Trends in Anaesthesia and Critical Care 3 (2013) 166–170

Contents lists available at SciVerse ScienceDirect

Trends in Anaesthesia and Critical Care

journal homepage: www.elsevier.com/locate/tacc

REVIEW

Control of blood pressure during spinal anaesthesia for caesarean section

Hon Sen Tan [a], Ban Leong Sng [b,*]

[a] Duke-NUS Graduate Medical School, Singapore
[b] Department of Women's Anaesthesia, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore

Keywords:
Blood pressure
Vasopressor
Spinal
Anaesthesia
Caesarean section

SUMMARY

Maternal hypotension during caesarean delivery under spinal anaesthesia may lead to adverse maternal and neonatal outcomes. Vasopressors commonly administered include phenylephrine and ephedrine. Phenylephrine (alpha-1 agonist) is now an established 1st line vasopressor compared to ephedrine (alpha- and beta-agonist) as it has rapid onset, is efficacious and titratable. Over.administration of phenylephrine may result in reactive hypertension. Ephedrine may cause increased foetal acidosis from increased placental transfer with increased foetal metabolism and oxygen consumption. Recent advances in vasopressor algorithms and delivery systems, together with non-invasive haemodynamic (blood pressure, cardiac output) monitoring may lead to refinement in the management of hypotension whilst reducing reactive hypertension.

1. Introduction

Maternal hypotension during spinal anaesthesia for caesarean delivery is an extremely common clinical problem.[1] Severe intra-operative hypotension poses significant consequences to both mother, such as nausea, vomiting, headaches,[2] and neonate in the form of foetal acidosis and neurological injury resulting in weak rooting and suckling reflexes.[3,4] Despite being a focus of research and controversy for more than three decades, no strategy definitively prevents its occurrence. Strategies to counteract maternal hypotension include non-pharmacological methods such as intravenous hydration, lower limb bindings and compression, left-lateral tilt and pharmacological methods, by administration of vasopressors. Despite the latest Cochrane review concluding that no single method consistently eliminates maternal hypotension,[5] recent years have seen exciting developments in automated closed-loop vasopressor dosing systems that promise to improve efficacy and reliability in maternal haemodynamic control. The purpose of this review is to summarize and evaluate the latest developments.

2. Pharmacological management of hypotension

The severe limitations in the efficacy of non-pharmacological strategies[5] often mandate the use of vasopressors, however, the choice of vasopressor had been a subject of debate. The ideal vasopressor should be inexpensive, efficacious, able to improve maternal and uteroplacental haemodynamics with minimal placental transfer and adverse effects, and is easily titrated with fast onset and short duration of action. Obviously such a vasopressor does not exist although ephedrine and phenylephrine have well-established safety and efficacy profiles and are used by most obstetric centres worldwide, and is hence the focus of this review.

2.1. Ephedrine

A non-selective sympathomimetic, ephedrine exerts its predominant vasopressor effect via indirect release of noradrenaline from sympathetic nerve terminals, which mainly stimulates β1-adrenoceptors and increases cardiac output.

The use of ephedrine originated from the sheep model, with evidence that β-adrenergic agonists resulted in less uterine artery vasoconstriction and hence, better maintenance of uterine blood flow and foetal pH compared to α-agonists.[6] Subsequent research discovered that ephedrine possesses greater selectivity for systemic vessels with relative sparing of uterine arteries,[7] perhaps due to elevated levels of endothelial nitric oxide synthase[8] and lack of direct sympathetic innervation of uterine arteries.[9] This finding was confirmed by Ngan Kee et al. who found that ephedrine use in humans was associated with higher umbilical vein oxygen partial pressure (PO_2) compared to phenylephrine (selective α-agonist), presumably reflecting a reduction in placental blood flow with the latter.[10,11] Furthermore, ephedrine restored foetal cardiovascular haemodynamics to baseline values in the sheep model,[12] and may even prevent foetal late decelerations.[13] Hence, ephedrine was

* Corresponding author.
E-mail addresses: Sng.Ban.Leong@kkh.com.sg, blsngdr@yahoo.com.sg (B.L. Sng).

2210-8440/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tacc.2013.02.010

adopted as the vasopressor of choice in obstetrics, where it has seen widespread use for decades with minimal adverse maternal and neonatal outcomes. Its effectiveness as a vasopressor has been summarized in recent reviews.[5,14]

Nonetheless, ephedrine possesses several notable shortcomings, leading to some concerns in recent years. Its limited efficacy[14,15] and susceptibility to tachyphylaxis with a mean half-life of 15 min[16] translates to greater dosages required to maintain blood pressure and a concomitant increase in adverse effects. Ephedrine has been associated in a dose-related manner with foetal acidosis and decreased base excess[17–20] along with elevated lactate and catecholamine levels,[10] possibly due to its high placental transfer[10] exerting an increase in foetal metabolism[17,21,22] via β1-adrenergic stimulation of brown fat.[23] This hypothesis was corroborated by observations of decreased PO_2 and increased PCO_2 veno-arterial gradients,[11,17] suggesting that ephedrine resulted in increased oxygen *utilization*, and not decreased oxygen *delivery*. Furthermore, the discovery of an association between the β2-adrenergic receptor haplotype and foetal acidosis evinces the possibility of genetic susceptibility to significant acidosis even with small doses of ephedrine.[24] However, the clinical significance of these findings is unclear, as most studies failed to demonstrate an adverse outcome or drop in APGAR scores, though the studied population tended towards healthy, elective cases, with little research done on high-risk pregnancies. A recent meta-analysis demonstrated an association between foetal acidosis and poor outcomes, by showing a four-fold increase in neonatal mortality and a two-fold increase in morbidity resulting from umbilical artery pH < 7.20.[25] Several studies have reported that ephedrine use is associated with a lowered mean umbilical arterial pH of 7.18 to 7.27.[15,26,27] Furthermore, it is possible that accelerating foetal metabolism decreases the oxygen supply-to-demand ratio in the foetus, which may be clinically evident only in the presence of factors predisposing to adverse neonatal outcomes, such as placental insufficiency or pre-eclampsia.

Also, the predominant β-adrenergic effect of ephedrine not only fails to address vasodilation occurring during spinal anaesthesia, but further increases maternal cardiac stress through its chronotropic and inotropic effects. Moreover, the haemodynamic profile of ephedrine is not optimal for use in obstetric anaesthesia. Ephedrine possesses a relatively delayed onset of action, with a maximum effect observed at 89.8 s compared to 61.8 s for phenylephrine.[28] This, in combination with its longer duration of action, makes ephedrine harder to titrate in cases of rapid and precipitous blood pressure changes that often occur during spinal anaesthesia, potentially resulting in sustained abnormal blood pressures and further compromising maternal and neonatal outcomes.

2.2. Phenylephrine

For decades, α-adrenergic agonists such as phenylephrine was contraindicated in obstetrics due to its potential adverse effects on uteroplacental flow observed in the sheep model (*vide supra*), but is now gaining increasing acceptance and use. This revival is attributed to studies in the past two decades and summarized in a recent meta-analysis.[29] Although there were no significant differences in incidences of hypotension, reactive hypertension, and APGAR scores detected between phenylephrine and ephedrine, phenylephrine was associated with significantly higher pH and base excess. This finding may be due to phenylephrine's lesser extent of placental transfer[10] and lack of metabolic stimulation in the foetus. Furthermore, there was no conclusive evidence of phenylephrine impairing uterine blood flow in the two available studies utilizing Doppler velocimetry; one trial found an increase in vascular resistance in uterine and umbilical vessels,[30] while the other reported no significant difference.[27] This discrepancy between early experiments on the sheep model and subsequent human studies may be explained by difficulties in extrapolating results obtained from animal models to the vastly different physiology of humans.[31–34]

Furthermore, phenylephrine resulted in a lower incidence of maternal intraoperative nausea and vomiting,[35] perhaps attributable to its faster onset and shorter duration of action, making for easier dose-titration and minimized hypoperfusion to cerebrum and gut, thus avoiding activation of the vomiting centre[36] and release of emetogenic substances.[37] Moreover, phenylephrine directly addresses the vasodilation that occurs with spinal anaesthesia by α-adrenoceptor stimulation; does not appear to suffer from the tachphylaxis seen in ephedrine; and offers greater potency – equipotent dose of ephedrine is 83:1.[38] These characteristics results in lower doses of phenylephrine required and fewer adverse maternal and neonatal effects.

However, phenylephrine is commonly associated with decreasing maternal cardiac output (CO) and heart rate, sometimes necessitating the use of anticholinergic drugs.[27] Stewart et al. studied the effects of three phenylephrine infusion rates (25, 50, 100 μg min^{-1}) in caesarean section under spinal anaesthesia and reported a linear dose-dependant reduction in maternal CO, but the differences were small compared to inter-patient differences in baseline CO.[39] Gelman and Mushlin noted that 25% of total vascular volume is stored as an "unstressed" reservoir within splanchnic organs, which is converted to "stressed" (actively circulating) volume with venoconstriction by α1-adrenergic agonists.[40] In addition, this reservoir exists in parallel with the systemic circulation, and local venoconstriction would have little influence on total vascular resistance.[41] Thus, it appears that phenylephrine *increases* cardiac preload and CO, but at higher doses, it is unclear if the observed drop in CO stems from excessive venoconstriction restricting venous return, or is actually due to baroreceptor-mediated increase in vagal tone. The former implies excessive phenylephrine dosing; while anticholinergics may be beneficial in the latter.

With the current movement towards "goal-directed therapy", one must not forget that the target physiologic parameter is oxygen delivery, and not blood pressure or CO, which are merely surrogate measures of perfusion. Unfortunately, it is unclear how well CO and blood pressure correlate with uteroplacental perfusion. Robson et al. suggested that CO correlates better with uteroplacental perfusion than blood pressure.[42] The concern that phenylephrine-mediated drop in CO might decrease uteroplacental perfusion has been addressed by Ngan Kee et al., who concluded that there was little change in uterine blood flow (as determined by uterine pulsatility) with the use of metaraminol, an α1-adrenergic agonist which depresses maternal heart rate (and presumably CO) in a similar fashion as phenylephrine.[19] Hence, further research is required to (1) determine the effects of phenylephrine-induced decreases in maternal CO on uteroplacental perfusion, and (2) the best surrogate parameter for uteroplacental perfusion.

2.3. Ephedrine or phenylephrine?

Two meta-analyses were published comparing ephedrine versus phenylephrine use during caesarean section under spinal anaesthesia. Lin et al.[43] analysed 15 trials and found no differences in the incidence of maternal hypotension and umbilical artery pH values with *prophylactic* use of ephedrine or phenylephrine. However, when used to *treat* intraoperative hypotension, phenylephrine was associated with higher umbilical arterial and venous pH values, although there was no difference in the incidence of maternal hypotension. These results largely corroborate that of Veeser et al.,[29] who found that as a treatment modality, ephedrine was associated