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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References


(Accepted for publication January 8, 2010.)

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-

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.
yalphrine group (47% vs. 41%), but he has apparently misread 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 vasoressor on the systolic, mean, and diastolic blood pressure is a subject that has not received enough attention. 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 Gamblng. 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, 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. 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. 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. 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 bradycardias-rhythmias (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. In studies of healthy women undergoing elective cesarean section, it is unlikely that there will ever be significant numbers of or differences in poor Apgar scores. The fact that Dr. Gambling has been encouraging the use of phellylphrine in his and his colleague's practice for a decade is testament to both his forward thinking and to the evidence that phenylphrine, especially as a infusion, is an effective antihypoten-sive therapy in terms of maternal experience and (perhaps) neonatal outcome. Their conclusion that "(phenylephrine) could be used as a first-line treatment" but that they "would not want to see (ephrine) discarded," are statements I can endorse and is a reasonable summary of my practice.

My editorial was not meant to (and did not) suggest that phenylephrine use be mandated or ephedrine use be " outlawed" or curtailed in any organized or regulatory way. My comments were intended to illustrate what I believe was surprising—that for more than a decade, multiple studies on at least three continents, concerning a subject that has been central to obstetric anesthesia practice for two or three generations, have suggested that phenylephrine was as good as 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 admits as science that which is at least capable of being disproved. However, I do think that the burden of proof has shifted from those advocating phenylephrine infusion therapy to those opposing it. There is certainly a need for further investigation, not least in the area of women with preeclampsia, gestational hypertension, or other causes of uteroplacental insufficiency. 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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*(Accepted for publication January 8, 2010.)*

In Reply:

We thank the correspondents for their interest in our article.1 A number of points were raised, which we shall address in turn.

Dr. Kempen describes our methodology as “questionable” and criticizes us for providing limited disclosure and analysis of hemodynamic data. It would seem that he misunderstands the main objective of our study, which was, as stated, to quantify and compare placental transfer of ephedrine and phenylephrine and the effect of these vasopressors on a number of biochemical markers of metabolism in mother and newborn. As detailed in the article, we used a regimen for infusing vasopressors that we have previously described.2–5 In recent studies by our group2–5 and others,3,4 the hemodynamic effects of phenylephrine given by infusion, both in comparison with and in combination with ephedrine, have been well delineated, and a thorough analysis has been provided for hemodynamic parameters, including detailed assessment of accuracy of blood pressure control.5,6 Because this information is already published, we considered that a detailed repetition of these analyses in our article was not relevant to the objectives of the study and was of limited extra scientific value. Presumably, this belief was shared by the editor and reviewers who did not request extra data or analysis.

Dr. Kempen criticizes us for deviating from the so-called “standard” or “typical” care and methods. For example, he points out that our protocol (similar to our usual clinical practice) did not include the use of intravenous prehydration or routine supplemental oxygen. We make no excuse for this because we consider these practices are supported by little scientific evidence.7–10 Just because something has been done for a long time does not mean it is right. Dr. Kempen stated that we provided no indication of the number of patients given oxygen, but careful reading of our article reveals this information in the final sentence of the results.

We titrated vasopressors to maintain maternal blood pressure near to baseline values. Our estimations of the latter were indeed derived from “on the table” initial recordings after arrival in the operating room. We acknowledge that this may not be ideal, but we were careful to make multiple measurements, continued this until a degree of stability was achieved, and then averaged three recordings. Dr. Kempen suggests that it may have been better to rely on clinical outpatient measurements, but one might levy equal criticism at what would likely be single measurements using different equipment taken in nonstandardized hospital conditions. In addition, Dr. Kempen states that Chinese exhibit lower pressures than Americans but provides no reference for this. The calculated mean baseline systolic blood pressure for patients in our study was 114 mmHg (SD, 9.9 mmHg). We would not regard this as being particularly low (from being Chinese) or high (from being anxious).

We agree that oscillometric measurement of blood pressure is prone to motion artifact, but we persist in using this method because it remains the most common method in clinical practice. We agree that mean arterial pressure may be a better indicator of perfusion pressure, but nevertheless, systolic pressure remains a clinically useful endpoint on which to base therapy,11 and many clinicians and researchers continue to use it. Interestingly, Dr. Kempen refers to measurement of blood pressure in “Torr.” Our equipment is calibrated in millimeters of mercury, which numerically is close to “Torr” but is not exactly equivalent.*

Dr. Kempen states incorrectly that we “simply stopped” the infusion if systolic blood pressure was greater than base-