such data are available, do not "throw away" the ephedrine syringe, but rather use a common sense approach based on sound clinical judgment when treating maternal hypotension in this setting.

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Table 1. Umbilical Artery pH and Base Excess from Two Studies Comparing Ephedrine and Phenylephrine for the Treatment of Hypotension during Cesarean Delivery with Spinal Anesthesia

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Ephedrine</th>
<th>Parameter Measured</th>
<th>P Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.33 (7.30–7.35)</td>
<td>7.25 (7.14–7.29)</td>
<td>μA pH</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>−1.9</td>
<td>−4.8</td>
<td>Base excess</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>7.31</td>
<td>7.28</td>
<td>uA pH</td>
<td>NS</td>
<td>2</td>
</tr>
<tr>
<td>−1.34</td>
<td>−4.75</td>
<td>Base excess</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

The values are given as mean (range).

NS = not significant.

References


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In Reply:

I thank Drs. Kempen, Gambling, and McLaughlin for their interest and comments concerning the articles by Ngan Kee et al.1 and Dyer et al.2 regarding phenylephrine infusions during spinal anesthesia for cesarean section and my editorial3 about the relative lack of acceptance of phenylephrine, especially as an infusion, for the treatment or prevention of hypotension and other side effects in that clinical context.

Dr. Kempen provides a detailed and interesting discussion of the clinical and research protocol followed by the Ngan Kee group and raises possible alternative pharmacokinetic explanations for some of the findings. Many of these points were raised in the review process (of which I was a part), including issues concerning the dosing strategy and the determination of the "baseline blood pressure" in the operating room, as opposed to preoperatively as is perhaps more usual in studies of this kind. On balance, the other reviewers and I believed that the information obtained from the study far outweighed any limitations. Dr. Kempen refers to the dosing strategy in the study by Ngan Kee et al. as "high-dose vasopressor therapy for ASA1–2 [American Society of Anesthesiologists physical status 1 and 2] [patients]," suggesting that these healthy women were overtreated or unnecessarily treated to prevent hypotension. I had discussed this type of objection to phenylephrine infusions; basically that this is usually not a "life and death issue" and that the clinical differences compared with older, perhaps simpler, therapies (e.g., bolus ephedrine) are small.3 The thrust of my opinion was that I disagree with this view; obstetric anesthesiologists have been searching for a solution to the spinal hypotension problem for decades (hence the “Holy Grail” metaphor), and it is notable that when a reasonable solution appears within grasp, fewer clinicians than expected are using it or are even aware of the evidence for its safe use. Dr. Kempen states that there was an increased incidence of hypertension in the phen-

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In my editorial, I pointed out that phenylephrine infusions are a more than reasonable alternative to ephedrine, and most probably better for certain outcomes, and that not only was the use still relatively rare outside a few academic or other large obstetric centers (such as Dr. Gambling’s), but also that in fact the questions I was hearing at meetings and in hallways were of the sort asking “do you think it is actually permissible and accepted (i.e., not negligent) to use phenylephrine and to admit to using it?”

I do think that the work by Ngan Kee et al. has proven that phenylephrine infusions are a more than reasonable alternative to ephedrine or to boluses of ether drug, with strong evidence that maternal side effects, at least, are clinically significantly decreased. The title of my editorial, “Burden of Proof,” was not meant to imply that phenylephrine therapy was proven, because in science nothing ever is proven; the modern definition of science according to Karl Popper only endorses and is a reasonable summary of my practice. I remain hopeful that the work by Ngan Kee et al. and, to a much lesser extent, my editorial comments may allow us to do better than we had been doing at making the experience of and outcome from anesthesia for cesarean section as pleasant and successful as it can be.


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References

2. 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 maternal side effects compared with ephedrine.6–9 In my to a better control of blood pressure and a significant decrease clear from multiple studies that phenylephrine infusions lead better Apgar scores with phenylephrine issue to discuss, although at least one study has reported better metric to assess neonatal “outcome” is too complex an other evidence, it would be hard to argue that a drug (ephedrine group (47% vs. 41%), but he has apparently mis- read the lines in table 4; the incidences are not different (P = 0.55), rather it is the maximum-recorded systolic pressures that are slightly different, and probably not truly statistically so, given the multiple comparisons made (139 vs. 134 mmHg, P = 0.044). He also suggests that the one neonate with an Apgar score of less than 7 (it was 6), whose mother had been randomized to the phenylephrine group, may be a “subtle warning.” This suggestion based on one subject is hard to take seriously. The issue of whether to assess and treat patients based on systolic blood pressure or based on mean blood pressure is a valid point. The differential effects of vasopressor on the systolic, mean, and diastolic blood pressure is a subject that has not received enough attention.4 Right or wrong, however, the majority of anesthesiologists use the systolic blood pressure as their treatment target during cesarean delivery, and almost all previous studies have treated this based on the systolic blood pressure. Dr. Kempen also suggests that bolus dosing is less likely to result in “over- infusion,” by which he presumably means an increased incidence or severity of hypertension or perhaps bradycardia; this point is similar to that raised by Gambling. My editorial comments were not meant to recommend any particular dosing strategy for phenylephrine infusion, and specific protocols used in research studies may not always be the proper ones to use in general clinical practice,5 but the evidence is clear from multiple studies that phenylephrine infusions lead to a better control of blood pressure and a significant decrease in maternal side effects compared with ephedrine.6–9 In my personal practice, I tend to use a somewhat more moderate dosing strategy than that used by the Ngan Kee group, starting at 50 μg/min and titrating up to 100 μg/min or down to 25 μg/min or 0 μg/min each minute based on systolic blood pressure. A 100-μg/min on/off strategy used by Ngan Kee et al.10,11 has the undeniable advantage of simplicity.

Dr. Gambling’s comments are easier for me to address. I have the highest respect for his knowledge and judgment in the field of obstetric anesthesia because he has been in the forefront of research and practice for more than two decades, with early or groundbreaking work in several areas of clinical obstetric anesthesia.12–14 Thus, I am pleased that his and Dr. McLaughlin’s comments do not really contradict or refute any of the points I tried to raise in my editorial; in fact, I essentially agree with all of their statements. Certainly, phenylephrine is not always effective and can cause bradydysrhythmias (although I am not as sure that infusions are more likely to cause this), and the clinical importance of the small but consistent difference in acid–base status reported with phenylephrine is far from clear. However, in the absence of other evidence, it would be hard to argue that a drug (ephedrine) that results in a lower neonatal pH is preferable. The issue of whether Apgar scores or umbilical cord gases are the better metric to assess neonatal “outcome” is too complex an issue to discuss, although at least one study has reported better Apgar scores with phenylephrine versus ephedrine.1 In studies of healthy women undergoing elective cesarean sec-
We thank the correspondents for their interest in our article.1 A main objective of our study, which was, as stated, to quantify hemodynamic data. It would seem that he misunderstands the number of points were raised, which we shall address in turn.


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