieving adequate hemostatic control most likely prevented the subcapsular hematoma from expanding and increasing the risk of liver rupture.

One reason that recombinant factor VIIa has not been widely used in pregnant patients is the theoretical risk of thrombosis, particularly in patients with consumptive coagulopathy. Coagulopathy is not uncommon in patients with preeclampsia and HELLP syndrome.[7] Because randomized controlled trials to prove safety and efficacy cannot be performed in this subset of patients, inference has to be drawn from reported cases in which emergency use of recombinant factor VIIa is based on risk-and-benefit assessment. There are now reports of safe and effective use of recombinant factor VIIa in management of uncontrollable hemorrhage in patients

with disseminated intravascular coagulation.[8] In our 2 surviving patients, there was no evidence of thromboembolism or other adverse effects of recombinant factor VIIa. Additionally, an autopsy performed in the first patient did not reveal any evidence of systemic thrombosis. These results are in agreement with the earlier reports and suggest that recombinant factor VIIa can be used safely in such patients. Hedner and Erhardtsen[3] reviewed the safety of recombinant factor VIIa and concluded that in the limited number of thromboembolic events reported, most were due to predisposing factors, such as previous cardiovascular disease and advanced age. In data from more than 170,000 doses given, 5 patients with thromboembolic events were reported, 6 with acute myocardial infarction, and 4 with cerebrovascular disorders. Several studies done in swine liver-injury models have shown a decrease in blood loss and correction of coagulation parameters, with no evidence of associated thromboembolic events detected.[9,10] In summary, these cases add important clinical observations for treating patients with life-threatening hemorrhage that have failed conventional therapies. In particular, recombinant factor VIIa is an effective–and potentially life-saving–adjunct treatment in preeclamptic and HELLP syndrome patients experiencing subcapsular liver hematoma, with or without rupture. The role of recombinant factor VIIa in other obstetric bleeding emergencies should be explored further.

REFERENCES

1. Greenstein D, Henderson JM, Boyer TD. Liver hemorrhage: recurrent episodes during pregnancy complicated by preeclampsia. Gastroenterology 1994;106:1668–71.
2. Aziz S, Merrell RC, Collins JA. Spontaneous hepatic hemorrhage during pregnancy. Am J Surg 1983;146:680–2.
3. Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. Transfusion 2002;42:114–24.
4. Hedner U. Recombinant factor VIIa (NovoSeven) as a hemostatic agent. Semin Hematol 2001;38:43–7.
5. Eskandari N, Feldman N, Greenspoon JS. Factor VII deficiency in pregnancy treated with recombinant factor VIIa. Obstet Gynecol 2002;99:935–7.
6. 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;108:162–3.
7. Negrier C, Lienhart A. Overall experience with NovoSeven. Blood Coagul Fibrinolysis 2000;11 suppl:S19–24.
8. Moscardo F, Perez F, de la Rubia J, Balerdi B, Lorenzo JI, Senent ML, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. Br J Haematol 2001;113:174–6.
9. Jeroukhimov I, Jewelewicz D, Zaias J, Hensley G, MacLeod J, Cohn SM, et al. Early injection of high-dose recombinant factor VIIa decreases blood loss and prolongs time from injury to death in experimental liver injury. J Trauma 2002;53:1053–7.
10. Schreiber MA, Holcomb JB, Hedner U, Brundage SI, Macaitis JM, Hoots K. The effect of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. J Trauma 2002;53:252–7.

Received April 22, 2003. Received in revised form May 12, 2003. Accepted May 16, 2003.

An Accessory Uterine Cavity as a Cause of Pelvic Pain

Michael P. Steinkampf, MD, Michelle T. Manning, MD, Sejal Dharia, MD, and Kenneth Dean Burke, MD

Department of Obstetrics and Gynecology, University of Alabama at Birmingham; and Burke and Robinson, MD, PC, Birmingham, Alabama

BACKGROUND: Pelvic pain is a common gynecologic problem. We report a case of a noncommunicating accessory uterine cavity as a cause of pelvic pain in a young adolescent.

CASE: A 17-year-old nulligravida presented with worsening pelvic pain. Transvaginal ultrasound revealed a 3-cm cavity within the myometrium. Hysteroscopy revealed a normal uterine cavity. Surgical excision of the accessory cavity just lateral to the normal uterine cavity was achieved through laparotomy. Pathology confirmed endometrial tissue in the accessory cavity. Pelvic pain resolved after surgery.

CONCLUSION: A noncommunicating uterine cavity should be considered in the differential diagnosis of pelvic pain. (Obstet Gynecol 2004;103:1058–61. © 2004 by The American College of Obstetricians and Gynecologists.)

Address reprint requests to: Michael P. Steinkampf, MD, University of Alabama at Birmingham, Department of Obstetrics and Gynecology, 547 OHB, 619 19th Street South, Birmingham, AL 35249-7333; e-mail: msteinkampf@uabmc.edu.

The female genital tract develops from the müllerian or paramesonephric duct system. Incomplete development or canalization can result in obstructive congenital anom-

0029-7844/04/$30.00
doi:10.1097/01.AOG.0000127944.68645.58