

Regional Anesthesia for a Parturient with Venous Sinus Thrombosis and Placental Abruption Undergoing Fractional Heparin Therapy

Robert S. Holzman, M.D., F.A.A.P.,* Sibel Bessim, M.D., F.A.C.O.G.†

THE increased incidence of thrombosis and hypercoagulability during pregnancy are well recognized and require anticoagulation for symptomatic sequelae. The following case illustrates our perioperative treatment of a patient with vaginal bleeding while undergoing treatment for a transverse sinus thrombosis.

Case Report

A 32-yr-old gravida 1 para 0 woman at 34 $\frac{1}{2}$ weeks presented with abdominal pain and vaginal bleeding. She had a witnessed generalized seizure at home at 29 weeks of gestation, was brought to the hospital, and was diagnosed with a left transverse sinus thrombosis and left temporal lobe cortical infarct. Serial electroencephalograms showed interictal epileptiform activity, localized to the left temporal lobe. She was started on 80 mg enoxaparin subcutaneously twice a day and remained well until the day of admission, when she noted vaginal bleeding with abdominal cramping. A nonstress test was reactive, with a fetal heart rate in the 140s and good beat-to-beat variability. Membranes were intact. Intravenous access was established with two peripheral intravenous lines. In consultation with a local high-risk obstetric center, it was considered inadvisable to transport the patient because of the continued vaginal bleeding. They further advised protamine reversal for emergency surgery.

A plan of continuous monitoring next to the operating room was decided upon. At 12 h after the patient's enoxaparin dose, a planned cesarean delivery during spinal anesthesia would be performed. If clinical deterioration and nonreassuring fetal heart rate monitoring supervened, cesarean delivery would be performed with a general anesthetic.

Although there were brief episodes of late decelerations that responded to supplemental oxygen and repositioning, the majority of the time the fetal heart rate remained in the 140s with good beat-to-beat variability. Uterine resting tone was soft throughout. At 11.5 h after the enoxaparin dose, the patient reported increased abdominal discomfort, and a primary low transverse cesarean delivery was performed during spinal anesthesia using 8 mg bupivacaine (0.75%), 10 μ g fentanyl, and 0.25 mg preservative-free morphine through a 25-gauge Whitacre needle. No blood was noted in the needle before medication delivery. The operative time was 24 min. Placental abruption was confirmed, and the baby was delivered with Apgar scores of 9 (1 min; color) and 10 (5 min). The pathology specimen (placenta and adherent

clot) measured 18 \times 16 \times 5 cm. The patient was stable in the postanesthesia care unit after delivery and was discharged from there 115 min after arrival, with a pain score of 2/10. She recovered uneventfully and was discharged on postoperative day 4. Hematology and neurology consultants recommended resumption of enoxaparin for 5-6 weeks.

Discussion

Venous thromboembolism is estimated to occur in 5-10:10,000 pregnancies, approximately fivefold higher compared with nonpregnant women of similar age. Pregnancy is associated with an increased concentration of clotting factors, including I (fibrinogen), V, VII, VIII, IX, X, and XII. Thrombin generation also increases. Concurrent disorders such as obesity, lupus anticoagulant, protein S and C deficiencies, antithrombin III deficiency, and dysfibrinogenemia further increase the risk of thromboembolism.

Cerebral vein thrombosis is a subgroup of thrombotic disorders. The transverse sinus has the highest frequency of thrombosis (86%). Inherited prothrombotic tendencies such as factor V Leiden mutations, protein S and C deficiencies, and antithrombin III deficiencies account for 10-15% of cases of cerebral venous sinus thrombosis.¹ During pregnancy, prothrombotic risk factors or a direct cause can be identified in approximately 85% of patients with sinus thrombosis. During the last trimester of pregnancy and after delivery, the risk of sinus thrombosis is increased. The frequency of peripartum and postpartum sinus thrombosis is approximately 12 cases per 100,000 deliveries. Focal seizures with or without generalized seizures occur in 47% of affected patients. More than 80% have a good neurologic outcome.²

Hypercoagulability and abruption may indeed be a continuum because histologic examination of uteroplacental vessels and intervillous architecture in abruption typically reveals increased fibrin deposition, thrombosis, and hypoxia-associated endothelial and trophoblast changes.³ With perinatal mortality rates as high as 34%, placental abruption is a critical situation.⁴ Large retroplacental bleeding is associated with a mortality rate of 50% or greater.

Recommendations for anticoagulation after thrombotic events have included therapeutic unfractionated or low-molecular-weight heparin (LMWH) therapy throughout pregnancy, including the antepartum period until

* Department of Anesthesia, Newton-Wellesley Hospital. Associate Professor of Anaesthesia, Harvard Medical School, Boston, Massachusetts. † Staff Physician, Department of Obstetrics and Gynecology, Newton-Wellesley Hospital.

Received from the Department of Anesthesia and the Department of Obstetrics and Gynecology, Newton-Wellesley Hospital, Newton, Massachusetts. Submitted for publication December 28, 2005. Accepted for publication February 26, 2006. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Holzman: Department of Anesthesiology, Perioperative and Pain Medicine, Children's Hospital Boston, 300 Longwood Avenue, Boston, Massachusetts 02115. robert.holzman@childrens.harvard.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

labor. Because LMWH has greater antithrombotic activity (anti-factor Xa) than anticoagulant activity (anti-factor IIa), it does not affect the activated partial thromboplastin time. Monitoring of anti-factor Xa activity is not routinely performed. Peak anti-factor Xa activity occurs within 3–5 h of administration, and 50% of the total anti-factor Xa activity disappears within 6 h. So far, there have been no studies comparing the effect of LMWH with unfractionated heparin in the treatment of sinus thrombosis. LMWH seems to be a reasonable alternative to standard heparin therapy and has several specific advantages because it permits self-administration at home, does not require physiologic monitoring, and may reduce the risk of heparin-induced thrombocytopenia and osteoporosis. In a series of women (29 antenatal and 7 postpartum) treated with LMWH for venous thromboembolism in pregnancy, 15 received regional anesthesia for delivery and were given enoxaparin in a reduced dose of 40 mg daily, without complications.⁵

Given these issues and the inevitability of a surgical delivery, our concerns centered on balancing the risks and benefits of general and regional anesthesia. A general anesthetic could possibly have adverse effects on maternal intracranial pressure and volume and would likely have sedative effects on the infant if a deeper, stress-attenuating anesthetic technique were chosen. There were further considerations of impaired uterine tone and alteration of cerebral blood flow with the effects of positive-pressure ventilation. There is a small but finite increased risk of aspiration and airway difficulty with the administration of a general anesthetic in pregnancy. Monitoring of mental status would be impossible intraoperatively. Emergence possibly poses its own risks of even transient increases in intracranial pressure as well as alteration of the seizure threshold. Finally, choosing a general anesthetic prevents maternal and paternal participation in childbirth. A subarachnoid block with a small-gauge needle seemed an acceptable alternative. An epidural approach was not considered an acceptable choice. We therefore set our plans as outlined above.

There are several long-term implications for pregnant patients with a diagnosis of venous thromboembolism, including the need for prolonged heparin therapy during pregnancy and prophylaxis during subsequent pregnancies. Moreover, the optimal duration of oral anticoagulant treatment after the acute phase is unknown. With a history of thromboembolism during pregnancy, the incidence of recurrence during a subsequent pregnancy has been estimated at 4–15%. Unfortunately, without prospective studies, firm guidelines for antepartum prophylaxis are difficult to establish.⁶ For patients with a known hypercoagulable state or a history of venous thromboembolism unrelated to pregnancy, those with a deficiency of antithrombin III have a 70% incidence of recurrence, those with a deficiency of protein C have a

33% incidence, and those with a deficiency of protein S have a 17% incidence.^{7–9} Coumadin therapy, started after delivery, should be continued for at least 6 weeks, and longer (e.g., 3–6 months) for previous thromboembolic events.

Few guidelines, let alone studies, exist to inform decisions about the use and timing of regional anesthesia. The Working Group on Behalf of the Obstetric Medicine Group of Australasia, in a consensus-based guideline, suggested that therapeutic subcutaneous injections of LMWH or unfractionated heparin should be ceased at least 24 and preferably 36 h before regional anesthesia (no differentiation was made between epidural or spinal techniques).¹⁰ Given the clinical situation described above and our hope that a nontraumatic spinal anesthetic after a 12-h interval would strike a favorable balance for the risks involved, we preferred the recommendation from Horlocker and subsequently from the American Society for Regional Anesthesia that needle placement for a single-dose spinal anesthetic should occur at least 10–12 h after the last LMWH dose.¹¹

The suggestion for protamine reversal is controversial. Although standard heparin anticoagulant effects are antagonized by protamine, because of reduced protamine binding to LMWH fractions, only the anti-IIa activity of LMWH is completely reversed; anti-Xa activity is not fully neutralized. Moreover, anti-IIa and anti-Xa activity may return up to 3 h after protamine reversal, perhaps because of additional LMWH released from subcutaneous depots.¹¹

We emphasize that the decision to use regional anesthesia in uncommon and complex settings such as this one must be made on an individual basis, with the risks of spinal hematoma or general anesthesia judged against their benefits.

References

1. Deschiens M, Conard M, Horellou M, Ameri A, Preter M, Chedru F, Samama M, Bousser M: Coagulation studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. *Stroke* 1996; 27:1724–30
2. Stam J: Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005; 352:1791–8
3. Lockwood C: Inherited thrombophilias in pregnant patients: Detection and treatment paradigm. *Obstet Gynecol* 2002; 99:333–41
4. Yla-Outinen A, Palander M, Heinonen P: Abruptio-placentae: Risk factors and outcome of the newborn. *Eur J Obstet Gynaecol Reprod Biol* 1987; 25:23–8
5. Rodie V, Thomson A, Stewart F, Quinn A, Walker I, Greer I: Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: A case series. *Br J Obstet Gynaecol* 2002; 109:1020–4
6. Toglia M, Weg J: Venous thromboembolism during pregnancy. *N Engl J Med* 1996; 335:108–14
7. Brenner B, Shapira A, Bahari C, Haimovich L, Seligsohn U: Hereditary protein C deficiency during pregnancy. *Am J Obstet Gynecol* 1987; 157:1160–1
8. Finazzi G, Barbui T: Different incidence of venous thrombosis in patients with inherited deficiencies of antithrombin III, protein C and protein S. *Thromb Haemost* 1994; 71:15–8
9. Trausch-Van Horn J, EL C, Easterling T, Bovill E: Pregnancy loss and thrombosis with protein C deficiency. *Am J Obstet Gynecol* 1992; 167:968–72
10. Hague W, North R, Gallus A, Walters B, Orlikowski C, Burrows R, Cincotta R, Dekker G, Higgins J, Lowe S, Morris J, Peek M: Anticoagulation in pregnancy and the puerperium. *Med J Aust* 2001; 175:258–63
11. Horlocker T, Heit J: Low molecular weight heparin: Biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; 85:874–85

Severe Anaphylaxis after Albumin Infusion in a Patient with Ahaptoglobinemia

Noriko Shimode, M.D.,* Hiroaki Yasuoka, M.D.,* Masaharu Kinoshita, M.D.,† Kana Hirashima, M.D.,† Saburo Tsujimoto, M.D.,‡ Chikara Tashiro, M.D.,§ Akira Kokubunji, B.Sc.||

WE report a patient who developed severe anaphylactic shock and life-threatening ventricular fibrillation immediately after starting infusion of 5% human plasma protein fractions (Albuminar-5%; ZLB Behring, Tokyo, Japan) during general anesthesia. He was diagnosed postoperatively with ahaptoglobinemia associated with haptoglobin gene deletion. We postulated that this event may have occurred as a result of allergic reaction to a precipitating antibody to haptoglobin associated with use of plasma protein fractions.

Case Report

A 55-yr-old Japanese man was scheduled to undergo subtotal gastrectomy based on a diagnosis of gastric cancer. Ten days before his surgery, he was transfused with 2 units of packed erythrocytes (in Japan, 1 unit = 140 ml) for anemia (8.9 g/dl hemoglobin). On the next 2 days, he was also given 2 units of packed erythrocytes with no adverse events. The patient had hypertension, which was controlled by diet, and first degree atrioventricular block on electrocardiogram.

Before induction of general anesthesia, an epidural catheter was inserted. Anesthesia was induced using propofol, fentanyl, and vecuronium and was maintained with sevoflurane in nitrous oxide and oxygen. After approximately 90 min, blood pressure decreased from 101/71 to 69/44 mmHg, abruptly coincident with infusion of Albuminar-5% (ZLB Behring, Tokyo, Japan). Capnography showed a bronchospasm-like waveform, and peak inspiratory pressure increased significantly (39 cm H₂O). Pulse oxygen saturation also decreased from 98% to 82%. Blood pressure showed a much greater decrease (35/21 mmHg), and electrocardiogram showed bradycardia (44 beats/min) and ischemic changes. Circulatory collapse continued with injection of epinephrine and isosorbide mononitrate, and finally it led to ventricular fibrillation; we repeated administration of lidocaine, and the patient was defibrillated 10 times at 200 J and once at 300 J. With subsequent examination, it was found that he had a stenosis of the left anterior descending coronary. We could not control his circulation and finally introduced a percutaneous cardiopulmonary support system. We decided not to continue the operation, and the patient was transferred to the intensive care unit. We asked the Japanese Red Cross Center (Tokyo, Japan) to investigate this episode. The levels of various proteins were measured, and serum haptoglobin was undetectable in this patient. Antihaptoglobin antibody was detected by enzyme-linked immunosorbent assay and Western blotting analysis. His Hp del gene and

the Hp gene (exon 1) were analyzed too. Therefore, the patient was diagnosed as having ahaptoglobinemia and was homozygous for *Hp^{del}*. These episodes were caused by anaphylactic shock due to the antigen-antibody reaction between the patient's antihaptoglobin antibody and haptoglobin present in 5% human plasma protein fractions.

We planned a second operation and prepared frozen fresh plasma from the patient with ahaptoglobinemia and packed erythrocytes washed twice with 0.9% sodium chloride because of anemia. This second operation was uneventful, and the patient was discharged from our hospital 28 days after the operation.

Discussion

Haptoglobin is a plasma protein that is synthesized in the liver. Its main physiologic function is to prevent hemoglobin leakage from the kidney at hemolysis by specific combination with hemoglobin and formation of a stable complex. Haptoglobin synthesis is reduced in patients with hepatocellular diseases and hemolysis, but some studies have suggested that cases of hypo- or ahaptoglobinemia in tropical countries have a genetic origin.¹

The incidence of ahaptoglobinemia among Japanese people has been reported to be approximately 1/4,000 and is much higher than that of immunoglobulin A deficiency in the Japanese population (1/30,000). Moreover, the incidences of ahaptoglobinemia in the Chinese and Korean populations have been reported to be approximately 1/1,000 and 1/1,500, respectively. They suggested that approximately 0.025% Japanese people, 0.067% of Korean people, and 0.1% of Chinese people are at risk of producing an antibody against haptoglobin after repeated blood transfusions.²

In Japan, nonhemolytic side effects after blood transfusion were reported in 10 cases of ahaptoglobinemia, 6 cases of immunoglobulin A deficiency, and 3 cases of complement component 9 deficiency between 1993 and 2001.³

The characteristics of anaphylactic shock after transfusion in patients with ahaptoglobinemia are serious. For example, the patient shows circulatory shock or bronchospasm. Eight of 10 patients with ahaptoglobinemia developed anaphylactic shock immediately after transfusion.³ Anaphylactic reactions also occurred after administration of platelet concentrate of blood and 25% albumin. Most cases have a history of previous transfusion, but one patient was reported with no history of transfusion but was pregnant.⁴ There were no associations between age or sex and anaphylactic shock after transfusion in ahaptoglobinemic patients.³

Our patient had no serum haptoglobin, and antihapto-

* Instructor, † Fellow, || Medical Technologist, Department of Anesthesiology, § Professor and Chairman, Department of Transfusion Medicine, Hyogo College of Medicine, Hyogo, Japan. ‡ Chief, Department of Anesthesiology, Saiseikai Nakatsu Hospital, Osaka, Japan.

Received from the Department of Anesthesiology, Hyogo College of Medicine, Hyogo, Japan. Submitted for publication December 28, 2005. Accepted for publication March 27, 2006. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Shimode: Department of Anesthesiology, Hyogo College of Medicine, 1-1, Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan. nshimode@hyo-med.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

globin antibody was detected by enzyme-linked immunosorbent assay and Western blotting analysis. He received packed erythrocyte transfusion before the operation and developed an antibody to haptoglobin. Our observations suggested that ahaptoglobinemic patients exhibit anaphylactic transfusion reaction to plasma protein due to antibodies to haptoglobin. Haptoglobin is included in Albuminar-5% at a level of approximately 25 mg/dl, and the average content of haptoglobin is higher than other plasma proteins (3 mg/dl in Albumin-20%, 0.7 mg/dl in Albumin-25% from Japanese Red Cross Society). The relation between the volume of haptoglobin and anaphylactic shock is unknown, and no anaphylactic shock was observed with transfusions of autologous blood or washed packed erythrocytes. Therefore, anaphylactic transfusion reactions to plasma proteins are rare events, and transfusions of autologous blood or washed packed erythrocytes should be

useful in treating patients with known antibodies or histories of reactions.⁵

The authors thank Eiko Shimada, M.S., the Japanese Red Cross Central Blood Center, Tokyo, Japan, for the analysis of patient's serum and DNA and her helpful suggestions.

References

1. Bunn HF, Rosse W: Hemolytic anemias and acute blood loss, Harrison's Principles of Internal Medicine, 15th edition, Japanese translation. Edited by Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Tokyo, Medical Sciences International, 2003, pp 704-16
2. Koda Y, Watanabe Y, Soejima M, Shimada E, Nishimura M, Morishita K, Moriya S, Mitsunaga S, Tadokoro K, Kimura H: Simple PCR detection of haptoglobin gene deletion in anahaptoglobinemic patients with antihaptoglobin antibody that causes anaphylactic transfusion reactions. *Blood* 2000; 95:1138-43
3. Shimada E, Ikeda K, Mitsunaga S, Nakajima K, Tadokoro K: Anaphylactic transfusion reactions: Allergy-ka [in Japanese]. 2003; 16:550-9
4. Morishita K, Shimada E, Watanabe Y, Kimura H: Anaphylactic transfusion reactions associated with anti-haptoglobin in a patient with ahaptoglobinemia. *Transfusion* 2000; 40:120-1
5. Nishiki S, Hino M, Kumura T, Hashimoto S, Ohta K, Yamane T, Takubo T, Tatsumi N, Kitagawa S, Kamitani T, Watanabe Y, Shimada E, Juji T, Iida S: Effectiveness of washed platelet concentrate and red cell transfusions for a patient with anahaptoglobinemia with antihaptoglobin antibody. *Transfusion* 2002; 12:71-3