REVIEW ARTICLE

Recent advances in pre-eclampsia management: an anesthesiologist's perspective!

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ABSTRACT

Pre-eclampsia is an important cause of mortality and morbidity in parturients with varied presentations and controversial pathophysiology. The central pathology is a profound vasoconstriction in the vasculature leading to volume contraction and placental hypoperfusion. The management mainly involves a multi-disciplinary approach with the anesthesiologist playing a significant role for a positive outcome. Anesthesia for such parturients remains a challenge and starts with provision of labor analgesia which should be offered to all preeclamptic parturients. The neuraxial techniques of analgesia are most favourable for adequate pain relief and if contraindicated, intravenous PCA technique with the use of opioids should be used. Recent studies show favourable maternal and fetal outcomes with the use of patient controlled epidural analgesia technique with the combination of lower concentrations of local anesthetics with opioids. Regional anesthesia should be preferred in these parturients for cesarean section if not contraindicated. If general anesthesia is indicated, the techniques should be modified to prevent any stress response. A careful and prompt use of oxytocics should be done in all cases as the incidence of postpartum hemorrhage is high in these parturients.

Key words: Pre-eclampsia; Pre-eclampsia management, Pre-eclampsia risk factors, Labor analgesia; Anesthesia; Vasodilators; Cesarean section

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INTRODUCTION

Pre-eclampsia (disease of theories) is a controversial and complicated disease which needs active involvement of both the obstetrician and the anesthesiologist. It is one of the important cause of maternal morbidity and mortality characterized by hypertension and multiorgan system involvement. It complicates about 4-7 % of pregnancies.[1]The pathogenesis is still controversial. Intracerebral haemorrhage, eclamptic seizures, abruptio placentae, acute pulmonary edema, organ failure and coagulation abnormalities leads to maternal morbidity and mortality in severe preeclampsia.[2,3,4] Intrauterine growth retardation, preterm delivery and intrauterine fetal demise are some of the important fetal complications.[5] It is, however, a preventable condition with a multi-disciplinary team management approach. Current scientific evidence should be incorporated in institutional clinical practice.

DEFINITION

Pre-eclampsia can be defined as 'a blood pressure ≥140/90 mmHg after 20 weeks of gestation and involvement of one or more organ systems with previously normal blood pressure'.

The American College of Obstetricians and Gynecologists defines preeclampsia as 'the development of hypertension with proteinuria, edema or both (the traditional triad) induced by pregnancy after the 20th week of gestation'.[1, 6]

The International Society for the Study of Hypertension (ISSH) in its definition of preeclampsia does not include edema because it may be detected in 80% of normotensive pregnant women most of whom are healthy.[7] Severe pre-eclampsia includes severe hypertension and proteinuria with one or more of the following signs/symptoms e.g. severe headache not responding to treatment, seizures,

pulmonary edema, vision disturbances with papilledema, liver tenderness, vomiting, elevated liver enzymes, thrombocytopenia, hyperreflexia, absent or reversed umbilical/uterine artery end diastolic blood flow.[8]

SEARCH STRATEGY

We conducted this review to highlight the recent concepts in the pathophysiology and management of pre-eclamptic parturients with special consideration to the current strategies for anesthetic management of such parturients. A systematic literature search was done using search engines like PubMed and Google Scholar with the use of following single text words and combinations: pre-eclampsia, labor analgesia, anesthesia, vasodilators, cesarean section. The PubMed search was made from the year 1990 till date. The references of the relevant articles were cross checked and the articles describing labor analgesia in pre-eclampsia and anesthetic management in pre-eclampsia were included.

HELLP Syndrome

This is a severe form of pre-eclampsia. According to Sibai and Martin,[9,10] it is a syndrome of hemolysis as evidenced with elevated serum lactate dehydrogenase, elevated liver transaminases > 70 IU /L plus platelet count of <100 x 10^9/litre. In pregnancy other causes of hypertension may be there which may make the diagnosis of pre-eclampsia very challenging. Cocaine and amphetamine use, renal disease, pheochromocytoma and cardiovascular diseases such as coarctation, vasculitis and subclavian stenosis should be kept in mind.[11]

Pathophysiologic concepts in Pre-eclampsia

The exact etiology of pre-eclampsia is still unknown but placenta has been implicated in some hypotheses. Triad of physiological derangements include vasospasm, plasma volume contraction and local or disseminated intravascular coagulation. Placental hypoperfusion leads to release of various factors that triggers endothelial activation or dysfunction. Due to increased production or increased sensitivity to vasoconstrictors (angiotensin II, serotonin and endothelin) and decreased production or decreased sensitivity to vasodilators (nitric oxide and prostacyclin), vasospasm takes place which in turn leads to plasma volume contraction, increased capillary permeability and low plasma oncotic pressure. Peripheral tissue edema occurs due to redistribution of fluid from intravascular compartment to interstitial fluid space. Reduced production of anti-thrombin III and platelets activation leads to intravascular coagulation. Brain, liver and kidney are the most commonly affected systems due to organ hypoperfusion, which is the net effect. Obesity, chronic hypertension, chronic renal disease, diabetes type-I / gestational diabetes, connective tissue disease and multiple gestation are some of the risk factors for pre-eclampsia.

CONSERVATIVE MANAGEMENT OF PRE-ECLAMPSIA

Risk of mortality decreases by reduction of severe hypertension.[12] With the help of antihypertensive drugs peripheral resistance decreases and perfusion of uterus increases, which in turn help in decreasing fetal complications.

For systolic BP between 140-159 mmHg and diastolic BP 90-109 mmHg, oral labetalol is the drug of choice.[13,14] Methyl dopa and nifedipine are safe alternatives. For systolic BP ≥ 160 mmHg and diastolic BP ≥ 110 mmHg, the choice of drug should depend upon experience with that particular agent.[15] The preferred drugs include oral or intravenous labetalol, oral nifedipine (sublingual not recommended) and intravenous hydralazine (5-10 mg boluses every 20 min upto a cumulative dose of 30 mg). Cautious preloading with 500 ml crystalloid is recommended to avoid maternal hypotension.[13] Labetalol is not suitable for asthmatics. Nifedipine may cause profound muscle weakness and maternal hypotension with fetal distress in patients receiving magnesium sulphate.[16] Labetalol and nifedipine are better choices than hydralazine as recent evidences suggests.[17] In all cases blood pressure should be monitored carefully along with fetal heart rate monitoring.[18] In patients with pre-eclampsia and acute pulmonary edema, the preferred drug is glyceryl trinitrate as an intravenous infusion at the rate of 5 μg/min which can be increased every 3-5 min to a maximum dose of 100 μg/min.[4]

Eclampsia is associated with a mortality rate of 3.1%.[2,19] Drug of choice for eclampsia is magnesium sulphate. The risk of seizure recurrence is significantly reduced by the use of magnesium sulphate in comparison to diazepam, phenytoin and lytic cocktail (chlorpromazine + promethazine + pethidine).[20,21] Intensive care unit admission and morbidity related to mechanical ventilation and pneumonia is significantly reduced with magnesium sulphate compared with phenytoin.[22] Collaborative Eclampsia Trial regimen is 4-5 gm magnesium sulphate intravenously over 5 minute followed by infusion of 1 gm of magnesium sulphate every hour for 24 hours.[23] When magnesium sulphate is used in conjunction with other clinical parameters infusion may be stopped earlier (12 hours post-partum)[24,25] The other ultra-short protocol of magnesium sulphate which was found to be effective in 92.6% eclamptic patients is to give 4 gm magnesium sulphate intravenously followed by 10 gm intramuscularly.[26] Evidence suggests that use of magnesium sulphate reduces the risk of eclamptic seizures by 50%.[27] Monitoring of urine output, respiratory rate, oxygen saturation and patellar reflexes should be done with measurement of serum

magnesium levels. Intravenous 10% calcium gluconate is used slowly over 10 min to reverse its toxicity.

After corticosteroid administration to achieve fetal lung maturity, delivery is appropriate any time after 34 weeks of gestation in severe pre-eclampsia. Before 34 weeks, delivery is indicated if hypertension is refractory to treatment[28, 29] or there is maternal/fetal compromise.

ANESTHETIC MANAGEMENT

The selection of suitable anesthetic technique for patients with pre-eclampsia or eclampsia is a challenge for the attending anesthesiologist. The expertise of an experienced anesthesiologist is required with particular attention on fluid management, stabilization of blood pressure and seizure prevention.[30]

Fluid management; how much is too much?

A serious complication of severe pre-eclampsia is acute pulmonary edema which is frequent cause of intensive care unit admission and can lead to increased maternal mortality with perinatal mortality (up to 50%).[31] The intravascular volume may be decreased due to vasoconstriction rather than due to decreased blood volume.[32] A systematic review showed no advantage of volume expansion over no volume expansion.[33,34] Evidence suggests that in patients with normal renal function and stable serum creatinine levels volume expansion to treat oliguria is not recommended.[33]

Pain relief in labor; recent concepts in pre-eclampsia

It is a well-known fact that process of labor induces various physiological and metabolic changes in mother which may be deleterious to the fetal well-being. Maternal pain during labor induces a stressful condition with release of catecholamines, cortisol and adrenocorticotrophin hormone, all of which reduce the uterine perfusion and can have effects on fetal well-being. Maternal hyperglycemia, with poor insulin release, lipolysis and increased levels of fatty acids, causes fetal acidosis and increased fetal oxygen requirements. Analgesia during labor mitigates all these deleterious effects and thus improves overall maternal satisfaction and fetal well-being. Due to these beneficial effects of labor analgesia, its acceptance is on the rise, especially among the developed countries. In a report by NHS Maternity Statistics in United Kingdom in a period from 2005 to 2006, it was found that one third of the laboring women chose epidural analgesia.[35] In India, the awareness and acceptance of labor analgesia is still lacking and is only limited to few centres only.

Preferred methods of analgesia for labor

These are broadly classified into three categories;

1. Non-Pharmacological

This includes Transcutaneous Electrical Nerve Stimulation (TENS), touch and massage therapy, intradermal sterile water injections, acupuncture, water bath and hypnosis. These methods have been found to be effective but fail to provide scientific data analysis of quality of pain relief.[36]

2. Pharmacological

Two routes are preferred i.e. intravenous and regional. Intravenous route includes use of intravenous analgesics mainly the opioids either by boluses or by continuous infusion using infusion pumps. Use of patient-controlled analgesia (PCA) has been recently found to be a safe and effective method of achieving analgesia in laboring parturients.[37] El-Kerdawy et al used PCA with remifentanil in a loading dose of 0.5 μg/kg with the pump settings; lockout interval 5 min, bolus dose 0.25 μg/kg and continuous infusion at 0.05 μg/kg/min in 30 preeclamptic women and found to be equally effective for control of labor pain with minimal effect on mother as well as fetus.[38]

Abu- Halaweh et al reported a case of laboring woman with pre-eclampsia and diabetes who refused epidural analgesia and was successfully managed with the use of intravenous dexmedetomidine infusion. Although dexmedetomidine is not recommended for use in pregnant patient but this report suggests its beneficial role in labor analgesia in pre-eclampsia as it has blood pressure stabilizing effects with no deleterious maternal or fetal effects.[39]

3. Regional Analgesia

Neuraxial analgesia remains the best mode of analgesia in laboring women[40] and is also the preferred method in pre-eclamptic women as it maintains the uteroplacental perfusion abnormalities often seen in pre-eclampsia and helps in to diminish hypertensive response to pain.[41] The various techniques are lumbar epidural analgesia and combined spinal epidural analgesia. Patel et al used epidural analgesia in 100 pre-eclamptic laboring women and compared them with normotensive laboring women and with those pre-eclamptic laboring women who did not received epidural analgesia and found to be effective with no increase in cesarean section rate or any other obstetric complications.[42] Moir et al used epidural analgesia in 150 women with pre-eclampsia and found a 20% reduction in blood pressure with favorable maternal and fetal outcomes and advised it to be used along with the anticonvulsant therapy.[43]

Recently patient controlled epidural analgesia (PCEA) has been extensively studied in normotensive laboring women and has been found to have following advantages over continuous epidural infusion (CEI). Firstly amount of local anesthetic can be reduced with this technique, and

secondly higher maternal satisfaction is achieved as patient has control over the dose of the drug to be received. Also number of unscheduled clinician top ups can be significantly reduced due to maintenance of adequate level of analgesia.[44]

The various local anesthetic drugs which can be used through PCEA are bupivacaine 0.0625-0.125% or ropivacaine 0.1-0.2% with 2 μg/ml fentanyl. It is given as continuous background infusion of 5-10 ml/hr with patient controlled bolus of 5 ml and lock out interval of 15 min.

There is not much clinical data of use of PCEA in pre-eclamptic laboring women but its advantages in normotensives can be extrapolated to the patients with pre-eclampsia.

The use of combined spinal epidural technique of labor analgesia in severe pre-eclampsia has been documented in literature with modest decrease in blood pressure and an effective control of labor pain when low doses of local anesthetics are used intrathecally which are then supplemented with drugs through epidural route.[45] Simmons et al, however, in their meta-analysis of comparison of traditional epidural technique with that of combined spinal epidural (CSE) technique of labor analgesia, found no added benefit of CSE in terms of maternal satisfaction, rate of cesarean birth and neonatal outcome with the only advantage being a slightly faster onset of analgesia with the CSE technique.[46]

Anesthesia for Cesarean Section- Is there any difference?

Neuraxial anesthesia is the technique of choice in the absence of any contraindications.[47] If the platelet count is >75x10^9/L with no other coagulation abnormality, the likelihood of major complications is minimal.[48] Titrated epidural, single shot spinal and combined spinal epidural are equally safe.[49] The incidence of hypotension after neuraxial anesthesia in pre-eclamptic patients is low and can be managed easily with titrated doses of intravenous ephedrine (3-5 mg) or phenylephrine (50-100μg) bolus.[47,50]

Though neuraxial anesthesia is the choice for cesarean section, GA may be required in patients with coagulopathy, pulmonary edema, eclampsia, and in extreme emergency where baby has to be delivered as soon as possible. The achievement of rapid and smooth induction is of utmost importance which may be challenging in these patients.[51] Hypertensive response during intubation should be ablated with extreme attention as this may lead to serious maternal mortality. Fentanyl, alfentanil, remifentanil, esmolol, lignocaine and magnesium sulphate may be used to blunt the hypertensive response but one should use familiar agent.[52, 53] Neonatal resuscitation facilities must be available as all opioids rapidly cross placenta. Respiratory depression by remifentanil is usually brief as it is rapidly metabolized by the neonate.[54] As pre-eclamptic patients are usually on magnesium sulphate, this may enhance the action of muscle relaxants, so appropriate neuromuscular monitoring is required. Maintenance of anesthesia is done by inhalational agents usually isoflurane. During emergence from anesthesia extreme caution is required to prevent hypertension, aspiration and acute pulmonary edema. The degree of safety with available anesthetic techniques may vary in different patients so the technique should be individualized and an adequate monitoring should be mandatory.

The drug of choice is intravenous oxytocin used in titrated doses according to hemodynamic response.[55] Ergometrine may cause hypertension so it should be avoided. Prostaglandins may be given carefully after weighing the risks with the benefits of this drug.

Postpartum acute pulmonary edema: a complication of special consideration!

In pre-eclampsia pulmonary edema may develop in up to 2.9% cases with about 70% cases developing after delivery.[56] Depending on severity of hypoxemia, oxygen may be administered either through a non-invasive ventilation device or through invasive ventilation (intubation). Patient positioning, intravenous furosemide, morphine and nitroglycerin are the main stay of management. Postpartum oliguria with normal renal function generally needs no treatment. Low dose dopamine or furosemide is not recommended.[57]

In the immediate postpartum period, blood pressure should be measured at 4-6 hours interval regularly. Blood tests should be done for platelets, transaminases and creatinine levels. Ideal drugs should have low milk to maternal plasma ratio. Methyl dopa, beta-blockers with high plasma protein binding (oxyprenolol), some dihydropyridine calcium channel blockers (nifedipine) and ACE inhibitors may be used.[58]

Preventative strategies

There are no established measures but calcium supplementation is found to be beneficial in high risk women. According to Cochrane systematic review, risk of pre-eclampsia approximately reduces to half with the reduction in preterm birth with calcium therapy.[59] In patients with abnormal uterine artery doppler studies, low dose aspirin started in early gestation(< 16 weeks) reduces the incidence of severe pre-eclampsia, intrauterine growth retardation and gestational hypertension.[60] The screening for and detection of onset of pre-eclampsia in a community has been studied and guidelines have been developed for its prevention (PRECOG).[61]

CONCLUSION

The etiology of pre-eclampsia is poorly understood but this condition is associated with varied presentation with a potential to develop some serious complications. The anesthetic management of these parturients for both analgesia and anesthesia is complicated. The labor analgesia in pre-eclamptic women is beneficial in reducing the hypertensive responses and thus in maintaining uteroplacental perfusion. The neuraxial techniques are most favourable and effective and if contraindicated patient controlled IV PCA technique using short-acting opioids is acceptable. By incorporating the current scientific evidence in clinical practice and with experienced multidisciplinary team approach, the mortality and morbidity of mother and the fetus can be significantly reduced.

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