Norepinephrine for Spinal Hypotension during Cesarean Delivery

Another Paradigm Shift?

Brendan Carvalho, M.B.B.Ch., F.R.C.A., Robert A. Dyer, F.C.A.(SA), Ph.D.

SPINAL anesthesia is the technique of choice for elective cesarean delivery; however, the technique results in hypotension in the vast majority of women if not actively prevented. The consequences of spinal hypotension in this setting are proportional to the severity and include nausea and vomiting, decrease in uteroplacental blood flow, fetal acidosis, and, rarely, cardiovascular collapse. There is now wide consensus that phenylephrine is the drug of choice for elective cesarean delivery to prevent and treat spinal hypotension. The majority of studies demonstrating the efficacy of phenylephrine and the superiority of phenylephrine compared to ephedrine have come from Ngan Kee *et al.* These investigators are credited with leading this evidence-based change in obstetric anesthesia practice.[1] Ngan Kee's studies have certainly changed our clinical practice from using ephedrine to administering phenylephrine as our primary vasopressor to prevent and treat spinal hypotension. Given this background, we were very interested to read Ngan Kee's latest study comparing phenylephrine with norepinephrine. In this issue of Anesthesiology, Ngan Kee *et al.*[2] report on a double-blinded, randomized clinical trial comparing norepinephrine and phenylephrine infusion for the maintenance of blood pressure during cesarean delivery under spinal anesthesia. The authors found that a computer-controlled infusion of norepinephrine maintained blood pressure as effectively as phenylephrine, but with less bradycardia and less decrease in cardiac output. No significant differences in neonatal outcomes were found. The authors hypothesize that the β-adrenergic receptor agonist activity in addition to the α-adrenergic receptor effects of norepinephrine may make it a preferable drug for maintaining blood pressure. The findings are very interesting and deserve much attention; however, the study does have a number of important methodological features that need to be considered before the role of norepinephrine in the obstetric anesthesia setting is determined.

"[F]uture research needs to address a number of questions before norepinephrine is considered preferable to phenylephrine for maintaining maternal hemodynamics."

Early research to prevent or minimize spinal hypotension has focused primarily on techniques to increase blood volume and venous return such as fluid loading, positioning to minimize aorto-caval compression, and leg wrapping. However, these techniques have proven largely ineffective.[3] More recent studies suggest that in fluid-replete parturients, spinal hypotension is primarily driven by a decrease in sympathetic tone in the arterial system and not by a reduction in central venous pressure due to increased venous capacitance. Studies using minimally invasive cardiac output monitors have demonstrated marked reduction in systemic vascular resistance and a modest *increase* in cardiac output, heart rate, and stroke volume after induction of spinal anesthesia.[4,5] This physiological observation is consistent with the findings that α-agonist vasopressors are the most reliable method for preventing and treating spinal hypotension during cesarean delivery.

The lower incidence of bradycardia and the smaller decrease in cardiac output observed with norepinephrine compared to phenylephrine in the study by Ngan Kee *et al.* are likely due to the inherent β-agonist activity in addition to the α-effects of norepinephrine. Despite the theoretical advantage of an added β-effect, previous studies using combinations of ephedrine and phenylephrine were not found to be superior to phenylephrine alone[6] although these studies focused on maintenance of

Image: ©iStock.

Corresponding article on page 736.

Accepted for publication December 18, 2014. From the Department of Anesthesia, Stanford University School of Medicine, Stanford, California (B.C.); and Department of Anesthesia, University of Cape Town, Cape Town, South Africa (R.A.D.).

 Anesthesiology 2015; 122:728-30

blood pressure, not cardiac output. Physiologic studies have shown a modest increase (not decrease) in heart rate and stroke volume after induction of spinal anesthesia,[4,5] so a β-effect may not be necessary in healthy patients with normal physiological response to afterload reduction after spinal anesthesia. Transient decreases in maternal heart rate and cardiac output in healthy women receiving phenylephrine are clearly accommodated without detrimental effects; however, the impact of these hemodynamic effects in women with compromised cardiac function or nonreassuring fetal status are not well known. Caution must be exercised when comparing drug efficacy in different clinical settings. For example, sepsis may be a logical reason to use norepinephrine, but this pathophysiology does not apply in healthy women undergoing spinal anesthesia.

The study used a computer-controlled system that the authors developed to infuse the vasopressors. This technology is for research purposes and currently not recommended or commercially available for clinical practice. An automated system focusing only on blood pressure (not integrating heart rate and/or cardiac output) may not be optimal. The vasopressor infusion rates using this computer-controlled system were based on intermittent noninvasive blood pressure measurements taken every minute that may have delayed infusion rate responses. The study results might have been different if the infusion algorithm included responses to continuous blood pressure, changes in heart rate, or beat by beat cardiac output measurements. In addition, safety considerations related to the influence of maternal movement and shivering artifacts on blood pressure readings used by a computerized system need to be considered.

The heart rate and cardiac output differences observed between women receiving phenylephrine and norepinephrine may be more of a dose than a drug effect. The authors compared norepinephrine 5 μg/ml *versus* phenylephrine 100 μg/ml based on a potency ratio of 20:1 determined in previous clinical studies; however, in the current study, median infusion rates required to maintain blood pressure were greater in the norepinephrine group. The true potency ratio in this setting or for a particular physiological endpoint (*e.g.*, blood pressure, cardiac output) is uncertain. Baroreceptor-mediated bradycardia with associated decreases in cardiac output are likely a result of overtreatment of blood pressure and are more frequent with high (75 to 100 μg/min) compared to lower (25 to 50 μg/min) phenylephrine infusion rates.[7,8]

Although it is well demonstrated that a vasopressor should be titrated to maintain blood pressure near or close to baseline values to minimize maternal symptoms (nausea or vomiting) and fetal acidosis,[9] what is uncertain is the relative importance of cardiac output and blood pressure maintenance to optimize uteroplacental perfusion. Blood pressure is a key driver of flow through the low resistance uteroplacental unit; however, cardiac output is an important component of oxygen delivery and would be particularly important in the setting of fetal hypoxemia. Studies and clinical practice have generally focused on blood pressure maintenance because cardiac output monitors are either unavailable or too invasive in this setting. Cardiac output monitoring is currently a research tool and not clinically indicated in healthy pregnant women undergoing cesarean delivery. However, in normal clinical practice, heart rate can potentially be used as a surrogate marker for cardiac output and to guide vasopressor dosing. Maternal heart rate is highly correlated ($r = 0.87$) to cardiac output in the setting of phenylephrine administration for spinal hypotension.[4]

Despite their encouraging results, the authors will likely struggle to institute another paradigm shift in vasopressor choice for cesarean delivery. Although there is strong evidence that phenylephrine is a superior agent to ephedrine (*e.g.*, faster onset of action, better fetal acid–base profile, less placental drug transfer, and more effective at increasing systemic vascular resistance), it took many years for clinicians to change practice and for phenylephrine to be considered the drug of choice in this setting. Phenylephrine is a drug readily used in the operating room and familiar to anesthesia care providers in the United States. In contrast, norepinephrine's use is generally limited to the setting of intensive care and cardiac anesthesia. Given this lack of familiarity, the shift toward using norepinephrine in the obstetric domain will be challenging. Tissue injury from norepinephrine extravasation and local vasoconstriction is also a potential safety concern which will necessitate large-bore intravenous access and dilute norepinephrine solutions.

In summary, Ngan Kee *et al.* need to be commended for producing a superb study and continuing the search for the optimal vasopressor to prevent and treat spinal hypotension during cesarean delivery. The current study provides further confirmation of how effective an α-adrenergic receptor agonist, delivered as a prophylactic infusion in combination with crystalloid coload, can be in preventing maternal spinal hypotension.[10] The findings of a lower incidence of bradycardia and a smaller decrease in cardiac output despite similar blood pressure maintenance with norepinephrine compared to phenylephrine are very encouraging. However, future research needs to address a number of questions before norepinephrine is considered preferable to phenylephrine for maintaining maternal hemodynamics. Anesthesia care providers will require much convincing before we are ready for another vasopressor paradigm shift in the management of spinal hypotension during cesarean delivery.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Carvalho: bcarvalho@stanford.edu

References

1. Smiley RM: Burden of proof. Anesthesiology 2009; 111:470–2
2. Ngan Kee WD, Lee S, Ng FF, Tan PE, Khaw KS: Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology 2015; 122:736–45

3. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW: Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev 2006:CD002251
4. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, Greenwood J, James MF: Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. ANESTHESIOLOGY 2009; 111:753–65
5. Langesaeter E, Rosseland LA, Stubhaug A: Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: A randomized, double-blind comparison of low-dose *versus* high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. ANESTHESIOLOGY 2008; 109:856–63
6. Ngan Kee WD, Lee A, Khaw KS, Ng FF, Karmakar MK, Gin T: A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: The effects on fetal acid-base status and hemodynamic control. Anesth Analg 2008; 107:1295–302
7. Allen TK, George RB, White WD, Muir HA, Habib AS: A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesth Analg 2010; 111:1221–9
8. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M: The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010; 111:1230–7
9. Ngan Kee WD, Khaw KS, Ng FF: Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. Br J Anaesth 2004; 92:469–74
10. Heesen M, Kölhr S, Rossaint R, Straube S: Prophylactic phenylephrine for caesarean section under spinal anaesthesia: Systematic review and meta-analysis. Anaesthesia 2014; 69:143–65

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Salt's Portable Ether Inhaler

Patented on March 5, 1847, this portable ether inhaler was manufactured by a cutlery and surgical instrument firm, M. Salt & Son of Birmingham, England. To prepare the inhaler for use, the physician or dentist had to simply: (1) remove the top, add ether to the main cylinder's sponges, and then replace the top; and then (2) partly or completely open the aeration holes at the base (*left*). In *The Pharmaceutical Journal* of London, this inhaler was noted to provide "the alternate admission of air and ether" so that "vapour may be regulated without the necessity of removing the apparatus from the [patient's] mouth." When Salt's portable ether inhaler was not in use, both its top and bottom ends could be sealed—a clever design ensuring both economy in ether use and fewer spills inside the jacket pocket of the etherist. Apparently, spilling this "Salt" was not bad luck!

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.