

Vasopressors in obstetric anesthesia: A current perspective

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acid-base status. This review article evaluates the present day evidence on the various vasopressors used in obstetric anesthesia today.

Key words: Vasopressor agents; Obstetrics; Cesarean section; Hypotension; Spinal anesthesia

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Core tip: Phenylephrine has emerged as the vasopressor of choice in Obstetrics. However, the present recommendations are essentially based on studies conducted in elective Cesarean sections. Further studies are needed in emergency and high risk Cesarean sections in order to clarify whether there is a benefit of phenylephrine over other vasopressors.

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Abstract

Vasopressors are routinely used to counteract hypotension after neuraxial anesthesia in Obstetrics. The understanding of the mechanism of hypotension and the choice of vasopressor has evolved over the years to a point where phenylephrine has become the preferred vasopressor. Due to the absence of definitive evidence showing absolute clinical benefit of one over the other, especially in emergency and high-risk Cesarean sections, our choice of phenylephrine over the other vasopressors like mephentermine, metaraminol, and ephedrine is guided by indirect evidence on fetal

INTRODUCTION

Neuraxial anesthesia remains the preferred choice for Cesarean deliveries across the world. Hypotension is the physiologic consequence of spinal anesthesia and can have a potentially deleterious maternal and fetal impact. Vasopressors, which lead to an increase in systemic vascular resistance and rise in mean arterial pressures^[1], have been traditionally used for the prevention and management of hypotension after neuraxial anesthesia. However, the understanding of hypotension after neuraxial anesthesia in obstetrics, and the use of vasopressors to counteract it, continues to evolve over the years. This review article briefly explores the present understanding of the mechanism causing hypotension before discussing the current use of

the various vasopressors in obstetric anesthesia today. The authors discuss the various vasopressors used in obstetric anesthesia and put the recent evidence into perspective to guide our clinical practice today.

HYPOTENSION AFTER NEURAXIAL ANESTHESIA

The sympathectomy resulting from the neuraxial blockade is exaggerated by the physiological changes of pregnancy and puerperium, leading to hypotension in as much as 55%-90% of the mothers receiving spinal anesthesia for Cesarean section^[2]. Holmes *et al*^[3] and Lees *et al*^[4] indicated that the compression of the vena cava by gravid uterus impeded the venous return and caused hypotension. Marx^[5] postulated that the subarachnoid block resulted in venous pooling of blood in the lower legs, leading to decreased venous return and reduced cardiac output. Although our present interpretation of the mechanism causing hypotension are still based on these principles, prophylactic therapeutic interventions based upon this understanding do not definitively prevent hypotension after neuraxial anaesthesia in Cesarean sections^[6].

Based on studies on pre-eclamptic women, Sharwood-Smith *et al*^[6] challenged the understanding that reduced central venous pressure led to decreased cardiac output and arterial pressures. They suggested that “venous capacitance” rather than venous pressure maybe the determinant in causing hypotension after spinal anesthesia in obstetrics. The “endothelium-dependent alteration of vascular smooth muscle function” and increased presence of “vasodilator prostaglandins and nitric oxide” during pregnancy have a vasodilatory effect which is counteracted by the intrinsic sympathetic vascular tone^[6]. This intrinsic vascular tone is adversely impacted after spinal anesthesia, leading to exaggerated fall in blood pressure. Studies now show that cardiac output remains nearly unchanged even after sympathetic blockade^[7], challenging the concept that in parturients, spinal anesthesia results in decrease in cardiac output^[8]. Despite the varied understanding of hypotension following neuraxial anesthesia in pregnancy, vasopressors remain the cornerstone in restoring the arterial pressure and mitigating the possible adverse maternal and fetal impact.

VASOPRESSORS USED IN OBSTETRICS

Vasopressors which have been used in obstetrics primarily include the directly acting selective α_1 receptors agonists, phenylephrine and methoxamine, and both directly and indirectly acting mephentermine, metaraminol and ephedrine.

METHOXAMINE

Methoxamine is an α_1 receptor agonist which causes intense vasoconstriction following parenteral administration, raising arterial blood pressure and may result in reflex

vagal inhibition of the heart rate^[9]. It is devoid of any inotropic or chronotropic effect^[9] and has been used to counteract the hypotension caused by spinal anesthesia^[10]. Tachyphylaxis has seldom been observed with methoxamine^[11]. While the peak vasopressor effect after a single intravenous dose of 2-4 mg has been observed after 0.5-2 min, its duration of action has been reported to be 10-15 min^[12]. Intramuscular administration of a 10-40 mg dose has its peak onset of action at 15-20 min and its action lasts for about 1.5 h^[12]. Its use in clinical obstetrics has fallen out of favor decades ago owing to concerns regarding decreased uterine blood flow and adverse impact on fetal acid-base status in animal studies^[12,13].

MEPENTERMINE

It has a mixed α and β receptor agonist action with both direct and indirect effect due to release of norepinephrine and epinephrine^[14]. Its impact on the heart rate is dependent on the vagal tone. Its use in hypotension after a neuraxial blockade in obstetrics is due to its ability to increase the blood pressures by augmenting the cardiac output^[14]. Tachyphylaxis to the pressor action of mephentermine develops rapidly^[15]. While there is immediate onset of action peaking at 5 min and lasting 15-30 min after an intravenous dose, an intramuscular dose starts acting after 5-15 min and has a variable duration of action from 1-4 h. It is commonly used as a 3-5 mg intravenous bolus or intravenous infusion of 2-5 mg/min^[16], or 25-50 mg intramuscularly^[17]. There is scarce literature evidence on the fetal metabolic effect and placental transfer of mephentermine^[18]. However, a few studies have shown that mephentermine is as effective as phenylephrine in preventing maternal hypotension after spinal anesthesia and has similar effect on neonatal outcome^[19]. It is being widely used in developing countries like India as it is much more economical^[19] than phenylephrine. Moreover, unlike phenylephrine which needs multiple dilutions from the single use 10 mg/mL (1 mL) ampoules, mephentermine offers ease of use as it does not necessitates multiple dilutions.

METARAMINOL

Although it has both mixed α and β receptor agonist action, its primary clinical use is to counteract the hypotension after spinal anesthesia in obstetrics. It has significant direct effect on vascular α adrenergic receptors along with its indirect action due to the release of norepinephrine^[20,21]. Tachyphylaxis develops due to the displacement of norepinephrine from the sympathetic nerve endings by metaraminol and its action as a false neurotransmitter having inhibited vasopressor effect^[17]. While an intravenous bolus dose of 0.5-5 mg has its onset of action in 1-2 min, peak action is at 10 min and duration of action is 20-60 min. An intramuscular dose of 2-10 mg has its onset by 10 min and duration of action of 1-1.5 h^[22].

PHENYLEPHRINE

At clinically relevant doses, it is a selective α_1 receptor agonist and β agonist action is only seen at much higher doses^[20]. It is frequently used in obstetric anesthesia to counteract the hypotension after spinal anesthesia due to marked arterial vasoconstriction caused by its α_1 agonist action. Potential negative chronotropic effect is due to reflex bradycardia and decreased cardiac output might not adversely influence the fetus in elective cases^[23], but during emergency Cesarean sections with presence of fetal acidosis, any fall in cardiac output may further jeopardize the compromised fetus^[23]. However, definitive understanding on the effect of phenylephrine in emergency situations awaits further research^[21]. Tachyphylaxis with phenylephrine is possibly caused by the down-regulation of α adrenergic receptors. Its potential to be reversed by hydrocortisone has not been evaluated in an obstetric setting^[24].

An intravenous dose of phenylephrine has immediate onset and duration of action of 5-10 min^[17]. The optimum regimen for administration of phenylephrine has not yet been defined^[25]. Prophylactic administration is associated with a higher incidence of hypertension and bradycardia^[26] and treatment after onset of hypotension is associated with higher “incidence and severity of maternal predelivery hypotension”^[26]. Despite some studies suggesting that to prevent spinal anesthesia induced hypotension, as an intravenous intermittent bolus dose (ED95) of phenylephrine should be at least 122-147 μg ^[27,28], 40-100 μg bolus dose remains the common clinical practice^[25].

Prophylactic infusions have been advocated in the range of 25-100 $\mu\text{g}/\text{min}$ in various studies, but claims have been made that a fixed dose of 50 $\mu\text{g}/\text{min}$ minimizes the risk of higher incidence of hypotension at lower doses and reactive hypertension, bradycardia and decreased cardiac output at higher doses^[23,25,26].

However, prophylactic fixed dose concept has been challenged^[26], necessitating further studies to find the advantages of phenylephrine infusion.

It was even suggested in 2010 that “prophylactic fixed rate infusions may have limited application in clinical practice” and further studies into variable rate of phenylephrine infusion is needed^[26]. A recent study by Siddik-Sayyid *et al*^[29] has failed to demonstrate any difference in neonatal outcome with a variable rate regimen adjusted in response to changes in arterial blood pressure, as compared to prophylactic fixed rate infusion regimen. However, with respect to limiting maternal symptoms, the variable rate regimen was more effective than relying on rescue phenylephrine^[29].

Despite these studies, obstetric anesthesiologists are unable to arrive at a consensus opinion on the ideal regimen for administration of phenylephrine because other studies have demonstrated that with intermittent boluses, the total dose requirement is smaller, blood pressure was better maintained in the 1st 6 min after

induction, and indeed, good blood pressure control is achievable by intermittent boluses^[30], which is not only simple, but also does not need the setting up of a syringe pump^[31].

Although not much literature is available on the efficacy of intramuscular phenylephrine, Ayorinde *et al*^[32] reported that 4 mg of intramuscular pre-emptive phenylephrine decreased the severity of hypotension and the need for rescue vasopressors in spinal anesthesia induced hypotension.

EPHEDRINE

It has both direct α and β agonist action, but indirect action is more prominent due to the “release of norepinephrine from sympathetic neurons”^[20]. It increases the blood pressure by β_1 receptor stimulation with increased heart rate and cardiac contractility, whereas the α agonist action causes peripheral vasoconstriction^[21,33]. Prophylactic doses of 30 mg intravenous ephedrine had been suggested by Ngan Kee *et al*^[34] to achieve significant reduction in the incidence of hypotension, but it was associated with the risk of reactive hypertension in as much as 45% of the patients. Subsequent studies by Kol *et al*^[35] also failed to demonstrate beneficial effect of prophylactic intravenous ephedrine at 0.5 mg/kg. Even for a reduction in the need for rescue boluses of ephedrine, at least 12 mg intravenous prophylactic dose of ephedrine is needed after spinal anesthesia for Cesarean sections^[36]. Ephedrine’s limited ability to prevent hypotension induced by neuraxial anesthesia is probably related to its slower onset of action^[34]. As a rescue vasopressor, 5-15 mg intravenous boluses are most commonly advocated for the treatment of hypotension following neuraxial anesthesia. Its clinical effect is primarily due to its indirect action of releasing norepinephrine from postganglionic nerve endings. The drug not only has delayed onset of action, it also has a longer duration of action of about 60 min. Depletion of presynaptic norepinephrine stores also lead to tachyphylaxis^[35]. Due to its delayed onset of action, it should only be repeated after 5-10 min as it was observed that larger doses of ephedrine were required in the first 10 min and often caused overshoot of the desired target systolic pressures after 10 min^[37]. Intravenous boluses are therefore preferred to continuous intravenous infusions as the drug exhibits delayed onset of action and tachyphylaxis.

CHOICE OF VASOPRESSOR: THE RECENT EVIDENCE

The ideal vasopressor would be one which is reliable and easy to use, has rapid onset, short duration of action, easily titrable, can potentially be used prophylactically and lack any adverse maternal and fetal impact. A Comparative analysis of the commonly used vasopressors in obstetric anesthesia is illustrated in Table 1.

Table 1 Comparative analysis of vasopressors used in obstetric anesthesia

No.	Drug	Mechanism of Action	Advantage	Disadvantage
1	Methoxamine	α_1 receptor agonist	No inotropic or chronotropic effect. Tachyphylaxis has seldom been observed	Reflex bradycardia. Adverse effect on fetal acid-base status
2	Mephentermine	α and β receptor agonist.	Economical and does not need multiple dilutions as compared to Phenylephrine	Tachyphylaxis. Little evidence available on placental transfer and its fetal metabolic impact
3	Metaraminol	Both direct and indirectly acting α and β receptor agonist.	No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis
4	Phenylephrine	Both direct and indirectly acting Selective α_1 receptor agonist at clinical doses	Immediate onset and short duration of action. Ideal for continuous infusion. No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis. Reflex bradycardia and concerns regarding decreased maternal cardiac output
5	Ephedrine	α and β receptor agonist. Both direct and indirectly acting	Economical and does not need multiple dilutions as compared to Phenylephrine. No bradycardia	Tachyphylaxis. Adverse effect on fetal acid-base status as compared to Phenylephrine

In 2002, Lee *et al*^[38] challenged the “traditional idea that ephedrine is the preferred choice”. for use as a vasopressor to combat hypotension after spinal anesthesia for Cesarean sections. In a quantitative systemic review they concluded that for elective Cesarean sections, phenylephrine was associated with better fetal acid-base status, although no clinical outcome difference based on the Apgar scores could be established^[38].

In patients treated with ephedrine, the cause of decreased pH, base excess and oxygen content in umbilical cord arterial blood is controversial. While earlier studies indicated towards differential action of various vasopressors on uteroplacental circulation^[39], studies by Ngan Kee *et al*^[40] showed that depressed fetal acid base status was possibly due to ephedrine crossing the placenta and causing depression of fetal pH by its “metabolic effects secondary to stimulation of fetal β -adrenergic receptors”. A recent study by Landau *et al*^[41] has given a new direction to this debate. They showed that the neonatal homozygosity for Arg16 of *ADRB2* protected from neonatal acidemia in mothers treated with ephedrine^[41]. The presence of this genotype in greater than 30% of the Chinese cohort and the fact that their genotype differs considerably from their North Americans indicate that clinicians should be wary of extrapolating studies of one ethnic population group on another^[41].

Despite evidence in favor of phenylephrine as a superior choice, there remains widespread variation in the “choice, dosing, and method of administration of vasopressors”^[25]. The United Kingdom National Institute for Health and Care Excellence Guidelines state that ephedrine and phenylephrine are equally efficacious as vasopressors in obstetric anesthesia^[42]. The American Society of Anesthesiologists Task Force on Obstetric Anesthesia states that while ephedrine and phenylephrine are both acceptable, “phenylephrine may be preferable because of improved fetal acid-base status in uncomplicated pregnancies”^[43]. There is much more clarity in the Canadian guidelines which state that there is “general agreement among experts to recommend the use of phenylephrine” as the first line therapy^[8]. Belgian guidelines also recommend phenylephrine as the preferred

vasopressor in absence of maternal bradycardia (Grade 1, A)^[44].

While there is abundant literature evidence claiming superiority of phenylephrine over ephedrine in healthy parturients undergoing elective Cesarean section based on fetal acid-base status, there is dearth of evidence showing benefit in clinical outcome. Meta-analysis of 142 studies comparing phenylephrine and ephedrine failed to show the superiority of one over the other while comparing the Apgar scores^[45]. However recent systematic review and meta-analysis do show that fetal acidosis defined as pH < 7.20 was associated with four- and two-fold increase in mortality and morbidity, respectively^[46].

Due to a dearth of studies on the vasopressor of choice during non-elective Cesarean sections^[47], it is suggested that further research is needed in high-risk pregnancies, intra uterine growth retardation, placental insufficiency, pre-eclampsia^[25] and in emergency Caesareans due to fetal distress.

In one study in 2008 by Ngan Kee *et al*^[48] in non-elective Cesarean sections, there was “no differences in fetal acid-base status or clinical neonatal outcome” between 100 μ g phenylephrine and 10 mg ephedrine boluses to manage spinal anesthesia induced hypotension. Similarly, a retrospective study by Cooper *et al*^[49] on the choice of vasopressor between phenylephrine and ephedrine in high-risk Cesarean sections, there was no statistically significant difference in the umbilical artery pH between the two groups.

There is also scarce literature available on the other vasopressors^[50]. Kansal *et al*^[16] concluded that mephentermine can be used as safely as ephedrine in the management of spinal anesthesia-induced hypotension in Cesarean sections. Similarly, Mohta *et al*^[19] concluded that phenylephrine and mephentermine are equally effective in preventing hypotension after a spinal anesthesia for Cesarean section. Both the studies compared the Apgar scores and the neonatal acid-base status while evaluating the vasopressors^[16,19]. In 2014, studies by de Aragão *et al*^[50] compared an infusion of metaraminol with phenylephrine and ephedrine and did not find any difference in the incidence of maternal hypotension or

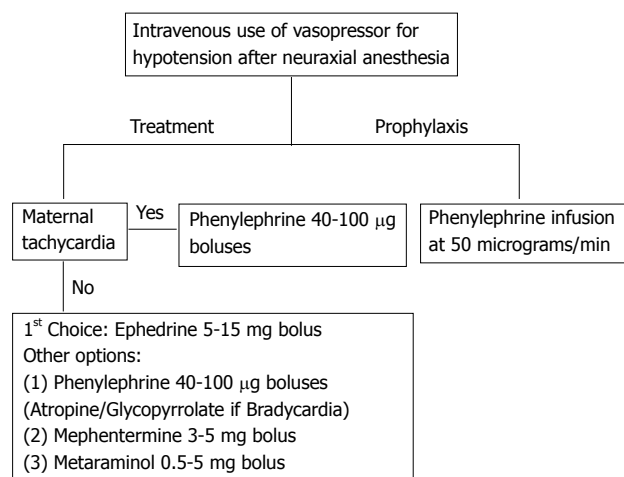


Figure 1 Suggested clinical protocol for intravenous use of vasopressor for Hypotension after Neuraxial Anaesthesia in Obstetrics.

neonatal Apgar scores. Comparison of phenylephrine, metaraminol and ephedrine showed that Ephedrine treated mothers had lower pH and base excess in their newborns^[50]. However those treated with metaraminol needed fewer rescue boluses as compared to ephedrine, but not phenylephrine^[50].

Combination of phenylephrine and ephedrine infusion has also demonstrated deterioration in fetal acid-base status and maternal hemodynamic control with the proportionate increase in the dose of ephedrine^[51-53].

CONCLUSION

Current literature supports the use of phenylephrine as the vasopressors of choice while considering the influence on fetomaternal physiology^[25,47]. However, this concept is mostly based on studies conducted in elective Cesarean sections. Therefore, this same principle cannot be extrapolated in emergency Cesarean sections and high-risk pregnancies.

Due to its potential for possible adverse impact on placental perfusion^[25] when it causes bradycardia and decreased cardiac output, further studies on phenylephrine are needed, especially in presence of pre-existing fetal compromise.

Certain clinical protocols support the use of phenylephrine in the presence of maternal tachycardia (heart rate > 110/min) and ephedrine at lower heart rates (< 80/min)^[54]. A suggested clinical protocol for intravenous use of vasopressor for hypotension after neuraxial anaesthesia in obstetrics is given in Figure 1.

Today, in obstetric anesthesia, both phenylephrine and ephedrine continue to be used in the “absence of relevant evidence, rather than any evidence of the absence of an effect”^[55]. The same appears to be true for mephentermine and metaraminol also. Larger trials, especially in non-elective Cesarean sections, would be needed to give further direction to the obstetric anesthesiologists in choosing their preferred vasopressor.

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