Vasopressors in obstetrics: what should we be using?

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Purpose of review

Historically, ephedrine has been recommended as the best vasopressor in obstetrics because animal studies showed it caused less reduction in uterine blood flow compared with α-agonists. Recent clinical evidence, however, suggests that this is not as important as initially thought. This review evaluates current data with a focus on spinal anesthesia for cesarean section.

Recent findings

Ephedrine and phenylephrine have been most investigated. Advantages of ephedrine include familiarity, long history and low propensity for uteroplacental vasoconstriction. Ephedrine, however, has limited efficacy, is difficult to titrate, causes maternal tachycardia and depresses fetal pH and base excess. Advantages of phenylephrine include high efficacy, ease of titration and the ability to use liberal doses to maintain maternal blood pressure near normal and then prevent nausea and vomiting without causing fetal acidosis. Phenylephrine, however, may decrease maternal heart rate and cardiac output and few data are available on its use in high-risk cases. Combination of a phenylephrine infusion and rapid crystalloid cohydration is the first method described that reliably prevents hypotension.

Summary

When current evidence is considered, in the authors' opinion, phenylephrine is the vasopressor that most closely meets the criteria for the best vasopressor in obstetrics.

Keywords

ephedrine, hypotension, obstetric anesthesia, phenylephrine, vasopressors

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Introduction

The choice of vasopressor in obstetric patients is controversial [1], particularly regarding the issues of efficacy and hemodynamic effects, adverse effects on uteroplacental blood flow and effects on fetal acid–base status. The purpose of this review is to highlight developments and research into the choice and use of vasopressors in obstetrics. Because hypotension is most likely to be a problem during spinal anesthesia for cesarean section, the emphasis will be on the use of vasopressors in this context.

Significance of hypotension

Hypotension in obstetric patients is important for many reasons: it is more common and severe than in nonobstetric patients, it causes a high incidence of maternal symptoms and it may have adverse effects on the fetus. Several large series have shown an association between spinal anesthesia and a greater risk of fetal acidosis during cesarean section [2,3]. This finding was confirmed in a meta-analysis by Reynolds and Seed [4•], who suggested that, from the perspective of fetal well-being, spinal anesthesia could not be regarded as the optimal technique for cesarean section, particularly in the presence of a compromised fetus. This is controversial [5] and rather than abandoning the use of spinal anesthesia it is more appropriate to focus on refining and improving its use [6]. In this respect, the management of hypotension, particularly the choice of vasopressor, is of key importance. Many strategies have been described to prevent and treat hypotension in obstetric patients. Nonpharmacological techniques include use of lateral uterine displacement, intravenous prehydration (preload) and lower limb wrapping. Unfortunately, these are not very effective [7] and it is usually necessary to use a vasopressor. There is, however, poor consensus on the best drug to use.

Physiological considerations

During spinal anesthesia, sympathetic block causes blood pressure to fall as a result of decreased systemic vascular resistance and cardiac output, the latter being secondary to reduced venous return and sometimes decreased heart rate. Hypotension is more frequent and severe in pregnant compared with nonpregnant women for several reasons. Greater sensitivity to local anesthetics may result in higher blocks, compounded by the effects of aortocaval compression. During pregnancy, there is a change in autonomic balance in favor of

a relative increase in sympathetic compared with parasympathetic activity [8] which predisposes to a greater risk of hypotension. Analysis of heart rate variability has been shown to be potentially useful for predicting which patients are most at risk of hypotension [9,10•]. Hanss *et al*. [10•] used power spectral analysis of heart rate variability as an indicator of autonomic balance and found that parturients with higher baseline sympathetic activity experienced more severe hypotension during spinal anesthesia. Many questions remain unanswered as to if this will prove to be a clinically useful tool [11]. Pregnant women show an attenuated response to vasopressors, which may be partly related to increased baroreceptor sensitivity [12] and increased endothelial nitric oxide synthase activity [13]. Relatively large doses of vasopressors, therefore, are often required to maintain maternal blood pressure, which may accentuate some of their adverse effects. The recent demonstration that the genotype of the β-2-adrenergic receptor influences vasopressor requirement [14] suggests the enticing future possibility of tailoring management of hypotension specifically to the individual patient's genetic makeup.

Historical considerations

In the 1960s and 1970s several animal models were developed to investigate the effect of vasopressors on uteroplacental blood flow. The results of these experiments affected clinical practice in a number of important ways. The demonstration that vasopressors can cause vasoconstriction in the uteroplacental circulation led to an emphasis on nonpharmacological methods of prevention such as prehydration and it was recommended that vasopressors not be used until nonpharmacological methods had failed [15]. Because ephedrine appeared to cause less uteroplacental vasoconstriction than α-agonists it was established as the vasopressor of choice in obstetrics [16]. These practices are now being challenged. Nonpharmacological methods have been shown to have poor efficacy [17,18] and, on the basis of clinical studies, the superiority of ephedrine has been questioned [19–21].

Available vasopressors

In choosing an appropriate vasopressor in obstetrics, several factors need to be considered. These include efficacy, maternal effects other than increasing blood pressure, ease of use, direct and indirect fetal effects, cost and availability. Drugs that have been described include ephedrine, phenylephrine, metaraminol, mephentermine, cafedrin/theodrenaline, eltiferamine, methoxamine, dopamine and angiotensin II. To an extent, the drug used will vary according to local experience and availability. The most widely available and commonly used drugs for which most data are available, however, are ephedrine and phenylephrine. Accordingly, this review will focus on these two drugs.

Ephedrine

Ephedrine is a long-established drug that is readily available in most countries and most anesthesiologists are familiar with its use.

Advantages of ephedrine

After decades of use in obstetrics, there are few reports of adverse clinical outcomes for mother or baby with ephedrine. Ephedrine increases blood pressure with minimal effect on uteroplacental blood flow. Several reasons have been proposed to explain this. Ephedrine is a nonspecific adrenergic agonist and increases blood pressure mainly by increasing cardiac output via stimulation of cardiac β-1 receptors with a smaller contribution from vasoconstriction. Ephedrine's action is considered to be mainly indirect, via stimulating release of norepinephrine from sympathetic nerve terminals; because the uteroplacental circulation is largely devoid of direct sympathetic innervation, it is relatively resistant to the vasoconstrictive effects of ephedrine [22]. Controversy remains, however. For example, recent studies in rats have had conflicting results in their support for indirect [22] and direct [23] actions of ephedrine. Further support for the use of ephedrine comes from laboratory experiments that showed that, compared with α-agonists, ephedrine exhibited greater selectivity for constriction of systemic (femoral) blood vessels compared with uterine blood vessels during pregnancy [24].

Disadvantages of ephedrine

Despite its widespread acceptance, ephedrine has a number of shortcomings. Ephedrine has limited efficacy [25,26]. To maintain blood pressure and prevent maternal symptoms, large doses may be required. Phenylephrine may need to be added when ephedrine is ineffective or when a large dose has been given [27,28]. The major action of ephedrine (cardiac stimulation) does not address the fundamental physiological derangement of spinal anesthesia (vasodilatation). Acute tolerance to ephedrine develops. This factor was demonstrated by Persky *et al*. [29] who showed that tolerance to the pressor (but not the chronotropic) effects of oral ephedrine in nonpregnant volunteers developed with a mean half-life of 15 min (range 6–140 min). The mechanism for this may involve reduction in receptor number, counter regulation, depletion of neurotransmitter pool or receptor desensitization.

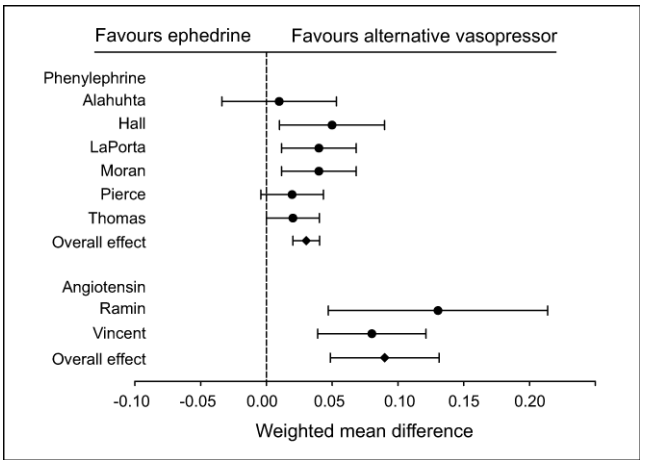
Ephedrine has a slow onset of action and a relatively long duration of action. These facts make accurate titration difficult and when large doses are used to restore

blood pressure, sustained increases above baseline may occur [20]. Increased heart rate and contractility are likely to increase myocardial oxygen demand. Marked increases in heart rate may be associated with unpleasant palpitations, atrial and ventricular ectopic beats and tachyarrhythmias [30].

An important concern about ephedrine in obstetrics has been the demonstration of an association between its use and a depression of fetal pH and base excess [19,20,31]. Lee *et al.* [32] showed that this occurs in a dose-related manner. Meta-analysis showed that umbilical arterial pH is significantly lower with the use of ephedrine compared with phenylephrine (Fig. 1) [19] and a multivariate analysis showed use of ephedrine to be a major factor predicting low umbilical arterial pH and base excess [33]. When ephedrine is used liberally, in doses required to confidently prevent maternal nausea and vomiting, very low values of umbilical arterial pH and base excess are sometimes seen [20,26]. This is an important limitation to the use of ephedrine.

How does ephedrine depress fetal pH and base excess? Although a decrease in uteroplacental blood flow is a possible explanation, the data from animal studies suggest that this is unlikely. An alternative explanation is a direct stimulating effect on fetal metabolism [31,33]. Ephedrine has metabolic stimulatory effects that has led to its use for weight loss [34] and athletic performance enhancement in adults [35]. Metabolic stimulation is particularly noted in brown adipocytes and is thought to be mediated by stimulation of β-adrenoreceptors [36], although the relative importance of the β-1, β-2 and β-3 receptors has been debated [37,38]. Ephedrine crosses the placenta and increases fetal catecholamine concentrations [39,40]. An increase in umbilical arterial norepinephrine concentrations was shown to correlate with decreasing pH [39]. Maternally administered ephedrine increases fetal heart rate [41] and, in clinical practice, a fetal tachycardia can often be observed on the cardiotocograph when large doses of ephedrine are given before delivery. Supporting animal evidence for a metabolic effect in the fetus is found in the observation that, in fetal lambs, β-stimulation increased oxygen consumption and lactate concentrations and decreased blood pH [42]. In a clinical study, Cooper *et al.* [31] showed that fetal acidemia induced by ephedrine was associated with an increasing umbilical arterio-venous $p(CO_2)$ difference; this is suggestive of increased CO_2 production in the fetus and is evidence for an ephedrine-induced increase in fetal metabolic rate.

Figure 1 Meta-analysis of trials comparing phenylephrine and ephedrine for management of hypotension during spinal anesthesia for cesarean section



This shows the effect of choice of vasopressor on umbilical cord arterial pH. Data are mean difference with 95% confidence intervals. (Adapted with permission from [19].)

What is the clinical significance of fetal acidosis induced by ephedrine? Although some studies have shown marked depression of fetal pH and base excess with ephedrine, evidence for a measurable clinical adverse effect is lacking. This, however, does not necessarily mean that ephedrine-induced fetal acidosis is not important. The majority of studies in this area have been performed in low-risk elective cases in which neonatal outcome is expected to be good, regardless of the technique of anesthesia. In the presence of nonanesthetic factors predisposing to adverse fetal outcomes, however, the contribution of ephedrine is more likely to be clinically relevant. In particular, an increase in oxygen consumption caused by ephedrine may compound obstetric causes of fetal hypoxia. Conversely, birth is an inherently stressful event for the fetus and it has been suggested that stimulation of β-receptors may have beneficial effects such as promotion of neonatal respiratory and metabolic adaptation [43]. Further work is required in this area.

Phenylephrine

Traditionally, phenylephrine was contraindicated in obstetrics because of concern about uteroplacental constriction and it was reserved as a second-line drug for use when ephedrine was not effective. These recommendations for practice, however, were extrapolated from the results of the animal experiments with few corroborating clinical data. In fact, recent clinical studies have failed to show any evidence of adverse fetal or neonatal effects when this class of drug is used. A number of possible explanations for this exist.

Most early studies utilized chronically instrumented animals, often under general anesthesia or no anesthesia, in which vasopressors were titrated to increase blood pressure above baseline values. This finding is likely to be a poor representation of the normal clinical situation when vasopressors are used to restore blood pressure towards normal values following a sympathectomy induced by spinal anesthesia.

Models of oxygen transport across the near-term human placenta suggest that the latter functions as a relatively inefficient venous equilibrator [44]. Adequate gas exchange is ensured because of a large uteroplacental blood flow. This arrangement confers a biological margin of safety in that oxygen transfer is less sensitive to reductions in uterine blood flow compared with species, such as the rabbit, that have more efficient countercurrent exchange arrangements and higher oxygen extraction coefficients [45]. For ethical and practical reasons, data on human placental physiology are limited. Placental exchange in the sheep, however, is also considered to function as a venous equilibrator and it is thought that, under normal physiological conditions, oxygen supply to the fetus is approximately double that required to maintain adequate fetal oxygen uptake and normal base excess [46]. Erkinaro *et al.* [47] compared phenylephrine and ephedrine for treating epidural-induced hypotension after an induced period of hypoxemia and showed that although phenylephrine had less favorable effects on uterine and placental circulation, there was no difference in fetal acid–base status and lactate concentration. The evidence that uteroplacental vasoconstriction is more likely with phenylephrine and other α-agonists compared with ephedrine may not have the clinical importance that has been historically assumed.

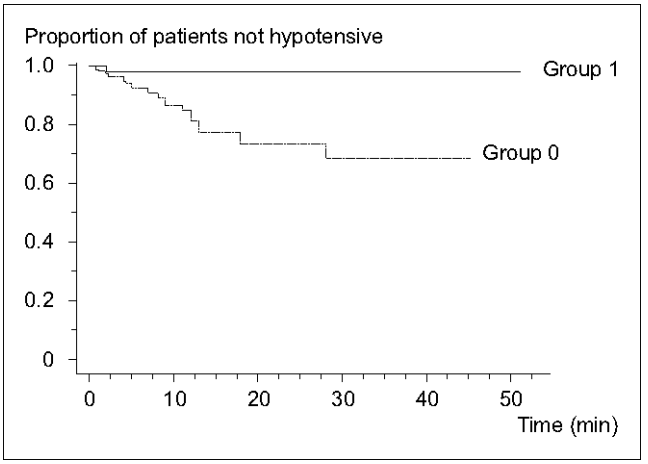
Advantages of phenylephrine

Phenylephrine is a potent, rapidly acting vasopressor with a short duration of action. Accordingly, it has high efficacy and is easy to titrate. Physiologically, it makes sense to treat vasodilatation with a vasoconstrictor. Phenylephrine titrated aggressively to maintain maternal blood pressure near to baseline reduces the incidence of nausea and vomiting without causing fetal acidosis [48,49]. A combination of a high-dose phenylephrine infusion and rapid crystalloid cohydration is the only technique to date that has been shown to be effective in virtually eliminating hypotension (Fig. 2) [50•].

Disadvantages of phenylephrine

Although in normal term fetuses, no adverse effects have been shown with use of phenylephrine, few data are available for its use in preterm, emergency, laboring or hypertensive patients, or in cases in which there is preexisting fetal compromise. A reflex decrease in heart rate is common with phenylephrine and occasionally treatment with an anticholinergic drug is required [51]. A decrease in cardiac output may accompany the decrease in heart rate although the clinical importance of this is uncertain [52]. Phenylephrine is commonly supplied commercially as a 10 mg/ml preparation and care is required to avoid dosage and dilution errors [53]. The short duration of phenylephrine means that it is particularly suited to delivery by infusion. Some anesthesiologists may be unfamiliar with this. A recent study suggested that rostral spread of spinal anesthesia might be reduced when a phenylephrine infusion is used, but the clinical importance of this is undetermined [54].

Figure 2 Comparison of phenylephrine infusion and rapid crystalloid cohydration (Group 1) with phenylephrine infusion alone (Group 0) for preventing hypotension during spinal anesthesia for cesarean section



Kaplan–Meier survival curve showing that the proportion of patients remaining not hypotensive until uterine incision was greater in Group 1 compared with Group 0 ($P = 0.0002$). The incidence of hypotension was 1.9% (95% confidence interval 0.3 – 9.9%) in Group 1. (Reproduced with permission from [50].)

Other vasopressors

Infusion of metaraminol resulted in better fetal acid–base status with no difference in uterine artery pulsatility index compared with ephedrine [20]. Mephentermine was shown to have similar efficacy and neonatal outcome compared with ephedrine [55]. A comparison of cafedrine/theodrenaline, etilefrine and ephedrine during epidural anesthesia in pregnant sheep showed that all three drugs corrected hypotension, although the effect of cafedrine/theodrenaline was slower and associated with a delay in restoration of uterine perfusion [56].

Combinations of vasopressors

Several authors have reported use of combination of phenylephrine and ephedrine together [31,57,58]. In theory, the positive chronotropic and inotropic effects of ephedrine may be useful to counter the reflex decreases in heart rate and cardiac output that phenylephrine may induce. The optimal combination ratio is unknown however, and there is little evidence that this approach is superior to phenylephrine alone [31].

Conclusion

The choice of vasopressor for obstetric patients remains controversial. Recent evidence from clinical trials suggests that concerns about uteroplacental vasoconstriction caused by phenylephrine and other α-agonists are exaggerated. Evidence that ephedrine may stimulate metabolism in the fetus leading to decreased pH and base excess exists. Compared with ephedrine, phenylephrine has a more physiologically appropriate action, which is reflected in greater efficacy for treating and preventing hypotension. Its fast onset and short duration of action make it easier to titrate. Unlike ephedrine, phenylephrine can be administered in doses sufficient to maintain maternal blood pressure and prevent nausea and vomiting without inducing fetal acidosis. On the other hand, use of phenylephrine is associated with reflex decreases in heart rate and cardiac output. Few data are available on the use of phenylephrine in emergency and high-risk cases. Although further work is still required in this area, when currently available evidence is taken into account, in the authors' opinion, phenylephrine is the vasopressor that most closely meets the criteria for the best vasopressor to use in obstetric patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 346).

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