Prophylactic Angiotensin II Infusion during Spinal Anesthesia for Elective Cesarean Delivery

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Background: Angiotensin II may prove useful in treating regional anesthesia-induced hypotension in obstetric patients, because it causes less uterine vasoconstriction than do other vasoconstrictor drugs (such as phelyphrine). This study compared (1) maternal blood pressure and heart rate and (2) fetal status at delivery in parturients given either prophylactic angiotensin II or ephedrine infusion during spinal anesthesia for elective cesarean delivery.

Methods: Fifty-four women were randomized to receive either angiotensin II or ephedrine infusion intravenously during spinal anesthesia for elective cesarean section delivery. Simultaneous with subarachnoid injection, infusion of angiotensin II (2.5 μg/ml) or ephedrine (5 mg/ml) was initiated at 10 ng kg⁻¹ min⁻¹ and 50 μg kg⁻¹ min⁻¹, respectively. The rate of each infusion was adjusted to maintain maternal systolic blood pressure at 90–100% of baseline.

Results: Cumulative vasopressor doses (mean ± SD) through 10, 20, and 30 min were 150 ± 100, 310 ± 180, and 500 ± 320 ng/kg in the angiotensin group and 480 ± 210, 660 ± 390, and 790 ± 640 μg/kg in the ephedrine group. Maternal heart rate was significantly higher (P < 0.001) during vasopressor infusion in the ephedrine group than in the angiotensin group. Umbilical arterial and venous blood pH and base excess were all significantly higher (P < 0.05) in the angiotensin group than in the ephedrine group.

Conclusions: Angiotensin II infusion maintained maternal systolic blood pressure during spinal anesthesia without increasing maternal heart rate or causing fetal acidosis. (Key words: Anesthetic techniques; angiotensin II; ephedrine; obstetric anesthesia; subarachnoid; vasoconstrictor agents.)

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Materials and Methods

The institutional review boards of the University of Mississippi Medical Center and the University of Ala-
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Bama Hospital at Birmingham approved the study protocol. After obtaining written informed consent, 54 women scheduled for elective cesarean section were randomized by selection of the next in a series of sequentially numbered opaque envelopes indicating angiotensin or ephedrine infusion. Exclusion criteria included active labor, rupture of amniotic membranes, chronic or pregnancy-induced hypertension, insulin-dependent diabetes mellitus, multiple gestation, oligohydramnios, and a preoperative diagnosis of small-for-gestational-age fetus.

Baseline maternal BP and HR values were derived from the mean of four consecutive noninvasive oscillometric measurements obtained at 1 min intervals before intravenous hydration. Hemodynamic measurements were repeated after an intravenous preload of 15 ml/kg lactated Ringer’s solution (not to exceed 1,500 ml) given in 20–40 min. Oxygen (3 l/min) was administered via nasal cannula before induction of spinal anesthesia and was continued through the time of delivery. Spinal anesthesia was induced with 0.75% hyperbaric bupivacaine (10.5 to 13.5 mg with or without 25 µg fentanyl or 0.2 mg morphine) using a 25-gauge Whitacre or 24-gauge Sprotte needle. Immediately after subarachnoid injection (time-zero), the patient was placed supine with left uterine displacement, and noninvasive BP measurements were performed at 1-min intervals. At that time, a prophylactic infusion of either 2.5 µg/ml angiotensin amide (Hypertensin; Ciba-Geigy, Summit, NJ) or 5 mg/ml ephedrine sulfate was initiated via a syringe pump (Medfusion 2010 or 2010I; Medex Inc., Rockville, MD). The syringe pump was piggybacked to an intravenous infusion of lactated Ringer’s solution that was running at 600 ml/h. The initial infusion rates of angiotensin and ephedrine were 10 ng·kg^{-1}·min^{-1} and 50 µg·kg^{-1}·min^{-1}, respectively. The rate of each infusion was adjusted to maintain systolic BP at 90–100% of baseline measurements. If systolic BP exceeded baseline BP at any time after 1 min, the vasopressor infusion was either temporarily interrupted or reduced at the discretion of the attending anesthesiologist. Both study drug infusions were continued (if necessary to maintain systolic BP within the predetermined range) for at least 30 min. If delivery occurred after 30 min, BP was maintained at 90–100% of baseline with infusion of the study drug until the umbilical cord was clamped. Administration of alternative vasopressors (i.e., ephedrine in the angiotensin group and phenylephrine or mephentermine in the ephedrine group) or atropine was allowed at the discretion of the attending anesthesiologist. Episodes of maternal vomiting or retching were recorded through 30 min, and metoclopramide was administered when this symptom was persistent. The times of both amnionatomy and delivery were recorded, and the difference of the two times was used to calculate the uterine incision-to-delivery interval.

After delivery, umbilical arterial and venous blood specimens were obtained from a double-clamped segment of the umbilical cord. Umbilical arterial and venous blood-gas and acid–base data were excluded if only one sample was obtained or if the pH difference of the two specimens was <0.05 (indicating that the two samples were both venous or both arterial). Sample size calculations indicated that 21 acid–base measurements per group would have an 80% power to detect a significant difference between the mean (± SD) umbilical arterial pH of 7.30 ± 0.06 and 7.25 ± 0.06 in the two treatment groups. Repeated-measures analysis of variance tests were used to compare the HR and BP responses between groups over time. Analysis of variance tests were used to compare demographic data, induction-to-delivery intervals, uterine incision-to-delivery intervals, and fetal blood-gas and acid–base data between groups. Regression analysis was used to compare induction-to-delivery interval and total vasopressor dose with umbilical arterial pH. Discrete data were compared using the chi-squared or Mann–Whitney U tests. Probability values <0.05 were considered significant.

Results

Maternal and fetal demographic data were similar in the angiotensin (n = 29) and ephedrine (n = 25) groups (table 1). The indications for cesarean delivery and the number of previous cesarean deliveries were also similar in both groups (data not shown). The median sensory level of spinal anesthesia at 10, 20, and 30 min was T3, T2, and T2 in the angiotensin group and T3, T3, and T2 in the ephedrine group. Cumulative vasopressor doses (mean ± SD) through 10, 20, and 30 min were 150 ± 100, 310 ± 180, and 500 ± 320 ng/kg in the angiotensin group and 480 ± 210, 660 ± 390, and 790 ± 640 µg/kg in the ephedrine group. Seven women in each group vomited or retched during the initial 30 min of spinal anesthesia. One woman in the angiotensin group and two in the ephedrine group received metoclopramide intravenously to treat nausea or vomiting during this period (P = NS).
Table 1. Maternal and Fetal Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Angiotensin (n = 29)</th>
<th>Ephedrine (n = 25)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
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<tr>
<td>Age (yr)</td>
<td>25 ± 6</td>
<td>24 ± 4</td>
<td>NS</td>
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<tr>
<td>Weight (kg)</td>
<td>82 ± 19</td>
<td>91 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
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<tr>
<td>Systolic</td>
<td>121 ± 10</td>
<td>118 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>64 ± 10</td>
<td>66 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Mean</td>
<td>83 ± 11</td>
<td>85 ± 13</td>
<td>NS</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td></td>
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<tr>
<td></td>
<td>91 ± 12</td>
<td>86 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
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<tr>
<td>Estimated gestational age (wk)</td>
<td>39 ± 2</td>
<td>38 ± 2</td>
<td>NS</td>
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<tr>
<td>Weight (g)</td>
<td>3,225 ± 638</td>
<td>3,388 ± 669</td>
<td>NS</td>
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<td>Presentation (number)</td>
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<td>Vertex</td>
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<td>21</td>
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</tr>
<tr>
<td>Nonvertex</td>
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<td>4</td>
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</tbody>
</table>

Continuous data are mean ± SD.
NS = not significant.

During vasopressor infusion, maternal HR was significantly lower (P < 0.001) in the angiotensin group than in the ephedrine group (Fig. 1). Systolic BP was easily maintained within the desired range using angiotensin infusion (Fig. 2). In contrast, maternal BP was slightly greater than the desired range between 12 and 30 min with ephedrine infusion. Systolic BP was significantly higher (P = 0.004) over time in the ephedrine group than in the angiotensin group.

Specific intraoperative hemodynamic events in several patients deserve amplification. In the angiotensin group, one patient received 0.2 mg atropine given intravenously at 6 min for sinus bradycardia (maternal HR, 51 beats/min) and hypotension (systolic BP, 73 mmHg). Transient sinus tachycardia (159 beats/min) associated with hypotension (systolic BP, 95 mmHg) developed at 6 min in another patient in this group. In the ephedrine group, two women received 50 μg phenylephrine intravenously for sinus tachycardia (HRs, 159 and 164 beats/min) and hypotension (systolic BPs, 95 and 84 mmHg) at 4 and 8 min, respectively. A third woman in the ephedrine group received several intravenous boluses of mephentermine (total 6 mg) for sinus tachycardia (maximum HR = 156 beats/min) and persistent hypotension (systolic BP = 68–76 mmHg between 6 and 12 min). Subsequently hypertension (systolic BP = 175 mmHg at 16 min) developed in this patient and was treated with 20 mg hydralazine given intravenously. The HR of a fourth patient in the ephedrine group was 48 beats/min associated with ventricular bigeminy and hypertension (systolic BP = 168 mmHg) 4 min after she received only 7 mg ephedrine intravenously. This dysrhythmia resolved spontaneously after the ephedrine infusion was terminated.

The interval between initiation of vasopressor administration and delivery (induction-to-delivery interval) was 27 ± 6.8 min in the angiotensin group and 25.8 ± 9.2 min in the ephedrine group (P = NS). The uterine
incision-to-delivery interval was 1.4 ± 1.2 min in the angiotensin group and 1.8 ± 1.1 min in the ephedrine group (P = NS). Umbilical arterial and venous pH and base excess were all significantly higher (P < 0.05) in the angiotensin group than in the ephedrine group (Table 2). Umbilical blood-gas and acid–base data were excluded from two patients with oligohydramnios who were inadvertently included in the study. There was no significant correlation between induction-to-delivery interval or total vasopressor dose (through 30 min) and umbilical arterial pH in either group. The number of 1-min Apgar scores <7 was two in the angiotensin group and three in the ephedrine group (P = NS). Only one neonate (angiotensin group) had an Apgar score <7 at 5 min. Umbilical arterial and venous pH were 7.32 and 7.36 U, respectively, in this neonate, whose 5-min Apgar score was 6.

Discussion

Ramin et al. recently suggested that angiotensin II (not ephedrine) may be the vasopressor of choice for use in women receiving spinal anesthesia for cesarean section delivery. Surprisingly, they reported that umbilical arterial pH measurements were significantly higher when a prophylactic infusion of angiotensin II was used to maintain maternal BP than when prophylaxis was provided with an infusion of ephedrine. They speculated the difference was a result of less constriction of the uterine vasculature during angiotensin II infusion than during ephedrine infusion. Furthermore, they observed that umbilical arterial pH was lower in the ephedrine group than in a control group of patients who did not receive any prophylactic vasopressor.

Intravenous infusions of angiotensin and ephedrine were initiated before intravenous hydration and induction of spinal anesthesia in the study of Ramin et al. In contrast, we initiated vasopressor infusions simultaneously with subarachnoid injection, which is more consistent with prophylactic vasopressor administration in clinical practice. Despite the differences in methods, we also observed that umbilical arterial and venous acid–base status were superior among the neonates of women given angiotensin II infusion to support BP compared with those of a similar group given ephedrine infusion. The present results and those of Ramin et al. appear to contradict the conclusions of previous authors who have advocated aggressive use of intravenous ephedrine to maintain maternal BP during spinal anesthesia for cesarean delivery. For example, Datta et al. compared umbilical blood-gas and acid–base measurements for women given ephedrine intravenously either (1) when any decrease in systolic BP was detected or (2) when systolic BP decreased 30 mmHg or to <100 mmHg. They reported that umbilical venous pH and umbilical arterial pH and base excess were all significantly higher among the women in the former group.

Opposite effects of small and large doses of ephedrine on vascular resistance may explain, in part, increased fetal acidemia among women given ephedrine infusion. For example, Wagner et al. observed that 0.1 mg/kg ephedrine given intravenously decreased systemic vascular resistance, whereas a larger dose (0.25 mg/kg intravenously) resulted in increased systemic vascular resistance in anesthetized dogs. Similarly, small doses of ephedrine may affect uterine vascular resistance differently than much larger doses (e.g., as given in the present study at 72 ± 53 mg over 30 min). We hypothesize that at some point continued administration of the ephedrine infusion became counterproductive (i.e., the resulting increase in uterine vascular resistance offset the additional increment in maternal BP, leading to decreased umbilical cord blood pH and base excess).

We did not anticipate the large doses of ephedrine that would be required to initially support maternal BP (44 ± 21 mg through 10 min) and the frequent overshoot in maternal BP that often occurred despite termination of the infusion of ephedrine. We acknowledge that the observed differences in umbilical blood acid-
base status might have not occurred if this BP overshoot in the ephedrine group had been prevented. We endeavored to maintain systolic BP at 90–100% of baseline measurements during spinal anesthesia because there is evidence that maintaining BP in this range would optimize fetal status and minimize maternal symptoms of nausea in both groups.\textsuperscript{9,10,11} For example, Kang\textit{ et al.}\textsuperscript{10} showed that maternal nausea and vomiting occurred less frequently when systolic BP was maintained within 10% of baseline rather than when ephedrine was withheld until systolic BP decreased to 80% of baseline measurements. In addition, they could not demonstrate any effect of fetal status from efforts to tightly control maternal BP. (However, the total mean dose of ephedrine given was similar in both treatment groups [32 and 27 mg] and was much less than that used in the present study).

We do not recommend that angiotensin II replace ephedrine as the primary vasopressor to prevent or treat hypotension during regional anesthesia. Angiotensin II has an ultrashort duration of action (15 s half-life), and thus must be given by continuous infusion rather than by intermittent bolus technique.\textsuperscript{13} Further, the extraordinary potency of angiotensin II mandates that BP be checked at frequent intervals and that the drug be administered with an infusion pump. Although there were no episodes of exaggerated hypertension during angiotensin infusion in the present study, a dilution or infusion mistake could lead to significant maternal morbidity. Finally, it is unfortunate that Ciba-Geigy recently suspended the production of angiotensin amide (Hypertensin) for clinical use. Thus it is unlikely that the drug will be available to most anesthesiologists in the foreseeable future.

It is unproved whether modest differences in umbilical acid–base status at delivery correlate with significant neonatal morbidity in unassisted fetuses of healthy women given spinal anesthesia for elective cesarean section. For example, Ramin\textit{ et al.}\textsuperscript{4} also observed no difference in Apgar scores between groups despite the presence of significantly lower umbilical artery pH among the infants of women given ephedrine (rather than angiotensin II) infusion during spinal anesthesia. In the present study, the only infant with a 5-min Apgar score <7 was in the angiotensin group. Interestingly, umbilical arterial and venous \(pH\) measurements (7.32 and 7.36, respectively) were both very reassuring in this specific instance. It is possible that the choice of vasopressor (or technique of vasopressor administration) might increase in importance in situations of decreased fetal reserve.

In conclusion, prophylactic infusion of angiotensin II resulted in higher umbilical blood \(pH\) and base excess with tighter BP control and lower HR than did prophylactic ephedrine infusion during spinal anesthesia for cesarean section delivery. Infusion of angiotensin II may be useful in those few cases in which a marked increase in HR could produce hemodynamic instability, such as in patients with mitral valve or aortic stenosis.

\textbf{References}


