International Journal of Obstetric Anesthesia (2017) **29**, 1–4
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2017.01.002

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EDITORIAL

More perfect?

The prevention and treatment of maternal hypotension during neuraxial (mostly spinal) anesthesia for cesarean delivery has been one of the central issues in obstetric anesthesia since the 1970s.[1] In the first decade of the 21st century, high-quality studies from a number of investigators, but most notably from Ngan Kee et al. in Hong Kong, demonstrated that, contrary to prior opinions and recommendations, pure α-1 adrenoceptor agonists (first metaraminol and then in later studies phenylephrine) were effective and safe for maintaining maternal blood pressure and were better than mixed α- and β- agonists (ephedrine), for preventing some of the side effects of maternal hypotension, most notably nausea and vomiting.[2–6] In addition, it became clear that ephedrine causes a dose-dependent, although usually mild, acidosis in the fetus, probably due to direct stimulation of fetal metabolism.[6] In 2009, I opined that the "burden of proof" had been met,[7] and phenylephrine, probably by continuous infusion, ought to be the standard method of maintaining maternal blood pressure during spinal anesthesia for cesarean delivery. This now appears to be the widespread consensus.[8–10]

Last year, Ngan Kee et al. published another high-quality study concerning the maintenance of maternal blood pressure during spinal anesthesia, this time comparing infusions of norepinephrine and phenylephrine.[11] The rationale for the use of norepinephrine is that phenylephrine, as an α_1-adrenoceptor agonist without β-agonist properties, may cause a decrease in heart rate in response to increases in systemic resistance and blood pressure, and a related decrease in cardiac output. Norepinephrine, with moderate β_1-agonist activity, might be expected to cause less bradycardia, and perhaps promote cardiac inotropy, better maintaining maternal cardiac output by maintaining heart rate. In any discussion of maternal cardiac output in this context, it is useful to note that the effect of spinal anesthesia is usually to *increase* maternal cardiac output, and many studies of the effect of phenylephrine that report a decrease in cardiac output, are in fact reporting a return to approximately the pre-anesthetic baseline, not an absolute decrease.[12] Ngan Kee et al. compared computer-controlled infusions of norepinephrine or phenylephrine targeted at maintaining maternal systolic blood pressure at baseline. The primary outcome was maternal cardiac output, measured every 5 minutes until delivery. As expected, they demonstrated that cardiac output was approximately 10% higher in the norepinephrine group, systemic vascular resistance was lower, and the incidence of bradycardia, defined as a heart rate <60 beats/min, was lower. Other neonatal and maternal endpoints, including umbilical arterial and venous pH and blood gas values, were similar between groups. Related to the point above about spinal anesthesia generally increasing cardiac output, it should be noted that except for the five minute mark when cardiac output in the phenylephrine group was at 94% of baseline, cardiac output was above pre-anesthetic baseline in both groups at all measured timepoints. The editorial that accompanied the article commended the authors for the continued quest for the optimal (perfect?) vasopressor, noting that the results are consistent with the pharmacologic properties of norepinephrine, but concluded that many more studies and much "convincing" would be needed before another shift in vasopressor recommendations and usage.[10]

In this issue of the journal, Vallejo et al. report on another comparison of phenylephrine to norepinephrine for blood pressure maintenance during spinal anesthesia for elective cesarean delivery in 85 women.[13] They compared *fixed* dose infusions of the two drugs, and examined the need for "rescue" boluses of phenylephrine for hypotension, or ephedrine for bradycardia with hypotension. They reported similar need for phenylephrine, but increased need for ephedrine boluses (24% versus 2%) in the phenylephrine group, reflecting somewhat better maintenance of heart rate in the norepinephrine group, although statistically there were few differences in maternal hemodynamics between groups, and no differences in umbilical blood gases or pH. At first glance, this study would appear to support the idea that norepinephrine is similar, perhaps slightly "better" than phenylephrine in the context studied. However, some of the details of the study design and execution must be discussed before this work can be added to the small (but presumably growing) list of such comparisons of norepinephrine to phenylephrine.

While all clinical studies can be criticized, this one has more than the usual number of issues. Perhaps most importantly, the study was not blinded, which is a serious limitation to any clinical study, since we have learned over decades that unblinding can result in investigator bias that is very hard to sense as an investigator, or detect or prevent as an editor, reviewer or reader. The reason for this non-blinded study design was apparently

that the Institutional Review Board (IRB) at the investigators' institution would not allow a blinded study, due to concerns about patient safety in this "vulnerable population." As a clinical investigator in the area of obstetrics and obstetric anesthesia, and as member of the IRB at my home institution, I have dealt with this kind of issue of clinical research in pregnant women from both sides of the IRB application process, and believe this is a serious error on the part of the IRB, the investigators, or both. At one point in the 1990s, the Columbia University IRB actually stated to me that they did not think that clinical research of any kind should be done in pregnant women, because of the risks. I responded that this would mean that they did not believe that pregnant women deserved to get better care in 2025 than in 1995, because the only way to facilitate safe progress in clinical care was through high-quality clinical research, which includes blinding of studies whenever feasible. Somewhat surprisingly, the Columbia IRB came to agree with this position. The type of investigation by Vallejo et al. is actually very easy to blind, compared to other types of clinical studies in obstetric anesthesia (e.g. comparison of epidural analgesia to other forms of analgesia, where blinding is almost impossible). In practice, the presence of blinding in this study would have had no effect on safety, as the possible "harm," an effect on the fetus, cannot be discovered until after delivery anyway, and the measured effect of the drug choice on the mother, blood pressure, was being monitored continuously.

Second, the use of a fixed-rate infusion is unusual, and perhaps not clinically relevant, in that both of the studied medications are well-known to have rapid onset and offset of their actions, thus a variable/adjusted rate infusion makes more pharmacological sense. The infusion rate chosen for phenylephrine, 0.1 μg/kg/min, is also very low, at approximately 7–10 μg/min. Most studies have found that an effective dose of phenylephrine, whether fixed or adjusted, is in the range of 25–100 μg/min, so the investigated dose may be almost an order of magnitude too low. The norepinephrine infusion was fixed at 0.05 μg/kg/min, 50% of the phenylephrine dose. This norepinephrine dose is almost certainly more potent than the phenylephrine dose, since the relative potency, while not completely determined in this context, is almost certainly not 1:2.[11,14] Because of this study design, much of the vasopressor used to maintain maternal blood pressure, especially in the phenylephrine group, was given as "rescue boluses" of phenylephrine, rather than in the infusions of phenylephrine or norepinephrine, making it more difficult to detect true differences in drug effects or side effects. In addition, the blood pressure goal in this study was to maintain systolic blood pressure in the range of 100–120% of baseline; boluses of phenylephrine were administered whenever systolic pressure was below baseline. This goal, rather than, for example, aiming at 90–100% of baseline, will necessarily require more vasopressor. With the study design of fixed rate infusions this will again tend to increase the percentage of vasopressor given in phenylephrine bolus form.

There are several other more minor, but still significant limitations or study design flaws. The spinal dose was not standardized, as subjects were allowed to receive "12–15 mg" bupivacaine. This is probably a minor issue, as the dose of bupivacaine in this range probably does not have much of a differential effect on blood pressure. Blood pressure was measured with the Nexfin® finger cuff, rather than a traditional blood pressure cuff. While the Nexfin® delivers continuous blood pressure data, theoretically making it easier to respond to maternal hypotension in a more timely manner, it is not completely validated in pregnancy, and has been mostly compared to invasive (i.e., arterial catheters) measurements, not the external blood pressure cuff that is and will be the standard detection device during most elective cesarean deliveries.[15,16] Especially in a non-blinded study, the availability of continuous blood pressure data might actually make it more likely for investigator bias to enter into decisions to intervene with rescue boluses of vasopressor. Another minor possible flaw in the study is the choice of endpoint; the investigators chose to examine the total number of rescue boluses needed, rather than the number of patients who needed to be "rescued" or who became hypotensive. This design could potentially have allowed a few subjects who needed many rescue boluses to skew the data.

In most investigations of vasopressor use during cesarean delivery umbilical pH and base excess is a primary or important secondary outcome. In this study umbilical blood was only obtained when "clinically indicated as part of routine care," so umbilical venous gases are only reported for five neonates in the phenylephrine group, and seven in the norepinephrine group. No umbilical arterial gases are reported. With the small numbers and possibility of selection bias of subjects who had umbilical samples measured, no conclusions can be reached from the neonatal blood gas data, which were not different between groups.

The investigators planned to include 85 subjects based on a sample size/power analysis, and did, but it is unclear why 47 subjects were randomized to norepinephrine with only 38 randomized to phenylephrine. The explanation in the manuscript is that "the enrolment difference between groups was due to each patient being randomly assigned to one of two groups without restriction to an equal size," but it is not clear why this should be the case if a set of envelopes with group assignments were prepared, with a study size of 85 subjects pre-planned.

With all the above caveats and limitations what can we learn from this investigation? The hemodynamic differences between groups were minor, and no adverse