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Management of Preeclampsia in Perioperative Conditions

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Abstract

Anaesthetists are the key member of a multidisciplinary team providing management to a preeclamptic patient. Anaesthetist's responsibility starts before the surgery at the moment of stabilising patient's hemodynamic status and guiding to an obstetrician about administration of antihypertensives and seizure prophylaxis. Recent literature about antihypertensives and seizure prophylaxis is reviewed. Labetolol, hydralazine, diazoxide and nifedipine is considered as the most common used drugs and their dosage is revised in the light of the recent literatures. Magnesium sulphate is the most effective agent for seizure prophylaxis. Platelet transfusion threshold is determined as 50000/mm^3 in acutely bleeding patient. We discussed the advantages and limitations of spinal anesthesia in the setting of severe preeclampsia. We emphasized the difficulties encountered in general anesthesia. The benefits of neuroaxial anesthesia in labour are well established. Potential maternal life-threating complications include acute pulmonary edema, oliguria and acute renal failure, intracranial hemorrhagies and stroke and also the treatment options in intensive care unit at the postnatal period is summarized. Plasmapheresis is discussed as an alternative successful treatment option in preeclamptic patients whose platelet consumption persisted after delivery.

Keywords: Preeclampsia; Anesthesia

Introduction

Preeclampsia, along with the other hypertensive disorders of pregnancy is a leading cause of maternal morbidity and mortality [1]. Preeclampsia affects the 5-8% of all pregnancies worldwide [2]. Deaths are due to intracranial haemorrhage, respiratory failure and hepatic failure or rupture [2,3].

Pre-eclampsia is generally defined as new hypertension (systolic blood pressure ≥140 mmHg diastolic blood pressure of ≥90 mm Hg) and substantial proteinuria (≥300 mg in 24 h) at or after 20 weeks of gestation [4]. Eclampsia is defined as the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions before, during, or after labour [5]. Risk factors are defined as genetic and familial factors (angiotensin T-235), chronic renal failure, preexisting hypertension, anticardiolipin syndrome, multiple pregnancies, elder pregnants and diabetes by the American College of Obstetrics and Gynecologists [6].

Pathophysiology of preeclampsia is associated with fetoplacental unit [7]. It is clear that abnormal placentation (development and arrangement of the placenta) and placental function are strong predisposing factors for preeclampsia. The effects of preeclampsia consist of uteroplacental hypoxia, an imbalance in angiogenic and anti-angiogenic proteins, oxidative stress, maternal endothelial dysfunction, and elevated systemic inflammation [8]. Severe vasoconstriction causes endothelial cell injury, tromboxan A2 levels increase and coagulation cascade activates. As a result of this cascade fibrin deposits accumulation in the vessels, blood flow to fetoplacental unit and all maternal organs decrease. This causes to ischemia in entire body [7].

Effects of Preeclampsia on Organ Systems

Maternal organ systems that are susceptible to excessive inflammation and endothelial damage are the CNS, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart.

Cardiovascular Changes

Bosio et al. [9] conducted a longitudinal study of 400 primigravidas who were monitored throughout pregnancy using Doppler echocardiography. Preeclampsia developed in 20 of the patients. Women who had preeclampsia had significantly elevated cardiac outputs before clinical diagnosis, but total peripheral resistance was not significantly different during this latent phase. During the clinical phase of preeclampsia, there was a marked reduction in cardiac output and increase in peripheral resistance. Belfort et al. [10] reported decreased pulmoner capillary wedge pressure and elevated systemic vascular resistance in thirty-two patients with severe preeclampsia (blood pressure >160/110 mm Hg; 3 to 4+ proteinuria) who were monitored with a pulmonary artery catheter. In preeclampsia, both a hyperdynamic state with high cardiac output and low vascular resistance and a hypodynamic state with high resistances, low cardiac output and low plasma volume are described. These differences in haemodynamics have been recently ascribed to two different disease entities. Early-onset preeclampsia before 34 weeks of gestation is characterized by high resistance and low cardiac output, whereas late onset preeclampsia is dominated by high cardiac output and low vascular resistance [11].

Central Nervous System

Hypertension above the normal cerebral autoregulation pressure causes an increase in cerebral blood flow that prompts cerebral haemorrhage. The detachment in blood brain barrier raises the interstitial edema. Cerebral vasospasm, ischemia, edema, hemorrhage,

and hypertensive encephalopathy are probably associated in the pathogenesis of eclampsia [12]. Although uncommon, temporary blindness also may accompany severe preeclampsia and eclampsia. Other nervous system manifestations include headache, blurred vision, scotomata, and hyperreflexia [13].

Hematologic System

Preeclampsia is commonly responsible for thrombocytopenia occurring in the 2nd and 3rd trimester. Roughly 20-50% of women with preeclampsia will develop thrombocytopenia and although thrombocytopenia is occasionally the sole manifestation of preeclampsia, the severity of thrombocytopenia typically parallels the underlying preeclampsia. Less than 5% of preeclamptic women will develop severe thrombocytopenia (platelets <50,000/uL) making the use of platelet transfusions rarely necessary [14].

The HELLP syndrome occurs in 10% of women with preeclampsia and is characterized by Hemolysis, Elevated Liver enzymes and Low Platelets. The microangiopathic hemolytic anemia, elevated lactate dehydrogenase (LDH >600 U/mL), increased aspartate aminotransferase (≥70 U/mL) and thrombocytopenia (platelets <100,000/uL) helps to identify this entity in women with preeclampsia [15].

Hepatic System

Hepatic functions significantly altered in women with severe preeclampsia. Alanine aminotransferase and aspartate aminotransferase may be elevated. Hyperbilirubinemia may occur, especially in the presence of hemolysis. Hepatic hemorrhage, which usually manifests as a subcapsular hematoma, also may occur, especially in women with preeclampsia and upper abdominal pain. Rarely, hepatic rupture, which is associated with a high mortality rate, occurs.

Gracia et al. [16] reviewed case reports of hepatic hematoma and rupture in women with pre-eclampsia and eclampsia between 1990 and 2010 on the MEDLINE, SciELO, and LILACS databases. 12 (6.7%) of 180 cases of hepatic hematoma or rupture were associated with eclampsia plus HELLP syndrome were identified.

Renal System

Both renal blood, effective renal blood flow and GFR decrease in preeclampsia. Increased proteinuria is a hallmark of the preeclamptic syndrome, those preeclamptic patients also facing vasoconstriction plus enhanced vascular reactivity, and glomerular endothelial swelling producing capillary obstruction lead to postglomerular ischemia and acute tubular necrosis [17].

Management of Care

Multidisiplinary team approach has been emphasised in many recent publications [18,19]. Involving the anaesthetist to the team is an important step for providing the preeclamptic patient's stabilisation before delivery. The basis of the management of pre-eclampsia is antihypertensive therapy, seizure prophylaxis, facilitated delivery and critical care management.

Antihypertensive Therapy

When the diagnosis is preeclampsia, the gestational age, as well as the level of BP, influences the use of antihypertensive therapy. At term, women with preeclampsia are likely to be delivered, treatment of hypertension (unless severe) can be delayed, and BP can be reevaluated postpartum. If preeclampsia develops remote from term, and expectant management is undertaken, treatment of severe hypertension is initiated, and BP can usually be safely lowered to 140/90 mm Hg with oral medications as methyldopa, labetalol, nifedipine or isradipine, and some β-adrenoceptor blockers (metoprolol, pindolol, and propranolol) and low dose diazoxide [20].

It should be emphasized that there are no studies addressing safe BP treatment targets for pregnant women, and guidelines and reviews generally recommend treating to BP levels that are likely to be protective against acute adverse cerebrovascular or cardiovascular events, which is usually in the range of 140 to 155/90 to 105 mm Hg [21]. When antihypertensive therapy is used in women with preeclampsia, fetal monitoring is helpful to recognize any signs of fetal distress. There is consensus that severe hypertension in pregnancy, defined as >160/110 mm Hg, requires treatment, because these women are at an increased risk of intracerebral hemorrhage, and that treatment decreases the risk of maternal death [22]. Drugs that can be safely used include labetalol (oral or intravenous), nifedipine (oral) and hydralazine (intravenous). The choice should be made depending on the experience of the clinican with a particular agent [23]. Hidralazine is usually administered by intermittent bolus of 5 mg intravenously or intramuscularly. A continuous infusion of 0.5–10.0 mg.h) 1 is also typically employed in more refractory cases [24].

Labetolol is usually administered 10 to 20 mg IV, then 20 to 80 mg every 20 minutes, a continous infusion dosage 1 to 2 mg/min recommended. Nifedipine is recommended by oral route only 10 to 30 mg PO, repeat in 45 minutes if needed. Diazoxide is usually administered 30 to 50 mg IV every 5 to 15 minutes. Sodium nitroprusside is rarely used in pregnancy and has known maternal adverse effects of hypotension and paradoxical bradycardia in women with severe preeclampsia. Fetal cyanide toxicity is a complication of prolonged treatment. Sodium nitroprusside should be used with extreme caution in situations of life-threatening hypertension, immediately before delivery in circumstances where clinicians are familiar with its use [22].

Seizure Prophylaxis

Magnesium sulphate with a loading dose of 4-6 g followed by continuous infusion of 1-2 g/h is recommended as prophylaxis for eclampsia. The Magpie Trial previously demonstrated that the risk of respiratory depression is low, even if magnesium therapy is monitored with clinical signs such as deep tendon reflexes and respiratory rate in the absence of plasma level measurements [25]. The prolongation effect of high doses magnesium on nondepolarizing muscle relaxants should be kept in mind.

Platelet Transfusions

A significant decrease in platelet numbers may be associated with abnormal bleeding. It is recommended that platelet counts should not be allowed to decrease below 50 × 103 in the acutely bleeding pregnant woman [26].

Single cases indicate that plasmapheresis seems to be a treatment with low risk during pregnancy and could be a promising treatment option for otherwise refractory preeclampsia [27-29].

Deile et al. [30] recommended only use this therapy in specialized centers with first class experience and when performing plasmapheresis in preeclampsia measures to respond to blood pressure drops must always be available and vital signs must be controlled during and after the entire session. This includes continuous electronic foetal heart rate monitoring and cardiovascular monitoring of the mother.

Neuroaxial Anesthesia

Historically, a common belief about the spinal anesthesia in patients with severe preeclampsia is causing severe hypotension and decreasing uteroplacental perfusion which prevents the widespread use of spinal anesthesia in preeclampsia. After recent studies, comparing general and regional anesthesia risk-benefit considerations strongly favor neuraxial techniques over general anesthesia for cesarean delivery in the setting of severe preeclampsia as long as neuraxial anesthesia is not contraindicated [31,32]. Two small prospective studies by Wallace et al. [33] and Sharwood-Smith et al. [34] have shown that the hemodynamic effects of spinal anesthesia were similar to those seen with epidural anesthesia in severely preeclamptic patients; Visalyaputra et al. [35] have shown that the incidence of hypotension was more frequent in the spinal group than in the epidural group (51% versus 23%) in a large population. But they also showed hypotension was easily treated in all patients. They conclude that the results of this large prospective study support the use of spinal anesthesia for cesarean delivery in severely preeclamptic patients.

Berends et al. [36] conducted a prospective trial among 30 patients whom were randomised into three groups: epidural anesthesia with prophylactic fluid loading (EA-F), combined spinal epidural anesthesia with prophylactic fluid loading (CSE-F), or combined spinal epidural anesthesia with prophylactic ephedrine (CSE-V). They concluded that combined spinal and epidural anesthesia (CSE) is a safe alternative to conventional epidural anesthesia in severe preeclamptic women and that the prophylactic use of ephedrine is effective and safe to prevent and treat spinal hypotension after combined spinal and epidural anesthesia for Cesarean section in severe preeclamptic women. However, the small study sample means that the conclusions from this study should be viewed with caution.

Karinen et al. [37] studied a prophylactic crystalloid bolus before spinal anesthesia in preeclamptic patients mean central venous pressure increased significantly after preload, but decreased to baseline shortly after induction of spinal anesthesia. Visalyaputra et al. [35] and Sharwood-Smith et al. [34] showed the transient impact of IV fluid boluses on CVP. Prophylactic phenylephrine infusions have not been studied in the setting of uteroplacental insufficiency, and there is insufficient evidence to suggest their evidence-based use in the preeclamptic population [31].

An important absolute contraindication for neuroaxial anesthesia is coagulation disorders. As discussed earlier preeclampsia is commonly responsible for thrombocytopenia occurring in the 2nd and 3rd trimester. Sharma et al. [38] used thromboelastography and showed that platelet count >100 × 103/mm^3 there were no abnormalities of coagulation detectable. They also concluded severe preeclamptic women with a platelet count <100,000/mm^3 are hypocoagulable when compared to healthy pregnant women and other preeclamptic women. Orlikowski et al. [39] have measured platelet count, bleeding time and thrombelastography (TEG) variables and the correlation between these variables in 49 pregnant patients presenting with pre-eclampsia or eclampsia. They figured out in the patients with severe thrombocytopenia a platelet count of 75 × 103/mm^3 should be associated with adequate haemostasis. Taken together in the absence of other coagulation abnormalities, the risk of haemotoma associated with neuroaxial anaesthesia with platelet counts >75 × 103/mm^3 is very low. There is no proposed data for a "safe" platelet count. Based on a consensus statement from the AmericanSociety of Regional Anesthesia [40] many anesthesiologists require a platelet count of at least 75,000 or 80,000/μL (and, if the platelet count is <150,000/μL, normal partial thromboplastin [PTT] and prothrombin [PT] times) before initiating spinal anesthesia in patients with severe preeclampsia. The ASA practice guidelines advise that "the use of a platelet count may reduce the risk of anesthesia-related complications" in preeclampsia. The Association of Anaesthetists of Great Britain & Ireland, The Obstetric Anaesthetists' Association Regional Anaesthesia UK evaluated relative risks related to neuroaxial blocks in obstetric patients with abnormalities of coagulation; they formed 4 groups of relative risks in idiopathic trombocytopenic pregnants. They grouped patients with Platelet count >75 × 103/mm^3 within 24 h of block in normal risk and platelet count <75 × 103/mm^3 in increased risk group [41].

As emphasized by practice guidelines from the American Society of Anesthesiologists (ASA) and American College of Obstetricians and Gynecologists (ACOG), neuraxial anesthetic techniques, when feasible, are strongly preferred to general anesthesia for preeclamptic parturients.

General Anesthesia

Specific indications for general anaesthesia for caesarean section include coagulopathy, pulmonary edema and imminent fetal distress.

Moodley et al. [42] compared retrospectively the outcome of caesarean section under epidural anaesthesia. 66 women fulfilled the criteria of being `stable'. Of the 66 women, 37 received epidural, 27 general, and 2 spinal anaesthesia. There were no major complications with either general or epidural anaesthesia. Epidural anaesthesia was associated with higher one±minute Apgar scores. Authors indicate that both maternal and neonatal outcomes are not affected adversely by the use of epidural anaesthesia in selected cases of eclampsia. When you are considering the use of regional anaesthesia in parturients who have had an eclamptic seizure you have to determine the signs or symptoms of cerebral edema. If cerebral edema is present, regional anaesthesia is not recommended [43].

General anesthesia has some dangers in preeclamptic patients. Tracheal intubation may be difficult due to mucosal edema in oral cavity and glottis. Low diameter endotracheal tube had a guide in it should be readied for intubation. Intubation during the shallow anesthesia can cause serious response in systemic and pulmonary arterial hypertension [7]. Alfentanil, fentanyl, remifentanyl, $MgSO_4$, lidocaine, esmolol, nitroglycerine have been used to ablate the hypertensive response to intubation [44] Induction agents with sympathomymetic activity (eg ketamin) should be avoided [7] Emergence from anaesthesia should be handled carefully to avoid hypertension, aspiration and acute pulmonary edema [44].

Monitorization Options

Blood pressure measurement should be done carefully and correctly. Intra-arterial blood pressure measurement enables continuous blood pressure recording, facilitates repeated blood sampling shows cardiac output by minimally invasive cardiac output monitors [44]. Transthoracic echocardiography provides structural and functional information about cardiac performance, diastolic function, and responses to interventions [45-47].

American College of Obstetricians and Gynecologists (ACOG) listed invasive monitorization indications in obstetric patients as follows [7]:

1. Septic patients with refractory hypotension and/or oliguria
2. Unexplained or refractory pulmonary edema or persistant oliguria
3. Gestational hypertension with pulmonary edema or oliguria
4. Cardiovascular decompansation intraoperatively
5. Massive blood or volüme lost or replacement
6. ARDS
7. Shock with unknown etiology
8. New York Heart Association Class III or IV cardiac disease
9. Perioperative or peripartum coronary artery disease.

Analgesia for Labour

In preeclampsia epidural anesthesia for delivery reduces circulating catecholamine levels and increases plasental perfusion. To start, hydration with 0.5-1 l of crystalloid is necessary. Maternal electrocardiogram, blood pressure, as well as fetal heart rate should be monitored continuously. Administration of oxygen with a facemask or nasal cannula is beneficial. Among the local anesthetics, a low concentration of bupivacaine, 0.125%, with 2 μg/ml of fentanyl as an initial bolus provides excellent analgesia with minimal motor block. Lesser the motor block, greater the benefits with regard to fetal head rotation [48]. In addition the presence of a functioning epidural catheter enables the use of the epidural catheter for titrating local anaesthetic to ensure surgical anaesthesia if delivery turns to cesarean section [49].

Critical Care

Potential maternal life-threatening complications include cerebral infarction or hemorrhage, congestive heart failure or pulmonary edema, renal failure, or death. Maternal outcome is usually good in those with only isolated hypertension or preeclampsia, whereas it is poor with pheochromocytoma, stroke, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome and with delayed diagnosis and inadequate control of persistent severe hypertension [50].

Acute Pulmonary Edema

Pulmonary edema refers to an excessive accumulation of fluid in the pulmonary interstitial and alveolar spaces. It may develop in up to 2.9% of pregnancies complicated by preeclampsia [51].

Oxygen supplementation either via non-invasive ventilation devices or intubation and ventilation are used depending on the severity of the respiratory compromise. Morphine sulfate should be administered intravenously at a dose of 2 to 5 mg to reduce the adrenergic vasoconstrictor stimuli to the pulmonary arteriolar and venous beds. Furosemide administered intravenously to promote diuresis. Head elevation should also be used [52].

Pulmonary edema may occur 30% of cases with preeclampsia in the antenatal period [52]. In addition to the therapy discussed above, a multidisciplinary careful decision about delivery should be done with new-born specialists.

Oliguria and Acute Renal Failure

Oliguria in the postpartum period may occur in the partriurent who has normal renal functions.

Steyn et al. [53] assessed the effects of low dose dopamine for oliguria in severe eclampsia. It is suggested that dopamine should first be tested in non-pregnant women with very low urine output before it is considered for trials with pregnant women because of the potential for severe adverse effects if the dose is exceeded.

Prerenal and intrarenal pathology (acute tubular necrosis) accounts for 83-90% of all cases of acute renal failure in preeclampsia [54,55]. Renal damage secondary to these pathologic changes is seen most commonly in preeclampsia and usually resolves completely after delivery.

The management of acute renal failure in the setting of preeclampsia should focus on reversible conditions as dehydration. Blood pressure control, correcting fluid and electrolyte imbalance, and maintaining adequate nutrition is supportive. Persistent acidemia, hyperkalemia, volüme overload and uraemia are indications for renal replacement therapy [44].

Cerebral Hemorrhage and Stroke

Cerebral hemorrhage has been reported to be the most common cause of death in patients with eclampsia [56,57]. Stroke is known to be the most common cause of death (45%) in women with HELLP syndrome who receive traditional nonsteroid obstetric and medical management [58]. Hypertension may persist in the postpartum period. These patients deserve immediate and special attention in intensive care units and antihypertensive therapy to reduce their risk of such neurological events.

Postpartum Plasmapheresis in Severe Preeclampsia

Scwartz et al. reported a case of severe preeclampsia in which hemolysis and rapid platelet consumption persisted after delivery. Exchange plasmapheresis with fresh frozen plasma were begun on the eighth postpartum day, but the hemolysis and rapid platelet consumption did not begin to improve until the 12th postpartum day. The authors proposed the use of plasmapheresis in highly selected cases of severe preeclampsia with hemolysis and thrombocytopenia that do not resolve after delivery [59]. In 1986 fourteen cases of plasmapheresis with fresh frozen plasma for maternal indications in selected cases of preeclampsia and eclampsia were reviewed and the possible role of plasmapheresis in treating the selested cases is emphasized [60].

Martin et al. [61] assessed the postpartum use of plasma exchange with fresh-frozen plasma in a group of seven women with severe preeclampsia-eclampsia and HELLP syndrome that persisted <72 hours after delivery. Within 48 hours of exchange plasmapheresis, they achieved a decreasing trend in lactate dehydrogenase levels and platelet counts increased 4.5 times after 72 hours.

Katz et al. [62] proposed plasma exchange as a therapeutic option when clinical deterioration occurs due to microangiopathic disease.

There is no animal model based study about this issue. Consequently more studies has to be done on this field [30].

Conclusion

For patients with preeclampsia an anaesthesist should be aware of the following:

1. Preoperative assesment of the preeclamptic patient involves fluid balance, hemodynamic situation, coagulation profile and careful airway examination
2. Neuraxial anesthetic techniques, when feasible, are strongly preferred to general anesthesia for preeclamptic parturients
3. Tracheal intubation may be difficult due to mucosal edema. Difficult airway management devices should be readied for intubation. Adequate sedation and analgesia is needed to control the stress response to intubation
4. Emergence from anaesthesia should be handled carefully to avoid hypertension, aspiration and acute pulmonary edema.
5. Invasive monitoring for guiding succesful fluid management are supportive
6. Multiple organ failure can be prevented by obsevation of high risk severe preeclamptic patients in intensive care unit setting in antenatal and postnatal period.

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