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Review Article

Role and efficacy of vasopressors in post-spinal hypotension in cesarean section. Is norepinephrine a newer choice?

Vikash Bansal[1], **Ripon Choudhary**[2], **Ridhima Sharma**[3], **Lalit Gupta**[4]*

[1]*Dept. of Anaesthesiology and Intensive Care, All India Institute of Medical Sciences, Deoghar, Jharkhand, India*
[2]*Dept. of Anaesthesiology and Intensive Care, Datta Meghe Medical College & Shalinitai Meghe Hospital & Research Centre, Wanadongri, Maharashtra, India*
[3]*Dept. of Anaesthesiology and Intensive Care, All India Institute of Medical Sciences, Nagpur, Maharashtra, India*
[4]*Dept. of Anaesthesiology and Critical Care, Maulana Azad Medical College and Associated Hospital, Delhi, India*

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ABSTRACT

In elective cesarean section, spinal anesthesia-related hypotension is routinely prevented or treated with fluids and vasopressors. From the use of fluid preloading to co-loading and different vasopressors, Phenylephrine remains the vasopressor of choice in the management of hypotension during cesarean section under spinal anesthesia for a long time. However, in recent studies, Norepinephrine has also been found as effective as phenylephrine but its routine use has not been recommended till now for the same as a vasopressor agent, and among all the vasopressors, phenylephrine has emerged as the recommended one. Phenylephrine is chosen as a vasopressor over mephenteramine, metaraminol, and ephedrine due to the lack of conclusive evidence about the clinical benefits of one over the other, especially in emergency and high-risk Cesarean sections, and is determined by indirect evidence on fetal acid-base status. Norepinephrine is preferable to phenylephrine, according to recent studies, the present recommendations are mostly based on studies done in elective Cesarean sections. Further studies are warranted in elective, emergency, and high-risk Cesarean sections to use phenylephrine over other vasopressors.

1. Introduction

For elective and uncomplicated cesarean sections, subarachnoid blockade (SAB) has become the preferred method.[1] The most common side effect of spinal anesthesia is hypotension, defined as systolic blood pressure (SBP) lower than 70–80% of baseline or an absolute value lower than 90 mm Hg.[1,2] Low blood pressure leads to cerebral hypoperfusion and hypoperfusion of the stomach which activates the vomiting center and production of emetogenic chemicals (such as serotonin) respectively that results in intraoperative nausea and vomiting (IONV).[3] Fetal acidosis, hypoxia, and brain damage are all serious consequences for the fetus if there is a decrease in uteroplacental blood flow caused by hypotension.[1,4] In addition, uterine flow can be low due to decreased perfusion pressure caused by the supine position, hemorrhage/hypovolemia, hypotension due to venocaval compression, drug-induced hypotension, skeletal muscle hypotension, increased vascular resistance, endogenous catecholamines during stress, vasopressin or exogenous vasoconstrictors, i.e. adrenaline, vasopressors (ephedrine/phenylephrine) or local anesthetics at a higher concentration. Hypotension, inadvertent intravenous injection of local anesthetic or epinephrine, absorbed local anesthetic decreases uterine blood flow while adequate pain relief, decreased sympathetic activity, and decreased maternal hyperventilation increases the uterine

* *Corresponding author*.
E-mail address: lalit.doc@gmail.com (L. Gupta).

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flow.[5,6] There is greater sensitivity to local anesthetics in the parturient, which can lead to a higher block, which is further exacerbated by the effects of aortocaval compression of the gravid uterus. Many strategies have been described to prevent and treat hypotension associated with spinal anesthesia. Nonpharmacologic techniques include the use of lateral uterine displacement, preoperative intravenous hydration, and a lower extremity wrap. Improved hemodynamic control with lower maternal nausea scores can be achieved by proper choice, timing, and methods of vasopressor administration. Commonly used vasopressors are phenylephrine, ephedrine, mephenteramine, and recently norepinephrine has been used in recent studies. Vasopressor infusion together with rapid co-loading of crystalloids is the modality of choice that is effective for preventing hypotension in cesarean sections under spinal anesthesia.[4]

Changes in maternal BP do not always mirror changes in maternal cardiac output (CO) because of changes in peripheral resistance, and it is the shift in CO that may put the fetus at risk.It is better to prevent hypotension than to treat its symptoms.Rapid administration of crystalloid solutions to correct established hypotension was first advocated by Greiss and Crandell.[7] For the last many decades, left uterine displacement and volume overloading before SAB have been the cornerstones of the prevention of hypotension.Several investigators have recently shown that increasing the amount of crystalloid does not eliminate the incidence of hypotension or ephedrine requirement after spinal anesthesia.[8] Fluid preloading at one time positively encouraged is now no longer recommended.[8] In a study, it was reported that preloading with 1000 ml crystalloid reduces the incidence of hypotension from 92% to 57% but doesn't eliminate it.[9]

Since formal preloading with crystalloids is not effective, many authors have abandoned the routine use of preloading. Because of the brief intravascular half-life, crystalloid preloading might not be able to properly prevent hypotension,[9] a large amount of crystalloid fluid may also reduce the blood's ability to carry oxygen or raise the danger of pulmonary edema. Additionally, colloid solutions containing 5% albumin, 6% HES, and gelatin are utilized to stop the hypotension brought on by SAB.[8] Colloids are, however, rather pricey, and recent trial has focused on potential morbidity related to them.

2. Role of Vasopressors in Treating or Preventing Hypotension

With the commencement of spinal block brought on by sympathetic nerve blockade, there is an increase in venous capacitance and a decrease in systemic vascular resistance, which results in hypotension.[10] It would seem rational to combat hypotension using vasopressors like Norepinephrine, Ephedrine, Phenylephrine, and Mephenteramine that stimulate adrenoreceptors.[11] Preload does not give any therapeutic advantages, and prophylactic vasopressors started just after spinal anesthesia are just as effective, according to studies substituting the typical preload.

3. Vasopressors

3.1. Phenylephrine

It is a pure $\alpha 1$ agonist and the most used vasopressor for spinal anesthesia-related hypotension during cesarean sections.[12] The International Consensus Statement on the management of hypotension with vasopressors during cesarean section recommends phenylephrine as the vasopressor of choice due to the availability of enough supporting evidence of its advantages.[13] When phenylephrine is taken or titrated to maintain SBP near baseline levels, it is a strong $\alpha 1$-receptor agonist without adrenergic receptor action at common clinical doses, reducing the incidence of nausea and vomiting without leading to fetal acidosis. Due to its quick onset of action, it is appropriate for infusion.[4] Although the ideal dose has not yet been established, intermittent intravenous bolus doses of 25–100μg are commonly utilized. It can be administered intravenously as a bolus or by an infusion approach, it is recommended to administer a preventive infusion dose between 25 and 100 μg/min; a lower dose reduces the risk of reactive hypertension, bradycardia, and decreased cardiac output. For better hemodynamics and fewer side effects, the infusion rate can be adjusted as needed.[14] Phenylephrine is less likely to cause fetal acidosis when used alone than when combined with other vasopressors.[14] The following characteristics make phenylephrine the preferred vasopressor in obstetrics: it is simple to titrate, has a quicker start, and is more effective at raising systemic vascular resistance. improves fetal pH and reduces maternal hypertension and tachycardia.[2,15]

Peripheral vascular resistance may considerably rise as a result of secondary hypertension brought on by adrenergic activation. This raises the left ventricular filling pressure by diverting blood from the peripheral circulation into the pulmonary vasculature, which is less susceptible to the effects of vasoconstrictors. Phenylephrine's duration of action is brief, and hypertension may resolve on its own before treatment is begun. Before administering antihypertensive drugs, mild to moderate phenylephrine-induced hypertension in a healthy person should be cautiously watched for 10 to 15 minutes.[16]

Its use is often associated with a dose-related reflexive slowing of maternal HR and a corresponding decrease in CO.[3,17–19] But this decrease in CO due to reflex decrease in HR can be attenuated or prevented by using anticholinergic drugs along with phenylephrine infusion.[20] Atropine and glycopyrrolate are the most commonly

used anticholinergic drugs. Glycopyrrolate is a quaternary ammonium anticholinergic drug which in contrast to atropine does not affect fetal heart rate (FHR) or HR variability since it does not penetrate placental barriers in significant amounts.20There are few studies on the effect of glycopyrrolate pretreatment on hemodynamic effects when used before phenylephrine infusion for the prevention of hypotension under spinal anesthesia in cesarean section. In a study done by Bansal V et al, they found that glycopyrrolate 0.1 mg is more effective in maintaining better hemodynamics than 0.2mg related to phenylephrine infusion.[21] However, its routine use with phenylephrine is not recommended as per international consensus guidelines.[13]

According to the consensus opinion, phenylephrine infusion should be started @ 25-50μg/min and increased or decreased in accordance with blood pressure response. If necessary, top-up boluses can be given. SBP should be kept at or above 90% of baseline, a dip below 80% should be avoided. The most commonly used bolus dose of phenylephrine is 100μg.[13,22,23]

3.2. Ephedrine

Ephedrine is an indirectly acting α and β adrenergic agonist[7] and action results from direct and indirect activation of α and β adrenoreceptors. The major mechanism of its indirect action is considered to be the release of norepinephrine from peripheral sympathetic neurons and possibly inhibition of neuronal norepinephrine uptake, rather than a centrally mediated action.[5] As uteroplacental circulation is devoid of sympathetic innervations, it is relatively resistant to the vasoconstrictive effect of ephedrine.[24] It increases SBP and maternal HR but decreases fetal pH, base excess, and umbilical artery oxygen content[5,18,25] as it crosses the placenta and causes β adrenergic ally mediated increase in fetal metabolic rate,[19,26] resulting in increased concentrations of lactate, glucose, norepinephrine, epinephrine and catecholamine in fetal blood which leads to fetal acidosis and lower base excess.[5,18,19,21,24,26,27] Ephedrine-induced β adrenergic stimulation of the fetus is a possible mechanism for fetal acidemia that doesn't involve uteroplacental or fetoplacental circulation. It can increase fetal heart rate and catecholamine levels.Historically ephedrine has been preferred for the treatment of hypotension and studies showed that it was more effective in maintaining uteroplacental circulation than phenylephrine and methoxamine. Intravenous boluses of 5 to 15 mg are most commonly advocated as rescue therapy. The onset of action of ephedrine is slightly delayed as compared to phenylephrine, so a repeat dose should be given after 5-10 min. Tachyphylaxis is also seen with it due to the depletion of presynaptic norepinephrine. Intravenous boluses are preferred as compared to the infusion method due to their delayed onset of action and tachyphylaxis. On the other hand, phenylephrine which is a pure α agonist was associated with higher umbilical pH and base excess than ephedrine despite the use of very large doses and is the first line of agent for the treatment of hypotension during cesarean section.[5,14,25,26]

4. Ephedrine vs Phenylephrine

Ephedrine was shown to be more effective than non-pharmacological control maneuvers in preventing hypotension. The risk of hypotension for a woman who received ephedrine is 14 to 37% less frequent than compared to a woman receiving control therapy.[11] The α agonist phenylephrine has been compared with ephedrine in terms of BP and cord blood gas but results were inconsistent initially with more episodes of bradycardia with phenylephrine. Ephedrine was used as the sole vasopressor in the United Kingdom at time.[5] α adrenergic such as phenylephrine was used less frequently because earlier work with it was found to be associated with reduced uteroplacental circulation compared with ephedrine.

In a randomized control trial by Anna Lee et al,[28] it was concluded that for the management of maternal hypotension, there was no difference between phenylephrine and ephedrine. Maternal bradycardia was more likely to occur with phenylephrine. Neonates in the phenylephrine group showed higher umbilical arterial pH than those with ephedrine. Acidotic changes in umbilical artery pH are sensitive indicators of reduced uteroplacental circulation and the finding was indirect evidence that uterine blood flow may in fact be better with phenylephrine as compared to ephedrine. They didn't support the traditional idea that ephedrine is the preferred choice for the management of maternal hypotension during spinal anesthesia.[28]

Although vasopressors have a role in the treatment of hypotension their prophylactic use is more controversial. Several studies have shown no significant reduction of maternal hypotension with prophylactic use of ephedrine compared with the control. In some studies, women who were given ephedrine before or during the induction of spinal anesthesia had a lower incidence of maternal hypotension compared with those who didn't receive it.[29]

In a study by David W. Cooper et al, it was concluded that giving prophylactic phenylephrine alone by infusion was associated with a lower incidence of fetal acidosis and maternal nausea and vomiting than giving ephedrine alone or a combination of phenylephrine and ephedrine infusion.[15] The increased incidence of fetal acidosis associated with ephedrine alone could have been caused by reduced uteroplacental perfusion from decreased maternal artery pressure, reduced uteroplacental perfusion from ephedrine-induced vasoconstriction or by the direct fetal effect of ephedrine.[15] Prophylactic ephedrine even in larger doses has limited efficacy and doesn't reduce the incidence

of fetal acidosis.[30,31] There is evidence that ephedrine may adversely affect the fetus when given in a parturient with labor.

Recent data support the use of phenylephrine to maintain BP during spinal anesthesia for cesarean section.[32,33] Umbilical artery pH and the incidence of nausea and vomiting are least when phenylephrine is titrated with the aim of maintaining maternal BP at 100% of baseline.[32] Studies have shown that prophylactic phenylephrine infusion starting immediately after induction of anesthesia is more effective for reducing both the incidence and frequency of hypotension.[33] Faster onset and short duration of phenylephrine make its administration by infusion more convenient, appropriate, and effective.[34] Phenylephrine infusion leads to less fluctuation in BP and is more effective in maintaining the BP near baseline values than boluses of phenylephrine.[34–36]

In a systemic review, 14 clinical trials were identified by Anna Lee including data from a total of 641 parturient, they concluded that prophylactic ephedrine is more effective for preventing hypotension during spinal anesthesia for elective cesarean delivery but has a clinically relevant positive effect on neonatal outcome was not observed. They didn't support the prophylactic routine use of ephedrine to prevent any adverse effects of maternal hypotension following spinal anesthesia for cesarean section.[29]

Ngan Kee et al randomized 125 parturient to receive an i.v. infusion of phenylephrine and ephedrine combined in 1 of 5 different ratios. Decreasing the concentration of phenylephrine and increasing the concentration of ephedrine was associated with increased incidences of hypotension and nausea/vomiting, increased maternal HR, decreased fetal pH and base excess, and decreased umbilical artery O2 content. They concluded that the combination of these two drugs offers no advantage compared with phenylephrine alone for the prevention of hypotension.[37]

Doherty et al gave a bolus of phenylephrine when the BP decreases from baseline and compared it with phenylephrine infusion and found that there was no difference in episodes of hypotension and bradycardia in the two groups and a lesser amount of phenylephrine was consumed in the bolus group.[38]

Siddik-Sayyid et al, however, suggested that repeated manual injection is more labor-intensive and arguably less convenient than infusion.[36] There is a reduced rate of maternal hypotension after prophylactic phenylephrine infusion both before and after the birth of the fetus.[38] Combinations of phenylephrine and ephedrine appear to have no advantage over phenylephrine alone when administered by infusion for the prevention of hypotension associated with spinal anesthesia for cesarean delivery.[37] Combination of high-dose phenylephrine infusion and rapid crystalloid co-loading is the first technique to be described that is effective for preventing hypotension during spinal anesthesia in cesarean section.[4,25]

4.1. Methoxamine

It acts as α 1 receptor agonist and causes severe vasoconstriction, and increases arterial blood pressure, but may also cause a decrease in the heart rate. It has no inotropic or chronotropic effects and is used to stop the hypotension brought on by SAB. Tachyphylaxis has been linked to methoxamine. The action usually lasts for around 10 minutes after I.V dose. Concerns about the fetal acid-base balance in animal investigations are the reason it is no longer used in clinical obstetrics.

4.2. Mephenteramine

It acts by both direct and indirect release of norepinephrine and epinephrine by mixed action on both α and β receptors. The heart rate is affected by the vagal tone. The effect of mephenteramine quickly develops. There is a peak of 5 min and a duration of 15 min after injection. It can be administered either as a 25–50mg dose or as a 2–5mg/min injection. There are no studies on mephenteramine's impact on fetal metabolism. A few studies have shown that mephenteramine has the same effect on newborns as phenylephrine in avoiding maternal hypotension. Due to economic reasons, it is being used more and more in our country.[39–42]

4.3. Metaraminol

It is a mixture of α and β receptor agonists, that is used to avoid hypotension. In addition to its indirect action, the release of norepinephrine has a direct effect on the cardiovascular system. The dose starts to work in 1–2 minutes, peaks in 10 minutes and lasts for 20–60 minutes.[43–45]

Norepinephrine:Norepinephrine has a weak β adrenergic receptor agonistic activity in addition to potent α adrenergic receptor activity and has fewer tendencies to decrease HR and CO compared with phenylephrine. In order to reduce post-spinal hypotension, Gupta et al. examined the effects of phenylephrine and norepinephrine when provided as boluses. They randomly assigned the group as NE and PE and a prophylactic dose of either NE 4μg or PE 50μg was given.[46] They noted that the mean HR was higher with the norepinephrine group than with phenylephrine at the 2nd to 4th minute after injection. However, there was no discernible difference in the incidence of bradycardia between the groups. There were no differences in the prevalence of hypotension, maternal nausea, or neonatal outcomes. Ngan Kee et al studied 104 healthy parturient undergoing cesarean delivery and randomized them to have SBP maintained with a computer-controlled infusion of norepinephrine or phenylephrine and they found that norepinephrine was effective for maintaining BP and was

associated with greater HR and CO as compared to phenylephrine. It is HR rather than BP which is a surrogate marker of uteroplacental circulation and is best preserved by norepinephrine.[12]

In a study Mohta M, concluded that 100 μg phenylephrine and 5 μg noradrenaline boluses had similar efficacy for treating hypotension in patients undergoing elective cesarean section under subarachnoid block, no significant difference was found in the incidence of maternal bradycardia. But they warranted to study of the placental transfer and fetal metabolic effects of noradrenaline as its use was associated with lower umbilical artery pH, bicarbonate, and base excess in the noradrenaline group.[47]

Hasanin et al compared the effect of prophylactic infusion of norepinephrine vs phenylephrine and concluded that in a manually adjusted infusion, norepinephrine effectively maintained maternal SBP during cesarean delivery under spinal anesthesia with a lower number of physician interventions, and likely less incidence of reactive hypertension and bradycardia compared to phenylephrine.[48]

Thoracic bioreactance was used by Belin et al. to assess cardiac index while manually controlling infusions of phenylephrine or norepinephrine.[49] With norepinephrine infusion rather than phenylephrine infusion, the cardiac index was kept at greater levels.

Norepinephrine 8μg or phenylephrine 100μg were administered right away following spinal anesthesia by Wang et al. to prevent hypotension.[50] If the patient had hypotension the doses were repeated. In comparison to patients who received phenylephrine boluses, those receiving norepinephrine had decreased incidence of bradycardia and higher cardiac output.

There are very few studies on norepinephrine for the prevention of hypotension under spinal anesthesia in cesarean section and results have shown that it is better than phenylephrine in maintaining maternal BP, HR, and CO. But as per ASA guidelines, it is not approved right now for use in the same. If equipotent doses of norepinephrine are considered, an infusion beginning at 2–4 μg/min or a bolus dose of 8 μg should be used. Recently, many workers have used weight-based doses of both these agents.[51]

5. Conclusion

According to current recommendations and guidelines, phenylephrine should be used as the preferred vasopressor in cases of hypotension after cesarean delivery. All of these suggestions are based on research done on elective cesarean sections. It is not possible to apply the same recommendations to high-risk pregnancies and emergency C-sections, especially when there is pre-existing fetal distress which can result in severe bradycardia and decreased cardiac output. Further research on phenylephrine in these contexts is needed.

Recent data and research indicate that norepinephrine and phenylephrine are equally effective for maintaining maternal cardiac output. However, more research is necessary before the regular use of norepinephrine can be recommended. Among all vasopressors, phenylephrine maintains better hemodynamics and is associated with fewer fetal problems. Larger studies in cesarean sections, both elective and high-risk, are required to provide anesthesiologists with more guidance in selecting their preferred vasopressor and managing hypotension.

So far, no study has demonstrated superior neonatal outcomes with the use of norepinephrine versus phenylephrine. In conclusion, both phenylephrine and norepinephrine are safe and effective for the prevention and treatment of post-spinal hypotension during cesarean delivery. Although norepinephrine maintains higher maternal heart rate and cardiac output, no additional advantage in terms of maternal and neonatal outcomes has been demonstrated. Thus, the evidence available at present does not support replacing phenylephrine with norepinephrine as the vasopressor of choice.

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None.

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Author's biography

Vikash Bansal, Assistant Professor https://orcid.org/0000-0002-9716-9261

Ripon Choudhary, Associate Professor https://orcid.org/0000-0001-7205-1876

Ridhima Sharma, Associate Professor https://orcid.org/0000-0001-9661-7547

Lalit Gupta, Professor https://orcid.org/0000-0001-7291-5961

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