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EDITORIAL

Adrenaline or noradrenaline for spinal hypotension during caesarean section – beware; the cure may be worse than the disease

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The management of spinal hypotension during caesarean section remains an important clinical challenge. Currently, more women are reported to die during spinal- than general anaesthesia in obstetrics, according to the Report on Confidential Enquiries into Maternal Deaths in South Africa.[1]

Research on spinal anaesthesia in obstetrics over the past two decades has achieved two main goals. Firstly, the haemodynamic changes induced by spinal anaesthesia in pregnant women have been elucidated. The main findings, using minimally invasive cardiac output monitoring, are typically arteriolar dilatation[2] with some venodilatation,[3] resulting in hypotension accompanied by an increased heart rate, and a partially compensatory increase in cardiac output. Secondly, the optimal pharmacological management of the haemodynamic changes associated with the usual sensory block (T2-4, as measured by cold sensitivity) has been thoroughly debated and settled. A recent international consensus review clearly recommends phenylephrine as the first-line vasopressor to reverse the peripheral dilatation, hypotension, and increased cardiac output.[4] The goal is to maintain systolic blood pressure at ≥ 90% of the baseline value, ideally using a prophylactic phenylephrine infusion, or alternatively treatment boluses in response to a decrease in blood pressure, in combination with crystalloid or colloid coload. This approach not only ensures adequate uteroplacental blood flow, but also minimises maternal nausea and vomiting.

An animal study has shown the dependence of the haemodynamic effects of phenylephrine on the volume status. During general anaesthesia in euvolaemic pigs, phenylephrine causes a dose-related reduction in cardiac output, due to peripheral arteriolar vasoconstriction and an increase in systemic vascular resistance. By contrast, in hypovolaemic pigs, phenylephrine causes a dose-related *increase* in cardiac output, mainly due to splanchnic venoconstriction, which results in an increase in the central filling pressure and venous return.[5]

Bradycardia may occur in three scenarios during spinal anaesthesia. Firstly, phenylephrine may induce a baroreceptor-mediated slowing of the heart rate in response to an increased in blood pressure above baseline. This is best managed by reducing the phenylephrine dose, and *not* by administering an anticholinergic agent, which could cause tachycardia and severe hypertension. Secondly, and far less commonly, a sudden decreased filling of the left ventricle during spinal anaesthesia may result in stimulation of ventricular afferents from the ventricle to the medulla, with resultant profound vagal activation, bradycardia and hypotension (Bezold-Jarisch reflex).[6] This usually responds well to prompt administration of anticholinergic agents, but may require full resuscitation, including adrenaline. It should be noted that the effect of prior administration of phenylephrine on the expression of the Bezold-Jarisch reflex in susceptible patients is unknown. Finally, sensory blockade to higher than T1 (high spinal anaesthesia) results in cardiac sympathectomy, bradycardia, hypotension and apnoea, which may require adrenaline, and ventilatory support.[7]

In summary, phenylephrine is the drug of first choice for spinal hypotension in obstetrics in the absence of bradycardia, for the following reasons:

1. A continuous, variable rate prophylactic phenylephrine infusion reliably reverses the known haemodynamic cause of spinal hypotension, namely arteriolar dilatation.
2. The pharmacokinetic profile of phenylephrine is ideal: rapid onset and offset, with a short elimination half-life allowing for rapid achievement of steady state levels during continuous infusion. Even in limited-resource environments its use is safe, with a recent study showing the effectiveness and safety of simply running an infusion of 500 µg in one litre of crystalloid solution, which is easy for the inexperienced practitioner.[8]
3. Phenylephrine is easily supplemented with small doses of ephedrine, which has a low potency, or an anticholinergic agent, should an increase in heart rate be required in the setting of hypotension. No single drug addresses every presentation of spinal hypotension and change in heart rate.
4. Neonatal acid base status is stable, with minimal changes in umbilical arterial pH and base deficit, because phenylephrine crosses the placenta to a lesser extent than ephedrine.
5. Tight control of systolic blood pressure at ≥ 90% of the baseline value reduces nausea and vomiting to a minimum.[5]

Smiley has commented in an editorial that the "burden of proof" should be met before anaesthetists change established practice.[9] In the matter of spinal hypotension, he pointed out that it is now

well known that large doses of ephedrine cause fetal acidosis due to placental absorption and increased fetal metabolic rate.[10] Furthermore, many papers have demonstrated the well understood benefits and safety of phenylephrine, so that there is general consensus that phenylephrine is the drug of choice for the pharmacological management of spinal hypotension.[11]

In this edition of SAJAA, Thejane et al have performed a thorough systematic review of available literature on the use of adrenaline for obstetric spinal hypotension.[12] Three papers were identified, of which only one was of high quality. The authors point out that adrenaline should only be used for routine obstetric spinal anaesthesia in the absence of availability of phenylephrine and the less potent ephedrine and anticholinergic agents. Hospital procurement committees should be informed of the evidence-based research for a particular agent, and the inexpensive phenylephrine should be on the essential drug list in every country. National guidelines should be published in South Africa emphasising the correct pharmacotherapy of spinal hypotension. In situations in which the recommended agents are unavailable, small boluses doses or low-dose infusions of adrenaline may be considered, but as the authors comment, there is very little research to inform such practice. Even the recommendations for the use of adrenaline in the published consensus guideline are only based upon expert opinion.[4]

So, should we be initiating major randomised trials on the use of adrenaline? The answer appears to lie in the findings of the recent spate of papers on the use of noradrenaline for spinal hypotension in obstetrics. In 2014, research began on the use of noradrenaline.[13] The rationale for this research was outlined in a narrative review, which stated that some patients experience bradycardia and a decreased blood pressure in response to phenylephrine, i.e. bradycardia that is not the usual baroreceptor-mediated slowing in response to an increase in blood pressure.[14] However, there was no scientific evidence for this comment. It was suggested that noradrenaline, which has some β1 effects, could have advantages over phenylephrine in this regard. This was followed by considerable research comparing phenylephrine and noradrenaline for spinal hypotension, including a dose response curve for noradrenaline.[15,16]

We performed a literature search in 2024, which produced 104 papers regarding noradrenaline for obstetric spinal hypotension, published during the past 10 years. Very little of the research on noradrenaline has gone beyond demonstrating non-inferiority to phenylephrine.[17,18] Limitations to the conclusions include the fact that the main outcomes of many papers were dose-related effects on, for example, cardiac output and neonatal cord gases, and not drug-related haemodynamic changes.[19-21] Some papers did not use doses of phenylephrine and noradrenaline with equivalent potency.[19,22,23] At least one study was not blinded.[24] In many studies, dilute noradrenaline was administered via a peripheral line with no invasive blood pressure monitoring. Overall, there remains considerable doubt as to the clinical value of the β-effects of noradrenaline, since bradycardia using phenylephrine seldom requires treatment. The futility and waste of resources should be avoided by discontinuing studies that merely show non-inferiority of an alternative agent and which are only (arguably) safe in the protected research environment. The findings of such research may not be generalisable to anaesthesia providers at large, particularly inexperienced clinicians.

In the light of the evidence that noradrenaline is at best non-inferior to phenylephrine, is its use associated with potential risk to our patients? Let us remember the wisdom of the age-old adage: "primum non nocere" – first, do no harm. Randomised controlled trials offer the strongest evidence in medical research. Well-designed studies with adequate sample sizes allow us to draw conclusions about causality, demonstrating whether a given intervention is effective and safe. However, high-risk clinical research trials potentially compromising the safety of the vulnerable mother and fetus, should be ethically justified, and kept to a minimum, particularly in the presence of pregnancy-specific conditions such as preeclampsia. An editorial written in 2015,[25] and subsequent narrative reviews on spinal hypotension[26] and preeclampsia,[27] cautioned against the very real risks posed by noradrenaline, which is approximately 13 times as potent as phenylephrine.[15] In inexperienced hands, the use of noradrenaline could result in morbidity and mortality, particularly if there were drug errors or if syringe drivers were not available. In addition, in limited-resource environments, patient triage is often very poor; consequently there are often undiagnosed cardiac comorbidities. In these centres, noradrenaline is usually expensive and not widely available, resulting in unfamiliarity with this vasopressor. Our opinion is that the burden of proof has still not been met for a change from phenylephrine to noradrenaline in patients with normal cardiac function, and that despite the findings of four randomised trials on its use in preeclampsia, this drug should be contraindicated for spinal hypotension in hypertensive disorders of pregnancy.

Based on these findings and on the above rationale related to the investigation of noradrenaline, further research on adrenaline for obstetric spinal hypotension would be of dubious value and potentially associated with increased risk to patients. A better approach would be to collect and share safety data when adrenaline is used if the first-line agent is unavailable.

In conclusion, phenylephrine remains the first-line drug to prevent and treat spinal hypotension, supplemented as necessary by ephedrine and anticholinergic agents. Adrenaline should only be used when resuscitation is required; let the cure not be worse than the disease.

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