



# The use of vasopressors during spinal anaesthesia for caesarean section

Warwick D. Ngan Kee

## Purpose of review

Hypotension remains one of the most researched subjects in obstetric anaesthesia. The purpose of this study is to review the most recent published articles on the use of vasopressors during spinal anaesthesia for caesarean section.

## Recent findings

Despite continued research indicating advantages of phenylephrine over ephedrine, practitioners in some countries continue to favour ephedrine. Recent research has continued to compare the two drugs with some work emerging on high-risk patients. Concern about reflexive bradycardia during phenylephrine use has led to consideration of alternatives. Norepinephrine which has mild  $\beta$ -adrenergic activity has been shown to have equivalent pressor activity but with less depressant effect on heart rate and cardiac output versus phenylephrine. Research continues to focus on methods of vasopressor administration. Prophylactic infusions of phenylephrine have been shown to be effective and may require less physician intervention compared with intermittent boluses. Automated computer-controlled systems have been further investigated using multiple agents and continuous noninvasive blood pressure monitoring.

## Summary

Evidence continues to support phenylephrine as the first-line vasopressor in obstetrics. However, recent research is emerging to suggest that low-dose norepinephrine may be a better alternative. Prophylactic infusions are effective and automated systems have potential for the future.

## Keywords

caesarean section, hypotension, norepinephrine, phenylephrine, spinal anaesthesia, vasopressors

## INTRODUCTION

Hypotension during spinal anaesthesia remains one of the most researched subjects in obstetric anaesthesia. Yet, many controversies still remain, in particular regarding the choice and use of vasopressors. Several recent editorials have focussed on the subject [1<sup>a</sup>,2,3<sup>a</sup>]. The purpose of this study is to review the most recent published articles on the use of vasopressors during spinal anaesthesia for caesarean section.

## RATIONALE FOR THE USE OF VASOPRESSORS

Previously, the mechanism of hypotension was thought to be related to aortocaval compression and its detrimental effect on venous return, cardiac filling, and cardiac output. This led to a reliance on intravenous fluid loading, which has now shown to have limited efficacy. More recently, the emphasis has changed toward proactive and liberal administration of vasopressors. Vasopressors directly

counter the primary physiological derangement induced by the sympathetic block: arteriolar vasodilation and decreased systemic vascular resistance [2]. Additionally, by restoring and maintaining vascular tone in venous and splanchnic vessels (the capacitance side of the circulation) vasopressors also maintain venous return and cardiac filling.

## CHOICE OF VASOPRESSOR: PHENYLEPHRINE VERSUS EPHEDRINE

A survey of European practice revealed considerable differences in practice among different countries

Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China

Correspondence to Warwick D. Ngan Kee, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China. Tel: +852 2632 2735; fax: +852 2637 2422; e-mail: wngankee@gmail.com

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## KEY POINTS

- Vasopressor use in obstetric patients varies among different countries.
- Recent research continues to support use of phenylephrine over ephedrine.
- Research is emerging showing that low-dose norepinephrine is an effective alternative to phenylephrine with the advantage of less depression of maternal HR and cardiac output.
- Vasopressors may be given by intermittent boluses or by infusion although infusions may provide tighter BP control with fewer clinician interventions.
- Automated computer-controlled systems are being developed that hold promise for the future.

regarding the choice and method of administration of vasopressors in obstetric patients with ephedrine still the mostly widely used agent [4], despite most experts now recommending phenylephrine. Ephedrine was historically recommended based on animal studies that suggested less detrimental effects on uteroplacental blood flow. However, phenylephrine has been shown to have greater efficacy, lower placental transfer, and smaller propensity to depress fetal pH [5].

Veeser *et al.* [6] performed an updated meta-analysis of studies that compared phenylephrine and ephedrine. Results from 20 trials, including 1069 patients showed that the risk ratio for fetal acidosis (umbilical arterial pH < 7.2) was 5.29 [95% confidence interval (CI) 1.62–17.25] for ephedrine versus phenylephrine. In an accompanying editorial, Dyer and Biccard [2] commented that adverse neonatal outcomes including mortality are associated with low fetal pH, that phenylephrine more appropriately counters the physiological changes induced by spinal anaesthesia, and the delayed pressor response of ephedrine may contribute to a higher incidence of nausea and vomiting.

Guo *et al.* [7] used Doppler ultrasonography to evaluate placental vascular resistance in 60 patients randomized to receive phenylephrine 50 µg/ml or ephedrine 4 mg/ml, titrated to maintain systolic blood pressure (SBP) at baseline. There was no difference between groups in resistance index or systolic peak velocity/diastolic velocity in uterine and umbilical arteries suggesting no detrimental effect on uteroplacental vascular resistance. The authors suggested that the discrepancy between their results and previous animal studies are ascribable to species differences in placental structure and function and possibility differences in placental adrenergic

receptor type and distribution. No power analysis was included so the likelihood of a type 2 statistical error cannot be evaluated; nevertheless the results support previous work and add to evidence for the safety of phenylephrine in obstetric patients.

Jeon *et al.* [8] in an impact study evaluated a range of clinical measures of neonatal outcome during 2-year periods before and after changing from infusing a mixture of phenylephrine (25 µg/min) and ephedrine (2 mg/min) to phenylephrine alone (50 µg/min). They reported a smaller incidence of Apgar scores less than 7 at 1 min during the phenylephrine-only period (0.8%) versus the phenylephrine/ephedrine period (2.0%; relative risk 0.39 (95% CI 0.21–0.70,  $P=0.002$ ). This study is unusual because although previous studies have demonstrated advantages of phenylephrine for biochemical outcomes, clinically assessed neonatal outcomes have been similar. However, some caution is required when interpreting the results of this study. The clinical significance of the findings is uncertain; many different clinical outcomes were assessed without adjustment for multiple comparisons which inflates the risk of a type 1 statistical error (false positive); and there may have been unidentified changes in practice during the study period.

## OTHER VASOPRESSORS: METARAMINOL, METHOXAMINE, AND NOREPINEPHRINE

Several other vasopressors have been used for maintaining blood pressure (BP) in obstetric patients. Bhardwaj *et al.* [9] found no difference in effectiveness or fetal pH between phenylephrine (bolus 30 µg and infusion 15 µg/min), metaraminol (bolus 0.5 mg and infusion 0.25 mg/min), and ephedrine (bolus 5 mg and infusion 2.5 mg/min). Previous work has shown that metaraminol, like phenylephrine, has less propensity to depress fetal pH than ephedrine. Further, larger studies would be of interest to better determine the relative dose requirements for metaraminol and whether it has any clinical advantages or disadvantages compared with phenylephrine.

Luo *et al.* [10] reported a randomized trial of methoxamine 2 mg alone or combined with one of three doses of atropine (0.1 mg, 0.2 mg, or 0.3 mg). They reported similar efficacy among groups for restoring BP. Patients who received the two higher doses of atropine had a lower incidence of maternal bradycardia compared with the other two groups. Neonatal condition was good in all groups although the authors reported that early neonatal heart rate (HR) was higher in patients who received the two higher doses of atropine; this may reflect placental

transfer of atropine which suggests that a more suitable anticholinergic, should it be required, would be glycopyrrolate which has a quaternary ammonium structure in contrast to the tertiary structure of atropine. Of note, in the study by Luo *et al.* [10] there was no comparison with other vasopressors. More data are required before methoxamine should be considered for routine use in obstetric patients.

One of the well known disadvantages of phenylephrine is its propensity to decrease maternal HR and, therefore, decrease cardiac output. Although the clinical significance of this has not been defined, it is generally considered undesirable and may precipitate the administration of anticholinergic agents with associated risk of severe reactive hypertension. The decrease in HR is thought to be mediated via a baroreceptor reflex which has led to suggestions that phenylephrine should not be administered in doses that decrease maternal HR, or even that its administration should actually be titrated to HR [2]; however, the clinical reality is not so simple. In the author's opinion, one of the most important clinical endpoints when using vasopressors during caesarean section is the prevention of maternal symptoms such as nausea, vomiting, and dizziness. These can largely be prevented by appropriate and early use of effective doses of phenylephrine. However, to reliably prevent maternal symptoms, it can be difficult to avoid decreases in maternal HR. Of note, the latter can occur even when BP is not elevated above baseline, suggesting that maternal bradycardia is not simply a reflection of relative overdose of phenylephrine.

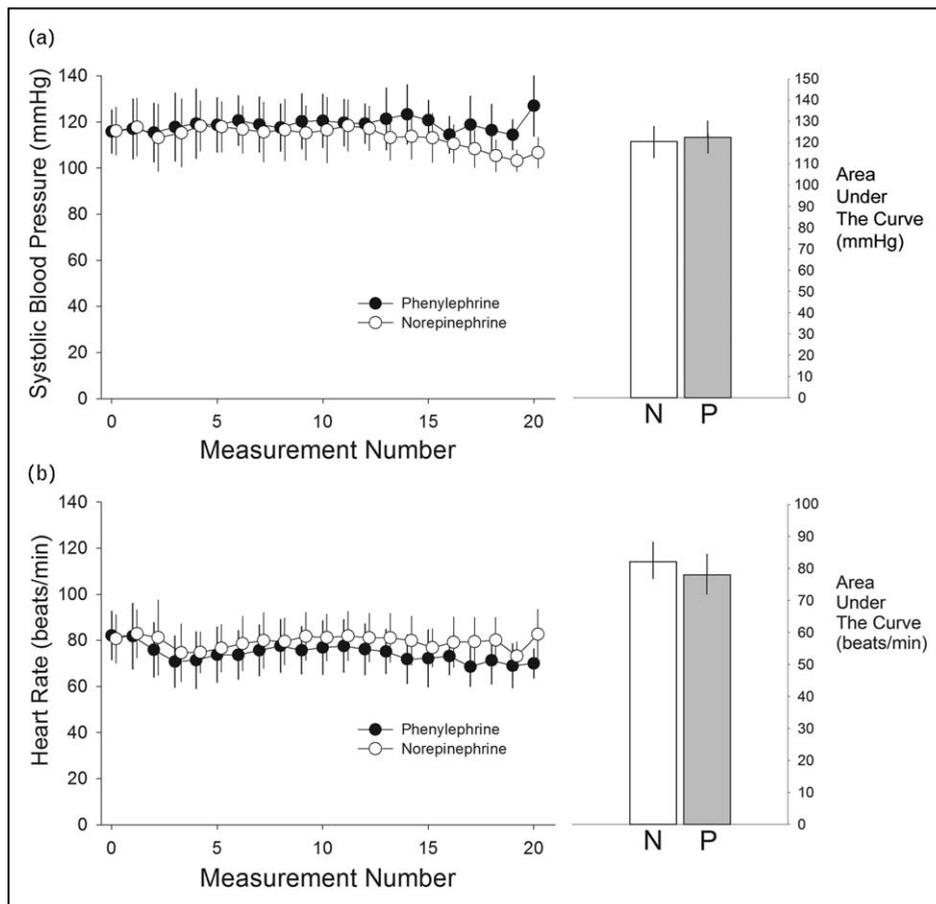
In response to the problem of bradycardia with phenylephrine, Ngan Kee *et al.* [11<sup>■</sup>] investigated the use of low-dose norepinephrine (noradrenaline) as an alternative to phenylephrine. Norepinephrine is a potent  $\alpha$ -adrenergic agonist and thus shares similar vasoconstrictor efficacy to phenylephrine. However, in contrast to phenylephrine, norepinephrine also possesses weak  $\beta$ -adrenergic agonist properties which act to counteract the baroreceptor response to the  $\alpha$ -effects. In a randomized controlled trial, 104 patients having elective caesarean delivery had BP maintained using a computer-controlled infusion of either phenylephrine (100  $\mu$ g/ml) or norepinephrine (5  $\mu$ g/ml). The concentration of norepinephrine was chosen to have approximately equipotent vasoconstrictor activity as estimated from a previous study on human saphenous vein. The results of the study showed that norepinephrine had similar efficacy for maintaining BP but with maintenance of HR at a higher level, closer to baseline (Fig. 1) and associated greater values for cardiac output (Fig. 2). In an accompanying editorial,

Carvalho and Dyer [12<sup>■</sup>] commented that because HR normally increases after induction of spinal anaesthesia, a vasopressor with  $\beta$ -effects may not be necessary, but this ignores the aforementioned baroreceptor response to pure  $\alpha$  agonists. They also commented that possible tissue injury from norepinephrine extravasation and local vasoconstriction are important considerations; however, these considerations are exactly the same as when using equipotent concentrations of phenylephrine.

Carvalho and Dyer [12<sup>■</sup>] suggested that more investigations of norepinephrine using simpler methods of delivery than computer-controlled systems are required. Such studies are now emerging. Vallejo *et al.* [13] performed an open-labelled comparison of continuous infusion of norepinephrine (0.05  $\mu$ g/kg/min) versus phenylephrine (0.1  $\mu$ g/kg/min), with rescue bolus or phenylephrine (for hypotension) or ephedrine (for bradycardia with hypotension). They found that use of phenylephrine boluses was similar between groups but more patients in the phenylephrine group required rescue ephedrine. Additionally, there was a greater incidence of vomiting in the phenylephrine group. An important limitation of this study was that the vasopressor infusions were not equipotent and were not titrated. Nevertheless, the authors concluded that a fixed-rate norepinephrine infusion can be considered as an alternative to phenylephrine.

Onwochei *et al.* [14<sup>■</sup>] performed a comparative dose-finding study of given as intermittent boluses to maintain SBP at or above 80% of the baseline value. Using sequential up-down methodology with a biased-coin design, they estimated the ED<sub>90</sub> (dose that is effective in 90% of patients) dose of norepinephrine to be 5.49  $\mu$ g (95% CI 5.15–5.83  $\mu$ g). For everyday clinical use, they suggested that doses of 6  $\mu$ g should be considered. In practice, a solution of norepinephrine 6  $\mu$ g/ml can easily be prepared by adding 0.6 ml of the commercial preparation (1 mg/ml) to a 100 ml bag of saline. This is not dissimilar to the common practice of making up a solution of phenylephrine 100  $\mu$ g/ml by adding 1 ml of the commercial preparation of phenylephrine (10 mg/ml) to a 100 ml bag of saline. Of note, this solution of norepinephrine is much more dilute than typically used in the ICU and can be administered via a peripheral vein, although it is prudent to use a large vein and deliver the solution into a running intravenous fluid solution.

Ngan Kee [15] described the experience of using norepinephrine 6  $\mu$ g/ml as the primary obstetric vasopressor over a 1-year period. During this time, norepinephrine was given to 256 (197 elective and 59 nonelective) patients having spinal anaesthesia for caesarean section. The mean rate of



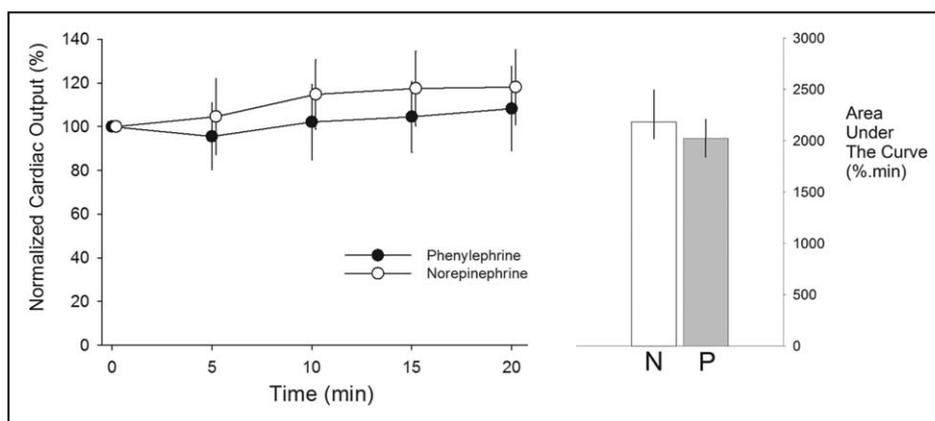
**FIGURE 1.** Changes in SBP and HR. Serial changes in SBP (a) and HR (b) during infusion of norepinephrine or phenylephrine. The left side shows serial data for the first 20 measurements (mean  $\pm$  SD). The right side shows standardized area under the curve. SBP was similar between groups ( $P=0.36$ ), but HR was greater over time in the norepinephrine group versus the phenylephrine group ( $P=0.039$ ). Adapted with permission [11]. HR, heart rate; N, norepinephrine; P, phenylephrine; SBP, systolic blood pressure.

norepinephrine administration until delivery was 2.14 (SD 0.99)  $\mu\text{g}/\text{min}$  for elective cases and 1.81 (SD 0.84)  $\mu\text{g}/\text{min}$  for nonelective cases. No adverse outcomes attributable to the use of norepinephrine were reported. In the author’s opinion, norepinephrine has the potential to be an ideal agent for maintaining BP during spinal anaesthesia for caesarean section. However, the results of further research are awaited.

**NON-ELECTIVE AND HIGH-RISK PATIENTS**

An important consideration when assessing current evidence for the use of vasopressors in obstetrics is that the vast majority of clinical trials have been performed in low-risk elective cases. Practical and ethical issues make research on high-risk and emergency obstetric cases difficult to include in randomized clinical trials, yet these are the very patients for whom the most benefit – or harm – is likely. In a

previous randomized study of 204 patients having spinal anaesthesia for nonelective cases we reported no difference in fetal pH and base excess between patients who received phenylephrine or ephedrine [16]. However, fetal compromise was thought to be present in only a relatively small proportion (24%) of patients included and not all patients actually required a vasopressor. More recently, Jain *et al.* [17] reported a randomized trial comparing phenylephrine and ephedrine in 90 patients, all of whom had acute intrapartum fetal compromise. The results showed a similar incidence of fetal acidosis (defined as umbilical arterial pH < 7.2) in the phenylephrine group (20%) compared with the ephedrine group (31%). The incidence of nausea and vomiting was higher in patients who received ephedrine, whereas the incidence of maternal bradycardia was higher in patients who received phenylephrine. These results support the appropriateness of using phenylephrine in emergency caesarean section when there is



**FIGURE 2.** Changes in cardiac output. Serial changes in cardiac output during infusion of norepinephrine or phenylephrine. The left side shows serial data for the first 20 measurements (median + IQR). The right side shows standardized area under the curve. Cardiac output was greater over time ( $P < 0.001$ ) in the norepinephrine group compared with the phenylephrine group. Adapted with permission [11<sup>■</sup>]. N, norepinephrine; P, phenylephrine.

potential fetal compromise. Further large studies in this area, in particular with a noninferiority design, would be of interest.

Parturients with preeclampsia constitute another high risk group for which data on vasopressors are sparse. Ituk *et al.* [18<sup>■</sup>] retrospectively reviewed a single-institution database to compare outcomes for preeclamptic patients who had spinal anaesthesia for caesarean section during a 10-year period. They found no difference in umbilical arterial pH in patients who received phenylephrine compared with those who received ephedrine. This provides some reassurance for the appropriateness of using phenylephrine in preeclamptic patients although the retrospective nonrandomized nature of this study is a clear limitation.

Overall, despite the limited data available for high-risk patients, in the author's opinion, given the lack of data showing any adverse fetal effect, it seems reasonable to consider phenylephrine as a suitable alternative to ephedrine in these patients.

#### **METHODS OF ADMINISTRATION: BOLUSES, INFUSION, AND COMPUTER-CONTROLLED DELIVERY**

There is controversy regarding the optimal dosing regimen and the optimal method of administration for phenylephrine. Liu *et al.* [19] performed a dose-finding study of phenylephrine and reported that the ED90 for phenylephrine was approximately 100  $\mu\text{g}$ . This value is smaller than previous estimates, which may reflect differences in methodology and definitions. Of note, many practitioners may choose to use a dose less than ED90/ED95 while

being prepared to repeat doses as necessary; this may reduce the risk of hypertension and bradycardia associated with the use of large doses.

Although use of intermittent boluses is a simple technique, there has been much interest in the use of titrated continuous infusions. Siddik-Sayyid *et al.* [20] compared variable rate phenylephrine infusions versus rescue boluses and found that in the infusion group BP was maintained closer to baseline with less nausea/vomiting. Importantly, fewer physician interventions were required when infusions were used suggesting that infusions may be less work and/or easier to use [21].

Heesen *et al.* [22] performed a systematic review of prophylactic phenylephrine. They found that the relative risk of hypotension with a phenylephrine infusion was 0.36 (95% CI 0.18–0.73) versus an ephedrine infusion and nausea and vomiting were reduced. They commented that the use of prophylactic infusions does expose those patients who are not prone to hypotension to phenylephrine unnecessarily with potential for adverse effects; however, no harmful effects were detected in their analysis.

Mwaura *et al.* [23] reported that a weight-adjusted (0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) infusion of phenylephrine resulted in a lower incidence of hypotension versus a fixed rate (37  $\mu\text{g}/\text{min}$ ) infusion (18.6 versus 35.2%). Although adjusting dose according to weight makes pharmacological sense, many clinicians may prefer to use titrated non weight-adjusted infusions for simplicity.

Finally, several studies have reported on the use of automated computer-controlled systems for vasopressor delivery. Initial descriptions of this

technology used simple closed-loop feedback to control an infusion of phenylephrine [24,25]. Sng *et al.* [26,27] extended the concept by describing the use of multiple vasopressors and the use of continuous noninvasive BP monitoring. Ngan Kee *et al.* [28] showed that the precision of BP control was greater for computer-controlled infusion of norepinephrine versus phenylephrine and was also greater for computer-controlled boluses versus infusion of phenylephrine [29].

## CONCLUSION

Research on vasopressors in obstetric anaesthesia continues to inform clinical practice. Continued evidence for the advantages of phenylephrine over ephedrine is likely to continue to induce changes of practice in favour of phenylephrine. Investigation of other agents is a current focus of research with particular interest in norepinephrine as an effective alternative to phenylephrine that has the advantage of more stable HR and cardiac output. Methods of administration are being refined with automated computer-controlled systems showing potential promise.

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## Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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