A Random-allocation Graded Dose–Response Study of Norepinephrine and Phenylephrine for Treating Hypotension during Spinal Anesthesia for Cesarean Delivery

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ABSTRACT

Background: Norepinephrine has been investigated as a potential alterative to phenylephrine for maintaining blood pressure during spinal anesthesia for cesarean delivery with the advantage of less depression of maternal heart rate and cardiac output. However, the relative potencies of these two vasopressors have not been fully determined in this context.

Methods: In a random-allocation, graded dose–response study, 180 healthy patients undergoing spinal anesthesia for elective cesarean delivery received a single bolus of norepinephrine in one of six different doses ranging from 4 to 12 μg or phenylephrine in one of six different doses ranging from 60 to 200 μg to treat the first episode of hypotension. The magnitude of response was measured as the percentage of full restoration of systolic blood pressure to the baseline value. Dose–response analysis was performed using nonlinear regression to derive four-parameter logistic dose–response curves, which were compared to determine relative potency.

Results: Data were analyzed for 180 patients. The estimated ED_{50} values (dose giving a 50% response) were norepinephrine 10 μg (95% CI, 6 to 17 μg) and phenylephrine 137 μg (95% CI, 79 to 236 μg). The estimated relative potency ratio for the two drugs was 13.1 μg (95% CI, 10.4 to 15.8 μg).

Conclusions: Comparative dose–response analysis was completed for norepinephrine and phenylephrine given as a bolus to treat the first episode of hypotension in patients undergoing spinal anesthesia for cesarean delivery. The estimated dose equivalent to phenylephrine 100 μg was norepinephrine 8 μg (95% CI, 6 to 10 μg). These results may be useful to inform the design of future comparative studies. **(Anesthesiology 2017; 127:934-41)**

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CURRENTLY phenylephrine is established as a preferred first-line vasopressor for maintaining blood pressure (BP) during spinal anesthesia for cesarean delivery.[1] However, because phenylephrine at usual clinical doses is a pure vasoconstrictor, its use is often associated with a reflex decrease in heart rate (HR) and an associated decrease in cardiac output (CO).[2] As a result, this has encouraged the investigation of alternative agents such as dilute norepinephrine.[3–5] Norepinephrine is similar to phenylephrine in being a potent α-adrenergic agonist, but in addition norepinephrine also possesses weak β-adrenergic agonist activity. The latter counteracts the reflex slowing of HR, which potentially may result in a more stable hemodynamic profile when norepinephrine is used to maintain BP during neuraxial anesthesia.

To determine the possible utility of norepinephrine as a suitable vasopressor in obstetric patients, comparison with the current standard, phenylephrine, is appropriate. Although a number of such comparisons have been published recently, the relative doses of norepinephrine and phenylephrine have varied.[3–5] To facilitate accurate comparison and also to guide clinical administration, determination of the relative potencies of norepinephrine and phenylephrine in obstetric patients is required. Therefore, the author performed a random-allocation, graded dose–response study of norepinephrine and phenylephrine. The aim of the study was to determine the relative potencies of these drugs when

What We Already Know about This Topic

- Norepinephrine is suggested as an alternative to phenylephrine for maintaining blood pressure during spinal anesthesia for cesarean delivery
- Although a recent dose-finding study reported 6 μg norepinephrine bolus injection effective for the purpose, the relative potencies of these two vasopressors have not been fully determined

What This Article Tells Us That Is New

- In this random-allocation, graded dose–response study, the relative potencies of the vasopressors were assessed by the proportion of full restoration of systolic blood pressure to the baseline in response to a bolus injection of one of six different doses of the vasopressors in 180 healthy patients undergoing spinal anesthesia for elective cesarean delivery
- The estimated dose equivalent to phenylephrine 100 μg was norepinephrine 7.6 μg (95% CI, 6.3 to 9.6 μg)

This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast.

Submitted for publication March 9, 2017. Accepted for publication August 10, 2017. From the Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China.

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<zdoi;10.1097/ALN.0000000000001880>

given as a bolus to treat hypotension during spinal anesthesia for cesarean delivery.

Materials and Methods

This randomized, double-blinded study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Shatin, Hong Kong, China) and was registered in the Chinese Clinical Trial Registry (registration No. ChiCTR-TRC-14005206). All of the patients gave written informed consent to participate. The study was conducted in the operating rooms in the labor ward of a university-affiliated teaching hospital.

Patients scheduled for routine elective cesarean delivery under spinal anesthesia were enrolled. Inclusion criteria were nonlaboring, normotensive parturients with term singleton pregnancy with baseline systolic BP within the range 90 to 140 mmHg. Exclusion criteria were American Society of Anesthesiologists physical status of 3 or higher, known fetal abnormality, preexisting or pregnancy-induced hypertension, known cardiovascular or cerebrovascular disease, thrombocytopenia, coagulopathy, any medical contraindication to spinal anesthesia, known allergy to phenylephrine or norepinephrine, weight less than 50 kg or greater than 100 kg, height less than 140 cm or greater than 180 cm, inability or refusal to give informed consent, and age less than 18 yr.

After routine fasting and antacid premedication, patients were transferred to the operating room and routine monitoring was attached. BP was recorded noninvasively on the right arm using the standard monitor (Infinity C500, Dräger Medical AG & Co., Germany) set to cycle at 1-min intervals. Baseline systolic BP and HR were determined as the mean of three consecutive measurements with a difference of not more than 10%. A wide-bore intravenous catheter (default size 16-gauge) was inserted under local anesthesia in the left forearm or hand. Patients were then turned to the right lateral position and, after skin disinfection and skin infiltration with lidocaine, a 25-gauge Whitacre spinal needle was inserted *via* an introducer at the estimated L3 to 4 or L4 to 5 vertebral interspace. Eleven milligrams hyperbaric bupivacaine 0.5% w/v and 15 μg fentanyl were injected intrathecally, after which the patient was turned to the supine position with left lateral tilt, and rapid intravenous (IV) cohydration up to 2 l was started using Plasma-Lyte-A solution (Baxter Healthcare Corporation, USA) by fully opening the IV fluid-giving set with the bag suspended at a height of approximately 1 m above the midpoint of the operating table. Block height was assessed using ice and was considered adequate if at the T6 dermatome or above. If an adequate block was not achieved, the patient was excluded, and the randomization code was reused for the next eligible enrolled subject.

The noninvasive BP monitor was set to cycle at 1-min intervals starting 1 min after the start of intrathecal injection. *Hypotension* was defined as a decrease in systolic BP to less than 80% of the baseline value. Immediately after the first episode of hypotension, the patient was given the study drug as a rapid IV bolus *via* a three-way stopcock attached directly to the IV catheter, followed immediately by a 1-ml saline flush. If a patient did not have an episode of hypotension before the time of uterine incision, she was excluded from the study, and the randomization code was reused for the next consecutive patient enrolled.

The study drugs were prepared by a research nurse who was not involved with patient management or study data collection. Block randomization was performed in groups of 12 using shuffled, opaque numbered envelopes. Each patient received a single IV bolus of either norepinephrine at a dose of 4, 5, 6, 8, 10, or 12 μg or phenylephrine at a dose of 60, 80, 100, 120, 160, or 200 μg. The doses of phenylephrine were chosen to cover the approximate usual range of doses used clinically, with dose sizes chosen so that their logarithms were approximately evenly spaced, with doses rounded to convenient sizes for ease of preparation. The doses of norepinephrine were chosen to be approximately equivalent to the doses of phenylephrine based on an estimated potency ratio of 16:1 for norepinephrine:phenylephrine; this estimated ratio was our best approximation according to data from a previous study.[3] All of the study drugs were prepared by a research nurse in identical 10-ml syringes that were each labeled *study drug* and were diluted to a total volume of 10 ml with saline. The investigator who administered the study drug was blinded to the group allocation.

After injection of the study drug, the BP monitor cycle was stopped. BP measurement was restarted 60 s after the completion of injection of the study drug. The first BP measurement at that time was recorded and used to derive response data. *Response* was defined according to the following equation:

$$Response = \frac{C - B}{A - B} \times 100\% \quad (1)$$

where A = baseline systolic BP, B = systolic BP at first episode of hypotension, and C = systolic BP of the measurement started 60 s after injection of the study drug. The decision to assess BP response 60 s after vasopressor injection was based on previous work that showed that the peak pressor effect of phenylephrine occurred between 32 and 47 s after central venous injection.[6]

After completion of the response measurement, the study was terminated. An infusion of norepinephrine 6 μg/ml was titrated as required to maintain BP near baseline, and additional management was according to usual clinical practice. The usual assessments of the neonate were performed, including measurement of Apgar scores and umbilical cord blood gases.

Statistical Analysis

Sample size was determined based on the previous recommendation by Tallarida *et al.*,[7] who suggested that, for efficient design of dose–response studies using regression analysis, six doses be administered with a minimum of 10 subjects per

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dose. Based on previously published work,[8] this study empirically increased the sample size to 15 patients per group to achieve more narrow confidence limits of dose estimates.

Univariate data were assessed for normality using the Kolmogorov–Smirnov test and were compared between the patients who received norepinephrine and those who received phenylephrine using Student's *t* test or the Mann–Whitney U test, as appropriate. Categorical data were compared using the chi-square test. These analyses were performed using IBM SPSS Statistics for Windows Version 21 (IBM Corp., USA). Values of $P < 0.05$ were considered significant.

Dose–response data were analyzed with nonlinear regression using GraphPad Prism 5.01 (GraphPad Software Inc., USA), as described previously.[8] Response data were entered as *x* values and were log-transformed. A four-parameter logistic model was fitted to the data sets of the drugs according to the following equation:

$$Y = \frac{100 \times dose^{\gamma}}{dose^{\gamma} + ED_{50}{}^{\gamma}} \quad (2)$$

where Y is the response as a percentage and γ is the Hill coefficient or Hill slope and ED_{50} is the dose giving a 50% response.

The best fit was obtained by using a model in which the bottom (minimum response), top (maximum response), and Hill coefficient were shared between data sets for both drugs. Log-dose–response curves were generated, and values for ED_{50}[9] with 95% CI were derived. The relative potency ratio of the two drugs with 95% CI was derived using the EC_{50} shift equation of GraphPad Prism.[8,10] For reference purposes, values for ED_{90} with 95% CIs for both drugs were also derived by substituting Y = 90% into the regression equations.[8,11]

Results

Data collection was completed between September 2014 and April 2016. Patient recruitment and flow are summarized in figure 1. Of the patients who were eligible for entry into the study and received successful standardized spinal anesthesia, excluding one patient in whom accurate BP measurement was prevented by excessive shivering, 180 (69%) of 259 had at least one episode of hypotension before delivery and were allocated a dose of study drug; characteristics of these patients are shown in table 1. Baseline systolic BP was not different between patients who received norepinephrine (mean = 114 ± 10 mmHg)

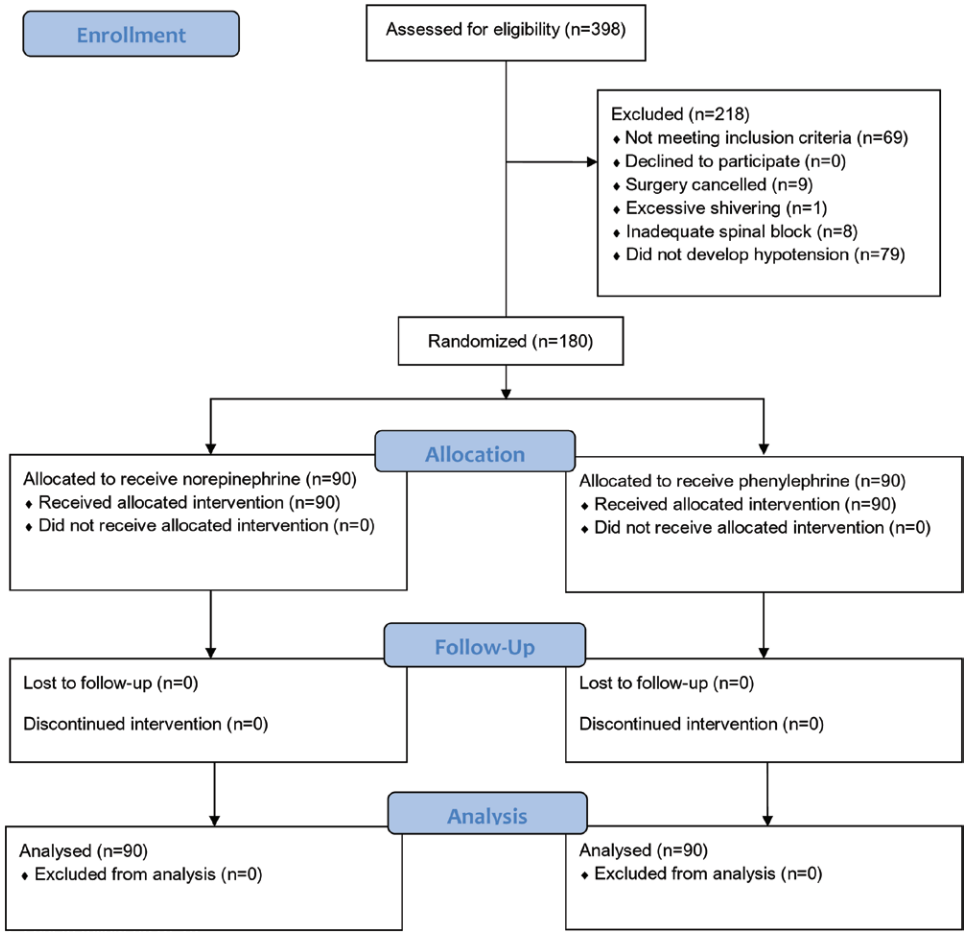

Fig. 1. Consolidated Standards of Reporting Trials flow diagram showing recruitment and flow of patients.

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and patients who received phenylephrine (114 ± 9 mmHg; P = 0.79). The first episode of hypotension occurred at a mean time of 100 ± 39 s in patients who received phenylephrine and 101 ± 32 s in patients who received norepinephrine (P = 0.23). The mean systolic BP at the first episode of hypotension was 83 ± 10 mmHg in patients who received phenylephrine and 83 ± 11 mmHg in patients who received norepinephrine (P = 0.99).

BP changes for each dose subgroup before and after administration of the study vasopressor dose are shown in table 2, A and B. The dose–response curves generated from these data are shown in figure 2. Derived parameters for the models are shown in table 3. The calculated ED_{50} value for norepinephrine was 10 μg (95% CI, 6 to 17 μg) and for phenylephrine was 137 μg (95% CI, 79 to 236 μg). The calculated relative potency ratio for the two drugs was 13.1 (95% CI, 10.4 to 15.8). The calculated ED_{90} values were 18 μg (95% CI, 5 to 63 μg) for norepinephrine and 239 μg (95% CI, 66 to 869 μg) for phenylephrine.

HR changes at the time of the first episode of hypotension and at the time of the first BP measurement after administration of the study vasopressor dose, as well as their differences, are shown in table 4, A and B. Analysis of data pooled for all of the dose categories for each vasopressor showed that the median magnitude of decrease of HR was greater for phenylephrine *versus* norepinephrine (P = 0.036).

Neonatal outcome is summarized in table 5, A and B. For the patients who received phenylephrine, one neonate had a 1-min Apgar score less than 7, no neonate had a 5-min Apgar score less than 8, and five neonates had umbilical arterial cord blood pH lower than 7.2. For the patients who received norepinephrine, no neonate had a 1-min Apgar score less than 7, no neonate had a 5-min Apgar score less than 8, and four neonates had umbilical arterial cord blood pH lower than 7.2.

Table 1. Patient Characteristics

	Patients Who Received Norepinephrine (n = 90)	Patients Who Received Phenylephrine (n = 90)
Age, yr	34 ± 4	33 ± 5
Weight, kg	67 ± 12	67 ± 8
Height, m	1.57 ± 0.13	1.57 ± 0.06
Block height at 5 min, dermatome	T4 (T3 to T5)	T4 (T3 to T5)

Values are mean ± SD or median (interquartile range).

Discussion

In this study, the dose–response relationships for norepinephrine and phenylephrine given as a single IV bolus to treat the first episode of hypotension in patients undergoing spinal anesthesia for elective cesarean delivery were determined. The calculated potency ratio for norepinephrine:phenylephrine was 13.1 (95% CI, 10.4 to 15.8), which suggests that, under the conditions of the study, compared with a typical dose of phenylephrine of 100 μg, the equivalent dose of norepinephrine is 8 μg (95% CI, 6 to 10 μg) in obstetric patients.

Table 2A. Systolic Blood Pressure Changes and Response to Vasopressor Dose: Norepinephrine

	Dose					
Variable	4 μg (n = 15)	5 μg (n = 15)	6 μg (n = 15)	8 μg (n = 15)	10 μg (n = 15)	12 μg (n = 15)
Baseline systolic BP, mmHg	115 ± 30	118 ± 30	116 ± 30	113 ± 30	109 ± 28	116 ± 30
Systolic BP at first episode of hypotension, mmHg	83 ± 22	85 ± 23	82 ± 23	84 ± 24	80 ± 22	85 ± 24
Time after induction of first episode of hypotension, s	96 ± 25	107 ± 38	97 ± 26	97 ± 26	104 ± 35	120 ± 69
Systolic BP after vasopressor dose, mmHg	94 ± 30	91 ± 30	93 ± 31	105 ± 31	104 ± 28	115 ± 35
Response, %	31.7 ± 55.8	19.9 ± 44.5	38.7 ± 51.5	74.2 ± 34.5	86.2 ± 44.6	95.1 ± 69.4

Calculation of response is explained in the text. Values are mean ± SD.
BP = blood pressure.

Table 2B. Systolic Blood Pressure Changes and Response to Vasopressor Dose: Phenylephrine

	Dose					
Variable	60 μg (n = 15)	80 μg (n = 15)	100 μg (n = 15)	120 μg (n = 15)	160 μg (n = 15)	200 μg (n = 15)
Baseline systolic BP, mmHg	111 ± 29	115 ± 29	111 ± 29	116 ± 30	116 ± 32	115 ± 31
Systolic BP at first episode of hypotension, mmHg	81 ± 22	84 ± 22	75 ± 21	84 ± 22	89 ± 25	84 ± 23
Time after induction of first episode of hypotension, s	124 ± 66	109 ± 49	99 ± 27	104 ± 30	103 ± 29	122 ± 62
Systolic BP after vasopressor dose, mmHg	97 ± 27	95 ± 27	94 ± 29	105 ± 35	117 ± 34	122 ± 35
Response, %	54.7 ± 61.3	40.4 ± 46.9	48.7 ± 31.0	74.0 ± 59.1	107.8 ± 58.5	127.4 ± 55.0

Calculation of response is explained in the text. Values are mean ± SD.
BP = blood pressure.

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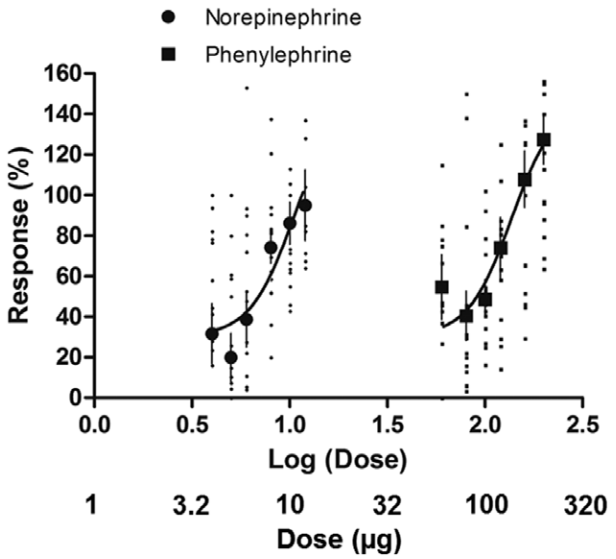

Fig. 2. Four-parameter logistic sigmoidal dose–response curves for norepinephrine and phenylephrine generated by nonlinear regression. Response is shown as the percentage of full restoration of systolic blood pressure to the baseline value. Data points for all patients are shown with mean and SD superimposed. The *horizontal axis* is on a logarithmic scale. Antilog values for dose are shown below log(dose) values to aid interpretation.

Table 3. Calculated Parameters Derived by Fitting Four-Parameter Logistic Sigmoidal Dose–Response Curves to Data Sets for Norepinephrine and Phenylephrine Using Nonlinear Regression

Parameter	Norepinephrine	Phenylephrine
$Log(ED_{50})$	1.02 (95% CI, 0.81–1.23)	2.14 (95% CI, 1.90–2.37)*
ED_{50}, mg	10 (95% CI, 6–17)	137 (95% CI, 79–236)*
Hill coefficient	3.93 (95% CI, –1.79 to 9.6)	3.93 (95% CI, –1.79 to 9.6)
R^2	0.23	0.27
$Log(ED_{90})$	1.26 (95% CI, 0.72–1.80)	2.38 (95% CI, 1.82–2.94)*
ED_{90}, mg	18 (95% CI, 5–63)	239 (95% CI, 66–869)*

The estimated values for ED_{90} were above the range of doses tested so should be viewed as approximations only.

*Significant difference between groups, $P < 0.0001$.

In this study, nonlinear regression was used to determine values for ED_{50} and ED_{90}. With this type of analysis, these values represent the doses that result in responses of 50% and 90% magnitude, respectively. This should not be confused with the use of the same terms in more traditional quantal dose–response methodology. In the latter, the term ED_x refers to the dose that results in a predefined response in X% of patients. To differentiate between these different interpretations, it been suggested that, when describing the dose associated with magnitude of response, the term *Dx* can be used as an alternative.[9]

A number of recent studies have compared the use of norepinephrine and phenylephrine in patients undergoing spinal anesthesia for cesarean delivery, but these studies have used a range of different relative concentrations or doses. The author's group previously described infusions of norepinephrine 5 μg/ml *versus* phenylephrine 100 μg/ml administered by closed-loop feedback, computer-controlled infusion.[3] In that study, given the lack of suitable comparative dose studies in obstetric patients, the relative doses of the drugs were estimated from a previous study that compared the potency of the two vasopressors for causing vasoconstriction in the human saphenous vein and suggested an approximate potency ratio of 20:1.[12] However, in the previous study, the average rate of administration and total volume of vasopressor given were greater for the norepinephrine group compared with the phenylephrine group. This suggests that the true potency ratio of the drugs is likely to be less than 20:1. The results of the current study are consistent with this observation.

Recently Vallejo *et al.*[5] compared fixed-rate infusions of norepinephrine 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with phenylephrine 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is equivalent to a dosing ratio of 1:2. However, in an accompanying editorial, Smiley[13] commented that the solutions compared in that study were almost certainly not equipotent. Onwochei *et al.*[4] performed a dose-finding study of intermittent boluses of norepinephrine for preventing hypotension during spinal anesthesia for cesarean delivery. They calculated that the ED_{90} of norepinephrine in the context of their study was 5.80 μg (95% CI, 5.01 to 6.59 μg); for practical usage they recommended use of a dose of 6 μg. Consistent with this, the author of the current study used norepinephrine at a concentration of 6 μg/ml in obstetric patients in routine clinical practice, having previously used phenylephrine 100 μg/ml.[14] The value of norepinephrine 6 μg falls within the 95% confidence limits of the estimated equivalent to phenylephrine 100 μg calculated in the current study.

Norepinephrine is a relatively new drug in the context of obstetric anesthesia. In the author's opinion, the lower propensity of norepinephrine to cause maternal bradycardia compared with phenylephrine is a potential advantage.[3,15] Although ephedrine also possesses combined α- and β-adrenergic agonist properties, use of this vasopressor in obstetric anesthesia has declined in recent times because it has the disadvantages of a slow onset and prolonged duration of action and a propensity to cross the placenta and depress fetal pH *via* presumed stimulation of fetal metabolism.[16] Although no study to date has assessed placental transfer of norepinephrine, the absence of any observable detrimental effect on fetal acid-base status argues for a lack of an adverse effect on fetal metabolism and suggests that norepinephrine should be preferred to ephedrine in obstetric patients.[3] To date there is no evidence that the use of norepinephrine is associated with any difference in neonatal outcome compared with phenylephrine. Although a decrease in HR caused by phenylephrine may be associated with a decrease in maternal CO,[2] there is insufficient evidence

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Table 4A. Heart Rate before and after Vasopressor Dose: Norepinephrine

Heart Rate	Dose					
	4 μg (n = 15)	5 μg (n = 15)	6 μg (n = 15)	8 μg (n = 15)	10 μg (n = 15)	12 μg (n = 15)
Heart rate at time of first episode of hypotension, beats/min	94 (87–106)	88 (84–104)	97 (73–115)	92 (80–100)	86 (80–104)	94 (82–114)
Heart rate at time of first BP measurement after study vasopressor dose, beats/min	83 (79–95)	82 (73–93)	86 (64–107)	81 (67–90)	73 (69–85)	74 (70–84)
Heart rate difference, beats/min	–6 (14 to –4)	–7 (–11 to –3)	–10 (–17 to –2)	–14 (–18 to –3)	–14 (–20 to –2)	–18 (–37 to –10)

Values are median (interquartile range).
BP = blood pressure.

Table 4B. Heart Rate before and after Vasopressor Dose: Phenylephrine

Heart Rate	Dose					
	60 μg (n = 15)	80 μg (n = 15)	100 μg (n = 15)	120 μg (n = 15)	160 μg (n = 15)	200 μg (n = 15)
Heart rate at time of first episode of hypotension, beats/min	95 (84–107)	93 (79–99)	93 (79–99)	96 (93–101)	94 (84–108)	95 (83–113)
Heart rate at time of first BP measurement after study vasopressor dose, beats/min	80 (78–89)	78 (71–95)	75 (72–78)	82 (73–87)	70 (66–76)	72 (61–74)
Heart rate difference, beats/min	–8 (–25 to –2)	–7 (–15 to –6)	–17 (–25 to –3)	–18 (–25 to –9)	–21 (–34 to –13)	–28 (–36 to –20)

Values are median (interquartile range).
BP = blood pressure.

to determine whether this has potential to be detrimental to the fetus. Current available data are limited to use in low-risk elective cases. No data are available for nonelective cases where it is possible that changes in CO and possible effects on uteroplacental blood flow could have more significance. Additional research in this area would be of interest.

There may be concern about the administration of norepinephrine *via* peripheral veins.[13,17] However, when dilute solutions of norepinephrine are used that are equivalent in vasoconstrictor potency to phenylephrine in commonly used concentrations, the risks of the drugs should be the same. Therefore, considerations for the peripheral administration of norepinephrine should be the same as those for the peripheral administration of phenylephrine; the latter currently is widely used in clinical practice.

This study has a number of limitations. The dose–response analysis was based on the treatment of the first episode of hypotension after induction of spinal anesthesia; responses might be different for treatment of subsequent episodes of hypotension. Furthermore, it is unknown whether it is valid to extrapolate the potency calculation to the use of the vasopressors by infusions. In addition, patients included in the study were all elective cases; the findings may not be applicable to laboring patients in whom the vasopressor requirement is lower.[18]

In conclusion, the relative potency for norepinephrine: phenylephrine when given as a bolus for restoring BP in hypotensive obstetric patients undergoing spinal anesthesia was estimated to be 13.1:1.0. This information may inform the design of other comparative studies of norepinephrine *versus* phenylephrine in obstetric patients and may also be useful as a clinical guide for anesthesiologists who may wish to use norepinephrine but are more familiar with dosing regimens for phenylephrine.

Acknowledgments

The author thanks Floria F. Ng, R.N., B.A.Sc., research nurse, Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong (Shatin, Hong Kong, China), for her assistance with recruiting patients and preparing study drugs.

Research Support

Supported by the Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong (Shatin, Hong Kong, China).

Competing Interests

The author declares no competing interests.

Reproducible Science

Full protocol available at: wngankee@gmail.com. Raw data available at: wngankee@gmail.com.

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Table 5A. Neonatal Outcome: Norepinephrine

	Dose					
Outcome	4 μg	5 μg	6 μg	8 μg	10 μg	12 μg
Birth weight, kg	3.23 ± 0.31	3.05 ± 0.43	3.43 ± 0.42	3.33 ± 0.32	3.07 ± 0.44	3.54 ± 1.16
Apgar score at 1 min	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)
Apgar score at 5 min	10 (10–10)	10 (10–10)	10.0 (10.0–9.5)	10 (10–10)	10 (10–10)	10 (10–10)
Umbilical arterial blood gases						
pH	7.30 ± 0.04	7.28 ± 0.03	7.31 ± 0.02	7.28 ± 0.05	7.26 ± 0.06	7.32 ± 0.06
P_{CO_2}, mmHg	48.3 ± 7.4	49.5 ± 6.7	47.6 ± 6.5	46.8 ± 9.0	50.1 ± 7.5	43.4 ± 6.2
P_{O_2}, mmHg	14.5 ± 4.2	13.5 ± 4.2	16.8 ± 4.5	14.4 ± 2.5	13.3 ± 3.4	19.1 ± 6.4
Base excess, mM	–3.6 ± 2.0	–4.1 ± 2.6	–3.3 ± 2.5	–5.6 ± 3.6	–5.3 ± 2.8	–4.1 ± 3.3
Umbilical venous blood gases						
pH	7.35 ± 0.03	7.34 ± 0.04	7.35 ± 0.03	7.34 ± 0.06	7.32 ± 0.05	7.35 ± 0.03
P_{CO_2}, mmHg	38.6 ± 5.2	39.0 ± 7.5	38.5 ± 5.7	39.9 ± 7.1	41.0 ± 8.8	40.6 ± 6.5
P_{O_2}, mmHg	25.5 ± 3.6	25.4 ± 6.1	26.0 ± 5.4	26.3 ± 4.7	24.8 ± 5.7	24.7 ± 6.8
Base excess, mM	–4.2 ± 1.7	–4.5 ± 2.5	–4.2 ± 2.7	–4.6 ± 2.9	–5.1 ± 3.1	–3.3 ± 2.9

Values are mean ± SD or median (interquartile range). Umbilical cord blood gas results were incomplete for four patients who received norepinephrine. For 12 patients who received norepinephrine, values for P_{O_2} were below the lower limit of detection of the blood gas analyzer; for these results the data values were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$.

Table 5B. Neonatal Outcome: Phenylephrine

	Dose					
Outcome	4 μg	5 μg	6 μg	8 μg	10 μg	12 μg
Birth weight, kg	3.26 ± 0.40	3.08 ± 0.27	3.17 ± 0.37	3.12 ± 0.39	3.08 ± 0.37	3.27 ± 0.42
Apgar score at 1 min	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)	9 (9–9)
Apgar score at 5 min	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)
Umbilical arterial blood gases						
pH	7.30 ± 0.06	7.31 ± 0.05	7.27 ± 0.05	7.30 ± 0.09	7.29 ± 0.07	7.29 ± 0.03
P_{CO_2}, mmHg	45.9 ± 9.1	42.5 ± 10.6	48.6 ± 9.6	48.6 ± 13.8	46.6 ± 5.9	45.7 ± 7.1
P_{O_2}, mmHg	14.8 ± 4.4	16.6 ± 5.4	13.1 ± 3.9	14.4 ± 5.0	16.6 ± 4.9	15.0 ± 4.7
Base excess, mM	–4.4 ± 3.3	–5.5 ± 4.1	–5.3 ± 3.5	–3.8 ± 3.2	–5.1 ± 3.7	–4.9 ± 2.5
Umbilical venous blood gases						
pH	7.35 ± 0.05	7.35 ± 0.05	7.33 ± 0.04	7.34 ± 0.09	7.32 ± 0.06	7.35 ± 0.03
P_{CO_2}, mmHg	38.1 ± 3.4	39.3 ± 6.4	40.3 ± 7.9	41.0 ± 12.5	41.4 ± 6.2	38.2 ± 6.1
P_{O_2}, mmHg	25.7 ± 6.5	27.6 ± 5.9	24.5 ± 5.8	24.6 ± 5.9	24.3 ± 5.7	27.0 ± 3.9
Base excess, mM	–4.3 ± 2.8	–3.9 ± 1.9	–4.6 ± 3.8	–4.2 ± 2.3	–4.8 ± 2.5	–4.3 ± 2.9

Values are mean ± SD or median (interquartile range). Umbilical cord blood gas results were incomplete for three patients who received phenylephrine. For six patients who received phenylephrine, values for P_{O_2} were below the lower limit of detection of the blood gas analyzer; for these results the data values were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$.

References

1. Ngan Kee WD, Khaw KS: Vasopressors in obstetrics: What should we be using? Curr Opin Anaesthesiol 2006; 19:238–43
2. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M: The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010; 111:1230–7
3. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS: Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology 2015; 122:736–45
4. Onwochei DN, Ngan Kee WD, Fung L, Downey K, Ye XY, Carvalho JCA: Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: A Sequential allocation dose-finding study. Anesth Analg 2017; 125:212–8
5. Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, Shapiro RE, Ranganathan P: An open-label randomized controlled clinical trial for comparison of continuous phenylephrine *versus* norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. Int J Obstet Anesth 2017; 29:18–25
6. Goertz AW, Seeling W, Heinrich H, Lindner KH, Rockemann MG, Georgieff M: Effect of phenylephrine bolus administration on left ventricular function during high thoracic and lumbar epidural anesthesia combined with general anesthesia. Anesth Analg 1993; 76:541–5
7. Tallarida RJ, Stone DJ Jr, Raffa RB: Efficient designs for studying synergistic drug combinations. Life Sci 1997; 61:PL 417–25
8. Ngan Kee WD, Ng FF, Khaw KS, Lee A, Gin T: Determination and comparison of graded dose-response curves for epidural bupivacaine and ropivacaine for analgesia in laboring nulliparous women. Anesthesiology 2010; 113:445–53
9. Tallarida RJ: Drug Synergism and Dose-Effect Data Analysis. Boca Raton, Chapman & Hall/CRC, 2000, pp. 21–39

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10. GraphPad Software. Frequently Asked Questions. Available at: http://www.graphpad.com/support/faqid/901/. Accessed May 19, 2017
11. Motulsky HJ, Christopoulos A: Fitting Models to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting. San Diego, GraphPad Software Inc, 2003, pp. 256–65
12. Sjöberg T, Norgren L, Andersson KE, Steen S: Comparative effects of the alpha-adrenoceptor agonists noradrenaline, phenylephrine and clonidine in the human saphenous vein *in vivo* and *in vitro*. Acta Physiol Scand 1989; 136:463–71
13. Smiley RM: More perfect? Int J Obstet Anesth 2017; 29:1–4
14. Ngan Kee WD: Norepinephrine for maintaining blood pressure during spinal anaesthesia for caesarean section: A 12-month review of individual use. Int J Obstet Anesth 2017; 30:73–4
15. Ngan Kee WD: The use of vasopressors during spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol 2017; 30:319–25
16. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK: Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. ANESTHESIOLOGY 2009; 111:506–12
17. Carvalho B, Dyer RA: Norepinephrine for spinal hypotension during cesarean delivery: Another paradigm shift? ANESTHESIOLOGY 2015; 122:728–30
18. Ngan Kee WD, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL: Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section. Anaesthesia 2008; 63:1319–26

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Brown Describes Bolivian Coca-Leaf Chewing: A Remedy Gathered *versus* Altitude and Attitude?

In 1876 author Robert Brown, Ph.D., began publishing his book series, *The Countries of the World: Being a Popular Description of the Various Continents, Islands, Rivers, Seas, and Peoples of the Globe*. In the third volume, he depicted the coca shrub, the pesticide-like cocaine of which wards off insects. However, the stimulant properties of the cocaine alkaloid led to what Brown captioned as "Gathering the Coca Plant (*Erythroxylon coca*) in Bolivia" (*above*). As landlocked descendants of the Incans, many indigenous Bolivians kept laboring on the steep Andes or on the highland plateau by carrying a "little leathern bag of the dried [coca] leaves, and a gourd of powdered [quick]lime." According to Brown, the coca leaves were "chewed four times a day, mixed, either with the powdered lime, or with the ashes of Cecropia, or quinoa." Cheekfuls of coca leaves provided trace amounts of cocaine, which were prized as an appetite-suppressing and energizing remedy against the attitudinal lows (fatigue) and perhaps the altitudinal heights. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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