Vasopressors and tight control of maternal blood pressure during cesarean delivery: A rocky alliance

Maternal hemodynamics during cesarean delivery, under spinal anesthesia and following administration of vasopressors like alpha and beta adrenergic receptor agonists and pure alpha adrenergic agonists, has generated a lot of controversy. Both vasopressors (phenylephrine and ephedrine) have been found to correct the fall in maternal blood pressure with return of systolic pressures to basal values. However, there is evidence that as compared to phenylephrine, ephedrine crosses the placenta to a greater extent and undergoes early metabolism and redistribution, causing direct fetal metabolic acidosis, which makes ephedrine less desirable as the first-line treatment. Use of phenylephrine as a first choice vasopressor for arterial blood pressure management during cesarean delivery under spinal anesthesia has consequently increased.[1]

Hypotension and incidence of intraoperative nausea and vomiting (IONV) are the two major concerns during spinal anesthesia for cesarean delivery. It has been suggested that, following spinal anesthesia, hypotension leads to a decrease in cerebral perfusion with brainstem ischemia and activation of the vomiting center[2] along with release of emetogenic substances like serotonin, due to gut hypo perfusion.[3]

Improved hemodynamic control with lower maternal nausea scores can be achieved by the correct choice, timing and method of administration of vasopressors. The use of bolus doses of phenylephrine (100mcg) and ephedrine (6-10mg) were found to have a similar incidence and frequency of hypotension though phenylephrine is found to have a faster onset of action with a lower incidence of IONV.[4,5]

Prophylactic infusions of phenylephrine (ranging from 33mcg/min to 100mcg/min), as compared to ephedrine infusions (1-8mg/min), have been found to reduce the incidence of both IONV and hypotension more effectively.[6-8] Varying the doses of infusions of vasopressors or their combinations is found to significantly affect the incidence of IONV and hypotension.[6,9-12] Kee further showed that incidence of IONV was significantly reduced in parturients whose systolic blood pressure (SBP) was controlled to 100% of baseline with a phenylephrine infusion, compared with groups controlled to 80% and 90% of baseline SBP.[10]

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Although a continuous infusion of prophylactic phenylephrine might be more effective in maintaining baseline systolic pressures, recent reports have expressed concern over the large doses of phenylephrine required to maintain maternal blood pressure, as it may cause bradycardia and consequently a reduction in cardiac output (CO). Till date, most of the work has concentrated on the cardiovascular effects of phenylephrine especially SBP and heart rate (HR). Phenylephrine administration was found to be associated with reflex bradycardia, as compared to ephedrine,[7,8] which is dose related[10,12] and seen more often with prophylactic infusions as compared to bolus doses.[10,13] Studies investigating CO changes with phenylephrine, have found a significant reduction in HR from pre-pressor values which strongly correlated with the CO.[6,12,13]

Measurements of SBP have been used as a surrogate marker for maternal CO in predicting uterine blood flow (UBF). Recently, non invasive monitoring of serial changes in maternal CO by the suprasternal Doppler LiDCO plus (minimally invasive lithium dilution technique) and pulse wave form analysis found that the administration of small boluses of phenylephrine in response to a decrease in mean arterial blood pressure (MABP) restored systemic vascular resistance (SVR) close to baseline with reduction of CO which strongly correlated with HR.[6,12-14] However, whenever large doses of phenylephrine are required to maintain the maternal SBP and if it is accompanied with bradycardia, one should initiate prompt and aggressive management of the slow HR, either by stopping the infusion or using a chronotropic drug.[12]

In an attempt to control the reductions in CO with fixed-rate phenylephrine infusion regimens,[10,12,15] a closed-loop variable rate algorithm has been found to provide a tighter and more accurate control of BP with no discernible effect on maternal and neonatal outcomes.[16]

Markers of neonatal outcome

To assess the effect of various vasopressors on neonatal well being, the uteroplacental blood flow (UPBF) umbilical

cord blood gases and APGAR scores have been estimated. The pulsatility index (PI) in maternal and fetal vessels has been calculated to assess the effect of vasopressors on the uteroplacental circulation with varying results.[17-20]

The usefulness of APGAR scores as a sensitive index of neonatal outcome has been questioned as there appears to be a poor correlation between APGAR scores and umbilical cord pH.[21] Umbilical cord blood gases and pH are considered as better predictors of neonatal outcome, when assessing perfusion and the impact of vasopressors on the fetus.

Standard base excess, which is also adjusted for pCO_2 gives a more accurate assessment of the metabolic status of the fetus, since base deficit may be a sign of prolonged O_2 debt and hence anerobic metabolism, however its usefulness as a practical measure to compare two vasopressors is doubtful.[20] It has been estimated that a pH value of 7.02 to 7.18 rather than 7.2 should represent the lower limit of normal umbilical artery pH.[22] Armstrong and Stenson[23] have gone a step further and stated that at a pH of >7.0 or base excess> -12mmol/L significant adverse outcome in the neonate is rare.

Phenylephrine use in low risk parturients undergoing elective cesarean delivery has been found to be associated with a higher umbilical artery pH and base excess as compared to ephedrine.[12,14] The more lipid soluble ephedrine stimulates the fetal beta adrenergic receptors and increases the metabolic activity to an extent that fetal oxygen demand exceeds its supply, thereby promoting anerobic metabolism.[6,7] The updated report on the Guidelines for Obstetric Anesthesia by the American Society of Anesthesiologists has recommended that, in the absence of maternal bradycardia, phenylephrine may be preferable to ephedrine because of improved fetal acid-base status in uncomplicated pregnancies.[23]

Lingering controversies in obstetric anesthesia[24] are a major cause for concern in ensuring safe obstetric anesthesia and unless obstetric audits[25] are carried out regularly in India, we will not be able to provide quality anesthesia services to our obstetric population.

Pharmacogenetics

Apart from the choice and doses of vasopressors to maintain maternal hemodynamics, genotyping of the mother and neonate is also found to influence the maternal and neonatal outcome following spinal anesthesia for cesarean delivery. Previous work in the obstetric population has demonstrated that the incidence and severity of maternal hypotension after spinal anesthesia for cesarean delivery and the response to treatment clearly are affected by the B2 adrenoceptor genotype (B2AR). Women who are Gly 16 homozygous carrying one or two Glu at position 27 of the beta 2 AR were found to require significantly lower doses of vasopressors for treatment of hypotension during spinal anesthesia.[26]

In a recent study, Landau *et al*,[27] found that the Chinese cohort as compared to the North American cohort had a low occurrence of Glu 27 homozygosity and that the ADRB2 genotype did not influence the dose of ephedrine administered to maintain maternal blood pressure during spinal anesthesia for cesarean delivery underlining the effect of ethnic background. The most clinically relevant and intriguing finding was that uterine artery pH was overall higher and uterine artery lactate was lower in neonates that were Arg 16 homozygous as compared to neonates with the two other genotypes of ADRB2. Furthermore, among neonates born to mothers who had received ephedrine, ephedrine dose was associated with neonatal academia (decreased uterine artery pH) only in neonates carrying a Gly 16 allele, but not in neonates who were Arg16 homozygous. The latter, seem to be protected, from the risk of developing acidemia, when exposed to ephedrine, irrespective of the maternal dose.

In summary, an infallible technique to prevent hypotension following spinal anesthesia for cesarean delivery is still not clear and remains a common, potentially adverse side effect, despite use of prophylactic doses of vasopressors. Clinical significance of a tight control regime of the SBP is debatable, as it can mask significant underlying hemodynamic disturbances in the parturient which are not evident with routine monitoring and could affect neonatal outcome. Future areas of research should focus attention on the dosing and timing of vasopressors in normal and high risk parturients; the ideal non invasive hemodynamic monitoring in the parturient; and maternal and neonatal genotyping in the Indian cohort.

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