Update on Anesthetic Management of Pre-eclampsia

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Hypertensive diseases of pregnancy are a leading cause of maternal and perinatal morbidity and mortality (1). Despite increases in cardiac output and total blood volume, the blood pressure of women during the second or third trimester of pregnancy is lower than that measured in nonpregnant women of similar age. The reason for this is due to a decrease in systemic vascular resistance related to the elaboration of progesterone and prostacyclin, and secondly, to the development of the placental unit, which has the effect of an arteriovenous fistula. The American College of Obstetricians and Gynecologists has defined hypertension occurring during pregnancy as a sustained systolic blood pressure of 140 mmHg or sustained diastolic hypertension of 90 mmHg (1). Hypertensive disorders of pregnancy can be classified into three broad categories: pregnancy induced, which includes preeclampsia, eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), chronic hypertension preceding pregnancy, and chronic hypertension with superimposed preeclampsia (1). This review will focus on the anesthetic management of the woman with preeclampsia.

Etiology

Preeclampsia is a disease unique to the human pregnancy and therefore advances in research have been limited by the lack of an adequate animal model to study the disease. The etiology of preeclampsia remains unknown.

The most accepted etiology of preeclampsia is that it is caused by an increase in placental thromboxane relative to prostacyclin (2). During a normal gestation, the placenta produces equivalent amounts of thromboxane and prostacyclin. An absolute or relative increase in thromboxane causes vasconstriction, platelet aggregation, increased uterine activity and uteroplacental hypoperfusion, features consistent with preeclampsia.

Whatever the initial event, placental ischemia results in the release of uterine renin which catalyses the conversion of angiotensinogen to angiotensin II. The elaboration of this neurohormone causes widespread arteriolar constriction, tissue hypoperfusion and hypoxia. Aldosterone secretion is likewise stimulated, causing renal reabsorption of sodium and edema. Ischemia causes the breakdown of placental architecture, which results in the release of trophoblastic material into the maternal circulation and widespread fibrin deposition and platelet aggregation at sites of endothelial damage. If severe, coagulopathy may ensue and, in the case of the kidney, fibrin deposition in the glomerular vessels causes proteinuria.

Pathophysiology

Central Nervous System: The CNS shows signs of hyperirritability such as headache, visual disturbances and hyperreflexia. Seizures, which define eclampsia, may be related to obstruction of the microcirculation by platelet and fibrin clots or, alternatively, due to hypoxia caused by intense arterial vasospasm. Cerebral edema and/or hypertensive encephalopathy may also be present. The severity of central nervous system manifestations does not necessarily correlate with the degree of hypertension. Cerebral hemorrhage accounts for 30-40% of maternal fatalities due to preeclampsia.

Hepatic

Increased SGOT, LDH and alkaline phosphatase are frequent findings during the course of normal pregnancy but may be even further increased by preeclampsia. Hyperbilirubinemia, however, is not a common feature and should jaundice occur, another disease process, such as HELLP, should be considered. Subcapsular hematoma of the liver can cause intense epigastric pain and, rarely, the liver may rupture. Hepatic blood flow can be markedly decreased in preeclampsia due to splanchnic vasoconstriction. Tissue sections of liver taken at biopsy or postmortem show severe periportal necrosis.

Renal

Renal plasma flow and glomerular filtration rate increase rapidly during pregnancy so that in the second trimester these are almost 50% greater than values for age matched nonpregnant females. Creatinine clearance is increased so that blood levels of urea nitrogen and creatinine are lower in pregnant compared to nonpregnant patients. Renal function in the preeclamptic patient is markedly abnormal due to renal arteriolar vasoconstriction, and obliteration of the vascular lumina due to swelling of the glomerular epithelial cells and fibrin deposition. Renal plasma flow and glomerular filtration are markedly diminished and BUN and creatinine levels

elevated. Hyperuricemia is present and tends to be an early sign of deteriorating renal function. Proteinuria, if severe, can be as much as 10-15 grams per day and contributes to hypolbuminemia.

Coagulation

A hypercoagulable state exists during pregnancy. For instance, platelet count is elevated, above 200,000 platelets/mm^3 and fibrinogen levels are higher than those observed in nonpregnant women. The most common coagulation disorder in preeclamptic patients is a relative thrombocytopenia (100-150,000 platelets per mm^3). Despite a normal platelet count, platelet function can be impaired. Consumption coagulopathy may occur as platelets adhere to sites of endothelial damage but it is relatively rare and more probably related to placental abruption which is associated with preeclampsia (3). In severe cases, the prothrombin and activated partial thromboplastin time are elevated.

Cardiovascular

A recent study compared hemodynamic data obtained from pregnant versus untreated preeclamptic mothers who were not in labor (4). Unlike previous studies performed in patients who were in labor or had been treated for preeclampsia with hydration or magnesium, this study showed that the preeclamptic patient had a low pulmonary capillary wedge pressure, a high systemic vascular resistance, a low cardiac index and an elevated heart rate compared with normotensive pregnant controls (4). Patients with mild preeclampsia may have small intravascular volume deficits, approximately 10%, but if severe, deficits of up to 40% may occur.

The composition of the intravascular volume is also altered in the preeclamptic patient. Although total body water and sodium content are increased in mothers with preeclampsia, there is nonetheless a shift of fluid and protein away from the central compartment into the extra vascular compartment resulting in hypovolemia, hypoproteinuria and peripheral edema. Hemoconcentration is present and is a useful guide in estimating the degree of intravascular fluid depletion. Colloid osmotic pressure in preeclamptic patients is lower than that found in normotensive pregnant patients, further compounding the risk of pulmonary edema (5,6). Pulmonary edema may occur in up to 2% of severe preeclamptic women due to ventricular dysfunction, low colloid oncotic pressure, increased intravascular hydrostatic pressure, or increased pulmonary capillary permeability (6).

Placenta

Using a radioactive xenon technique intervillous blood flow of the placenta in preeclamptic women has been shown to be approximately 2/3's that of normotensive women during the third trimester (7). There is widespread vasospasm and fibrin deposition in the decidual arteries of the placenta.

Hypoperfusion of the uteroplacental unit results in chronic fetal hypoxemia and intrauterine growth retardation. Indeed, the incidence of poor fetal outcome (small for gestational age, prematurity and prenatal death) may be 3-4 times greater in the preeclamptic pregnancy compared to the normotensive obstetric population. Placental abruption is also a more common occurrence in patients with preeclampsia.

Preeclampsia is severe with systolic blood pressure of 160 mm Hg or diastolic pressure of 110 mm Hg, proteinuria > 5 g in 24 hr, oliguria refractory to fluid challenge, cerebral/visual disturbances, pulmonary edema, hepatic rupture/impaired liver function, thrombocytopenia, fetal compromise, and HELLP syndrome.

Management

Women with mild preeclampsia and an immature fetus may be managed expectantly until near term. However, women with progression of disease, such as worsening hypertension, thrombocytopenia, hepatic/renal dysfunction, eclampsia and non-reassuring fetal status require delivery, even if the fetus is immature. The definitive therapy of preeclampsia is delivery of the fetoplacental unit. All other measures are supportive and focus on normalizing hemodynamics parameters, preventing and treating seizures and correcting coagulopathy should it occur.

Volume Repletion

The low cardiac output noted in preeclamptic mothers can be corrected by intravascular volume repletion. Once right and left sided cardiac filling pressures normalize, cardiac index improves and maternal heart rate and systemic vascular resistance decrease (4). Maternal systolic and diastolic hypertension likewise improve with careful hydration (4). Volume expansion and normalization of hemodynamic indices should be expected to improve tissue

and fetal perfusion. Indeed an increase in urine output occurs in severely preeclamptic women after judicious hydration.

In patients with severe preeclampsia careful monitoring may provide a rational basis for correction of volume deficit and improvement in hemodynamic indices. An indwelling arterial line for continuous monitoring of blood pressure may be necessary. Monitoring of cardiac filling pressures is useful in fulfilling therapeutic as well as diagnostic objectives, particularly in women with pulmonary edema, severe refractory hypertension and oliguria. The pulmonary artery catheter is more reliable in severely afflicted patients since simultaneous measurements of right and left sided cardiac filling pressures have failed to show a correlation between the two in about 50% of patients (8). The ability to perform serial determination of cardiac output by the thermodilution method and calculate systemic vascular resistance make placement of a Swan Ganz catheter preferable to a CVP. The benefits gained from invasive hemodynamic monitoring must be weighed carefully against the risks of inadvertent arterial puncture in a patient who may have a coagulopathy. An indwelling urinary catheter should be inserted and output and specific gravity measured frequently.

Anticonvulsant Therapy

Diazepam is frequently used in other parts of the world to control central nervous system hyperexcitability. However, in the United States, magnesium sulfate therapy is the most commonly used anticonvulsant. The mechanism of action of magnesium in preventing eclampsia is as yet unknown.

Usually the mother receives a loading dose of 4 grams of magnesium sulfate (20% solution) by intravenous injection followed by a 1-2 grams per hour infusion. Renal excretion is the primary route of magnesium clearance and the elimination half-life is approximately 20-30 minutes in the presence of good renal function. Magnesium blood levels should be determined, particularly if renal dysfunction and oliguria are present. Magnesium, 6-8 mg/1, is considered therapeutic, increasing magnesium ion concentration results in progressive cardiorespiratory depression. Blood levels of 12-14 mg/1 are associated with ventilatory insufficiency and cardiac asystole occurs at blood levels of 22-24 mg/1. Monitoring the deep tendon patellar reflex is fairly good in identifying rising magnesium blood levels since these disappear at blood levels of 9-10 mg/1, well before cardiorespiratory embarrassment occurs. Magnesium tends to have a temporary beneficial effect on maternal hemodynamic status resulting in a slight decrease in systemic vascular resistance and increase in cardiac index.

Should eclampsia occur despite adequate magnesium therapy; seizures may be terminated with the intravenous administration of a small dose of thiopental or diazepam. Thiopental is preferred in the prepartum period since large doses of diazepam may be associated with neonatal hypotonia and impaired thermoregulation. Intravenous solutions of diazepam also contain sodium benzoate, which may compete with bilirubin for binding sites on albumin. This is particularly hazardous for the preterm neonate in whom diazepam administration may precipitate kernicterus. Prevention of maternal hypoxemia and aspiration of gastric contents should be the foremost goal.

Magnesium therapy enhances the effects of muscle relaxants. Magnesium ion competes with calcium and causes a decrease in the amount of acetylcholine released at the myoneural junction. The net result is that the action of nondepolarizing muscle relaxants is enhanced (9). The duration of action of succinylcholine may be prolonged by magnesium (10). The use of muscle relaxants, if necessary, should not be avoided in patients receiving magnesium therapy, rather careful monitoring of peripheral nerve function with a train of four stimulator should be routine in order to avoid prolonged block.

The placentral transfer and fetal uptake of magnesium ion can result in neonatal hypermagnesemia and result in neonatal hypotonia, respiratory depression and low Apgar score. Neonatal well being, in the face of magnesium therapy, depends on the prevention of birth asphyxia and prematurity.

Vasodilator Therapy

Antihypertensive drugs are used in the management of preeclampsia so as to improve hemodynamic status and prevent cerebral hemorrhage when conservative measures, such as fluid therapy, left uterine displacement and magnesium sulfate therapy are not sufficient. Hydralazine is a potent vascular smooth muscle dilator and has good bioavailability by oral or parenteral routes and results in an increase in cardiac index and decrease in total peripheral resistance when used in conjunction with appropriate volume repletion (4). Its use also results in increased uteroplacental perfusion and renal blood flow. It is most frequently administered by intravenous injection. Its peak onset of antihypertensive effect is between 15-20 minutes and the drug has a duration of action which lasts for about

6 hours. Maternal heart rate may increase as a reflex sympathetic response to direct vasodilation. Placental transfer of hydralazine may result in neonatal hypotension without severe adverse effect on the baby. More potent vasodilators such as sodium nitroprusside (SNP) and nitroglycerine (NTG) may be used to prevent cerebral hemorrhage caused by hypertensive crisis or systolic hypertension during laryngoscopy and intubation. This class of drugs is ideally suited for this purpose since they are administered by the intravenous route, their onset of action is rapid and their effect short lived after terminating the infusion.

Placental transfer of sodium nitroprusside has been demonstrated in pregnant ewes and results in fetal cyanide toxicity and increased fetal wastage if large doses of the drug are given (11). Smaller doses (5-10 ug/kg/min) of the drug can be used safely without undue risk of cyanide intoxication to mother or fetus, as long as administration of the drug is not for an extended period of time. Nitroglycerine may be used as an alternative to SNP and has a lower risk of cyanide toxicity than the latter.

Anesthetic Management

Analgesia for labor and vaginal delivery can be provided with segmental lumbar epidural anesthesia using a dilute concentration of local anesthetic or a combined spinal-epidural technique. Prior to initiation of regional analgesia, platelet count should be obtained and intravascular volume should be normalized. Even though preeclampsia is associated with sodium and water retention, fluid and sodium restriction are not necessary, and, in fact, may further exacerbate the disease by increasing the production of renin-angiotensin and aldosterone. Hydration can be accomplished with a balanced salt solution depending upon the severity of the syndrome. Once hydrated, epidural analgesia has several beneficial effects on maternal hemodynamic status caused by sympathetic blockade and decrease in systemic vascular resistance. With adequate hydration, left uterine displacement, and gradual induction, epidural anesthesia does not result in significant maternal hypotension and improves urinary output. The technique also prevents wide swings in blood pressure resulting from anxiety and pain. A major advantage of having a functioning epidural catheter in place for labor is that it can be rapidly converted to a suitable anesthetic for cesarean delivery.

For the fetus too epidural analgesia has some beneficial effects. Intervillous blood flow in the placenta of preeclamptic patients increases by up to 75% with epidural anesthesia (12). In alleviating the pain of labor, the technique also abolishes the need for administering narcotic or sedative medications to the mother, which may later depress the infant.

For cesarean section, since the level of sensory anesthesia must extend to at least the fourth thoracic dermatome, careful prehydration, as well as frequent blood pressure monitoring, either by an arterial cannula or electronic device, are prudent. Should hypotension occur (systolic blood pressure 100 mmHg or 20% decrease in systolic pressure) it should be corrected with increasing left uterine displacement and the rate of intravenous fluid administration. If necessary, ephedrine, administered by intravenous injection, will usually restore the maternal systolic blood pressure.

The definitive therapy is delivery of the infant and placenta. However, only in the most urgent situations (i.e. placental abruption) is there not enough time to institute appropriate monitoring, assess and treat volume depletion, control hypertension and prevent central nervous system complication with magnesium sulfate therapy. If no coagulopathy exists and volume status has been corrected, properly conducted regional anesthesia is preferred to general anesthesia. Both epidural and spinal anesthesia have been used for cesarean delivery in severely preeclamptic women (13). In the past, there has been concern that a sudden sympathectomy associated

with the use of spinal anesthesia would result in catastrophic hypotension. However, studies to date have shown that the incidence and severity of hypotension is similar in women with severe preeclampsia having a cesarean delivery with spinal or epidural anesthesia (13,14) Careful consideration should be given to the total dose of local anesthetic administered to the preeclamptic patient. A recent study demonstrated that the total maternal body clearance of lidocaine was prolonged in preeclampsia presumably due to a lower hepatic blood flow (15). Repeated administration of amide local anesthetics may result in higher maternal blood levels and toxicity. In this regard, 2-chloroprocaine may be a safer alternative since it is rapidly metabolized by plasma esterase's and is not dependent on hepatic metabolism for elimination.

Whereas spinal anesthesia is a suitable alternative to general anesthesia in many emergency situations, general anesthesia may be required in patients with severe coagulapathy or hemorrhage. There are however several hazards to the use general anesthesia in preeclamptic women. Tracheal intubation may be difficult because of mucosal edema in the glottis and oral cavity. A small diameter endotracheal tube (6.0 mm) with stylet should be available;

intubation under light levels of anesthesia can result in severe systemic and pulmonary artery hypertension. These responses can be blunted with short-term antihypertensive therapy, either with sodium nitroprusside or nitroglycerine prior to induction and intubation. Care must be exercised in titrating potent vasodilators in patients whose volume repletion has not been complete. Drugs with sympathomimetic effects should obviously be avoided (ketamine, ergot alkaloids). Lastly, if magnesium therapy has been instituted, a peripheral nerve stimulator should be used in order to avoid prolonged neuromuscular blockade due to the interaction between magnesium and depolarizing/nondepolarzing muscle relaxants.

Summary

Preeclampsia is a multisystem disease of unknown etiology requiring multidisciplinary intervention by the perinatal team in order to lessen maternal and fetal morbidity and mortality. Once volume status has been normalized and no severe coagulopathy exists, regional anesthesia can be used safely for vaginal or abdominal delivery. In urgent situations – general anesthesia may be necessary.

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