Prophylactic Phenylephrine Infusions to Reduce Severe Spinal Anesthesia Hypotension During Cesarean Delivery in a Resource-Constrained Environment

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Phenylephrine infusions are considered as standard management for obstetric spinal hypotension, but there remains reluctance to implement them in resource-limited contexts. This prospective, alternating intervention study of patients undergoing elective or urgent cesarean delivery under spinal anesthesia compared a vasopressor bolus strategy to fixed-rate, low-dose prophylactic phenylephrine infusion with supplemental boluses. The primary outcome was the incidence of severe hypotension (mean arterial pressure <70% baseline or systolic blood pressure <80 mm Hg). Fewer patients receiving prophylactic phenylephrine infusions had severe hypotension (47.4% [n = 120/253] vs 62.1% [n = 157/253], P = .001, estimated relative risk 0.84, 95% confidence interval 0.69–1.02), with no significant difference in the rate of hypertension (15% [n = 39/253] vs 11% [n = 27/253], P = .11, estimated relative risk 1.39, confidence interval 0.87–2.20). Guidelines for resource-constrained settings should consider a fixed, low-dose phenylephrine infusion in combination with rescue vaspressor bolus therapy. (Anesth Analg 2017;125:904–6)

MATERIALS AND METHODS

Study Design
We undertook a single-center, prospective, alternating intervention study of patients undergoing cesarean delivery (CD) under SA. Ethics approval was given by the University of KwaZulu-Natal Ethics Committee (BFC013/15). Because the intervention for this study was at an institutional level and made use of management protocols with equivalent therapies and equivalent risk profiles, the local ethics and provincial ethics committees waived the need for consent. Patients were informed of the study and were given the opportunity to withdraw their data if they so desired.

Patients and Setting
Edendale Hospital is a regional referral center that caters to both routine and complex obstetric cases. The delivery rate is 700 births per month, with a CD rate of 30%. Both obstetric and anesthesia departments are staffed largely with inexperienced junior doctors. Medical officers with less than 1 year of anesthesia experience commonly provide obstetric anesthesia.

Recruitment and Protocols
Recruitment occurred from June 29, 2015, to November 25, 2015, in patients scheduled for CD under SA between 7:30 AM and 4:00 PM on normal working days. Alternating spinal hypotension protocols were used. The first protocol was used exclusively for a 2-week period, followed by the second for the subsequent 2 weeks. Choice of first protocol was decided by the flip of a coin.

Management and Data Collection
Before administering SA, baseline heart rate (HR) and noninvasive blood pressure were recorded by the attending anesthetist. Automated noninvasive blood pressure measurements were taken at 1-minute intervals. Patients received metoclopramide 10 mg intravenously and oral
sodium citrate 30 mL preoperatively. Spinal anesthesia was standardized: all patients received 9 mg of 0.5% hyperbaric bupivacaine with 10 μg fentanyl, administered in the sitting position and then immediately put into the supine position with left lateral tilt. A 1-L coload of Ringer’s lactate was administered via an 18-G intravenous line before delivery. After delivery, 3 international units (IU) of oxytocin were administered as a slow injection and 7 IU of oxytocin were given by infusion over the remainder of the operation.

Hypotension was managed either according to the bolus or the phenylephrine infusion protocol. The infusion protocol differed from the bolus protocol only by the addition of a fixed-rate 25 μg/min (50 μg/mL at 30 mL/h) prophylactic phenylephrine infusion commenced immediately after spinal insertion. Boluses were given in both protocols if mean arterial pressure (MAP) was less than 80% of baseline MAP or systolic blood pressure (SBP) was <90 mm Hg. If the HR was >70 beats per minute, phenylephrine (50–100 μg) was administered, and if the HR was less than 70 beats per minute, ephedrine was administered (5–10 mg). If the MAP increased to greater than 20% above baseline, the infusion was discontinued. Infusions were otherwise continued until after administration of oxytocin, and then weaned rapidly, aiming to maintain MAP within 20% of its initial value and SBP >90 mm Hg.

Hemodynamic data were recorded with Nihon-Kohden Lifescope monitors (BSM 3562; Nihon-Kohden, Tokyo, Japan). Intraoperative vomiting was assessed by direct observation. Blood loss was estimated by the anesthetist based on visual inspection of the abdominal swabs and suction containers, and discussion with the obstetric surgeon. Data were entered into a Microsoft Excel spreadsheet by a research assistant and checked by a study investigator. Data were then exported to a statistical program (StataCorp, 2013. Stata: Release 13. Statistical Software; StataCorp LP, College Station, TX) for further analysis.

OUTCOMES

The primary study outcome was severe hypotension defined as either MAP <70% below baseline or SBP <80 mm Hg. Hypertension was defined as MAP >20% above baseline. We also recorded adverse events: mortality within 24 hours of SA, intensive care unit admission within 24 hours of SA, conversion to general anesthesia (GA) due to loss of consciousness, intensive care unit admission due to on-table loss of consciousness, cardiac arrest requiring cardiopulmonary resuscitation, and emergent administration of atropine or adrenaline.

STATISTICAL ANALYSIS

Baseline demographics were compared using the Student t test and the χ² test. The Shapiro-Wilk test was used for testing whether data were normally distributed. The primary outcome was the incidence of severe hypotension: this was tested using a χ² test. For all analysis, an α value of <.05 defined statistical significance. A priori we deemed a 30% reduction in the primary outcome to be clinically important. Although initial sample size calculations were incorrect, the study was still adequately powered. With the achieved 253 patients per group, we had 93% power at the 0.5 significance level to detect a relative reduction of 30% in the proportion with severe hypotension, assuming a 50% incidence in the worst group. The STROBE guideline for the reporting of observational studies was followed.

RESULTS

A total of 523 patients were included in the study. Seventeen patients were excluded for the following reasons: 1 duplicate entry; 2 patients erroneously included who had a GA as the primary anesthetic; 1 received the incorrect bupivacaine dose; and 13 required conversion to GA during the study period. For the patients converted to GA, 11 of these had failed SA, 1 suffered postpartum hemorrhage (bolus group), and 1 had an iatrogenic bowel injury (bolus group). The final analysis included 506 patients: 253 in the bolus group and 253 in the phenylephrine infusion group. The patient characteristics of the 2 groups are outlined in the Table.

For the primary outcome of severe hypotension (MAP <70% of baseline or SBP <80 mm Hg), the estimated incidence in the phenylephrine group was 47.4% (n = 120/253) vs 62.1% (n = 157/253) in the bolus group. This constituted a 23.6% reduction in severe hypotension in the phenylephrine when compared with the bolus group (P = .001, estimated relative risk 0.84, 95% confidence interval, 0.69–1.02).

The estimated incidence of hypertension was 13% (n = 66/506) and was not different between 15% (n = 39/253) in the phenylephrine group and 11% (n = 27/253) in the bolus group (P = .11). Eleven patients became bradycardic (HR < 50) during the study period: 7 in the phenylephrine group and 4 in the bolus group. No patient required atropine administration.

DISCUSSION

This study found that fixed-rate, low-dose prophylactic phenylephrine infusions reduced the incidence of severe hypotension in real-world, resource-limited conditions. Although prophylactic phenylephrine infusions are increasingly becoming standard of care, there has been a reluctance to apply these recommendations to daily obstetric

### Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bolus Group (n = 253)</th>
<th>Phenylephrine Group (n = 253)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.3 (5.9)</td>
<td>27.4 (6.6)</td>
<td>.837</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.5 (16.8)</td>
<td>81.6 (18.4)</td>
<td>.960</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.3 (8.4)</td>
<td>158.1 (6.8)</td>
<td>.812</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.5 (1.6)</td>
<td>11.4 (1.5)</td>
<td>.661</td>
</tr>
<tr>
<td>HIV positive</td>
<td>122 (48.2%)</td>
<td>117 (46.2%)</td>
<td>.656</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>28 (11.1%)</td>
<td>44 (17.4%)</td>
<td>.059</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (2.0%)</td>
<td>4 (1.6%)</td>
<td>.737</td>
</tr>
<tr>
<td>Urgent cesarean delivery</td>
<td>77 (30.4%)</td>
<td>78 (30.8%)</td>
<td>.923</td>
</tr>
<tr>
<td>Baseline HR (/min)</td>
<td>90.7 (15.0)</td>
<td>92.8 (14.8)</td>
<td>.102</td>
</tr>
<tr>
<td>Baseline MAP (mm Hg)</td>
<td>96.1 (13.6)</td>
<td>97.8 (14.9)</td>
<td>.188</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>127.0 (15.8)</td>
<td>129.3 (17.8)</td>
<td>.139</td>
</tr>
<tr>
<td>Total intraoperative fluid (mL)</td>
<td>1466 (560)</td>
<td>1306 (515)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL)</td>
<td>588 (185)</td>
<td>568 (188)</td>
<td>.216</td>
</tr>
</tbody>
</table>

Continuous data expressed in mean with SD in brackets. Categorical data as count with percentage in brackets.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

*P < .05 for statistical significance.
anesthesia practice, even in similar clinical contexts to the research environment. Furthermore, because research in this field has been conducted predominantly in elective, healthy patients, both international and local guidelines reflect caution in generalizing applicability of the findings. This pragmatic study applied the protocols to a diverse heterogeneous population group and included any patient deemed fit for SA, including both elective and urgent CD.

Our study has several limitations. Initial power calculations were incorrectly calculated, but fortunately, the study was sufficiently powered for the primary outcome. We also used a composite hypotension definition of either an absolute SBP < 80 mm Hg or a reduction of MAP to < 70% of the baseline value. It is possible that this may overestimate the incidence of severe hypotension, because preoperative anxiety may elevate maternal blood pressure. This may have been compounded by the single blood pressure reading taken to establish the baseline, which was necessary to prevent delays in emergency surgery. This is likely to have affected both groups to the same degree. We also recorded the incidence of severe hypotension as a binary outcome and were thus unable to differentiate between isolated readings of severe hypotension and protracted periods of hypotension.

CONCLUSIONS
This pragmatic study, conducted in a resource-limited setting with inexperienced staff, has shown that a prophylactic low-dose phenylephrine infusion is able to significantly reduce the incidence of severe hypotension in patients undergoing both elective and urgent CD under SA. In the light of these findings, and the strong existing evidence base, we propose that consideration be given to the routine use of prophylactic phenylephrine infusions in low-resource environments.

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DISCLOSURES
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

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REFERENCES