Spinal Hypotension During Elective Cesarean Delivery: Closer to a Solution

Robert A. Dyer, FCA (SA), PhD, and Anthony R. Reed, FRCA

Hypotension during spinal anesthesia for cesarean delivery should be minimized, both for maternal safety and comfort, and fetal wellbeing. Traditional teaching is that aortocaval compression predisposes the parturient to decreased venous return and hence cardiac output and blood pressure during spinal anesthesia for cesarean delivery. However, a variety of measures to improve venous return, including lateral tilt and numerous fluid administration regimens, have failed to eliminate hypotension.[1] Recent studies focusing on the arterial circulation as a source for hypotension suggest that in the fluid-replete parturient undergoing elective cesarean delivery, moderate spinal hypotension (20% decrease from baseline) primarily reflects decreased systemic vascular resistance.[2–4] In most cases, venous return is initially maintained and consequently there is a partial compensatory *increase* in cardiac output, mediated by an increase in stroke volume and heart rate. In this situation, the rapidly acting α-agonist phenylephrine seems to be the best option to restore baseline hemodynamics rapidly. Although ephedrine has traditionally been used to treat spinal anesthesia–induced hypotension, recent evidence suggests that ephedrine causes neonatal acidosis, and large doses may be harmful in a compromised fetus, by increasing oxygen demand and anaerobic metabolism.[5,6] Ephedrine is also associated with a higher incidence of nausea and vomiting than phenylephrine.

The dose and method of administration of phenylephrine have been the subject of extensive investigation.[7–12] In this issue of *Anesthesia & Analgesia*, 2 articles address this subject. First, Allen et al.[13] compared placebo with the use of 4 different infusion rates of phenylephrine, in combination with a crystalloid coload, and assessed "hemodynamic stability" by heart rate and blood pressure. The aim was to maintain blood pressure within 20% of baseline values. They demonstrated that infusing phenylephrine at a fixed rate of 75 or 100 μg/min is associated with more episodes of hypertension than placebo, or the lower infusion rates of 25 or 50 μg/min, respectively. Seven patients in the group receiving 100 μg/min developed sinus bradycardia and were given glycopyrrolate. It may be more appropriate to treat baroreceptor-mediated bradycardia associated with a well-maintained blood pressure by discontinuing the infusion than by the administration of an anticholinergic. This would avert the reactive hypertension reported by the authors. This work suggests that to reduce hypotension and avoid hypertension and bradycardia, slower infusion rates of phenylephrine are a better starting point, with supplementary boluses as necessary, in keeping with the pharmacokinetic principle of the use of a bolus followed by an infusion to increase steady-state concentrations. Alternatively, the authors speculate, varying infusion rates could be used. The fact that some patients experienced bradycardia and hypertension even at the slower infusion rates suggests that bolus administration of phenylephrine, titrated as required in the individual case, may be a better option than prophylactic infusions.

In the second important contribution, Stewart et al.,[14] using a suprasternal Doppler flow technique, described cardiac output changes associated with infusions of 25, 50, and 100 μg/min phenylephrine, respectively, after the administration of a rapid crystalloid preload, during spinal anesthesia for elective cesarean delivery. The aim was to maintain baseline blood pressure. The infusion of phenylephrine at 100 μg/min for 20 minutes was associated with a reduction in heart rate from 80 to 58 bpm and a reduction in cardiac output from 5.1 to 4.0 L/min. Neonatal outcomes were similar among groups. This is in agreement with a recent investigation of the hemodynamic effects of boluses of ephedrine and phenylephrine using pulse power analysis. Bolus administration of phenylephrine in response to hypotension (20% decrease from baseline blood pressure) was shown to reduce maternal cardiac output to close to baseline values (an effect strongly correlated with maternal heart rate) and restore blood pressure.[2]

In the non-obstetric population, phenylephrine (1:20,000) added to epidural lidocaine,[15] and IV methoxamine administered during spinal anesthesia,[16] have been shown to reduce cardiac output. The studies published in this issue examining the effects of phenylephrine infusions during spinal anesthesia for cesarean delivery suggest that the use of phenylephrine in doses that cause hypertension and sinus bradycardia is inappropriate.

How does phenylephrine influence cardiac output? The effect of α-agonists on venous return is controversial.[17] It is

From the Department of Anaesthesia, University of Cape Town and New Groote Schuur Hospital, Cape Town, South Africa.

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Address correspondence and reprint requests to Robert A. Dyer, FCA (SA), PhD, D23, Department of Anaesthesia, University of Cape Town and New Groote Schuur Hospital, Anzio Rd., Observatory 7925, Cape Town, South Africa. Address e-mail to Robert.dyer@uct.ac.za.

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likely that low doses of phenylephrine increase venous return, and thus cardiac output, by causing some degree of increase in splanchnic venous tone,[18] particularly in the parturient at term, with her expanded blood volume. By contrast, high doses of phenylephrine cause a baroreceptor-mediated reduction in heart rate and dilation of splanchnic veins and a shift of blood into the splanchnic vasculature with a decrease in venous return.[19] Although the indirect baroreceptor reflex-mediated sympathetic effects on the splanchnic circulation are blocked under spinal anesthesia, the heart rate- and direct receptor-mediated effects of high-dose phenylephrine persist. The latter may cause a significant increase in splanchnic arterial resistance, resulting in a decrease in splanchnic blood flow.[20] Hepatic vein resistance may also be increased. Both effects would reduce venous return. It was interesting that Stewart et al. noted that larger doses of phenylephrine were required to maintain equivalent control of the blood pressure when the infusion rate was 100 μg/min. This would be in keeping with a dose-related decrease in venous return. Because the Corrected Flow Time Index is a measure of ventricular filling, the suprasternal Doppler flow technique, which incorporates this technology, could be used in future research to study a surrogate marker of cardiac filling and hence changes in venous return.

High-dose phenylephrine may also reduce cardiac output by decreasing stroke volume. Stroke volume may decrease in response to a marked increase in systemic vascular resistance and afterload. This decrease in stroke volume was not shown in the study by Stewart et al., because the effect is best demonstrated after bolus administration, using beat-by-beat measurements.[2] A compensatory increase in stroke volume may occur via the Anrep effect,[2,21] postulated to be the recovery from subendocardial ischemia induced by the increase in afterload, and subsequent correction by autoregulation of the coronary vascular bed.[22] This effect would be undesirable if there is either coronary artery disease or ventricular dysfunction.

Animal studies have shown that under normal physiological conditions, uterine blood flow is higher than required for fetal oxygen demand,[23] thus conferring a margin of safety under conditions of rapid changes in uterine flow. This could explain the lack of neonatal acidosis observed during the administration of large doses of phenylephrine, even in the face of decreases in cardiac output.[7–9] However, as Stewart et al. rightly pointed out, significant reductions in maternal cardiac output could have deleterious effects on the outcome of a compromised fetus.[14]

In the absence of cardiac output monitoring in everyday practice, heart rate is a good surrogate marker of cardiac output. Usually, the initial response to spinal anesthesia for elective cesarean delivery is an increase in heart rate and a well-maintained or increased cardiac output.[2,4] In this situation, restoring the heart rate to the baseline value using phenylephrine in conjunction with a rapid fluid coload should be the primary goal. Because a small proportion of patients respond to spinal anesthesia with hypotension and bradycardia,[24] which usually reflects a decrease in cardiac output, anticholinergics and ephedrine (and occasionally epinephrine) do have a role to play, together with increasing lateral tilt and fluid administration.

The primary goal should thus be the maintenance of the baseline heart rate. In many cases, this can be achieved by simply using boluses of phenylephrine.[25] Alternatively, variable rate infusions may be used, with supplementary boluses of phenylephrine (either administered as prophylaxis or in response to modest hypotension). These interventions will correct blood pressure and cardiac output simultaneously, and maintain the baseline resting physiological hemodynamics. This, after all, is what we are supposed to do as anesthesiologists.

Further research should explore the exact dose-related effects of phenylephrine on venous return in the term parturient. This would enable the anesthesiologist to fine-tune what is now a well-understood clinical scenario. The more difficult issue of establishing predictors for the rarer presentation of acute bradycardia and hypotension is far from resolved and requires further investigation.[26]

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A Double-Blind, Placebo-Controlled Trial of Four Fixed Rate Infusion Regimens of Phenylephrine for Hemodynamic Support During Spinal Anesthesia for Cesarean Delivery

Terrence K. Allen, MBBS, FRCA,* Ronald B. George, MD, FRCPC,† William D. White, MPH,* Holly A. Muir, MD, FRCPC,* and Ashraf S. Habib, MBBCh, MSc, FRCA*

BACKGROUND: The administration of prophylactic phenylephrine infusions in combination with fluid cohydration significantly reduces the incidence of hypotension in women having cesarean delivery under spinal anesthesia. The ideal dosing regimen for this purpose is not known. In this study, we investigated the dose of phenylephrine that, when administered as a prophylactic fixed rate infusion, is associated with the least interventions needed to maintain maternal systolic blood pressure (SBP) within 20% of baseline.

METHODS: Women undergoing elective cesarean delivery were randomly allocated to receive placebo or prophylactic phenylephrine infusion at 25, 50, 75, or 100 μg/min immediately after spinal anesthesia in combination with a 2-L fluid coload. Maternal SBP was maintained within the target range using a predetermined algorithm. The number of physician interventions, hemodynamic performance, intraoperative nausea and vomiting, and umbilical cord blood gases were compared among the groups.

RESULTS: One hundred one patients were included in the analysis. There were no differences between the placebo and phenylephrine groups in the number of interventions needed to maintain maternal SBP within the target range. Doses of phenylephrine of 25 and 50 μg/min were associated with significantly fewer interventions when compared with 100 μg/min ($P = 0.004$ vs 50 μg/min, $P = 0.02$ vs 25 μg/min). Predelivery hypotension was more frequent in the control group compared with all phenylephrine groups. Phenylephrine 75 and 100 μg/min groups were associated with a significantly higher incidence of predelivery hypertension compared with control ($P < 0.001$ vs 75 μg/min and 100 μg/min). There was a trend toward an increase in median magnitude of deviations of SBP above or below baseline ($P = 0.006$), and the bias of SBP to be above baseline ($P < 0.001$) with increasing rates of phenylephrine infusion. There were no differences in the incidence and severity of intraoperative nausea and vomiting and umbilical cord blood gases among the groups.

CONCLUSIONS: The use of prophylactic fixed rate phenylephrine infusions did not significantly reduce the number of physician interventions needed to maintain maternal predelivery SBP within 20% of baseline compared with placebo. However, prophylactic phenylephrine infusions reduced the incidence and severity of maternal predelivery hypotension. Phenylephrine 25 and 50 μg/min administered as a prophylactic fixed rate infusion provided greater maternal hemodynamic stability than phenylephrine 75 and 100 μg/min. Prophylactic fixed rate infusions may have limited application in clinical practice, and future studies assessing the accuracy of hemodynamic control with variable rate phenylephrine infusions are needed. (Anesth Analg 2010;111:1221–9)

The administration of a prophylactic phenylephrine infusion significantly reduces the incidence of hypotension associated with spinal anesthesia.[1–3] When administered with a fluid coload, hypotension is virtually eliminated.[4] However, concerns have been raised about the safety of this technique in terms of the frequent incidence of reactive hypertension and bradycardia.[5] Although it has been suggested that phenylephrine at a dose of 100 μg/min should be titrated to maintain maternal arterial blood pressure at or near baseline, there are no studies comparing this with other dosing regimens of prophylactic phenylephrine infusions.[2]

We designed a double-blind, placebo-controlled study to determine the dose of phenylephrine that, when administered as a prophylactic fixed rate continuous infusion, is associated with the least number of physician interventions needed to maintain maternal systolic blood pressure (SBP) within a set criteria during cesarean delivery under spinal anesthesia.

METHODS

After receiving IRB approval, ASA physical status I and II pregnant women with singleton gestation at a gestational

From the *Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; and †Department of Women's & Obstetric Anesthesia, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

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Reprints will not be available from the author.

Address Correspondence to Terrence K. Allen, MBBS, FRCA, Duke University Medical System, Box 3094, Durham, NC 27710-0001. Address e-mail to terrence.allen@duke.edu.

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age of >36 weeks scheduled for elective cesarean delivery under spinal anesthesia were recruited. All patients provided written informed consent. We excluded women who were in labor, had a body mass index >45 kg/m^2, Type 1 diabetes mellitus, hypertensive disease, cardiac disease, a fetus with severe congenital anomalies, history of monoamine oxidase inhibitor use, or those who were included in any other anesthesia drug studies.

Patients were admitted to the preoperative holding area on the morning of their cesarean delivery. They had an 18-gauge IV cannula inserted into a dorsal hand vein, which was then connected to a Y-connector flushed with normal saline. A fluid preload was not administered. Baseline arterial blood pressure and heart rate (HR) were measured in the supine position with left uterine displacement. We determined baseline SBP by calculating the mean of 3 consecutive SBP measurements taken 5 minutes apart when the patient was left undisturbed. The baseline SBP was then used to determine the acceptable range of ±20% outside of which a physician intervention would be indicated by study protocol. We used a lower limit of 90 mm Hg in patients in whom a 20% reduction in maternal baseline SBP was <90 mm Hg.

Patients were randomly allocated to a placebo group (PE 0) or 4 fixed rate phenylephrine infusion regimens: phenylephrine 25 μg/min (PE 25), phenylephrine 50 μg/min (PE 50), phenylephrine 75 μg/min (PE 75), and phenylephrine 100 μg/min (PE 100). Each syringe was identified by a study number according to a computer-generated randomization in blocks of 20. To maintain blinding, the infusions were prepared in identical 50-mL syringes containing normal saline (PE 0), or phenylephrine at a concentration of 25, 50, 75, and 100 μg/mL by a physician not involved in the study.

Patients were transferred to the operating room and after the administration of 30 mL oral sodium citrate, standard noninvasive monitoring was applied, including pulse oximetry, electrocardiography, and noninvasive blood pressure. Spinal anesthesia was performed in the sitting position at the L3-4 or L4-5 interspace using a 25-gauge Pencan® spinal needle (B Braun Medical, Inc., Bethlehem, PA) with fentanyl 15 μg, preservative-free morphine 150 μg, and 0.75% hyperbaric bupivacaine 1.6 mL. Immediately after the injection of the intrathecal medication, infusion of study drug was started at 60 mL/h in combination with a fluid coload. The study drug infusion was connected to the most distal drug administration port and a pressurized 1-L bag of room temperature lactated Ringer solution was infused, with the aim of administering at least 2 L before delivery of the baby. Patients were immediately laid supine with left uterine displacement. Noninvasive blood pressure readings were taken every minute for the first 10 minutes after spinal injection and every 2.5 minutes thereafter. After delivery, 5 U oxytocin was administered IV as a bolus followed by an infusion over the next 2 hours (25 U in 1 L lactated Ringer solution). The study drug was infused until 10 minutes after delivery, after which the study ended and further management was at the discretion of the anesthesiologist. The surgical technique was standardized and included uterine exteriorization.

The primary end point was the number of physician interventions needed to maintain maternal SBP within 20% of baseline and to treat bradycardia during the study period. Physician interventions were triggered by a change in any of the following hemodynamic variables: a decrease in SBP >20% of baseline or SBP <90 mm Hg was treated by administering a 100-μg bolus of phenylephrine; an increase in the SBP to >20% of baseline was treated by stopping the infusion. Infusions were only restarted when the SBP decreased to below the upper limit of the target range (>20% above baseline). Glycopyrrolate 0.4 mg was administered for bradycardia defined as HR <50 bpm. If the study drug infusion had to be stopped on 3 occasions, then it was stopped permanently and blood pressure was maintained with phenylephrine boluses for the remainder of the study. We recorded the number of patients who experienced any episode of hypotension (SBP <20% below baseline), reactive hypertension (SBP >20% above baseline), and bradycardia (HR <50 bpm) in each group. We also recorded the number of hypotensive and hypertensive episodes per patient in each group.

The cephalad extent of the sensory block at 5, 10, and 20 minutes after placement of the spinal anesthetic was recorded using loss of pinprick sensation. Patients were asked to rate the severity of their nausea at 5, 10, and 15 minutes after spinal injection and at the end of the study using an 11-point verbal rating scale (0 = no nausea, 10 = worst possible nausea). They were also asked to report nausea occurring at any other time. Intraoperative nausea or vomiting not related to hypotension was treated with ondansetron 4 mg IV. Intraoperative nausea or vomiting occurring immediately before or after a 20% reduction in maternal SBP was recorded as hypotension-induced nausea or vomiting.

Apgar scores at 1 and 5 minutes were recorded. Blood samples were collected from a double-clamped segment of the umbilical cord for the measurement of umbilical artery and umbilical vein blood gases. Samples were either read immediately or placed in an ice bath and read within 30 minutes of collection using a blood gas analyzer (ABL735 Blood Gas Analyzer; Radiometer America, Inc., Cleveland, OH).

Statistical Analysis

Based on data from a pilot study, we estimated that a sample size of 18 patients per group would provide 80% power to detect a mean difference of 2.5 interventions among groups in pairwise comparisons at $\alpha = 0.05$ adjusted for multiple comparisons. To compensate for possible patient withdrawals, we aimed to recruit at least 20 patients per group.

Numeric measures such as gestational age, number of interventions required, and changes in blood pressure were compared among treatment groups using Kruskal-Wallis rank tests. Categorical outcomes such as the incidence of hypertension or bradycardia were compared using χ^2 tests. Where an overall test of difference among groups was significant, rank sum or χ^2 tests compared groups pairwise, with adjustments for multiple tests using a step-down permutation method. Outcomes of hypotension and hypertension are presented as overall incidence (yes/no) as well as number of measurements when the SBP was >20% of baseline (hypertension) or <20% of baseline or <90 mm Hg (hypotension). Times to the first SBP measured outside the

Table 1. Demographic Data

	PE 0 (n = 20)	PE 25 (n = 20)	PE 50 (n = 20)	PE 75 (n = 19)	PE 100 (n = 22)	P value
Height (cm)	164 ± 5.5	164 ± 4.9	164 ± 6.1	164 ± 7.1	164 ± 5.6	0.98
Weight (kg)	80 ± 15	90 ± 20	87 ± 16	84 ± 16	81 ± 11	0.24
Gestational age (wk)	38 (38–39)	39 (38–39)	39 (37–39)	39 (37–39)	39 (39–39)	0.06
Highest sensory block (dermatome)	T2 (T2-4)	T4 (T3-4)	T3 (T2-4)	T4 (T3-4)	T4 (T2-4)	0.25
Skin incision to delivery time (min)	11 (9–16)	11 (9–13)	11 (8–16)	11 (10–14)	10 (8–12)	0.34
Uterine incision to delivery time (min)	2 (1–2)	1 (1–2)	1 (1–2)	1.5 (1–2)	1 (1–2)	0.48
Volume of lactated Ringer solution infused (mL)	2200 (2150–2300)	2200 (2100–2225)	2200 (2200–2400)	2225 (2150–2300)	2150 (2100–2200)	0.24
Estimated blood loss (mL)	800 (650–1000)	800 (700–850)	700 (550–800)	725 (600–800)	800 (600–900)	0.22
Total phenylephrine dose (μg)	255 ± 248	984 ± 444	1859 ± 559	2144 ± 990	2179 ± 1070	<0.001

PE = phenylephrine.
Data are mean ± SD or median (interquartile range).

20% target range were analyzed using the log-rank test with a Kaplan-Meier analysis. We analyzed data on an intention-to-treat basis.

To further compare the accuracy of blood pressure control among groups, we compared the performance among the different infusion regimens using parameters previously described for assessing the performance of computer-controlled infusion pumps and adapted for closed loop infusions.[6–10] The following parameters were calculated.

Percentage Performance Error

Percentage performance error was defined as the difference between each measured value of SBP and the baseline value, expressed as a percentage of the baseline value and was calculated for each patient as follows:

$$\text{Percentage PE}_{ij} = [(\text{meaSBP}_{ij} - \text{basSBP}_i) \times 100]/\text{basSBP}_i$$

where percentage PE_{ij} is the percentage performance error for the ith patient at the jth minute, $meaSBP_{ij}$ is the measured SBP for the ith patient at the jth minute, and $basSBP_i$ is the baseline SBP in the ith patient.

Median Performance Error

Median performance error (MDPE) is a measure of bias and describes the median of performance error for each patient's performance error values. These differences have a direction that may be positive, indicating SBP above baseline or negative, indicating an SBP below baseline. MDPE was calculated as follows:

$$\text{MDPE}_i = \text{median } [\text{PE}_{ij}, j = 1,. . . . . , \text{N}_i]$$

where $MDPE_i$ is the MDPE for the ith patient and N_i is the number of values for the performance error obtained for the ith patient.

Median Absolute Performance Error

Median absolute performance error (MDAPE) is similar to MDPE except that it only considers the magnitude of the difference between the measured and baseline SBP and not the direction. It is a measure of inaccuracy and is summarized as the median of the absolute values of the performance error for each patient as follows:

$$\text{MDAPE}_i = \text{median } \{|\text{PE}_{ij}|, j = 1,. . . . . , \text{N}_i\}$$

where $MDAPE_i$ is the MDAPE for the ith patient.

Wobble

Wobble is a measure of the intraindividual variability of performance error and it is directly related to the ability of a computer-controlled infusion to achieve a stable effect. It is calculated as follows:

$$\text{wobble}_i = \text{median } \{|\text{PE}_{ij} - \text{MDPE}_i|, j = 1,. . . . . , \text{N}_i\}$$

where $wobble_i$ is the wobble for the ith patient.

These measures of blood pressure stability were compared among the treatment groups using Kruskal-Wallis rank tests, followed by adjusted pairwise comparisons, as described previously. In addition, the Pearson correlation between these measures and dose was used as a test of trend to determine whether variability tended to increase with larger doses. Linearity of the trend was checked with Spearman and Jonckheere-Terpstra tests. Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

One hundred nine patients were initially recruited for this study. Eight patients did not complete the study because of inadequate or failed spinal anesthesia. Insufficient samples were obtained for umbilical cord blood gases for patients in all groups because of insufficient samples, clotted samples, or sampling errors (1 sample in PE 0, 2 in PE 25, 2 in PE 50, 1 in PE 75, and 5 in PE 100).

There were no significant differences among the groups in patient demographic characteristics, maximum height of the sensory block, skin incision to delivery time, uterine incision to delivery time, volume of lactated Ringer solution infused, and the estimated blood loss (Table 1). The

Table 2. Hemodynamic Variables

	PE 0 (n = 20)	PE 25 (n = 20)	PE 50 (n = 20)	PE 75 (n = 19)	PE 100 (n = 22)
No. of interventions	2 (1–3.5)	0.5 (0–4.5)	1.5 (0–3.5)	4 (1–6)	5 (4–6)*
Infusion permanently stopped	1 (5%)	5 (25%)	3 (15%)	9 (47%)	15 (68%)†
Predelivery hypotension	16 (80%)‡	6 (30%)	3 (15%)	2 (11%)	0 (0%)
Predelivery hypertension	2 (10%)§	5 (25%)	8 (40%)	14 (74%)	18 (82%)‖
Postdelivery hypotension	9 (45%)	5 (25%)	1 (5%)	4 (21%)	2 (22%)
Postdelivery hypertension	0 (0%)	0 (0%)	5 (25%)	2 (11%)	8 (36%)
No. of hypotensive episodes	2 (1–3)¶	0 (0–2)	0 (0–0)	0 (0–1)	0 (0–0)
No. of hypertensive episodes	0 (0–0)#	0 (0–0)**	0.5 (0–2)††	2 (0–5)	3 (2–6)
Maximum percent change in SBP	8.3 (4.7–15.5)‡‡	12.7 (5.0–19.8)§§	22 (14.4–27.1)	29.3 (19.9–37.2)	33.2 (23.9–46.5)
Minimum percent change in SBP	−26.9 (−30.5, −19.1)‖‖	−19.2 (−22.5, −13.1)	−9.8 (−15.1, −5.5)	−8.3 (−19.7, −0.4)	−11.8 (−17.6, −6.2)
Bradycardia	1 (5%)	3 (15%)	0 (0%)	6 (32%)	7 (32%)

PE = phenylephrine; SBP = systolic blood pressure.
Data are median (interquartile range) or number (%).
* $P = 0.004$ vs PE 50, $P = 0.02$ vs PE 25.
† $P < 0.001$ vs PE 0, $P = 0.0096$ vs PE 50.
‡ $P = 0.001$ vs PE 50, $P < 0.001$ vs PE 75 and PE 100.
§ $P < 0.001$ vs PE 75 and PE 100.
‖ $P = 0.0081$ vs PE 25.
¶ $P < 0.001$ vs PE 25, PE 50, PE 75, and PE 100.
# $P < 0.001$ vs PE 75 and PE 100.
** $P = 0.0027$ vs PE 75, $P < 0.001$ vs PE 100.
†† $P < 0.001$ vs PE 100.
‡‡ $P < 0.001$ vs PE 75 and PE 100.
§§ $P < 0.001$ vs PE 100.
‖‖ $P < 0.001$ vs PE 50, PE 75, and PE 100.

dose of phenylephrine administered was significantly different among the groups with the largest doses administered in the PE 75 and PE 100 groups.

Hemodynamic data are presented in Table 2. Doses of phenylephrine of 25 and 50 μg/min were associated with significantly fewer interventions to maintain target blood pressure compared with a dose of 100 μg/min. However, there were no differences in the number of interventions needed to maintain SBP within our target range among patients in the control group and those receiving phenylephrine infusions. The incidence of predelivery hypotension was significantly lower in groups PE 50, 75, and 100 compared with the control group. Hypotensive episodes were more frequent in the control group compared with all the PE groups. Both groups PE 75 and PE 100 were associated with a significantly higher incidence of predelivery hypertension compared with the control group. The incidence of predelivery hypertension was also significantly higher in the PE 100 group compared with PE 25. Similarly, hypertensive episodes were significantly more frequent in groups PE 100 and PE 75 compared with both lower infusion regimen groups PE 0 and PE 25. Hypertensive episodes were also more frequent in group PE 100 compared with PE 50. Infusions were permanently stopped for reactive hypertension in 15 patients (68%) in the PE 100 group compared with 3 patients (15%) in the PE 50 group. There were no significant differences in the incidence of postdelivery hypotension or hypertension among the groups.

Figure 1 presents the percentage performance error over time for all patients in each of the 5 groups. The performance measurements were calculated for each patient and the data for each group are presented in Figures 2 and 3. The MDPE was <0 in the PE 0 and PE 25 groups and >0 in the other 3 groups. MDPE was significantly different among the groups (Fig. 2). Pairwise comparisons of MDPE among the groups showed that MDPEs in the control and PE 25 groups were significantly less than baseline when compared with all the other groups. The PE 75 and PE 100 groups were significantly above baseline when compared with the PE 0 and the PE 25 groups. The MDPE of the PE 50 group was also significantly less than that of the PE 100. The MDAPE was different among the groups (Fig. 3). The PE 50 group had the smallest MDAPE among all the groups but was only significantly different from PE 100 after correction for multiple comparisons. Significant Pearson correlations for both MDPE ($P < 0.001$) and MDAPE ($P = 0.006$) showed that the measures of SBP distance from baseline tended to increase with increasing dose. The trend was linear with no significant nonlinearity. Wobble was also significantly different among the groups ($P = 0.0024$). Pairwise comparisons showed that wobble was significantly higher in the PE 100 group compared with all the other groups ($P < 0.001$ vs PE 0, $P = 0.0075$ vs PE 25, $P < 0.001$ vs PE 50, and $P = 0.0017$ vs PE 75). Phenylephrine infused at 25 and 50 μg/min was associated with longer times to the first SBP measured outside the 20% target range when compared with the higher doses of 75 and 100 μg/min, but there were no differences when compared with the control group (Fig. 4).

There were no differences in the incidence of bradycardia among the groups. Glycopyrrolate was administered to 1 patient in the control group, 3 patients in group PE 25, 2 patients in group PE 75, and 7 patients in group PE 100. When those patients who received glycopyrrolate for the treatment of bradycardia were excluded from the analysis, only the PE 25 group was associated with significantly fewer interventions than the PE 100 group ($P = 0.02$),

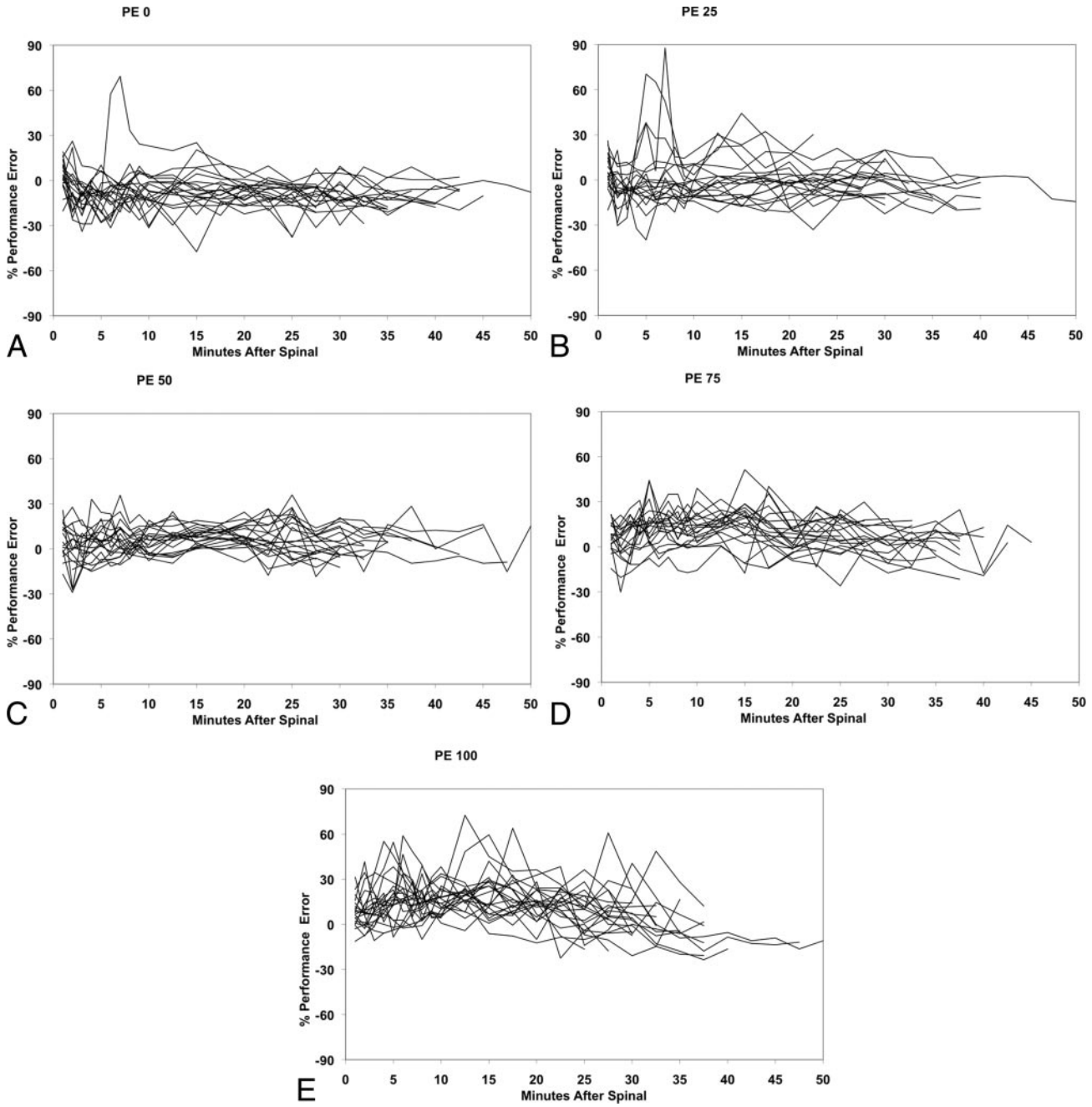

Figure 1. Percentage performance error for all patients in the control group and the phenylephrine infusion groups versus time from the time of administration of spinal anesthesia to the end of the study. The percentage performance error is a measure of the patient's systolic blood pressure (SBP) distance from baseline expressed as a percentage of that baseline. A, PE 0 (control group). B, PE 25 (phenylephrine 25 μg/min). C, PE 50 (phenylephrine 50 μg/min). D, PE 75 (phenylephrine 75 μg/min). E, PE 100 (phenylephrine 100 μg/min).

whereas the comparison with the PE 50 group was no longer statistically significant ($P = 0.06$).

There were no significant differences among groups with respect to the incidence of intraoperative nausea, vomiting, highest nausea scores, and the need for rescue antiemetics (Table 3). However, phenylephrine at a dose of 100 μg/min significantly reduced the incidence of hypotension-induced nausea when compared with the control group.

Three patients experienced adverse effects during the study period. Two of these were patients in the PE 100 group. Both events occurred after the administration of glycopyrrolate for the treatment of bradycardia, which was then followed by reactive hypertension. One patient developed headache and the other patient developed neck pain. Both events resolved spontaneously. One patient in the PE 50 group experienced an episode of ventricular bigeminy, which was not associated with any hemodynamic instability. The PE infusion was stopped but bigeminy persisted intraoperatively and resolved spontaneously in the postanesthesia care unit.

There were no significant differences in umbilical cord gases or in 1- and 5-minute Apgar scores among the

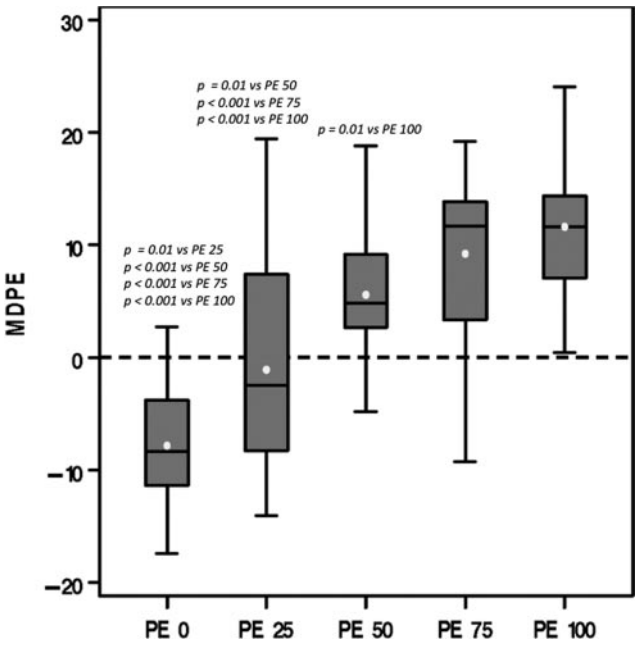

Figure 2. Box plots showing the median performance error (MDPE) in all groups. The MDPE represents the median differences in systolic blood pressure (SBP) from baseline SBP, as a percent of baseline for each patient. These differences have a direction, positive (SBP above baseline) and negative (SBP below baseline). The length of the box represents the interquartile range (IQR), with the top and bottom at the 25th and 75th percentiles, respectively. The mean is represented by the dot in the box and the horizontal line represents the median. The vertical lines extend to the farthest value observed within 1.5 times the IQR. Values outside of this range are identified by a circle. The MDPE was significantly different among the groups ($P < 0.001$). PE 0 = control group; PE 25 = phenylephrine 25 μg/min; PE 50 = phenylephrine 50 μg/min; PE 75 = phenylephrine 75 μg/min; PE 100 = phenylephrine 100 μg/min.

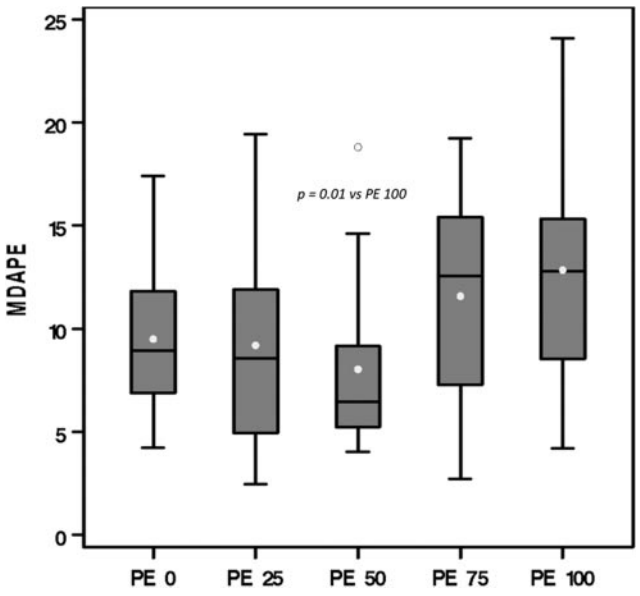

Figure 3. Box plots showing median absolute performance error (MDAPE) in all groups. The MDAPE represents the absolute magnitude of the median differences in systolic blood pressure (SBP) from baseline SBP, as a percent of baseline for each patient. The length of the box represents the interquartile range (IQR), with the top and bottom at the 25th and 75th percentiles, respectively. The mean is represented by the dot in the box and the horizontal line represents the median. The vertical lines extend to the farthest value observed within 1.5 times the IQR. Values outside of this range are identified by a circle. The MDAPE was significantly different among the groups ($P = 0.009$). PE 0 = control group; PE 25 = phenylephrine 25 μg/min; PE 50 = phenylephrine 50 μg/min; PE 75 = phenylephrine 75 μg/min; PE 100 = phenylephrine 100 μg/min.

groups (Table 4). There were also no differences in the incidence of fetal acidosis (umbilical artery pH <7.2) among the groups.

DISCUSSION

Although current evidence supports the use of phenylephrine as the vasopressor of choice for low-risk elective cesarean delivery, the dosing and mode of administration of this drug still remain an area warranting further research.[1–4,11–17] In this study, we found greater hemodynamic stability with the lower doses of phenylephrine administered as fixed rate infusions (25 and 50 μg/min) compared with the higher doses (75 and 100 μg/min). Of these regimens, phenylephrine at a dose of 50 μg/min was associated with a significant reduction in the incidence of predelivery hypotension and the number of hypotensive episodes compared with the control group. In addition, whereas the 25 μg/min infusion regimen had a lower incidence of predelivery hypertension when compared with the 100 μg/min group, both the lower infusion rates of 25 and 50 μg/min were associated with fewer episodes of reactive hypertension when compared with 100 μg/min. However, there were no differences in the number of interventions needed to maintain SBP within our target range among patients in the control group and those receiving phenylephrine infusions.

In a comparison of all the infusion regimens, there was a bias (MDPE) toward maintaining SBP below baseline with placebo and phenylephrine infused at 25 μg/min and a bias toward maintaining SBP above baseline with 50, 75, and 100 μg/min. This suggests that although increasing doses of phenylephrine reduce maternal hypotension, they also significantly increase the incidence of hypertension. Patients who received phenylephrine 50 μg/min had the fewest number of physician interventions and also had the lowest degree of inaccuracy (MDAPE) for SBP control of all the regimens; the median magnitude of the absolute performance error between each measured value of SBP and the target SBP was 6.5%. The performance of this regimen compares favorably with a previously described computer-controlled feedback algorithm used to provide hemodynamic support during cesarean delivery under spinal anesthesia.[7] Patients receiving the highest infusion rate of 100 μg/min had the greatest variability in performance error (wobble) compared with those receiving 25 to 75 μg/min and phenylephrine boluses only. These results suggest that an infusion regimen of 100 μg/min provides less maternal hemodynamic control and stability compared with all the other regimens studied. There were no differences in MDAPE between those patients receiving phenylephrine boluses and those receiving infusions, suggesting that the administration of phenylephrine by a fixed rate continuous infusion may not improve the accuracy of blood pressure control when compared with bolus administration.

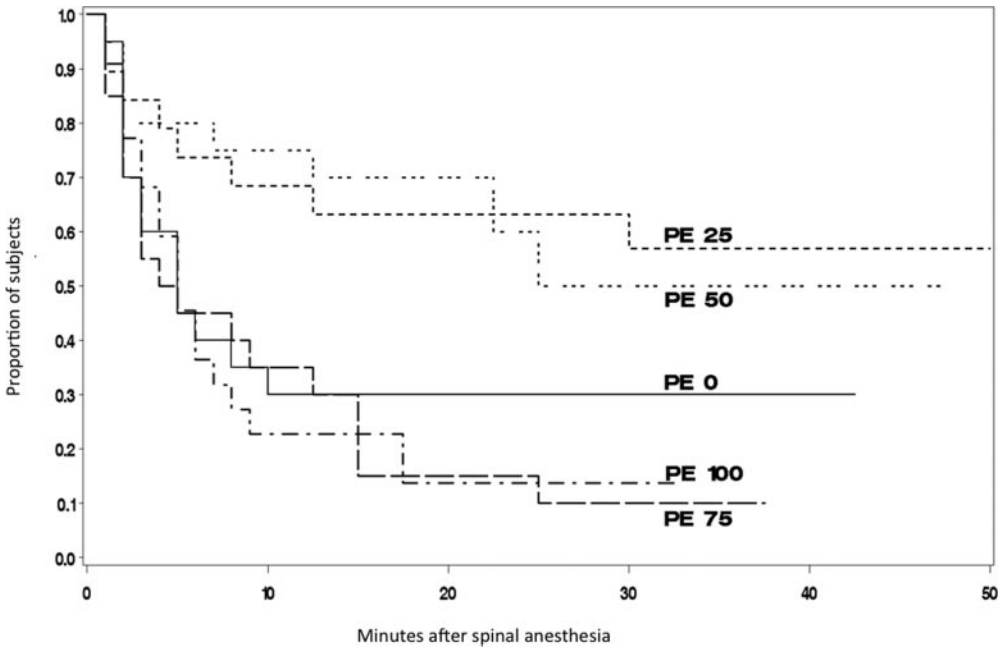

Figure 4. Kaplan-Meier survival curve—estimated time to first systolic blood pressure (SBP) outside the ±20% target range. Doses of phenylephrine of 25 and 50 μg/min were associated with a significantly longer time to a SBP outside the target range than doses of 75 (P = 0.006 vs PE 25, P = 0.004 vs PE 50) and 100 μg/min (P = 0.024 vs PE 25 and P = 0.021 vs PE 50). PE 0 = control group; PE 25 = phenylephrine 25 μg/min; PE 50 = phenylephrine 50 μg/min; PE 75 = phenylephrine 75 μg/min; PE 100 = phenylephrine 100 μg/min.

Table 3. Incidence of Intraoperative Nausea and Vomiting

	PE 0 (n = 20)	PE 25 (n = 20)	PE 50 (n = 20)	PE 75 (n = 19)	PE 100 (n = 22)
Intraoperative nausea	7 (35%)	8 (40%)	8 (40%)	6 (32%)	7 (32%)
Highest intraoperative nausea scores	0 (0–2.5)	0 (0–4.0)	0 (0–3.0)	0 (0–2.5)	0 (0–2.0)
Hypotension-induced nausea	7 (35%)	4 (20%)	1 (5%)	2 (11%)	0 (0%)*
Intraoperative vomiting	2 (10%)	2 (11)	0 (0%)	1 (5%)	1 (5%)
Need for antiemetics	4 (20%)	3 (15%)	2 (10%)	3 (16%)	2 (9%)

PE = phenylephrine.
Data are number (%) or median (interquartile range).
* P = 0.04 vs PE 0.

Table 4. Umbilical Cord Gas Data

	PE 0 (n = 19)	PE 25 (n = 18)	PE 50 (n = 18)	PE 75 (n = 18)	PE 100 (n = 17)	P value
Apgar score at 1 min	8 (5–9)	8 (8–9)	8 (8–9)	8 (8–9)	8 (8–9)	0.64
Apgar score at 5 min	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	0.52
UA pH	7.29 (7.24–7.32)	7.31 (7.29–7.31)	7.27 (7.25–7.30)	7.28 (7.23–7.30)	7.26 (7.24–7.29)	0.17
UA Po_2 (mm Hg)	19.7 ± 6.9	19.9 ± 4.8	16.7 ± 5.7	16.5 ± 4.9	16.9 ± 5.8	0.11
UA Pco_2 (mm Hg)	56.6 ± 10.7	52.3 ± 4.3	56.7 ± 5.9	59.3 ± 9.4	56.7 ± 6.8	0.12
UA base excess (mmol/L)	−2.5 ± 1.8	−1.8 ± 1.5	−2.0 ± 2.2	−2.5 ± 3.7	−2.8 ± 2.0	0.71
UA lactate (mmol/L)	2.8 ± 0.8	2.2 ± 0.5	2.7 ± 0.8	2.9 ± 1.6	2.6 ± 0.8	0.14
UA pH <7.20	2 (11)	0 (0)	0 (0)	2 (11)	0 (0)	0.51
UV pH	7.34 (7.30–7.36)	7.35 (7.33–7.37)	7.33 (7.32–7.35)	7.33 (7.31–7.36)	7.33 (7.30–7.35)	0.22
UV Po_2 (mm Hg)	26.9 ± 6.7	27.1 ± 6.0	24.9 ± 4.5	25.1 ± 7.4	24.9 ± 5.5	0.64
UV Pco_2 (mm Hg)	48.9 ± 8.4	44.5 ± 4.3	45.7 ± 4.6	48.4 ± 8.9	47.1 ± 4.3	0.25
UV base excess (mmol/L)	−2.0 ± 2.1	−1.6 ± 1.4	−1.8 ± 1.7	−2.6 ± 3.2	−2.2 ± 1.3	0.79
UV lactate (mmol/L)	2.2 ± 1.1	1.9 ± 0.5	2.0 ± 0.6	2.4 ± 1.5	2.0 ± 0.5	0.42

PE = phenylephrine; UA = umbilical artery; UV = umbilical vein.
Data are median (interquartile), mean ± SD, or number (%).

Reactive hypertension can be a problem and is a concern with the use of prophylactic phenylephrine infusions.[4,5] Ideally, the infusion should be stopped before reactive hypertension occurs. However, because factors predicting response to vasopressor administration are not clear, it is difficult to predict if and when a patient will develop reactive hypertension. In fact, even patients in the bolus group and 25 μg/min group developed reactive hypertension in this study. The incidence of hypertension was dose dependent, ranging from 25% to 82%. The administration of glycopyrrolate for the management of bradycardia may have also contributed to this. We elected to include this intervention in our treatment algorithm because we had a control group and bradycardia may be associated with hypotension and is not always a result of reactive hypertension. Phenylephrine administration has also been associated with profound bradycardia and hypotension.[2] In retrospect, managing bradycardia by stopping the phenylephrine infusion and restricting the administration of glycopyrrolate to cases of bradycardia associated with hypotension may have reduced its administration and limited the incidence and magnitude of hypertension. When we repeated the analysis on the number of physician interventions, by excluding patients who received glycopyrrolate, statistical significance remained only between the 25 and 100 μg/min groups. However, because a larger proportion of patients was excluded from the 100 μg/min group compared with the other groups (Pearson exact $P = 0.03$), this reduced the power to show statistical significance compared with the 50 μg/min group.

There were no differences in umbilical cord blood gas values among the groups despite a significantly higher incidence of maternal predelivery hypotension in the control group, probably because of the brief nature of those hypotensive episodes and their rapid treatment. This is in agreement with the results of a previous study showing no difference in fetal outcomes between patients receiving phenylephrine as a bolus or infusion.[3]

Whereas previous studies investigating the use of prophylactic phenylephrine infusions ended after uterine incision,[2–4,18] we decided to continue the infusions postdelivery to attenuate the potential hemodynamic changes associated with the administration of IV oxytocin.[19,20] Although the incidence of postdelivery hypotension was reduced from 45% in the control group to 5% to 25% in the phenylephrine groups, this difference was not statistically significant. However, our study was not powered to detect such a difference.

Hypotension has been identified as an important etiological factor for intraoperative nausea and vomiting.[21] Several studies have identified a reduction in the incidence of nausea and vomiting when using phenylephrine for cesarean delivery under spinal anesthesia.[1–3,6,22] The mechanism of this may be related to the attenuation of the increase in vagal tone accompanying the rapid decrease in preload associated with spinal anesthesia.[1,23] Even though all prophylactic infusion regimens reduced the incidence of hypotension-induced nausea compared with the control group, the result was only statistically significant in the 100 μg/min group. Our study was not powered to detect these differences. Overall, there were no significant reductions in the incidence of intraoperative nausea, vomiting, highest nausea scores, or the need for rescue antiemetics among the groups.

The current study has limitations. First, we investigated the use of simple fixed rate phenylephrine infusion regimens in conjunction with a 2-L crystalloid coload. Our findings may not be applicable to clinical situations in which IV fluids are not coadministered or an alternative volume of crystalloid or colloid is administered. The simple fixed rate infusion regimen used in this study was stopped when maternal SBP exceeded the set limits and lacked titration. In clinical practice, however, titrating the infusion rate in response to changes in blood pressure may be more appropriate. Such variable infusion rates could improve the accuracy of hemodynamic control over bolus administration. Furthermore, the best infusion rate for a fixed rate regimen might not be the best initial rate for a titrated infusion. Physician interventions were our primary end point and served as a surrogate marker of hemodynamic stability, but we did not measure other hemodynamic variables such as maternal cardiac output.[18] For the purposes of this study, we collected hemodynamic data at 1-minute intervals for the first 10 minutes only and then every 2.5 minutes until the end of the study period, and may have missed opportunities in this later time period to intervene to maintain maternal SBP within the target range, ultimately affecting our final outcome. In retrospect, the measurement of maternal blood pressure at 1-minute intervals during the entire study period, as has previously been described, would have been more appropriate.[4,6] For those practitioners using phenylephrine infusions, we recommend frequent blood pressure measurements, especially in patients receiving higher infusion rates and after the administration of oxytocic drugs.

In conclusion, prophylactic fixed rate infusions did not reduce the number of physician interventions needed to maintain maternal SBP within 20% of baseline or the accuracy of hemodynamic control when compared with placebo. However, prophylactic phenylephrine infusions reduced the incidence and severity of maternal predelivery hypotension. Among the fixed rate phenylephrine infusion regimens investigated, 25 and 50 μg/min were associated with greater maternal hemodynamic stability compared with 75 and 100 μg/min. Therefore, if a prophylactic fixed rate infusion is used in conjunction with a fluid coload, the lower rates are more appropriate. Future studies are needed to investigate variable rate infusion regimens for the prevention of hypotension in this patient population.

AUTHOR CONTRIBUTIONS

TKA, RBG, and ASH helped in study design, conduct of study, data collection, and manuscript preparation; WDW helped in study design, data analysis, and manuscript preparation; and HAM helped in study design, conduct of study, and manuscript preparation.

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The Dose-Dependent Effects of Phenylephrine for Elective Cesarean Delivery Under Spinal Anesthesia

Adrienne Stewart, FRCA,* Roshan Fernando, FRCA,* Sarah McDonald, FRCA,†
Rachel Hignett, FRCA,† Tanya Jones, FRCA,§ and Malachy Columb, FRCA‖

BACKGROUND: Hypotension is the most common serious side effect of spinal anesthesia for cesarean delivery. There has been a move recently toward the use of phenylephrine as a vasopressor infusion to improve maternal cardiovascular stability and fetal outcome. Although it seems safe in the elective setting, there have been concerns about its propensity for causing an increase in afterload and a baroreceptor-mediated bradycardia in the mother, with a consequent reduction in maternal cardiac output (CO). Using a noninvasive measure of CO, our aim was to investigate whether there were any dose-dependent effects of phenylephrine on maternal cardiovascular stability and, if so, any impact on fetal outcome.

METHODS: In this randomized, double-blind study, 75 women scheduled for elective cesarean delivery were allocated to receive a phenylephrine infusion at 25 μg/min, 50 μg/min, or 100 μg/min. This infusion was titrated to maintain maternal baseline systolic blood pressure (SBP), from induction of spinal anesthesia until delivery. The maternal cardiovascular variables recorded included heart rate (HR) and SBP. A suprasternal Doppler monitor measured CO and stroke volume, as well as measures of venous return (corrected flow time) and contractility, at baseline, and then every 5 minutes for 20 minutes after initiation of spinal anesthesia. Apgar scores and umbilical cord blood gases were recorded.

RESULTS: SBP control was satisfactory in all groups; however, the group receiving phenylephrine 100 μg/min required significantly higher doses to achieve arterial blood pressure control compared with the lower infusion rates. There were no significant differences in the number of times SBP decreased below 80% of baseline, or the numbers of boluses of ephedrine or phenylephrine required to maintain SBP above 80% of baseline. There were significant time and dose-dependent reductions in HR and CO with phenylephrine, such that HR and CO were seen to decrease with time in each group, and also with increasing concentrations of phenylephrine. Stroke volume remained stable throughout. Apgar scores and umbilical cord blood gases were similar among groups.

CONCLUSION: By infusing a higher concentration (100 μg/min), we subject the mother and fetus to a much higher dose of phenylephrine, with significant effects on maternal HR and CO (up to a 20% reduction). Future investigation is required to determine whether this reduction in maternal CO has detrimental effects when providing anesthesia for an emergency cesarean delivery for a compromised fetus. (Anesth Analg 2010;111:1230–7)

Widespread use of spinal anesthesia for cesarean delivery has been accompanied by a reduction in maternal mortality.[1] However, spinal anesthesia is associated with hypotension, and this is more common and profound in the pregnant population, with an incidence in excess of 80% without prophylactic management.[2] The resulting hypotension can cause nausea and vomiting, cardiovascular collapse, and loss of consciousness in the mother, as well as acidosis in the fetus.[3] Both spinal anesthesia and maternal physiological changes contribute to the hypotension. A reduction in systemic vascular resistance (SVR) as a consequence of sympathetic blockade, more extensive neuroblockade because of a contracted subarachnoid space, and aortocaval compression have all been implicated as mechanisms of the hypotension.[4]

Many strategies have been described to prevent and treat hypotension in the obstetric population. There has been growing evidence to support the use of coloading with IV fluids in combination with the use of vasopressors.[5,6] The ideal vasopressor would maintain maternal cardiovascular stability and prevent nausea and vomiting, but have little adverse effect on uteroplacental perfusion, therefore with no resulting compromise to the fetus. The ideal vasopressor has been the subject of much controversy and debate, but it is now widely accepted that the vasopressor of choice in the parturient is phenylephrine.[7–10] Large doses of vasopressor are often required during cesarean delivery after spinal anesthesia because of increased baroreceptor sensitivity.[11] There have been concerns that large doses of phenylephrine, although maintaining maternal systolic blood pressure (SBP), may cause reflex bradycardia and consequently a reduction in cardiac output (CO).[a]

Although previous work has shown that maternal CO correlates closely with uteroplacental blood flow,[12] most of the work done to date examining the cardiovascular effects of phenylephrine has concentrated on its effect on maternal

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Address correspondence and reprint requests to Roshan Fernando, FRCA, Department of Anesthesia, University College London Hospitals NHS Foundation Trust, London, NW1 2BU, UK. Address e-mail to r.fernando@btinternet.com.

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[a] Ashpole K, Fernando R, Tamilselvan P, Columb M. Maternal cardiac output changes with phenylephrine and ephedrine infusions after spinal anaesthesia for caesarean section [abstract]. Int J Obstet Anesth 2005;14:S5.

heart rate (HR) and SBP.[13] It is a long-held belief that measurements of SBP can be used as a surrogate for maternal CO in predicting uterine blood flow, in the absence of a reliable noninvasive method of assessing maternal CO.[14] However, with the advent of newer noninvasive techniques, maternal CO can now be measured reliably and accurately. The suprasternal measurement of aortic blood flow is a noninvasive technique for assessing the CO. It measures the stroke distance, in the aortic arch, providing a linear measure of CO. It has been validated against volumetric measures derived from thermodilution[15] and has been used successfully in the pregnant and nonpregnant populations.[16,17]

This double-blind, randomized, controlled study was designed to investigate the dose-dependent effects of 3 infusion doses of phenylephrine on maternal cardiovascular stability in women undergoing elective cesarean delivery under combined spinal-epidural anesthesia. The primary outcome measure was change in CO. Secondary outcomes included effects on HR, SBP, and measures of fetal well-being.

METHODS

After ethics committee (Royal Free Hampstead NHS Trust, London, UK) and MHRA (Medicines and Healthcare Regulatory Authority) approvals (EudraCT number 2006-004858-25), the study was conducted over a 7-month period from May until November 2007. Written informed consent was obtained from 75 healthy term parturients undergoing elective cesarean delivery under combined spinal-epidural anesthesia. Exclusion criteria included cardiovascular disease or cardiac medication, pregnancy-related hypertensive disease, height <150 cm or >180 cm, or weight <50 kg or >100 kg.

Randomization was performed using a computer-generated random number table. Parturients were randomly assigned to 1 of 3 groups of 3 infusion regimens of phenylephrine. Group assignments were sealed within opaque envelopes. All phenylephrine infusions were infused at the same rate, but the concentration differed among groups, such that the parturients received 25 μg/min (group 25), 50 μg/min (group 50), or 100 μg/min (group 100).

Three anesthesiologists were involved in the study. One anesthesiologist, unconnected with the clinical care or data collection, prepared the phenylephrine infusion according to the randomization group and instructions provided in the sealed envelope opened just before drug preparation. A second anesthesiologist monitored and recorded the HR and SBP every minute from the initiation of anesthesia (intrathecal injection) until delivery of the fetus and controlled the phenylephrine infusion. A third anesthesiologist performed all of the Doppler measurements of CO, as well as the combined spinal-epidural technique. The patient and second and third anesthesiologists were blinded to group assignment.

Baseline measurements (HR, SBP, and oxygen saturation) were obtained before the initiation of the fluid preload in the supine position with the bed tilted 15 degrees to the left. A handheld suprasternal ultrasound device (SupraQ® cardiac function monitor; Deltex Medical Ltd., Chichester, UK) was used to measure CO, stroke volume (SV), and other Doppler variables. Baseline HR and SBP were taken as an average of 3 readings, and 80% value of the baseline SBP was calculated.

Immediately after the measurement of the baseline hemodynamic variables a fluid preload of 500 mL Hartmann solution was infused over a 5-minute period through a wide-bore peripheral IV cannula with the aid of a simple pressurized infusion system. No further fluid was administered until after delivery of the fetus. On completion of the fluid preload, SBP, HR, CO, and other Doppler variables were measured, followed by initiation of anesthesia. HR and SBP were then recorded and acted upon every minute from the start of spinal injection until delivery of the fetus. CO, SV, and other Doppler measurements were performed at 5-minute intervals for a period of 20 minutes before the start of surgery. The incision was delayed for purposes of the study until the 20-minute measurement interval was completed.

Combined spinal-epidural anesthesia was initiated in the sitting position at the L3-4 or L4-5 interspace with 0.5% hyperbaric bupivacaine 11 mg and fentanyl 15 μg. Block height to cold and loss of touch were recorded at 5-minute intervals using ethyl chloride spray. If a block height of T5 to touch sensation was not achieved by 20 minutes, 5-mL boluses of levobupivacaine 0.5% were given via the epidural catheter to extend neuroblockade.

The phenylephrine infusion was administered at a rate of 120 mL/h from the time of the intrathecal injection until delivery of the fetus if SBP was at or below the baseline SBP. The infusion was stopped if the SBP went above the baseline. Hypotension, defined as an SBP <80% of baseline SBP for 2 consecutive readings, despite the phenylephrine infusion, was treated with a bolus of phenylephrine 100 μg. If no improvement was seen after a further 2 consecutive readings, a bolus of ephedrine 6 mg was administered. Bradycardia (HR <50 bpm) for 2 consecutive readings was treated by stopping the phenylephrine infusion if the SBP was at or above the baseline, but if the SBP was below the baseline, the phenylephrine infusion was continued and a bolus of glycopyrrolate 200 μg was administered. The presence of nausea and vomiting (none, mild, moderate, or severe) was assessed at 5-minute intervals until 20 minutes after spinal injection.

Obstetric data collected included time interval from the intrathecal injection to the start of surgery, uterine incision to delivery time, Apgar scores at 1 and 5 minutes, and umbilical arterial and venous blood gases obtained from a double-clamped segment of umbilical cord.

CO was measured using a suprasternal ultrasound device, the SupraQ cardiac function monitor (Deltex Medical Ltd.). All measurements were taken from the aortic arch and performed by a single operator trained over a 3-month period in suprasternal ultrasound techniques, so as to achieve reproducibility and reliability. All CO readings used for statistical analysis represented the mean of 3 readings taken in rapid succession at each measurement time. Apart from CO and SV, we also measured stroke distance, minute distance, corrected flow time, and peak velocity.

Data are presented as mean and frequency. Group effects were analyzed using 1-way analysis of variance for numerical data, linear trend for dose, and expanded Fisher

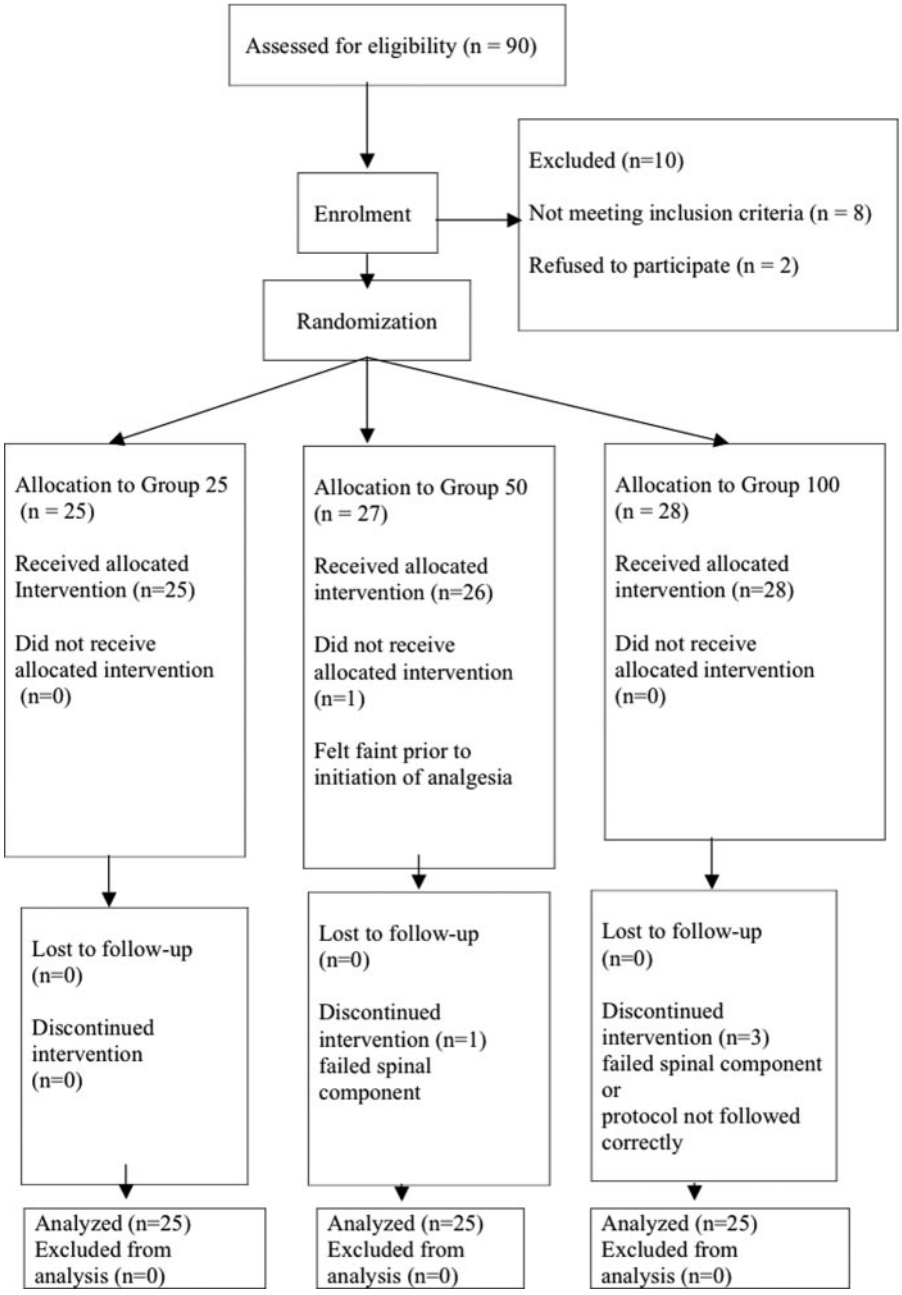

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) recommended description of patient recruitment to the phenylephrine infusion randomized, double-blind trial at the University College London Hospitals, UK.

exact tests for categorical data. Within- and among-group comparisons of hemodynamic variables from baseline to predefined time points were performed using repeated-measures analysis of variance, analysis of covariance (using baseline hemodynamic variables as covariates), and Tukey-Kramer multiple comparison tests. True group effects were tested at 4 time points, between 5 and 20 minutes after the spinal injection.

An a priori sample size analysis showed that a minimum of 23 patients in each of 3 groups would give 80% power to detect a 20% difference in CO (assuming a coefficient of variation of 20%), at an overall 2-sided $P < 0.05$ (threshold $P < 0.017$ with the Bonferroni adjustment for multiple comparisons). This sample size would also provide at least 90% power to detect differences of 20% in SBP and 25% in HR. Additionally, because the aim of the study was to provide similar SBP control in the groups, this was examined by an equivalence analysis approach, which was defined as significant ($P < 0.05$ after adjustment for multiple comparisons) if the 90% confidence interval estimates of the ratios were contained within the conventional 0.80 to 1.25 margin. Analyses were performed using the following software: Excel 2000 (Microsoft Corp., Redmond, WA), Number Cruncher Statistical Systems 2004 (NCSS Inc., Kaysville, UT), and Prism 5.0 (GraphPad Inc., San Diego, CA).

RESULTS

Data analysis was performed on 75 patients (Fig. 1). Details of maternal characteristics are summarized in Table 1. The

Table 1. Maternal Characteristics

Characteristic	Group 25 ($n = 25$)	Group 50 ($n = 25$)	Group 100 ($n = 25$)
Age (y)	32 ± 5	33 ± 6	34 ± 5
Weight (kg)	66 ± 12	61 ± 8	67 ± 13
Height (cm)	163.0 ± 8.0	161 ± 7	161 ± 7
BMI (kg/m^2)	25 ± 4	24 ± 3	26 ± 6

Values are mean ± SD.
BMI = body mass index.
There were no significant differences among groups.

Table 2. Baseline Cardiovascular Values

Baseline value	Group 25	Group 50	Group 100
Heart rate (bpm)	79 ± 16	77 ± 13	80 ± 14
Cardiac output (L/min)	5.1 ± 1.0	4.6 ± 0.8	5.1 ± 1.0
Systolic blood pressure (mm Hg)	122 ± 13	120 ± 12	124 ± 10
Stroke volume (mL)	67.0 ± 14.7	60.8 ± 12.0	64.8 ± 9.4

Values are mean ± SD.
There were no significant differences among groups.

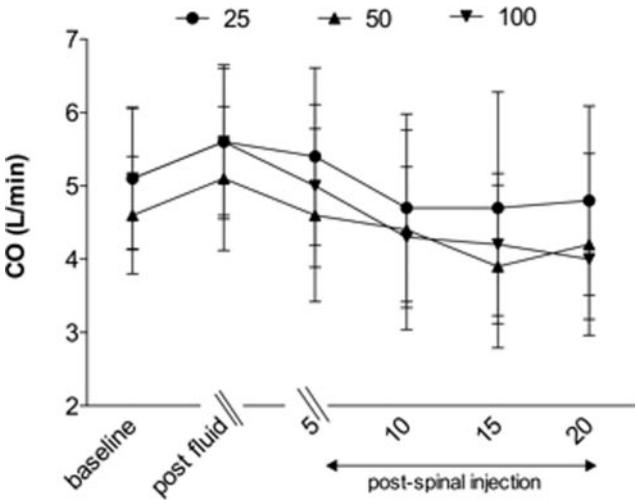

Figure 2. Cardiac output (CO) versus time (data are mean ± SD). Main effects after intrathecal injection: effect of phenylephrine dosing group ($P = 0.025$), concentration dependency (trend, $P = 0.007$). Effect of time ($P < 0.001$; trend, $P < 0.001$). Interaction of group × time ($P = 0.01$).

3 groups were similar with respect to maternal age, weight, height, and body mass index.

Baseline cardiovascular variables are detailed in Table 2. To control for differences in baseline CO values, any differences among groups after spinal anesthesia were compared using analysis of covariance. CO decreased significantly ($P < 0.001$) with time within each group (Fig. 2). Compared with baseline values, the reductions in CO at 20 minutes were 0.3, 0.4, and 1.1 L/min in groups 25, 50, and 100, respectively. There were significant between-group differences ($P = 0.03$) in CO that were concentration dependent (linear trend; $P = 0.007$). The maximum percentage reductions in CO from baseline values were 7.8%, 15.2%, and 22% in groups 25, 50, and 100, respectively. The decrease from baseline CO was highest in group 25 and lowest in group 100 at all time points.

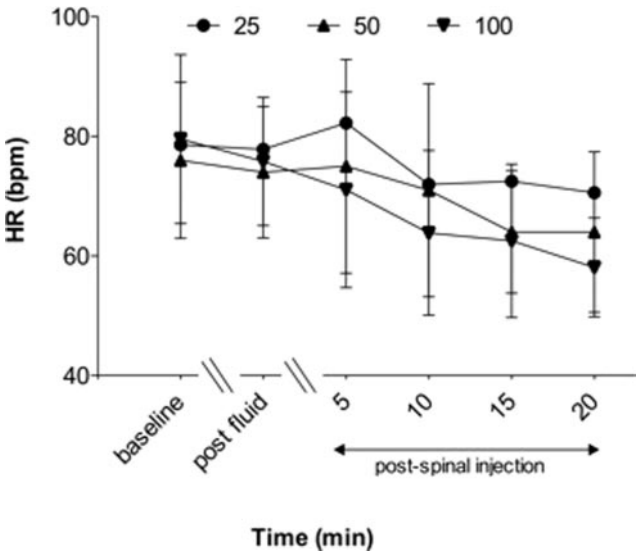

Figure 3. Heart rate (HR) versus time (data are mean ± SD). Main effects after intrathecal injection: effect of phenylephrine dosing group ($P = 0.02$), concentration dependency (trend, $P = 0.007$). Effect of time ($P < 0.001$; trend, $P < 0.001$). Interaction of group × time ($P > 0.20$).

There was a significant between-group difference in HR ($P = 0.02$), and HR decreased significantly with time in all groups (linear trend; $P < 0.001$) (Fig. 3). Compared with baseline values, the reductions in HR at 20 minutes were 8, 12, and 22 bpm in groups 25, 50, and 100, respectively. There were significant concentration-dependent reductions in HR (linear trend; $P < 0.007$). At all time points from the start of the phenylephrine infusion, the HR was the most rapid in group 25 and slowest in group 100. No significant differences were found in the number of glycopyrrolate boluses (Table 3).

SV remained stable with time within each group (Table 4). Other variables obtained from the Doppler readings, corrected flow time, mean acceleration, peak velocity, did not demonstrate any significant differences among the groups (data not shown).

There were small but significant differences in SBP among groups ($P = 0.04$) (Fig. 4), which were concentration dependent (linear trend; $P = 0.01$). Our results suggest that the highest concentration group had a more "stable" SBP compared with the lower concentrations, which tended to drift down with time. Although statistically significant, the difference among groups at any time point was <15 mm Hg and therefore less than the clinically significant minimum difference of 20% as demanded by the protocol.

At 20 minutes, the SBP was 110, 113, and 125 mm Hg in groups 25, 50, and 100, respectively. Overall, SBP was 6% higher ($P = 0.049$) in group 100 compared with group 25 (Fig. 4). These small differences were further examined by an equivalence analysis, which confirmed that there were no significant clinical deviations of SBP among the groups as the ratio 1.06 (95% confidence interval at 0.99–1.13) was wholly contained within the 0.80 to 1.25 interval ($P < 0.05$). The number of minutes SBP was recorded as above baseline was significantly higher in group 100 (linear trend; $P = 0.01$) (Table 3), and the number of minutes SBP was

Table 3. Phenylephrine, Ephedrine, and Glycopyrrolate Data

	Group 25	Group 50	Group 100
Phenylephrine infusion time (min)*	31.2 ± 9.9	27.6 ± 10.3	23.0 ± 8.5
Median (IQR) number of phenylephrine infusion interventions (stopping/starting) (*n*)	6 (3, 9)	7 (5, 10)	7 (7, 9)
Phenylephrine infusion dose (μg)*	779 ± 247	1380 ± 515	2300 ± 847
No. of patients receiving a phenylephrine bolus (*n*)†	9	4	2
Total phenylephrine dose (infusion + bolus) (μg)*	830 ± 289	1436 ± 542	2328 ± 865
No. of patients receiving an ephedrine bolus (*n*)	4	1	1
No. of patients receiving a phenylephrine and ephedrine bolus (*n*)†	10	5	3
No. of patients receiving a glycopyrrolate bolus	2	0	0
Time systolic blood pressure lower than baseline (min)*	26.8 ± 9.7	22.5 ± 9.3	20.3 ± 8.2
Time systolic blood pressure higher than baseline (min)*	10.2 ± 5.9	11.6 ± 8.5	16.2 ± 8.8

Values are mean ± SD or median (IQR).
*$P < 0.05$ linear trend in groups.
†$P < 0.05$ trend for proportions among groups.

Table 4. Stroke Volume Data

	Group 25 (mL)	Group 50 (mL)	Group 100 (mL)
Baseline	67.0 ± 14.7	60.8 ± 12.0	64.8 ± 9.4
5 min	69.1 ± 17.4	62.9 ± 13.5	70.7 ± 10.9
10 min	66.9 ± 16.9	62.4 ± 15.4	65.0 ± 9.8
15 min	65.4 ± 19.0	61.6 ± 13.9	66.0 ± 7.9
20 min	68.7 ± 14.3	64.4 ± 16.7	66.6 ± 9.4

Values are mean ± SD (mL).
There were no significant differences within or among the groups.

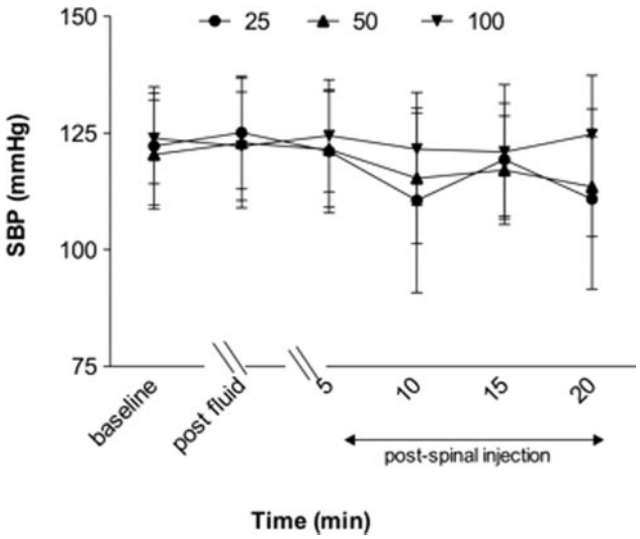

Figure 4. Systolic blood pressure (SBP) versus time (data are mean ± SD). Main effects after intrathecal injection: effect of phenylephrine dosing group ($P = 0.04$), concentration dependency (trend, $P = 0.01$). Effect of time ($P = 0.002$; trend, $P = 0.005$). Interaction of group × time ($P = 0.03$).

Table 5. Operative and Fetal Data

	Group 25	Group 50	Group 100
Spinal injection to skin incision interval (min)	33.9 ± 4.4	34.0 ± 5.5	33.3 ± 3.9
Spinal injection to delivery interval (min)	43.3 ± 7.8	41.7 ± 7.6	42.6 ± 7.6
Skin incision to delivery interval (min)	9.4 ± 5.6	7.7 ± 4.5	9.3 ± 4.9
UA pH	7.31 ± 0.03	7.31 ± 0.04	7.30 ± 0.03
UA BE (mEq/L)	−0.9 ± 1.6	−1.2 ± 1.5	−1.2 ± 1.5
UV pH	7.36 ± 0.02	7.35 ± 0.03	7.35 ± 0.03
UV BE (mEq/L)	−1.2 ± 1.6	−1.7 ± 1.1	−1.5 ± 1.3

Values are mean ± SD.
UA = umbilical artery; BE = base excess; UV = umbilical vein.
No significant differences among groups.

recorded below baseline was significantly lower in group 100 (linear trend; $P = 0.02$.)

There were significant concentration-dependent effects on the duration of the infusion, infusion dose, and total dose received (linear trend; $P < 0.05$). The lower the concentration of phenylephrine, the longer the infusion time, but with lower total dose (Table 3). There was no difference in the median number of interventions (i.e., stopping/starting the infusion) while receiving the phenylephrine infusion among groups. The median number of phenylephrine and ephedrine boluses required per patient was not significantly different among the groups. Fewer boluses of phenylephrine were administered as the phenylephrine infusion concentration increased (trend analysis for proportions, $P = 0.01$). There were no differences among groups in the number of patients requiring ephedrine boluses. Fewer patients received phenylephrine or ephedrine boluses (some patients received both) as the phenylephrine infusion concentration increased (trend analysis for proportions, $P < 0.02$).

All patients received a pretest 500-mL crystalloid preload after the baseline readings. Preload was associated with increases in SV and CO ($P < 0.001$) and a small reduction in HR ($P = 0.02$).

Before the start of surgery, all patients achieved a bilateral sensory anesthesia level to touch ranging from T5 to T2. Six patients needed supplementation with 0.5% wt/vol levobupivacaine (3 patients in group 25, 2 in group 50, and 1 in group 100). Six patients in group 25 (2 mild, 3 moderate, 1 severe), 1 patient in group 50 (mild), and no patients in group 100 had symptoms of nausea and vomiting ($P = 0.01$).

Obstetric data, including interval from spinal anesthesia to skin incision and delivery, as well as interval from skin incision to delivery, are shown in Table 5. There were no significant differences among groups. There were also no

significant differences in Apgar scores or neonatal cord gas values (Table 5).

DISCUSSION

The significantly larger dose of phenylephrine received by group 100 had a marked effect on maternal HR and CO. Maternal HR was decreased steadily with time in all groups, and at all times HR was slower in group 100, and this dose-dependent effect was significantly different 20 minutes after spinal anesthesia. The decrease in HR had a profound effect on maternal CO. SV remained stable, therefore we can attribute the changes that occurred in CO solely to a decrease in HR. Initiation of a phenylephrine infusion is usually associated with an increase in SVR, a consequent reduction in SV, and a baroreceptor-mediated bradycardia.[18] We did not commence Doppler recordings until 5 minutes after induction of spinal anesthesia, which may account for the fact that we did not see an initial decrease in SV values.

Previous work has also demonstrated a reduction in CO associated with phenylephrine infusions.[18,19] Work done by Langesaeter et al.[19] led to questioning the routine clinical practice of maintaining SBP at baseline with such high concentrations of phenylephrine, at the expense of a negative effect on maternal CO. Using the minimally invasive lithium dilution technique (LiDCO™ Plus; LiDCO Ltd., Lake Villa, IL), the investigators demonstrated that even a low-dose phenylephrine infusion (0.25 μg/kg/min [equivalent to 16 μg/min in a woman weighing 65 kg]) resulted in significantly lower HR and CO compared with a group receiving a placebo infusion.

Although the LiDCO Plus technique allows continuous measurement of CO, it can only be described as a minimally invasive technique because it requires arterial line placement. The technique has been recently criticized as a tool for assessing CO during periods of hemodynamic instability[20]; errors >33% were noted during cardiac surgery. In our study, we used a suprasternal Doppler technique that measures flow across the aortic arch to estimate serial changes in maternal CO. The advantage of this technique over the LiDCO Plus technique is that it is truly noninvasive, making it ideal in both the elective and emergency setting. It is a well-validated technique[15] and has been used in the pregnant and nonpregnant populations.[16,17] However, its main drawbacks are that it is an intermittent technique, it does not allow for continuous monitoring, and it does require some training in its use to achieve reproducibility. It gives a calculation of CO taken from across the descending part of the aortic arch, distal to the common carotid and subclavian arteries; therefore, it typically underestimates CO by approximately 10%. However, in our study, it was not actual values of CO that we were interested in, but the trend in each patient that was important.

Dyer et al.[21] studied hemodynamic changes associated with spinal anesthesia for cesarean delivery in severe preeclampsia using the LiDCO Plus and pulse wave form analysis. They found that the administration of small boluses of phenylephrine in response to a 20% decrease in mean arterial blood pressure restored SVR to levels close to baseline. This was associated with a trend toward a reduction in CO. The investigators suggested that further work was required to establish whether a mixed acting vasopressor with α and β agonist activity could have advantages for the mother with severe preeclampsia and her fetus.[21] In a more recent study, the same group compared the hemodynamic effects of bolus ephedrine and phenylephrine administered in response to a 20% decrease in mean arterial blood pressure. Bolus phenylephrine was found to reduce maternal CO, and CO changes correlated strongly with HR changes. It was concluded that a low bolus dose of phenylephrine is the most appropriate intervention in most cases to restore SVR and CO, and that HR is the best surrogate marker for CO.[18] Their findings support our view, based on the present study, that continuous infusions of phenylephrine sufficient to cause sinus bradycardia should be avoided.

This prospective, double-blind, randomized, controlled trial demonstrated that all 3 infusion regimens of phenylephrine maintained the maternal SBP equally. However, to achieve this control, those who received 100 μg/min, despite receiving a significantly shorter mean infusion time, received a significantly higher total dose of phenylephrine (twice that received by patients who received 50 μg/min and nearly 3 times that received by parturients who received 25 μg/min). Although there was a small and statistically significant 6% increase of SBP in the high-dose compared with the low-dose phenylephrine group, control in the 3 groups was deemed equivalent, as defined for usual clinical purposes. There was, however, a greater degree of variability in SBP measurements in the low-dose group, and this variability was reduced with higher doses of phenylephrine. Although the higher SBP observed in the high-dose group may have contributed to the lower incidence of nausea and vomiting, it is possible that the greater variability in SBP control in the low-dose group was the more important factor. This would support work done by Ngan Kee et al.,[22] which showed an improvement in the incidence of nausea and vomiting in a group of parturients whose SBP was controlled to 100% of baseline with a phenylephrine infusion, compared with groups controlled to 80% and 90% of baseline.

There is strong evidence to suggest that CO, specifically the maximum change in CO, correlates more closely with uteroplacental blood flow than upper arm blood pressure measurement.[23] Uterine blood flow increases throughout pregnancy, reaching 800 mL/min at term (10%–15% of the maternal CO). Uterine blood flow, and therefore oxygen delivery to the fetus, is dependent on the maternal CO. The fetus has no storage capacity for oxygen and is vulnerable if placental oxygen delivery should fail. The well-being of the fetus requires that maternal CO, uterine blood flow, and maternal Pao_2 are maintained at or above normal values for pregnancy.[24]

We did not see any adverse effects on the fetus in our study as indicated by Apgar scores and umbilical arterial and venous gases. However, this degree of decrease in CO may have a detrimental effect on the fetus in the emergency situation in which fetal acidosis might already be present. Under these circumstances, we should be doing all we can to improve oxygen delivery to the fetus by maintaining

maternal CO and blood pressure as near to normal as possible. Our study has demonstrated that a decrease in the maternal HR, with phenylephrine use, is associated with a similar decrease in maternal CO. Therefore, if high doses of phenylephrine are required to maintain the maternal SBP, and a decrease in HR is observed, the anesthesiologist should be alerted that the maternal CO is compromised and initiate prompt and aggressive treatment of the slow HR, either by stopping the phenylephrine infusion if SBP is satisfactory or by using a chronotropic drug.

Theoretically, treatment of decreasing HR should minimize the risk of a sustained decrease in maternal CO and optimize oxygen delivery to the fetus. However, no studies examining the effects of phenylephrine on maternal CO and/or umbilical cord gases have evaluated the effects on uteroplacental blood flow or oxygen delivery to the fetus. We suggest that further work in this area should incorporate Doppler measurements of umbilical blood flow. An additional limitation of our study design is that we did not include a control group. It was thought at the time that we could not have a group that received an infusion containing no phenylephrine because it is well recognized that a sustained decrease in maternal SBP is associated with nausea and vomiting in the mother and acidosis in the fetus. However, we could have included a bolus-only group and compared this with the other 3 infusion groups.

In summary, good SBP control using phenylephrine during elective cesarean delivery can mask significant underlying maternal hemodynamic effects that are not obvious to the anesthesiologist using routine monitoring. The dose-dependent decrease in HR associated with a continuous infusion of phenylephrine during spinal anesthesia for cesarean delivery is associated with a similar reduction in maternal CO. Infusion rates of phenylephrine insufficient to cause a sinus bradycardia should be used to maintain maternal CO and therefore oxygen delivery to the fetus.

AUTHOR AFFILIATIONS

From the *Department of Anesthesia, University College London Hospitals NHS Foundation Trust, London; †Department of Anesthesia, Guy's and St. Thomas' NHS Foundation Trust, London; ‡Department of Anesthesia, Royal Infirmary of Edinburgh, Edinburgh; §Department of Anesthesia, Royal Free Hampstead NHS Trust, London; and ‖Department of Anesthesia, University Hospital of South Manchester NHS Foundation Trust, Wythenshawe, Manchester, United Kingdom.

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