

## Burden of Proof

IN early 2009, a 2-day symposium on Obstetric Anesthesia had just ended and my colleague and I stepped onto the tram in Basel, Switzerland, to begin our respective journeys home. One of the final discussions at the conference had concerned treatment/prevention of hypotension during spinal anesthesia for Cesarean delivery. I had spoken about the evidence in favor of phenylephrine infusions, and my personal practices in using the drug. On the tram, I asked my colleague what he generally used to treat hypotension during Cesareans and he responded "Boluses of ephedrine or phenylephrine, as does most of the rest of my group." The following month, as I began a lecture at a continuing medical education course, I asked the audience, composed of a mixture of anesthesiologists and certified registered nurse anesthetists (CRNAs), "What is your first-line drug to treat hypotension at Cesarean section, ephedrine or phenylephrine?" Ninety percent responded ephedrine. The next week, one of our current departmental Fellows, who had done his residency in our institution and was quite familiar with both the evidence for and our practice in using phenylephrine infusions and who was about to sit for his oral American Board of Anesthesiologists examination, asked me, "What do I say if they ask me what drug I would use for hypotension during Cesarean section? Is phenylephrine an acceptable answer?" The response from the audience of predominantly nonobstetric anesthesia providers is perhaps not so shocking, despite the fact that there exists over a decade of fairly consistent evidence from well-designed, randomized, blinded studies in Europe,<sup>1,2</sup> the United States,<sup>3-5</sup> and Asia<sup>6,7</sup> supporting the proposition that phenylephrine is at least as safe and effective and probably preferable to ephedrine for the treatment or prevention of hypotension at Cesarean section. Not every anesthesiologist or CRNA reads every journal, interprets evidence correctly, is willing to change his or her practice on the basis of the available information, or even believes in the principle of evidence-based practice. The question from the Fellow reflects the fear and insecurity that all of us felt as we approached our oral exam, even when we thought we knew the answer to a clinical question. We wondered what those Board examiners knew (or didn't know) and

what they would accept as answers. The comments of my colleague on the tram, however, were a bit more surprising, as they came from the Editor-in-Chief of this Journal, whose clinical practice is and has been predominantly in obstetric anesthesia. A few weeks later, Dr. Eisenach emailed me to tell me that he had started using phenylephrine infusions, had convinced several colleagues at his institution to also do so, and invited me to write this editorial.

In this issue of ANESTHESIOLOGY, Ngan Kee *et al.* report on a blinded, randomized clinical trial comparing phenylephrine infusion to ephedrine infusion for the prevention and treatment of hypotension at Cesarean section under spinal anesthesia.<sup>8</sup> The question of how to prevent or treat hypotension during spinal anesthesia for Cesarean section has been a central question in obstetric anesthesia for decades. The answer has been called the Holy Grail of obstetric anesthesia.<sup>9</sup> For decades ephedrine was the drug of choice, based on classic studies in sheep that suggested deleterious effects of pure  $\alpha$ -adrenergic agonists on uteroplacental blood flow.<sup>10</sup> Multiple reports in the 1990s and early 21st century, many by Dr. Ngan Kee and his colleagues in Hong Kong,<sup>1,3-6,11-14</sup> have demonstrated that phenylephrine or other  $\alpha$ -agonists (e.g., metaraminol) are safe and generally more effective than ephedrine at preventing maternal hypotension and its symptoms (e.g., nausea and vomiting). In addition, it has become clear that ephedrine use often leads to lower neonatal pH and a higher incidence of neonatal acidosis than does the use of phenylephrine or other pure  $\alpha$ -agonists. The cause of this relative acidosis has been postulated not to be directly related to uteroplacental blood flow (fetal asphyxia) but rather to the effect of ephedrine as a metabolic stimulant within the fetus, resulting in a relatively hypermetabolic state. Indirect evidence for this theory was provided in a variety of ways: umbilical artery-vein differences, the dependence on ephedrine dose, and the lack of observable differences in uteroplacental perfusion that could otherwise explain a deleterious effect of ephedrine on neonatal pH or base excess.<sup>2,15</sup>

In the current study, Ngan Kee *et al.* randomly assigned 104 patients undergoing elective Cesarean section with spinal anesthesia to groups receiving infusions of either ephedrine (8 mg/ml) or phenylephrine (100  $\mu$ g/ml), titrated to maintain baseline preoperative systolic blood pressure. Blood pressure was better maintained in the phenylephrine group, with fewer episodes of hypotension and need for rescue boluses. Umbilical arterial pH was lower in the ephedrine group (7.25 *vs.* 7.33), with higher Pco<sub>2</sub> (56 mmHg *vs.* 49 mmHg) and a more negative base excess (-4.8 *vs.* -1.9). Maternal side effects were decreased with phenylephrine, with an incidence

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of nausea or vomiting of 35% in the ephedrine group *versus* 2% (1 patient) with phenylephrine. Concentrations of glucose, lactate, epinephrine, and norepinephrine were significantly higher in the umbilical blood of the ephedrine group. Most importantly, for the first time in studies comparing ephedrine and phenylephrine, the investigators measured maternal and umbilical arterial and venous phenylephrine and ephedrine concentrations. Fetal:maternal ratios of ephedrine were significantly higher than those for phenylephrine, with umbilical concentrations of phenylephrine 10–20% of maternal, whereas ephedrine concentrations were comparable to maternal concentrations. These findings confirm the previously held suspicion that ephedrine crosses the placenta more readily than phenylephrine and support the concept that an increase in fetal metabolism caused by ephedrine is the cause of the increase in base deficit and increase in other markers of fetal metabolic stress.

The current study is well-done, the results are almost certainly valid, and perhaps more importantly, it is consistent with almost every study done over the past 15 yr comparing the two interventions at comparable doses. What are we then to make of the fact that practice, even that of very well-informed anesthesiologists, does not seem to have changed in response to the evidence? If the Holy Grail has been found and is readily accessible, why are so few celebrating or drinking from it?

Several explanations suggest themselves. First, we should not be so quick to change long-accepted practices based on one (or two or perhaps three) studies. The “burden of proof” should be on the new therapy, especially when conventional therapy is reasonably effective and reasonably safe, as is the case with ephedrine boluses or infusions. Indeed, recent experience with perioperative  $\beta$ -adrenergic antagonist recommendations and some studies of tight glucose control suggest that clinicians should be appropriately wary of following every new evidenced-based trend. As many have learned in a different context, a buy-and-hold strategy may frequently be superior to a day-trader approach in which a clinician attempts to adopt every new trend and piece of evidence that presents itself, especially in a “safety-first” subspecialty such as obstetric anesthesiology that deals with a predominantly healthy population. Second, the phenylephrine *versus* ephedrine issue is perceived as not being quite a life and death issue. The pH and base deficit differences are consistent and statistically significant in most studies, but they are not all that dramatic, typically a pH difference of 0.02 or 0.05. Thus, many clinicians may just not think it worth their while to learn a new strategy. Third, setting up an infusion, the preferred method of administering phenylephrine (and probably ephedrine) based on the evidence, is a bit more time consuming than simply injecting boluses from a syringe. Fourth, some clinicians, even some who would

concede the evidence in favor of phenylephrine for routine elective Cesarean delivery, may argue that the safety and superiority of  $\alpha$ -agonist vasopressor treatment has not been demonstrated in parturients with severe preeclampsia or other scenarios with significantly decreased uteroplacental flow and/or increased resistance, and more work in this area is both needed and ongoing.<sup>16,17</sup> Fifth, it must be acknowledged that much of the work demonstrating the efficacy or superiority of phenylephrine comes from the Ngan Kee group, and confirmation from other centers and investigators should be required before widespread acceptance of any clinical recommendation. However, studies elsewhere have confirmed the major findings.<sup>1–5,13</sup> Finally, of course, there are those who still do not quite believe the evidence is convincing.<sup>18</sup>

However, thanks in large part to the consistent, high-quality, and productive clinical investigations of Ngan Kee and colleagues in Hong Kong, the evidence now is sufficient for a change in attitude and practice to be strongly encouraged. The weight of the evidence has now equaled the burden of proof, and our clinical burden should be to incorporate the evidence into our routine practice. This recommendation is finding its way into review articles from a variety of countries.<sup>19–22</sup> Titrated phenylephrine infusions minimize maternal nausea, vomiting, and episodes of hypotension, and they result in higher neonatal pH and lower base deficits. A variety of specific dosing strategies can be used and have been published,<sup>2,6,23,24</sup> but doses in the range of 25–100  $\mu\text{g}/\text{min}$  titrated to maintain maternal blood pressure near baseline values appears to be very effective and relatively easy to employ. It is the therapeutic strategy that most anesthesiologists would want for themselves or family members as patients, and it should probably be the default choice for prevention and treatment of hypotension during spinal anesthesia for elective Cesarean delivery in the absence of a specific contravening rationale or contraindication. As the famous Alka-Seltzer ad from the 1970s said, “Try it, you’ll like it,” and so will your patients.

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