Know Your Options for Peripartum Hemorrhage

A leading cause of maternal mortality, hemorrhage accounts for up to 18% of pregnancy-related deaths.

BY KERRI WACHTER
Senior Writer

ASHEVILLE, N.C. — Peripartum hemorrhage is one of the leading causes of maternal mortality, making it important to understand the myriad options for controlling bleeding, David C. Mayer, M.D., said at the Southern Obstetric and Gynecologic Seminar.

"Unfortunately, over the decades, hemorrhage has never been moved out of the top three causes of maternal mortality," said Dr. Mayer of the department of anesthesiology at the University of North Carolina at Chapel Hill.

Peripartum hemorrhage accounts for as much as 18% of pregnancy-related deaths in the United States, according to one estimate.

Resuscitation is the first goal in the management of peripartum hemorrhage (PPH). Make sure there is an adequate number of intravenous lines and maintain adequate volume by using crystalloids, colloids, packed red blood cells, fresh frozen plasma, or platelets, as necessary. Get baseline blood laboratory tests, including a coagulation profile, and monitor arterial blood gas levels and urinary output. Invasive monitoring with arterial or central venous lines may be necessary, as may consultation with specialists, cautioned Dr. Mayer.

There are a number of options to control bleeding: pharmacologic (such as prostaglandins), autologous blood transfusion, and selective arterial embolization. Pharmacologic therapy includes oxytocics, ergot alkaloids, prostaglandins, and recombinant activated factor VII (rFVIIa). Keep in mind almost all studies of pharmacologic therapies are based on routine elective cesarean sections.

"It may have very little applicability to a patient with an atonic uterus," Dr. Mayer said.

Oxytocin (Pitocin) is the pharmacologic therapy that most obstetricians go to first to control bleeding. The drug can be used as prophylaxis in women who are at high risk for PPH, with doses of 10-40 U/L administered intravenously. "For uterine atony, I'm very aggressive with oxytocin, except for giving a large bolus," Dr. Mayer said during the meeting.

He recommends using up to 40-60 U/L given intravenously. Avoid using an intravenous bolus greater than 2 IU. A bolus less than 2 IU can be effective and is unlikely to be problematic, especially if blood pressure is supported. "Just remember that if your patient is already hypotensive, it's probably not the thing to do—increasing the rate of oxytocin," said Dr. Mayer, also of the department of obstetrics and gynecology at the university.

Ergot alkaloids—ergonovine and methylergonovine—are very effective at inducing contractions. While the exact mechanism of action is unclear, ergot alkaloids are believed to have adrenergic, dopaminergic, and tryptaminergic effects. "Most people now think that it's the adrenergic effect that causes the increased uterine contractility," Dr. Mayer said.

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However, it's also thought that the adrenergic effect is responsible for some of the concerning side effects. Ergot alkaloids produce vasoconstriction that can last for 1-4 hours. These drugs are associated with hypertension, increased central blood volume, coronary vasospasm, pulmonary edema, and cerebrovascular accidents. The dopaminergic stimulation produces nausea and vomiting that can be severe in about 20% of patients. Ergot alkaloids should be given in a very controlled manner to avoid complications such as vasospasm and decreased ejection fractions.

The range of options in the prostaglandin family could grow in the future. "We don't have the whole armamentarium that they do in Europe and I think that someday we may," Dr. Mayer said. Prostaglandins available in the United States include carboprost (15-methyl prostaglandin $F_{2\alpha}$), misoprostol (prostaglandin E_1), dinoprost (prostaglandin $F_{2\alpha}$), and dinoprostone (prostaglandin E_2).

The side effect profile for these drugs is different from that of the oxytocics or ergot alkaloids. Prostaglandins do not contribute to significant vasoconstriction. One big drawback for these drugs is that they cannot be administered intravenously. Instead, prostaglandins can be administered intramuscularly and intramyometrially. Prostaglandins E_1 and E_2 also can be administered orally, vaginally, or rectally.

"There's nothing to suggest that there's a better drug than carboprost," Dr. Mayer said. Carboprost (Hemabate) is 10 times more potent than the parent compound (prostaglandin $F_{2\alpha}$). It has minimal effect on the cardiovascular system. Severe bronchial constriction is the one real problem associated with carboprost, even in patients without asthma. This can result in bronchospasm, regional ventilation perfusion mismatch, and arterial desaturation. Patients receiving carboprost should be monitored with a pulse oximeter until at least an hour after the last dose. Dosing is 250 mcg given every 15 to 45 minutes, up to a maximum of 8 doses.

Both carboprost and methylergonovine are contraindicated in patients with cardiovascular and respiratory problems. Misoprostol—a synthetic oral prostaglandin E_1 analog—may be one option for these patients. "Misoprostol plays a major role in [the management of] peripartum hemorrhage," Dr. Mayer said. It is not associated with bronchospasm, has no major cardiovascular effects, and can be stored for a long time without refrigeration.

Based on the literature, the evidence is not sufficient at this time to support routine use of misoprostol for the prevention of PPH. "The drug has such a high safety profile that it may be more useful in a treatment role" said Dr. Mayer. He recommends using 800-1,000 mcg administered rectally.

Many PPH cases have a major component of acquired coagulopathy, making rFVIIa (Novoseven) a treatment option, indicated for hemophilia A or B, with inhibitors of factor VII or factor IX. The drug induces hemostasis independent of factor VII or IX. It complexes with tissue factor to promote the conversion of factor IX to factor IXa, factor X to factor Xa, and prothrombin to thrombin—the key parts of the coagulation cascade. The drug produces clots, making it theoretically contraindicated in patients with disseminated intravascular coagulopathy.

The literature on the use of rFVIIa for PPH has been encouraging so far. In a recent study, 12 patients with severe PPH (estimated blood loss of 5-25 L) were treated with the drug (Br. J. Anaesth. 2005;94:592-5). All had previously undergone surgery, and one-third had arterial ligation. Eleven patients had a positive response.

"They're feeling was to give the drug at 1.5 L blood volume loss—it buys time," said Dr. Mayer.

However, the drug is very expensive. The cost equivalent of a single 90-mcg/kg dose is 50 units of packed red blood cells, 2 days in the ICU, or an embolization procedure. In patients for whom surgical options have been explored, for whom there are no vascular interventional radiology options, for whom significant blood products are required, and for whom results of the coagulation studies are elevated, "this is a very reasonable drug to give," Dr. Mayer said.

Intraoperative autologous transfusion should be considered when there is major blood loss and an inadequate amount of packed red blood cells is available. Potential risks associated with obstetric use include amniotic fluid embolism and maternal exposure to fetal red cells. However, in 400 exposures to intraoperative autologous transfusion, there has been only one case of amniotic fluid embolism that was not confirmed pathologically. Heparin toxicity also has been associated with the technique.

At the University of North Carolina at Chapel Hill, the cell saver has been used for 12 obstetric patients. "It's a perfect solution for Jehovah's Witnesses with risk factors, such as a known placenta percreta," said Dr. Mayer. Blood was autotransfused in only one case though. This patient received 1,200 mL of salvaged blood with no problems.

Selective arterial embolization is highly successful when it can be performed. There are very few complications—fever is the most common. The technique also can be used prophylactically using a balloon. Coagulopathy is not a contraindication, so it's a good option for these patients. ■

Valacyclovir Prophylaxis Cheapest Route for Prevention

BY SHARON WORCESTER
Southeast Bureau

CHARLESTON, S.C. — Oral valacyclovir was the most economically favorable treatment choice for the prevention of intrapartum herpes transmission in a recent analysis.

The clinical outcomes and costs of the three strategies, including oral valacyclovir, oral acyclovir, and no prophylaxis, were compared using a decision analysis model in a hypothetical cohort of 1 million women with recurrent herpes infection. All strategies included cesarean section for patients with active lesions during labor, Monique G. Lin, M.D., of the University of Alabama, Birmingham, and her colleagues reported in a poster at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

The valacyclovir model included 500 mg given twice daily beginning at 36 weeks' gestation; the oral acyclovir model included 200 mg given four times daily beginning at 36 weeks' gestation.

The investigators used the literature and "local sources" to determine baseline costs, and based their analysis on current treatment strategies that employ polymerase chain reaction, viral culture, and high-dose intravenous acyclovir for treatment of affected neonates. Using this model, the researchers showed that the total costs in the hypothetical cohort were $9.94 billion for valacyclovir, $9.93 billion for acyclovir, and $13.7 billion for no prophylaxis.

The number of cases of neonatal death or moderate-to-severe neonatal morbidity associated with each treatment in this model was 1,911 with valacyclovir, 2,111 with acyclovir, and 8,240 with no prophylaxis.

The number of cases prevented by using valacyclovir prophylaxis was 6,239, and the number prevented by using acyclovir prophylaxis was 6,129.

The cost per case prevented was $1.57 million for valacyclovir and $1.62 million for acyclovir, the investigators reported at the meeting. ■