IRJIF: 5.012

North Asian International Research Journal of Pharmaceutical & Medical Sciences

ISSN: 2456-8287 Vol. 6, Issue-1 January -2022

Index Copernicus Value: 55.07 DOI NUMBER: 10.5859/2456-8287.2022.00008.9 Fulfill MCI Criteria Citation Index

A Peer Reviewed Refereed Journal

COMPARISON OF HEMODYNAMIC RESPONSE AND NEONATAL OUTCOME BETWEEN NORMOTENSIVE AND PREECLAMPTIC WOMEN UNDERGOING CESAREAN SECTION UNDER SPINAL ANESTHESIA

***DR. ABDUL HAMID YATOO**

(POSTGRADUATE STUDENT)

DIPLOMA COURSE

2015

****DEPARTMENT OF ANAESTHESIOLOGY AND INTENSIVE CARE GOVERNMENT MEDICAL COLLEGE, JAMMU***

INTRODUCTION

Preeclampsia is defined as the association of pregnancy-induced hypertension and proteinuria with or without edema after 20 weeks of gestation The American College of Obstetricians and Gynecologists characterized preeclampsia as the development of hypertension with proteinuria, edema or both (the traditional triad) induced by pregnancy after the 20th week of gestation **(Landau and Irion, 2005; Winer and Tsasaris, 2008)**.It increases both maternal and fetal morbidity with the occurrence of eclampsia in 0.04 to 0.05% of the affected parturients with an estimated annual mortality rate of 50,000 parturients with preeclampsia worldwide**(Ness and Roberts, 1999; Duley, 2003; Villar *et al.*, 2003)**.

Preeclampsia may progress from mild to severe when the SBP becomes more than 160 mmHg or DBP more than 110 mmHg, proteinuria more than 5g per 24 hours or any sign of end organ damage **(Rath and Fischer, 2009)**. However, preeclampsia can be diagnosed in special situations in the absence of proteinuria. A significant deterioration of renal function with elevation of serum creatinine to levels greater than 0.9 g/L or oliguria <500 mL/day, severe epigastric pain along with elevated liver enzymes level indicating liver involvement with overstretching of the hepatic capsule, pulmonary edema manifested by dyspnea and oxygen desaturation, thrombocytopenia, hemolysis, disseminated intravascular coagulation (DIC), severe headache, persistent visual disturbance, hyperreflexia or intrauterine growth restriction (IUGR) reflect the most common systemic dysfunctions of severe preeclampsia **(Airoldi and Weinstein, 2007)**.

In normal pregnancy, the uterine blood flow is about 10% (500-600 ml/min) of cardiac output, with 80% of uterine blood flow normally supplying the placenta and the remaining 20% supplying the myometrium. In preeclampsia, there is an abnormal trophoblastic invasion of the maternal spiral arteries with impaired uteroplacental perfusion. There is release of vasoactive factors into the maternal circulation, resulting in endothelial dysfunction, vasoconstriction and hypertension **(Poston, 1996)**. These parturients have an elevated thromboxane/prostacyclin ratio, factor VIII antigen and fibronectin prior to the onset of clinical manifestation **(Rappaport *et al.*, 1990)**. Similarly, there is an exaggerated inflammatory response that affects every single organ in the body compared with normal pregnancy **(Redman *et al.*, 1999)**. However, there is limited evidence to the role of nitric oxide in the pathophysiology and management of preeclampsia. The assessment of uterine arteries by Doppler studies has shown higher uterine artery resistance in preeclamptic parturients compared to normal parturients **(Simmons *et al.*, 2000)**.

Preeclamptic parturients whose hypertension has been treated antepartum generally present for delivery with contracted plasma volume, normal or increased cardiac output, vasoconstriction, and hyperdynamic left ventricular function (although left ventricular systolic and diastolic dysfunction may develop). Additional manifestations include increased airway edema, decreased glomerular filtration, platelet dysfunction, and a spectrum of hemostatic derangements (typically accentuated hypercoagulability) **(ACOG 2002; Lindheimer *et al.*, 2008)**. In severe preeclampsia, chronic placental hypoperfusion is often significant. Since the uteroplacental circulation is not autoregulated, further decreases in perfusion may be poorly tolerated by the fetus. Primary peripartum goals in the severely preeclamptic parturient are the optimization of maternal blood pressure, cardiac output, and uteroplacental perfusion and the prevention of seizures and stroke**(Henke *et al.*, 2013)**.

The commonly performed regional anesthetic techniques among parturients with preeclampsia include spinal anesthesia, epidural analgesia/anesthesia or combined spinal epidural (CSE) anesthesia. Spinal anesthesia offers rapid onset, more reliable anesthetic with low local anesthetic requirement. Similarly, the addition of adjuvants prolongs the spinal anesthetic duration in addition to increased analgesic duration in the post-operative period. Hence, this technique has been widely used when these parturients present for cesarean section (CS) delivery. On the contrary, epidural analgesia/anesthesia offers top up doses, modification and extension of block through indwelling catheter with maintenance of hemodynamic stability compared to spinal anesthesia. The CSE anesthetic technique offers rapid onset, better quality of analgesia/anesthesia with the presence of epidural catheter allowing a top up for optimization and prolongation of spinal block. However, this technique is time consuming and technical difficulty is noted with inexperienced hands **(Ankichetty *et al.*, 2013)**.

Historically, a belief that spinal anesthesia in patients with severe preeclampsia causes severe hypotension and decreases uteroplacental perfusion prevented the widespread use of spinal anesthesia in these patients. However, studies show that parturients with severe preeclampsia experience less frequent, less severe hypotension than healthy parturients. Among patients with severe preeclampsia, spinal anesthesia may cause a greater degree of hypotension than epidural anesthesia; however, this hypotension is typically easily treated and short lived, and no studies have demonstrated clinically significant differences in outcomes when spinal anesthesia is compared with epidural or general 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. Therefore, spinal anesthesia is a reasonable anesthetic option in severe preeclampsia when cesarean delivery is indicated, and there is no indwelling epidural catheter or contraindication to spinal anesthesia **(Henke *et al.*, 2013)**.

Spinal anesthesia is a generally preferred anesthetic technique as it is simple to perform; it provides rapid onset and a dense block. It also provides excellent post-operative analgesia when intrathecal opioids are used **(Burns and Cowan, 2000; Gogarten, 2003; Sia *et al.*, 2010)**.It has no effect on Apgar scores and umbilical artery pH in preeclampsia as long as the systolic blood pressure is maintained greater than 80% or more of the baseline **(Karinen *et al.*, 1996)**.

The incidence of spinal induced hypotension and the vasopressor requirement were found to be two times lower in preeclamptic parturients when compared with normal parturients undergoing CS delivery **(Aya *et al.*, 2003; Aya *et al.*, 2005)**. The increased production of circulating factors with potent pressor effect and the increased sensitivity to vasopressor drugs in preeclampsia along with the use of hyperbaric bupivacaine (8-12 mg) with opioids could decrease the spinal induced hypotension in preeclamptic parturients. Cardiac output monitoring after spinal anesthesia has shown that neither spinal anesthesia nor the use of phenylephrine to treat hypotension reduce cardiac output during CS delivery, further supporting its safety in preeclamptic parturients **(Dyer *et al.*, 2008)**.

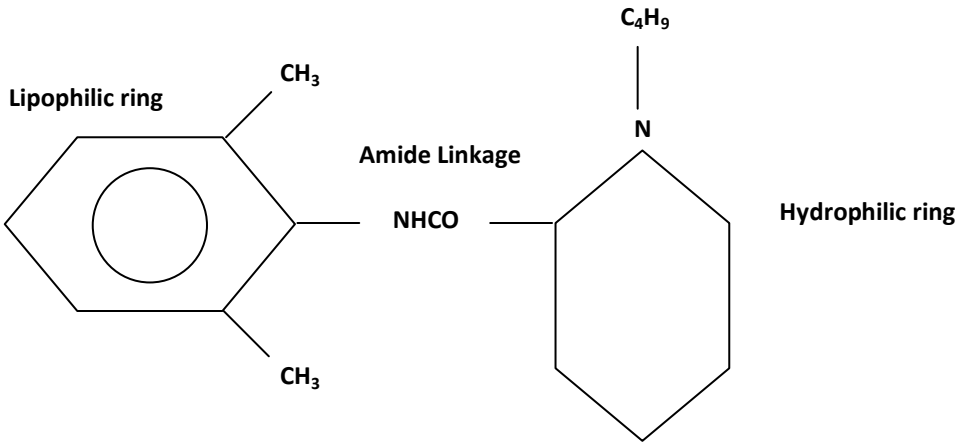
Cesarean delivery is a common method of terminating pregnancy in preeclamptic patients, more common when the latter becomes severe. Anesthesiologists are more likely to encounter a difficult airway in a severely preeclamptic patient. Furthermore the hazards related to the hemodynamic consequences of laryngoscopy and tracheal intubation in a severely preeclamptic patient is very much obvious **(Antoine *et al.*, 2003)**. So, general anesthesia in such patients may be resorted to only when regional anesthesia is contraindicated. Although spinal anesthesia has been usually avoided in these patients because of the risk of precipitous fall in BP and severe hypotension, and epidural anesthesia preferred, several studies are now available that show that the hemodynamic effects of spinal and epidural anesthesia are almost similar **(Wallace *et al.*, 1995; Karien *et al.*, 1996; Hood and Curry, 1999; Antoine *et al.*, 2003)**.

Owing to its simplicity, reliability and rapidity, spinal anesthesia may be considered as an alternative to general anesthesia for emergency cesarean delivery in preeclamptic women who have been adequately prepared with judicious amount of intravenous preload **(Santos and Birnbach, 2003)**.

The present study was undertaken to compare the changes in hemodynamic response, safetyand neonatal outcome between normotensive and preeclamptic women undergoing cesarean section under spinal anesthesia.

PHARMACOLOGY

BUPIVACAINE



Bupivacaine was synthesized by **Af Ekenstam and associates** in **1957**. First reports of its use were made in **1963** by **Telivuo**.Most useful feature of the drug appears to be duration of analgesia it produces.

Chemical structure:

It is an amide type local analgesic drug. Chemically it is designated as 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide. Its formula is $C_{18}H_{28}N_2O$. The pipecoloxylidides are chiral drugs because the molecules possess an asymmetrical carbon atom and they may have a left (sinister) or right (rectus) handed configuration. Bupivacaine is currently available for clinical use as a racemic mixture of enantiomers containing equal quantities (50:50) of the "S" and "R" forms.

Mechanism of action:

Bupivacaine prevents transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion selective sodium channels in nerve membranes. Failure of sodium ion channel permeability to increase slows the rate of depolarisation such that threshold potential is not reached and thus an action potential is not propagated **(Butterworth and Strichartz, 1990)**.

Physical properties:

Bupivacaine has a melting point of 258^0C, molecular weight 324.9, pka of 8.2, partition coefficient 346, protein binding 95.5% and pH of 3.5 with epinephrine 1:200,000. The hydrochloride is readily soluble in water and has a high degree of stability. Bupivacaine without adrenaline can withstand repeat autoclaving. Bupivacaine with adrenaline should not be autoclaved more than twice. It is 80 to 95% protein bound, highly lipid soluble and has potency approximately four times that of lignocaine or mepivacaine.

Pharmacokinetics:

Duration of action of local anaesthetic drugs correlate with binding to lipoproteins; albumin and alpha-1 acid glycoprotein, being two major binding proteins. Bupivacaine undergoes biotransformation in the liver. Hydroxylation of aromatic nucleus occurs to produce a compound which can be conjugated and so becomes solely water soluble. Six percent of bupivacaine dose is excreted unchanged. After bupivacaine administration,

approximately five percent of the dose is recovered as the N-dealkylated metabolite pipecoloxydide from urine. Epinephrine does not prolong effect but reduces toxicity of bupivacaine **(Boyes, 1975)**.

Indications:

* It is used for peripheral nerve blocks.
* It is useful in obstetrical analgesia because of low systemic toxicity to mother and foetus and is thus suitable for continuous epidural analgesia in labour.
* Bupivacaine is used as single dose epidural analgesic for surgery.
* Because of its prolonged duration of action, it is suitable for subarachnoid block for long surgical procedures.

Dosage:

The dosage of bupivacaine varies and depends upon the area to be anaesthetized, the vascularity of tissues, the number of neuronal segments to be blocked, individual tolerance and the technique of anaesthesia. Bupivacaine produces complete sensory and motor blockade with its concentration of 0.5% and above.

Adverse effects:

These include allergic reactions and systemic toxicity. Systemic adverse effects are dose related and are due to high plasma level due to overdosage, rapid absorption from injection site and unintentional intravascular injection.

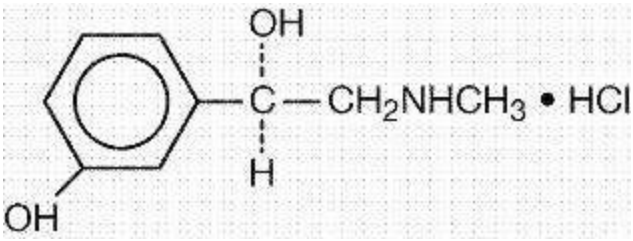
- **Central nervous system:** These include restlessness, vertigo, tinnitus, difficulty in focussing, slurred speech, skeletal muscle twitching, drowsiness, tonic clonic seizures, unconsciousness and respiratory arrest. Typical plasma concentration of bupivacaine associated with seizure is 4.5 – 5.5 μg/ml.

- **Cardiovascular system:** Accidental intravenous injection of bupivacaine may result in precipitous hypotension, cardiac dysrhythmias and atrio ventricular heart block **(Albright, 1979)**. Cardiotoxic plasma concentrations of bupivacaine are 8 to 10 μg/ml **(Timour *et al.*, 1990)**. Cardiac toxicity of bupivacaine is enhanced by arterial hypoxemia, acidosis or hypercarbia **(Rosen *et al.*, 1985)**. Pregnancy may increase sensitivity to cardiotoxic effects of bupivacaine **(Morishima *et al.*, 1985; McClure, 1996)**. The threshold for cardiac toxicity produced by bupivacaine may be decreased in patients being treated with drugs that inhibit myocardial impulse propagation (beta-adrenergic blockers, digitalis preparations, calcium channel blockers) **(Roitman *et al.*, 1993)**.

- **Hepatic effects:** Continuous or intermittent epidural administration of bupivacaine to treat postherpetic neuralgia has been associated with increased plasma concentrations of liver transaminases **(Yokoyama *et al.*, 2001)**.

Allergic reactions: These occur as a result of sensitivity to local anesthetic. These are urticaria, pruritus, erythema, tachycardia, nausea, vomiting, dizziness, syncope and anaphylactoid reaction.

PHENYLEPHRINE



Phenylephrine hydrochloride is a sympathomimetic amine salt which is chemically designated as (-)-m-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride. It occurs as white or nearly white crystals, having a bitter taste. It is freely soluble in water and alcohol. Phenylephrine hydrochloride is subject to oxidation and must be protected from light and air. It has a molecular weight of 203.67, a molecular formula of $C_9H_{13}NO_2$•HCl.

Indications:

For the treatment of ophthalmic disorders (hyperaemia of conjunctiva, posterior synechiae, acute atopic), nasal congestion, hemorrhoids, hypotension, shock, hypotension during spinal anesthesia, paroxysmal supraventricular tachycardia. It is also used as an aid in the diagnosis of heart murmurs and for prolongation of spinal anesthesia.

Pharmacology:

Phenylephrine is a powerful vasoconstrictor. It is used as a mydriatic, nasal decongestant, and cardiotonic agent. Phenylephrine is a postsynaptic alpha-receptor stimulant with little effect on the beta receptors of the heart. Parenteral administration of Phenylephrine causes a rise in systolic and diastolic pressures, cardiac output is slightly decreased and peripheral resistance is considerably increased, most vascular beds are constricted; renal, splanchnic, cutaneous, and limb blood flows are reduced but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised. This alpha receptor sympathetic agonist is also used locally because its vasoconstrictor and mydriatic action.

Mechanism of action:

Phenylephrine produces its ophthalmic and systemic actions by acting on alpha 1 adrenergic receptors in the pupillary dilator muscle and the vascular smooth musle, resulting in contraction of the dilator muscle and contraction of the smooth muscle in the arterioles of the conjunctiva and peripheral vasoconstriction. Phenylephrine decreases nasal congestion by acting on alpha 1 adrenergic receptors in the arterioles of the nasal mucosa to produce constriction.

Absorption:

Reduced bioavailability (compared to pseudoephedrine) following oral administration due to significant first-pass metabolism.

Biotransformation / Drug Metabolism:

Oral phenylephrine is extensively metabolised by monoamine oxidase, an enzyme which is present in the stomach and liver.

Contraindications:

Phenylephrine hydrochloride should not be used in patients with severe hypertension, ventricular tachycardia, or in patients who are hypersensitive to it or to any of the components.

Drug interactions:

Vasopressors, particularly metaraminol, may cause serious cardiac arrhythmias during halothane anesthesia and therefore should be used only with great caution or not at all.

MAO inhibitors:

The pressor effect of sympathomimetic pressor amines is markedly potentiated in patients receiving monoamine oxidase inhibitors (MAOI). Therefore, when initiating pressor therapy in these patients, the initial dose should be small and used with due caution. The pressor response of adrenergic agents may also be potentiated by tricyclic antidepressants.

REVIEW OF LITERATURE

The measurement of cardiac output during spinal anaesthesia for caesarean section in healthy parturients was performed as early as 1968, using an indicator dilution technique with indocyanine green **(Ueland *et al.*, 1968)**.

Employing pulmonary artery catheterisation, epidural anaesthesia for labour was found to be associated with remarkable haemodynamic stability in patients with severe pre-eclampsia who were receiving magnesium sulphate therapy **(Newsome *et al.*, 1986)**.

Gutsche (1988) in his study reported that in preeclampsia a rise of 20 mmHg mean arterial blood pressure (MABP) is significant even if previous blood pressure measurement is not available. A MABP of 105 mmHg or greater is considered abnormal.

The diagnosis of hypertension in pregnancy is reached when two blood pressure readings show a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg, taken over a period of 4 to 6 hours after 20 weeks gestation, in previously normotensive women**(Brown *et al.*, 2001)**.

In a prospective cohort study,**Aya *et al.* (2003)** found that patients with severe preeclampsia had a decreased hemodynamic response to a combined spinal epidural relative to healthy patients after volume loading with 1500 mL of crystalloid.

Spinal anaesthesia has been reported to be associated with a greater neonatal base deficit than general anaesthesia if the fetal heart trace is nonreassuring **(Dyer *et al.*, 2003)**.

Aya *et al.* (2005)evaluated the hemodynamic effects of spinal anesthesia in pre-eclamptic versus normotensive women when aortocaval compression was considered, for example by controlling fetal weight. For this purpose, the authors compared the incidence and magnitude of spinal hypotension in preeclamptic patients (n=65), with normotensive women (n=71) carrying preterm fetuses, undergoing cesarean delivery. Apgar scores and umbilical arterial blood pH were also studied. Neonatal and placental weights were similar between the groups. Hypotension was less frequent in preeclamptic patients than in women with preterm pregnancies (24.6% versus 40.8%, respectively). Although the magnitude of the decrease in systolic, diastolic, and mean arterial blood pressure was similar between groups, pre-eclamptic patients required less ephedrine than women in the preterm group to restore blood pressure to baseline levels (9.8±4.6 mg versus 15.8±6.2 mg, respectively). The risk of hypotension in

the pre-eclamptic group was almost 2 times less than that in the preterm group (relative risk=0.603). The impact on Apgar scores was minor, and umbilical arterial blood pH was not affected. The authors concluded that pre-eclampsia-associated factors, rather than a smaller uterine mass, account for the infrequent incidence of spinal hypotension in pre-eclamptic patients.

In normal pregnancy, there is reduced sensitivity to exogenous vasoconstrictors leading to increased vasopressor requirement to reverse the hypotensive effect after SAB. In preeclampsia, there is an increased sensitivity to vasoconstrictor agents, and less vasopressor is required **(Clark *et al.*, 2005)**.

Visalyaputra *et al.* (2005) in a prospective randomized multicenter study of severely preeclamptic women undergoing cesarean delivery showed that even when there was a period of increased hypotension in patients receiving spinal versus epidural anesthesia, there were no clinical differences in fetal or maternal outcomes.Spinal anaesthesia was associated with a higher incidence of hypotension and higher ephedrine requirement than epidural anaesthesia for caesarean section, but these differences were not of clinical significance.

Duley *et al.* (2006) opined that the suitable anesthetic technique for patients with preeclampsia and or eclampsia is a challenge because both general anesthesia and an epidural block are fraught with pitfalls. Opinions are controversial regarding the use of an epidural in preeclamptic or eclamptic patients undergoing caesarean section. The standard textbook, "Williams Obstetrics" in 1985 recommended avoiding regional anesthesia in preeclamptic patients because of concern for sudden severe hypotension.

Dyer *et al.* (2007)reviewed anaesthetist's role in the management of the patient with severe pre-eclampsia with particular emphasis on the role of regional anaesthesia. They concluded that the anaesthetist has a crucial role to play in the management of the pre-eclamptic parturient. Initial stabilisation of the severe pre-eclamptic patient includes careful fluid therapy. Regional anaesthesia is the mainstay of therapy both in labour and for caesarean section. In the absence of contraindications, single shot spinal anaesthesia for caesarean section, employing similar doses as in the healthy patient, and an emphasis on vasopressors rather than fluid infusion to treat hypotension, is safe. Spinal anaesthesia is associated with less hypotension, and probably less impairment of cardiac output than in the healthy parturient.

Ishrat and Raja (2007) in a prospective cohort study compared the incidence and severity of spinal anesthesia (SA) associated hypotension in preeclamptics (n=25) versus healthy parturients (n=25) undergoing cesarean delivery. After proper preloading, SA was administered with 0.5% hyperbaric bupivacaine. Blood pressure (BP) was recorded before performing SA (baseline BP), and then after SA, every 2 minutes for 30 minutes, and thereafter, every 5 minutes up to completion of surgery. The preeclamptic patients had a less frequent incidence of clinically significant hypotension, which was less severe and required less ephedrine. The risk of hypotension was significantly less in preeclamptic patients than that in healthy patients. The study concluded that spinal anesthesia seemed to be a useful and safe option, and alternative to epidural anesthesia, in preeclamptic patients in setting of large patient turn up for cesarean deliveries.

Preeclampsia/eclampsia, being a complex disease taxes the expertise of the most experienced anesthetist, who has to focus on blood pressure stabilization, optimization of fluid status and prevention of seizures **(Smith and Fretts, 2007)**.

Dyer (2008) with the use of lithium dilution cardiac output monitoring in severe preeclampsia, showed that neither spinal anesthesia nor treatment of hypotension with modest doses of phenylephrine reduces maternal cardiac output during cesarean delivery, further supporting safety in this patient population.

Chaudhary and Salhotra (2011) reviewed the literature with regards to the type of anesthesia for pregnancy-induced hypertension. Severe preeclampsia poses a dilemma for the anesthesiologist especially in emergency situations where caesarean deliveries are planned for uninvestigated or partially investigated parturients. The authors concluded that there is growing evidence to support the use of subarachnoid block in such situations when the platelet counts are >80,000 mm^{-3}. Better hemodynamic stability with the use of low-dose local anesthetic along with additives and better neonatal outcomes has been found with the use of subarachnoid block when compared to general anesthesia.

Hossain *et al.* (2011) observed the effect of magnesium sulphate on quality of subarachnoid block in terms of onset and duration of motor and sensory block, Apgar score of the neonates and haemodynamic status of the patients. Sixty parturients undergoing caesarian sections under subarachnoid block were enrolled for the study. They were divided into two groups. Group-A included normal parturient undergoing caesarian section and Group-B included pre-eclamptic parturient treated with magnesium sulphate within 1 to 2 hours before block. After recording of base line haemodynamic status (BP, HR, SPO_2) all patients received subarachnoid block with 2 ml (10 mg) hyperbaric bupivacaine at L3-4 level. Changes in systolic blood pressure in Group B patient was more and highly significant, for upto 60 min. But changes in diastolic blood pressure in Group B was only highly significant with Group A for upto 9 minutes. Apgar score was significantly low both in 1 minute and 5 minutes, in Group B patients which was 5.80 ± .61 at 1 minute and 7.73 ± .827 at 5 minutes and in Group A which was 6.60 ± .85 at 1 minute and 8.30 ± .595 (mean ± SD) at 5 minutes. Onset of sensory block and onset of motor block revealed no significant difference between groups. The study concluded that chance of hypotension is more in patients getting magnesium sulfate but it may be managed with adequate preloading and by pressor agent ephedrine.

Ankichetty *et al.* (2013) reviewed the regional anesthetic considerations when parturients with pregnancy induced hypertension present to the labor and delivery unit. According to them, the administration of regional anesthesia not only avoids the maternal complications with general anesthesia like difficult intubation, vasopressor response to intubation, but also improves uteroplacental blood flow and neonatal outcome. They concluded that parturients with mild preeclampsia may safely undergo regional anesthetic procedures for labor analgesia and cesarean section delivery. A thorough evaluation to detect underlying coagulopathy or thrombocytopenia is essential prior to considering regional anesthetic procedures in severe preeclamptic parturients. It may be safer to consider non-neuraxial techniques in eclamptic parturients with or without end organ damage.

According to **Henke *et al.* (2013)** spinal anesthesia is widely regarded as a reasonable anesthetic option for cesarean delivery in severe preeclampsia, provided there is no indwelling epidural catheter or contraindication to neuraxial anesthesia. Compared with healthy parturients, those with severe preeclampsia experience less frequent, less severe spinal-induced hypotension. In severe preeclampsia, spinal anesthesia may cause a higher incidence of hypotension than epidural anesthesia; however, this hypotension is typically easily treated and short lived and has not been linked to clinically significant differences in outcomes.

Saha *et al.* (2013) compared the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), phenylephrine requirement, and neonatal outcome between normotensive and severe pre-eclamptic women undergoing cesarean section under spinal anesthesia. The minimum SBP, DBP,

and MAP recorded were lower in normotensive, and the difference between two groups was statistically significant. The mean phenylephrine requirement in the normotensive group (151.1 ± 70) was significantly greater than that of pre-eclamptic group (48.3 ± 35). Apgar scores at 1 and 5 min after birth were comparable in both the groups. Thus, the authors concluded thatpre-eclamptics experience less hypotension following subarachnoid block (SAB) than normotensives and require less phenylephrine with comparable fetal Apgar scores.

According to **Abdo *et al.* (2014)**, preeclampsia in women is typically characterized by hypertension, proteinuria and edema, with the hemodynamic disturbances being the most prominent feature. These disturbances commence in early gestation and account for the development of the clinically apparent vasoconstriction and increase in arterial pressure as gestation progresses. Despite being one of the leading causes of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not yet been fully elucidated. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease. An initiating event in preeclampsia has been postulated to be reduced placental perfusion that leads to widespread dysfunction of the maternal vascular endothelium by mechanisms that remain to be defined.

AIMS AND OBJECTIVES

1. To compare the changes in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure between normotensive and preeclamptic women undergoing cesarean section under spinal anesthesia.
2. To compare the phenylephrine requirement, safety and neonatal outcomeafter spinal anesthesia in normotensive and preeclamptic women.

MATERIALS AND METHODS

The present study was conducted in the Postgraduate Department of Anaesthesiology and Intensive Care, Government Medical College, Jammu in collaboration with the Postgraduate Department of Obstetrics and Gynaecology, SMGS Hospital, Government Medical College, Jammu on 50 non-laboring parturients of ASA-I (age 18-30 years, weight 45-70 kg) carrying a singleton pregnancy and scheduled to have elective cesarean section. Before admission to the study, all the patients were informed about the aims, methods, anticipated benefits and potential hazards of the study. An informed written consent from the patients and approval from local ethics committee was obtained.

Parturients with cardiac disease, chronic hypertension, renal disease, diabetes mellitus, coagulopathy, and those who refused subarachnoid block (SAB) were excluded from the study.

Out of 50 women selected for the study, 25 women were normotensive (Group I) and 25 were pre-eclamptic (Group II) having BP ≥ 140/90 requiring antihypertensive therapy.

All parturients were premedicated with injection Aciloc (50 mg) and injectionOndansetron (4 mg) prior to the surgery. After establishing IV access with 18 G cannula prehydration was done with 10 ml/kg body weight of lactated ringer (RL) solution 15 to 20 minutes before surgery. Standard multichannel monitor was attached and baseline hemodynamic variables (HR, SBP, DBP, MAP) were recorded. Baseline BP was measured as the mean of the three readings taken 5 minutes after arrival in the operation theatre and before doing any invasive procedures.

After proper asepsis and draping, SAB was administered with 25G -spinal needle at L3-4 interspace in sitting posture with 12.5 mg hyperbaric 0.5% bupivacaine. Patient was then placed supine with a 10-cm wedge under the right buttock to prevent aortocaval compression. Infusion of RL was continued at the rate of 5 ml/kg/h. Surgery was allowed as soon as upper level of sensory block reached T_6.

Haemodynamic variables SAB, SBP, DBP, MAP, and HR were recorded every 2 minutestill deliveryand every 5 minutes thereafter until completion of surgery. Hypotension (defined as fall in MAP >20% of the baseline) was treated with 50 µg phenylephrine IV bolus and dose was repeated if required to maintain MAP within 20% of baseline. Bradycardia (HR < 60 beats/min) if associated with hypotension was treated with 0.36 mg IV atropine (maximum 1.8 mg). Lowest SBP, DBP, and MAP were noted for each patient and for the HR both the lowest and highest values were recorded. The total amount of phenylephrine consumed was also noted.

Apgar score at 1 and 5 minutes, birth weight, and gestational age of the baby were also compared.

25All the cases had adequate block for cesarean section and none of them had to be excluded from study due to inadequate block. All the pre-eclamptic parturients were stabilized by antihypertensive medication and did not have any clinical evidence of pulmonary edema.

Statistical analysis

Data was compiled in Microsoft Excel worksheet and student's t test was used to detect significant difference for difference of means and chi-square test was used for difference of proportions. A p-value of less than 0.05 was considered significant.

RESULTS

The present study was conducted on 50 non-laboring parturients of ASA-I (age 18-30 years, weight 50-75 kg) carrying a singleton pregnancy and scheduled to have elective cesarean section under spinal anesthesia. Out of 50 women selected for the study, 25 women were normotensive (Group I) and 25 were pre-eclamptic (Group II) having BP ≥ 140/90 requiring antihypertensive therapy. Baseline hemodynamic variables like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were recorded and subsequently after subarachnoid block (SAB), HR, SBP, DBP, MAP were recorded every 2 minutes for 10 minutes and every 5 minutes thereafter until completion of surgery in all the parturients. Following observations were noted during the course of the study.

Table 1: Mean baseline maternal characteristics of parturients inGroup I and Group II

Variable	**Group I (Normotensive women) Mean ± SD**	**Group II (Preeclamptic women) Mean ± SD**	**p-value**
Age (years)	26.24 ± 3.03	25.92 ± 3.01	0.709; Not significant
Weight (kg)	60.76 ± 6.60	60 ± 6.23	0.677; Not significant

Women in normotensive and preeclamptic groups were comparable regarding mean age and mean weight. Statistically there was no significant difference in the two variables.

Table 2: Mean baseline haemodynamic parameters of parturients inGroup I and Group II

Haemodynamic parameters	**Group I (Normotensive women) Mean ± SD**	**Group II (Preeclamptic women) Mean ± SD**	**p-value**
Systolic blood pressure (mmHg)	129.7 ± 7.2	164 ± 17	<0.0001; Highly significant
Diastolic blood pressure (mmHg)	87.5 ± 9.21	105.7 ± 10.2	<0.0001; Highly significant
Mean arterial blood pressure (mmHg)	100.1 ± 7.3	121.8 ± 9	<0.0001; Highly significant
Heart rate (beats/min)	87.84 ± 6.63	90.56 ± 14.51	0.394; Not significant

The mean baseline SBP, DBP and MAP were higher in the preeclamptic women (Group II),the differences between Group I and Group II in all three parameters being highly significant ($p<0.0001$). The mean baseline heart rate was comparable in both Group I and Group II. There was statistically no significant difference between the two groups.

Table 3: Trend of SBP in Group I and Group II after subarachnoid block

Time interval (in minutes)	Group I (Normotensive women) Mean values (mmHg)	Group II (Preeclamptic women) Mean values (mmHg)
2	120.2	145.28
4	99.50	135.84
6	108.16	123.60
8	115.36	124.32
10	116.68	125.48
15	116.56	128.44
20	119.84	128.48
25	117.28	129.92
30	118.88	131.32
35	119.32	129.16
40	123.28	128.12

The mean SBP decreased from the baseline in both Groups I and II following subarachnoid block (SAB). Minimum recorded SBP (99.5 mmHg) in normotensive women was lower than the preeclamptic women (123.6 mmHg).

Table 4: Trend of DBP in Group I and Group II after subarachnoid block

Time interval (in minutes)	Group I (Normotensive women) Mean values (mmHg)	Group II (Preeclamptic women) Mean values (mmHg)
2	71.36	88
4	61.5	87.21
6	67.72	81.70
8	71.24	87.6
10	69	84.52
15	67.4	86.2
20	66.76	87.6
25	66.12	84.52
30	67.68	86.2
35	70.4	88.2
40	70.64	89.6

The mean DBP decreased from the baseline in both Groups I and II following subarachnoid block (SAB). Minimum recorded SBP (61.5 mmHg) in normotensive women was lower than the preeclamptic women (81.7 mmHg).

Table 5: Trend of MAP in Group I and Group II after subarachnoid block

Time interval (in minutes)	Group I (Normotensive women) Mean values (mmHg)	Group II (Preeclamptic women) Mean values (mmHg)
2	91.08	107.4
4	71.5	96.76
6	87.88	94.5
8	88.12	96.08
10	85.24	91.68
15	85.88	97.52
20	87.2	95.36
25	87.72	95.92
30	86.76	98.16
35	89.6	94.12
40	91.4	97.56

The mean MAP decreased from the baseline in both Groups I and II following subarachnoid block (SAB). Minimum recorded MAP (71.5 mmHg) in normotensive women was lower than the preeclamptic women 94.5 mmHg).

Table 6: Trend of HR in Group I and Group II after subarachnoid block

Time interval (in minutes)	Group I (Normotensive women) Mean values (beats/minute)	Group II (Preeclamptic women) Mean values (beats/minute)
2	96.2	90.72
4	95.52	93.92
6	92.88	93.96
8	88.04	88.28
10	91.04	90.52
15	98.92	93.04
20	101.16	102
25	94.68	103.48
30	94.28	98.48
35	94.6	100.2
40	92.32	95.92

The mean HR in both Groups I and II were comparable following subarachnoid block (SAB). Minimum recorded HR in normotensive women was 88.04 beats/minute, while maximum recorded HR was 101.16 beats/minute.Similarly, minimum recorded HR in preeclamptic women was 90.52 beats/minute, while maximum recorded HR was 103.48 beats/minute.

Table 7: Mean changes in haemodynamic parameters after SAB in parturients of Group I and Group II

Variable	Group I (Normotensive women)	Group II (Preeclamptic women)	p-value
Systolic blood pressure			
Mean baseline value (mmHg)	129.7	164	<0.0001; Highly significant
Lowest value after SAB (mmHg)	99.5	123.6	<0.0001; Highly significant
Percentage decrease from baseline	23.28	24.63	>0.05; Not significant
Diastolic blood pressure			
Mean baseline value (mmHg)	87.50	105.7	<0.0001; Highly significant
Lowest value after SAB (mmHg)	61.50	81.7	<0.0001; Highly Significant
Percentage decrease from baseline	29.71	22.70	=0.01; Significant
Mean arterial blood pressure			
Mean baseline value (mmHg)	100.1	121.8	<0.0001; Highly significant
Lowest value after SAB (mmHg)	71.5	94.5	<0.0001; Highly significant
Percentage decrease from baseline	28.57	22.41	=0.04; Significant
Heart rate			
Mean baseline value (beats/minute)	87.84	90.56	>0.05; Not significant
Lowest value after SAB (beats/minute)	88.04	90.52	>0.05; Not significant
Highest value after SAB (beats/minute)	101.16	103.48	>0.05; Not significant

After establishing SAB, minimum mean SBP, DBP and MAP values recorded during the observation period were higher in the preeclamptic women (Group II) (123.6, 81.7, 94.5 mmHg respectively) in comparison with normotensive women (Group I) (99.5, 61.5, 71.5 mmHg respectively). The differences in all three parameters were statistically highly significant (p <0.0001).

The percentage of fall in SBP calculated from the baseline was comparable in both normotensive (23.28%) and preeclamptic (24.63%) groups. However, percentage of fallin DBP and MAP calculated from the baseline was significantly less in the preeclamptic women (22.70% and 22.41% respectively) as compared to normotensive women (29.71% and 28.57% respectively).

The difference between minimum as well as maximum mean heart rates (beats/minute) after SAB between normotensive and preeclamptic women, however, was not significant.

Table 8: Mean phenylephrine dosage required in Group I and Group II parturients

Variable	**Group I (Normotensive women) Mean ± SD**	**Group II (Preeclamptic women) Mean ± SD**	**p-value**
Mean phenylephrine dosage (µg)	65 ± 23.50	50 ± 0	=0.0025; Highly significant

Preeclamptic women needed less phenylephrine to treat hypotension as compared to normotensive women (50 µg vs 65 µg). The difference was statistically highly significant (p = 0.0025).

Moreover, there were two normotensive women who experienced bradycardia associated with hypotension which was treated with 0.36 mg IV atropine.

Table 9: Neonatal characteristics of Group I and Group II parturients after SAB

Variable	**Group I (Normotensive women) Mean ± SD**	**Group II (Preeclamptic women) Mean ± SD**	**p-value**
Mean birth weight (kg)	2.83 ± 0.24	2.79 ± 0.19	0.516; Not significant
Mean Apgar score at 1 minute	8.44 ± 1.47	7.84 ± 1.14	0.1134; Not significant
Mean Apgar score at 5 minutes	9.76 ± 0.43	9.8 ± 0.40	0.7349; Not significant

Neonatal parameters like mean birth weight and mean Apgar scores at 1 and 5 minutes were comparable in parturients of Group I and Group II. There were no significant differences observed between normotensive and preeclamptic women in these parameters.

DISCUSSION

The present study was conducted on 50 non-laboring parturients of ASA-I carrying a singleton pregnancy and scheduled to have elective cesarean section. Out of 50 women selected for the study, 25 women were normotensive (Group I) and 25 were pre-eclamptic (Group II) having BP ≥ 140/90 requiring antihypertensive therapy.

Spinal anesthesia is often the preferred technique of anesthesia for cesarean delivery (**Bourne *et al.*, 1997)**. It is suitable for use in preeclamptic patients **(Wallace *et al.*, 1995; Hood and Curry, 1999)**, even in cases with a nonreassuring fetal heart rate (HR) pattern **(Dyer *et al.*, 2003)**. Hypotension may occur as a side effect of this anesthetic technique. The present study was performed to evaluate the hemodynamic effects of spinal anesthesia and neonatal outcome in preeclamptic versus normotensive women.

In the present study, after establishing SAB, blood pressure decreased in both the groups from the baseline, but the minimum SBP, DBP, and MAP recorded during the observation period were always higher in the preeclamptic group (Group II) (123.6, 81.7, 94.5 mmHg respectively) in comparison with normotensive women (Group I) (99.5, 61.5, 71.5 respectively). The differences in all three parameters were statistically highly significant ($p < 0.0001$).

The percentage of fall in SBP calculated from the baseline was comparable in both normotensive (23.28%) and preeclamptic (24.63%) groups. However, percentage of fallin DBP and MAP calculated from the baseline was significantly less in the preeclamptic women (22.70% and 22.41% respectively) as compared to normotensive women (29.71% and 28.57% respectively).

The difference between minimum as well as maximum mean heart rates (beats/minute) after SAB between normotensive and preeclamptic women, however, was not significant.

It has been believed that preeclamptic patients may carry a high risk with use of spinal anesthesia owing to possibility of severe hypotension with maternal and fetal consequences because of reduced plasma volume and of need to limit IV fluids to avoid iatrogenic pulmonary edema, so use of spinal anesthesia has not been popular in preeclampsia **(Hays *et al.*, 1985; Cunningham *et al.*, 1989; Sibai *et al.*, 1997)**. At present several prospective and retrospective studies are available that clearly show that properly administered spinal anesthesia induces a similar incidence and severity of hypotension in patients with preeclampsia as epidural anesthesia **(Wallace *et al.*, 1995; Karien *et al.*, 1996; Hood and Curry, 1999)**.

In our study, we administered spinal anesthesia safely in preeclamptic parturients. Furthermore, incidence and severity of hypotension were less in preeclamptic patients compared to normotensive parturients in our study. We did not encounter any case of iatrogenic pulmonary edema with judicious preloading in preeclampsia in this study.

Saha *et al.* (2013) alsoreported in their study thatthe minimum SBP, DBP, and MAP recorded were lower in normotensive, and the difference between normotensive and preeclamptic groups was statistically significant. The results are in agreement with those of the present study.

The present study results corroborates with the study of**Aya*etal*.(2003)**comparing the incidence and severity of hypotension and ephedrine consumption in 30 pre-eclamptics and 30 healthy parturients. They found that SAB induced hypotension was 6 times less in preeclamptics group and they required significantly less ephedrine to treat it. **Clark *et al.* (2005)** have also reported similar results.

Ishrat and Raja (2007) in a prospective cohort study observed that the risk of hypotension was significantly less in preeclamptic patients than that in healthy patients. They concluded that spinal anesthesia seemed to be a useful and safe option, and alternative to epidural anesthesia, in preeclamptic patients in setting of large patient turn up for cesarean deliveries.

Even with varying incidence of hypotension and IV phenylephrine to treat it, we found comparable and good neonatal outcome in both the groups in respect to Apgar scores at 1 and 5 minutes after birth and also whenmean birth weight of the newborns in both the groups were compared.

Preeclamptic women needed less phenylephrine to treat hypotension as compared to normotensive women (50 µg vs 65 µg). The difference was statistically highly significant ($p = 0.0025$).

Moreover, there were two normotensive women who experienced bradycardia associated with hypotension which was treated with .36 mg IV atropine.

Saha *et al.* (2013) reported in their study that the mean phenylephrine requirement in the normotensive group was significantly greater than that of pre-eclamptic group. Apgar scores at 1 and 5 min after birth were comparable in both the groups. The results of this study are comparable with the present study.

CONCLUSION

In the present study, hypotension following spinal anesthesia administered for cesarean section was significantly less in severe preeclamptics than in healthy pregnant women.

Use of spinal anesthesia, when properly administered and monitored, is a safe alternative to epidural anesthesia in preeclamptic patients including severe preeclampsia.

Spinal anesthesia owing to its simplicity, reliability and quicker onset may save lot of time and so may be more practical method of anesthesia in preeclamptic parturients.

In addition, phenylephrine requirements were also less in preclamptic parturients and neonatal outcome was comparable between the two groups.

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ABBREVIATIONS

α	-	Alpha
%	-	Percentage
µg	-	Microgram
&	-	And
ANOVA	-	Analysis of Variance
ASA	-	American Society of Anaesthesiologists
BP	-	Blood Pressure
bpm	-	Beats per Minute
BT	-	Bleeding Time
CNS	-	Central Nervous System
CT	-	Clotting Time
DBP	-	Diastolic Blood Pressure
g	-	Gram
Hb	-	Hemoglobin
hr	-	Hour
HR	-	Heart Rate
I/V	-	Intravenous
JVP	-	Jugular Venous Pressure
kg	-	Kilogram
mg	-	Milligram
Min	-	Minutes
ml	-	Millilitre

mmHg	-	Millimeter of Mercury
PTI	-	Prothrombin Index
R/E	-	Routine Examination
RFTs	-	Renal Function Test
SBP	-	Systolic Blood Pressure
SD	-	Standard Deviation
SPO_2	-	Saturation of Hemoglobin with Oxygen
Yr	-	Year