INTRODUCTION

Pre-eclampsia is defined as a disorder that occurs in pregnancy after twenty weeks of gestation which manifests as hypertension and proteinuria with at least one maternal organ dysfunction involvement with an incidence of 5-10% of all pregnancies ***(Hull and Rucklidge, 2009).***

The use of spinal anesthesia in pre-eclamptic pregnant woman is of considerable benefit, as these patients present particular hazards with general anaesthesia, such as concerns for rapid airway control and cerebral blood flow alterations during induction of general anaesthesia and intubation ***(Henke et al., 2013).***

The incidence of hypotension is high during spinal anesthesia for cesarean section and it may approach values up to 95% ***(Banerjee et al., 2010; NganKee et al., 2010).*** However, the preeclamptic parturients experience less frequent and less severe hypotension and require smaller doses of vasopressors than normotensive parturients after initiation of spinal anesthesia ***(Aya et al., 2003; Clark et al., 2005)***.

Hypotension during spinal anesthesia for caesarean delivery is a result of decreased vascular resistance due to sympathetic blockade and decreased cardiac output due to blood pooling in blocked areas of the body and is treated by careful fluid therapy and vasopressors, such as phenylephrine or ephedrine, which should be given very cautiously and in much smaller doses than those used in non pre-eclamptic patients due to the

exaggerated vasoconstrictor response in parturients suffering from pre-eclampsia ***(Johnson, 2017).***

Magnesium ion is a natural calcium antagonist, it inhibits calcium entry into the cells *via* noncompetitive blockade of the dorsal horn *N*-methyl-D-aspartate (NMDA) receptor, which modulates or prevents central pain sensitization ***(Ramírez et al., 2013)***.

So the addition of magnesium to bupivacaine for spinal anaesthesia significantly improves the duration of postoperative analgesia and reduces the postoperative analgesic consumption in patients with preeclampsia undergoing caesarean section ***(Arora et al., 2015).***

Different doses of magnesium sulphate (50, 75, or 100 mg) can be added and provide safe and effective anesthesia, as it lead to a significant delay in the onset of both sensory and motor blockade, and prolong its duration, without increasing major side effects ***(Jabalameli and Pakzadmoghadam, 2012).***

Aim of the Work

Our study will examine the hemodynamic effects of adding two different doses of magnesium sulphate to bupivacaine in patients with severe preeclampsia undergoing caesarean section using spinal anesthesia.

REVIEW OF LITERATURE

Preeclampsia

Pre-eclampsia is defined as a disorder that occurs in pregnancy after twenty weeks of gestation which manifests as hypertension and proteinuria with at least one maternal organ dysfunction involvement with an incidence of 5-10% of all pregnancies ***(Hull and Rucklidge, 2009).***

Classification of preeclampsia

Preeclampsia is classified as either mild or severe. There is no moderate category. Preeclampsia is severe when the systolic arterial pressure is 160 mm Hg or more or the diastolic arterial pressure is 110 mm Hg or higher ***(Birnbach et al., 2000).***

Table (1): Factors that differentiate mild from severe preeclampsia ***(Birnbach et al., 2000)***

Factor	Mild PE	Severe PE
Systolic arterial pressure	<160 mm Hg	>160 mm Hg
Diastolic arterial pressure	<110 mm Hg	>110 mm Hg
Urinary protein	<5 g/24 h Dipstick +or ++	>5 g/24 h Dipstick+++or ++++
Urine output	>500 mL/24 h	<500 mL/24 h
Headache	No	Yes
Visual disturbances	No	Yes
Epigastric pain	No	Yes
Right upper quadrant abdominal pain	No	Yes
Pulmonary edema	No	Yes
Cyanosis	No	Yes
HELLP	No	Yes
Platelet count	>100,000/mm3	<100,000/mm3

Aetiology

The aetiology of preeclampsia remains an obstetric enigma. Several theories have been proposed but most have not withstood the test of time. Some of the suggested causes include abnormal trophoblast invasion of uterine vessels, immunologic intolerance between fetoplacental and maternal tissues, maladaptation to cardiovascular changes, inflammatory changes of pregnancy, abnormal angiogenesis, and genetic abnormalities ***(Steegers et al., 2010)***.

Some reported abnormalities of preeclampsia include placental ischemia, generalized vasospasm, abnormal hemostasis with activation of the coagulation system, vascular endothelial dysfunction, abnormal nitric oxide and lipid metabolism, leukocyte activation, and changes in various cytokines and growth factors ***(Suresh et al., 2013).***

There is substantial evidence suggesting that the pathophysiologic abnormalities of preeclampsia are caused by *abnormal angiogenesis,* particularly an imbalance in soluble fms like tyrosine kinase 1:Placental growth factor ratio (sFlt-1:PlGF ratio) as well as in soluble endoglin and serum levels of these markers have been suggested for the prediction of preeclampsia (Figure 1) ***(Khankin et al., 2010).***

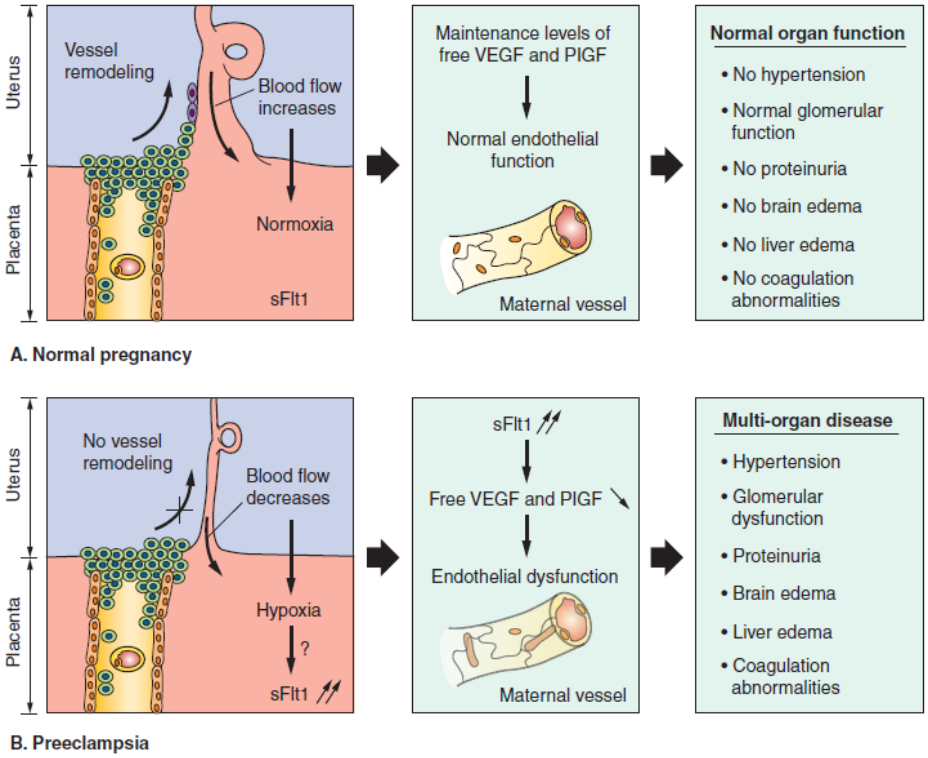

Figure (1): Hypothesis on the role of sFLt1 in preeclampsia ***(Khankin et al., 2010).***

A: During normal pregnancy, the uterine spiral arteries are infiltrated and remodeled by endovascular invasive trophoblasts, thereby increasing blood flow significantly in order to meet the oxygen and nutrient demands of the fetus. B: In the placenta of preeclamptic women, trophoblast invasion does not occur and blood flow is reduced, resulting in placental hypoxia. In addition, increased amounts of soluble Flt1 (sFlt1) are produced by the placenta and scavenge vascular endothelial growth factor (VEGF) and PlGF, thereby lowering circulating levels of unbound VEGF and PlGF.

Clinical Manifestations

Central nervous system

CNS manifestations include severe headache, visual disturbances, hyperexcitability, hyperreflexia, and coma ***(Okanloma and Moodley, 2000).***

Airway

In pregnant women, the internal diameter of the trachea is reduced because of mucosal capillary engorgement. In women with preeclampsia, these changes can be exaggerated along with upper airway narrowing as a result of pharyngolaryngeal edema, which may compromise visualization of airway landmarks during direct laryngoscopy. Subglottic edema can cause airway obstruction. Signs of airway obstruction include hoarseness, snoring, stridor, and hypoxemia ***(Munnur et al., 2005).***

Pulmonary

Pulmonary edema is a severe complication that occurs in approximately 3% of women with preeclampsia. Decreased colloid osmotic pressure, in combination with greater vascular permeability and the loss of intravascular fluid and protein into the interstitium, increases the risk of pulmonary edema and can result in the acute respiratory distress syndrome ***(Pacheco et al., 2015).***

Cardiovascular

Women with preeclampsia have increased vascular tone and greater sensitivity to vasoconstrictor influences, leading to the clinical manifestations of hypertension, vasospasm, and end-organ ischemia. Characteristically, blood pressure and systemic vascular resistance are elevated. In mild disease, plasma volume may be normal; however, it may be reduced as much as 40% in women with severe disease ***(Roberts and Cooper, 2001).***

Hematologic

Thrombocytopenia is the most common hematologic abnormality in women with preeclampsia, occurring in 15% to 20% of affected women. Platelet counts less than 100,000/mm^3 occur most commonly in women with severe disease or HELLP syndrome HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels) and correlate with both the severity of the disease process and the incidence of placental abruption ***(Gabbe et al., 2007).***

Hepatic

Hepatic manifestations of preeclampsia include periportal hemorrhage and fibrin deposition in hepatic sinusoids. Damage ranges from mild hepatocellular necrosis to the more ominous HELLP syndrome and can be associated with potential subcapsular bleeding and risk of hepatic rupture. Spontaneous hepatic rupture is rare but is associated with a 32% maternal mortality rate ***(Perronne et al., 2015).***

Renal

Renal manifestations of preeclampsia include persistent proteinuria, changes in the glomerular filtration rate, and hyperuricemia. The presence of proteinuria is a defining element of preeclampsia. Increasing urinary excretion of protein likely results from changes in the pore size or charge selectivity of the glomerular filter and impaired proximal tubular reabsorption. Notably, women with preeclampsia may have blood urea nitrogen (BUN) and creatinine measurements

in the normal range for nonpregnant women despite significantly decreased glomerular filtration rate (GFR) relative to normal pregnant women ***(Moran et al., 2003).***

Management

The only cure for preeclampsia is delivery. Timing is balanced by the safety of the mother against the risk of delivery of a potentially premature fetus ***(Koopmans et al., 2009).***

Table (2): Urgent indications for delivery in preeclampsia ***(Sibai and Barton, 2007)***

• Severe, refractory hypertension .24 hours
• Refractory renal failure
• Pulmonary edema
• Worsening thrombocytopenia, coagulopathy/disseminated intravascular coagulopathy
• Progressive liver dysfunction or hepatic hematoma/rupture
• Eclampsia or progression of neurologic symptoms
• Placental rupture
• Evidence of severe fetal growth restriction or oligohydramnios (may consider delay for betamethasone therapy)
• Fetal distress

Antihypertensive treatment is used to diminish the risk of maternal complications such as cerebral hemorrhage, eclampsia, or acute pulmonary edema. Medications commonly

used by obstetricians to treat hypertension associated with severe preeclampsia include hydralazine (5 mg IV slowly over 1 to 2 min 30–90 mg once daily, may be increased to maximum dose of 120 mg a day), labetalol (start with 20 mg IV bolus, may require double dose 10 min later), and nifedipine (start with 10 mg oral, may repeat dose 30 min later) ***(Duley et al., 2006).***

Seizure prophylaxis is routinely accomplished with magnesium sulphate using a 4–6 g intravenous loading dose, then a 1–2 g/hour infusion, with a goal serum concentration of 5–8 mg/dL. Due to the continued risk of eclampsia, the infusion continues for at least 24 hours postpartum ***(Duley et al., 2006)***

Spinal Anesthesia in Severe Preeclampsia

Spinal Anesthesia and hypotension in severe preeclampsia

The incidence of hypotension is high during spinal anesthesia for cesarean section and it may approach values up to 95% ***(Banerjee et al., 2010; NganKee et al., 2010).*** However, the preeclamptic parturients experience less frequent and less severe hypotension and require smaller doses of vasopressors than normotensive parturients after initiation of spinal anesthesia ***(Aya et al., 2003; Clark et al., 2005)***.

The normal pregnant patient is very sensitive to spinal anesthesia, because of an altered balance of vascular tone. Responses to endogenous pressors, particularly angiotensin II, are reduced. This is caused by an endothelium-dependent alteration of vascular smooth muscle function. Additionally, there is increased synthesis of vasodilator prostaglandins and nitric oxide. These effects increase dependence on sympathetic vascular tone in normal pregnancy ***(Sharwood-Smith et al., 2009)***.

The use of sympathomimetic vasopressors to sustain arteriolar tone and thus arterial pressure has become the most important strategy for safe spinal anesthesia in contemporary practice ***(Sharwood-Smith et al., 2009).***

In pre-eclampsia, vascular epithelium is damaged by a process involving placental-derived proteins, leading to an

imbalance between pro- and anti-angiogenic growth factors which results in persistent vasoconstriction ***(Romero et al., 2008)***.

Hypotension after spinal anesthesia in severely preeclamptic patients may reflect the rapid onset of sympathetic blockade, underlying intravascular volume depletion, and possible left ventricular dysfunction ***(Henke et al., 2013).***

Longstanding obstacles to widespread use of spinal anesthesia for patients with preeclampsia were concerns about (1) precipitous spinal anesthesia–induced hypotension, superimposed on (2) preexisting utero-placental-hypoperfusion and (3) the risk of inducing hypertension or pulmonary edema with subsequent efforts to correct the hypotension. While there was evidence as early as 1950 that preeclampsia actually attenuates spinal anesthesia–induced hypotension ***(Henke et al., 2013).***

It was not until the mid-1990s, when clinical trials demonstrated the safety of spinal and combined spinal–epidural (CSE) anesthesia in this patient population that spinal anesthesia gained acceptance as an alternative to epidural and general anesthesia for preeclamptic patients ***(Henke et al., 2013).***

Most trials assessing the severity of hypotension after spinal anesthesia among severely preeclamptic parturients exclude patients in active labor because labor itself attenuates the frequency and severity of the hypotensive response to neuroaxial anesthesia during cesarean delivery ***(Mubarak, 2015).***

Spinal versus general anesthesia in severe preeclampsia

For most of the severely preeclamptic population, the risk benefit profiles of spinal anesthesia and general anesthesia strongly favor the use of spinal anesthesia when feasible ***(Henke et al., 2013).***

In severely preeclamptic patients, spinal anesthesia–induced hypotension is typically easily treated, the risk of spinal/epidural hematoma is low, and there is no evidence that neonatal outcomes are compromised. In contrast, potential complications of general anesthesia, such as hypertensive crisis, stroke, and difficult airway management, are leading causes of morbidity and mortality in the preeclamptic population. Therefore, in the majority of severely preeclamptic patients,who are not coagulopathic or thrombocytopenic, the risk of difficult or failed airway management and delayed recognition of maternal stroke during a general anesthetic are felt to exceed the risk of adverse outcomes from spinal anesthesia induced hypotension or spinal/epidural hematoma ***(Santos and Birnbach, 2005).***

Peripartum pharyngeal and glottic edema are accentuated in preeclamptic parturients, and the risks of difficult/failed laryngoscopy and intubation are greater among preeclamptic parturients than healthy parturients ***(Munnur et al., 2005)***.

Traumatic laryngoscopy may trigger pharyngeal or hypopharyngeal bleeding, further obscuring visualization of the airway. Although the absolute risks of general anesthesia (failed/difficult airway management, hypertension with direct laryngoscopy, delayed recognition of stroke under general anesthesia, and aspiration) are low even among preeclamptic parturients, the risk of difficult airway management is a compelling reason to favor neuroaxial anesthesia ***(Munnur et al., 2005).***

Closed claims analysis from the United Kingdom from 2006 to 2008 identified poor management of preeclampsia as one of the main categories in which poor perioperative management may have contributed to maternal death. Severe preeclampsia is also a leading cause of peripartum hemorrhagic stroke ***(Bateman et al., 2006).***

During direct laryngoscopy and intubation, severely preeclamptic parturients experience significantly larger increases in arterial blood pressure and middle cerebral artery velocity compared with healthy parturients. Cerebral hypertension may, in turn, precipitate hemorrhagic stroke. Hemorrhagic stroke was the leading direct cause of mortality in patients with severe preeclampsia according to the analysis by the United Kingdom Center for Maternal and Child Enquiries. If general anesthesia is necessary, equipment should be immediately available to manage a difficult airway, and every effort should be made to blunt the hemodynamic response to laryngoscopy (e.g., via a bolus of an antihypertensive drug) ***(Dyer et al., 2003)***.

Adjuvants to spinal anesthesia in severe preeclampsia

Even though major advances have been made in local anesthetic chemistry, synthesis of an ideal agent remains illusive. An agent with a longer duration of action, shorter onset time, and a more selective sight of action is sought. In lieu of finding such an ideal agent, a number of adjuvants have been combined with local anesthetics (LAs) to improve the effectiveness of LAs ***(Swain et al., 2017).***

Intrathecal adjuvants are often administered during spinal anaesthesia in caesarean section of severe preeclamptic patients to provide significant analgesia. Intrathecal **midazolam** produces effective postoperative analgesia with no significant side effects ***(Dodawad et al., 2016).***

Opioids (Like morphine and fentanyl) can also be added to a spinal anaesthesia as a mean of extending the duration of pain relief and as a way of decreasing the dosage of LA required for pain treatment ***(Dienstfertig and Stein, 2010).***

Intrathecal 5 mcg **dexmedetomidine** potentiated hyperbaric bupivacaine by 31% in spinal anaesthesia for patients undergoing caesarean section and prolonged the spinal analgesia duration without additional side effects ***(Xia et al., 2018).***

The addition of **magnesium** to bupivacaine for spinal anaesthesia significantly improves the duration of postoperative analgesia and reduces the postoperative analgesic consumption in patients with preeclampsia undergoing caesarean section ***(Arora et al., 2015).***