BJA

British Journal of Anaesthesia, 125 (4): 588–595 (2020)

doi: 10.1016/j.bja.2020.05.057
Advance Access Publication Date: 15 July 2020
Obstetric Anaesthesia

Norepinephrine or phenylephrine during spinal anaesthesia for Caesarean delivery: a randomised double-blind pragmatic non-inferiority study of neonatal outcome

Warwick D. Ngan Kee[1,2,*], Shara W. Y. Lee[3], Floria F. Ng[1] and Anna Lee[1]

[1]Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China, [2]Department of Anesthesiology, Sidra Medicine, Doha, Qatar and [3]Department of Health Technology & Informatics, Hong Kong Polytechnic University, Kowloon, Hong Kong, China

*Corresponding author. E-mail: wngankee@gmail.com

Previously presented in part as a free paper at Obstetric Anaesthesia 2019, Newcastle, UK, May 23, 2019, with preliminary results published as an abstract in: Ngan Kee WD, Ng FF, Lee SWY, Lee A. Norepinephrine versus phenylephrine during spinal anaesthesia for Caesarean delivery: a randomised double-blinded pragmatic non-inferiority study comparing neonatal outcome. *Int J Obstet Anaesth* 2019; 39 (S1): S7.

Abstract

Background: Norepinephrine is an effective vasopressor during spinal anaesthesia for Caesarean delivery. However, before it can be fully recommended, possible adverse effects on neonatal outcome should be excluded. We aimed to test the hypothesis that umbilical arterial cord pH is at least as good (non-inferior) when norepinephrine is used compared with phenylephrine for treatment of hypotension.

Methods: We enrolled 668 subjects having elective and non-elective Caesarean delivery under spinal or combined spinal–epidural anaesthesia in this randomised, double-blind, two-arm parallel, non-inferiority clinical trial. Arterial blood pressure was maintained using norepinephrine 6 $\mu g\ ml^{-1}$ or phenylephrine 100 $\mu g\ ml^{-1}$ according to the practice of the anaesthetist, either prophylactically or therapeutically, as an infusion or bolus. The primary outcome was umbilical arterial pH with a chosen non-inferiority margin of 0.01 units.

Results: Of 664 subjects (531 elective and 133 non-elective) who completed the study, umbilical arterial cord blood was analysed for 351 samples from 332 subjects in the norepinephrine group and 343 samples from 332 subjects in the phenylephrine group. Umbilical arterial pH was non-inferior in the norepinephrine group (mean, 7.289; 95% confidence interval [CI], 7.284–7.294) compared with the phenylephrine group (mean, 7.287; 95% CI, 7.281–7.292) (mean difference between groups, 0.002; 95% CI, −0.005 to 0.009; P=0.017). Subgroup analysis confirmed the non-inferiority of norepinephrine for elective cases but was inconclusive for non-elective cases.

Conclusions: Norepinephrine was non-inferior to phenylephrine for neonatal outcome assessed by umbilical arterial pH. These results provide high-quality evidence supporting the fetal safety of norepinephrine in obstetric anaesthesia.

Clinical trial registration: ChiCTR-IPR-15006235.

Keywords: Caesarean delivery; hypotension; norepinephrine; obstetric anaesthesia; phenylephrine; spinal anaesthesia

Received: 19 February 2020; **Accepted:** 20 May 2020

Editor's key points

- Although norepinephrine has been suggested as a vasopressor during spinal anaesthesia for Caesarean delivery, it cannot be fully recommended until possible adverse effects on neonatal outcome are excluded.
- In a randomised, double-blind, two-arm parallel, non-inferiority trial, the effect on umbilical arterial cord pH of norepinephrine or phenylephrine for treatment of hypotension was compared.
- Umbilical arterial pH was non-inferior in the norepinephrine group compared with the phenylephrine group.

Norepinephrine has been investigated recently as a vasopressor for maintaining arterial BP during spinal anaesthesia for Caesarean delivery.[1–7] Like phenylephrine, norepinephrine is a potent alpha-adrenergic receptor agonist with similar vasoconstrictor efficacy. However, in contrast to phenylephrine, norepinephrine also has weak beta-adrenergic receptor agonist activity that counteracts the baroreflexive decreases in HR and cardiac output that commonly occur during unopposed stimulation of vascular alpha-adrenergic receptors. Consequently, greater maternal haemodynamic stability could result with use of norepinephrine compared with phenylephrine.[4,7] Accordingly, it has been suggested that norepinephrine is the superior vasopressor for use in obstetric spinal anaesthesia.[4,7] However, before norepinephrine can be fully recommended for general clinical use, it is important to exclude adverse effects on neonatal outcome. Analysis of umbilical arterial (UA) pH is commonly used as an objective measure of the latter.[8] We considered that absence of a significant depressive effect on UA pH would be evidence for the fetal safety of norepinephrine used as a vasopressor during obstetric anaesthesia.

The objective of this randomised, double-blinded, two-arm parallel, non-inferiority study was to test the hypothesis that neonatal outcome, as assessed by UA pH, is at least as good (non-inferior) when norepinephrine is used to maintain BP during spinal or combined spinal–epidural (CSE) anaesthesia for Caesarean delivery compared with the current standard, phenylephrine. We adopted a pragmatic study design[9] in order to increase the applicability of results to normal clinical practice and to increase the generalisability of the results. UA base excess (BE) was compared between groups as a secondary outcome.

Methods

Approval was obtained in February 2015 from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and the protocol was registered in April 2015 in the Chinese Clinical Trial Registry (registration no. ChiCTR-IPR-15006235). A Certificate for Clinical Trial/Medicinal Test was obtained in June 2015 from the Department of Health of the Government of the Hong Kong Special Administrative Region, Hong Kong, China.

We enrolled 668 subjects who were scheduled for elective or non-elective Caesarean delivery under spinal or CSE anaesthesia during normal working hours at the Prince of Wales Hospital, Shatin, Hong Kong, China between November 2015 and December 2016. Exclusion criteria were inability or refusal to give informed consent, age <18 yr, allergy to phenylephrine or norepinephrine, known fetal abnormality, mesenteric or peripheral vascular thrombosis, renal impairment, and current usage of monoamine oxidase inhibitors or tricyclic antidepressants. Informed consent was obtained from all subjects. For elective cases and other cases transferred from the antenatal ward, consent was obtained in the ward before transfer to the operating theatre. For non-elective cases transferred from the birthing area, consent was obtained in a two-stage process in which patients considered to have a likelihood of requiring Caesarean delivery were initially approached, given explanation of the study and asked to give preliminary verbal consent to participate. Subsequently, if they proceeded to Caesarean delivery, agreement to participate was confirmed and signed consent was obtained at the time of consent for anaesthesia.

Subjects were randomly assigned in a 1:1 ratio using computer-generated randomisation codes to intraoperative BP maintenance using either norepinephrine 6 $\mu g\ ml^{-1}$ (norepinephrine group) or phenylephrine 100 $\mu g\ ml^{-1}$ (phenylephrine group). The randomisation codes were concealed in consecutively numbered, sealed opaque envelopes. Randomisation was stratified, with separate code sequences generated for subjects who had Caesarean delivery for elective or for non-elective indications. The block size for the randomisation was mixed, with randomly permuted blocks of four, six, and eight subjects generated using nQuery version 7.0 (Statsols, Cork, Ireland). The randomisation sequences were not revealed until completion of subject enrolment.

At the start of each day, a research nurse prepared a batch of identical 25 ml syringes containing dilute solutions of the study vasopressors according to the randomisation. Two syringes with identical contents were prepared for each subject, each labelled with the name 'study vasopressor' and with the randomisation code number. Syringes were stored in a refrigerator until use. Any unused syringes were discarded after the shift, and the randomisation codes were reused the next day. In the norepinephrine group, the syringes contained norepinephrine 6 $\mu g\ ml^{-1}$ prepared by adding 0.6 ml norepinephrine 1 $mg\ ml^{-1}$, measured using a 1 ml syringe, to a 100 ml bag of sterile saline. In the phenylephrine group, the syringes contained phenylephrine 100 $\mu g\ ml^{-1}$ prepared by adding 1.0 ml phenylephrine 10 $mg\ ml^{-1}$, measured using a 1 ml syringe, to a 100 ml bag of sterile saline. The prepared solution bags were agitated thoroughly before the study solutions were aspirated into syringes. The assigned syringes were given to the anaesthetists by the research nurse at the start of each case. Subjects and staff caring for the patients were blinded to the subjects' group assignment. The method of vasopressor preparation by which a small volume of concentrated drug was added to a 100 ml bag of saline reflected the normal unit practice for vasopressor preparation. The concentration of phenylephrine selected was identical to that used in routine departmental practice. The concentration of norepinephrine was selected to be approximately equivalent in potency to phenylephrine 100 $\mu g\ ml^{-1}$ based on our previous results.[4]

According to the pragmatic study design,[9] no practice constraints were imposed on the staff and the anaesthetists were not restricted in their clinical management other than to use the allocated vasopressor which they were at liberty to administer at their discretion according to their usual practice. All patients were given antacid premedication according to

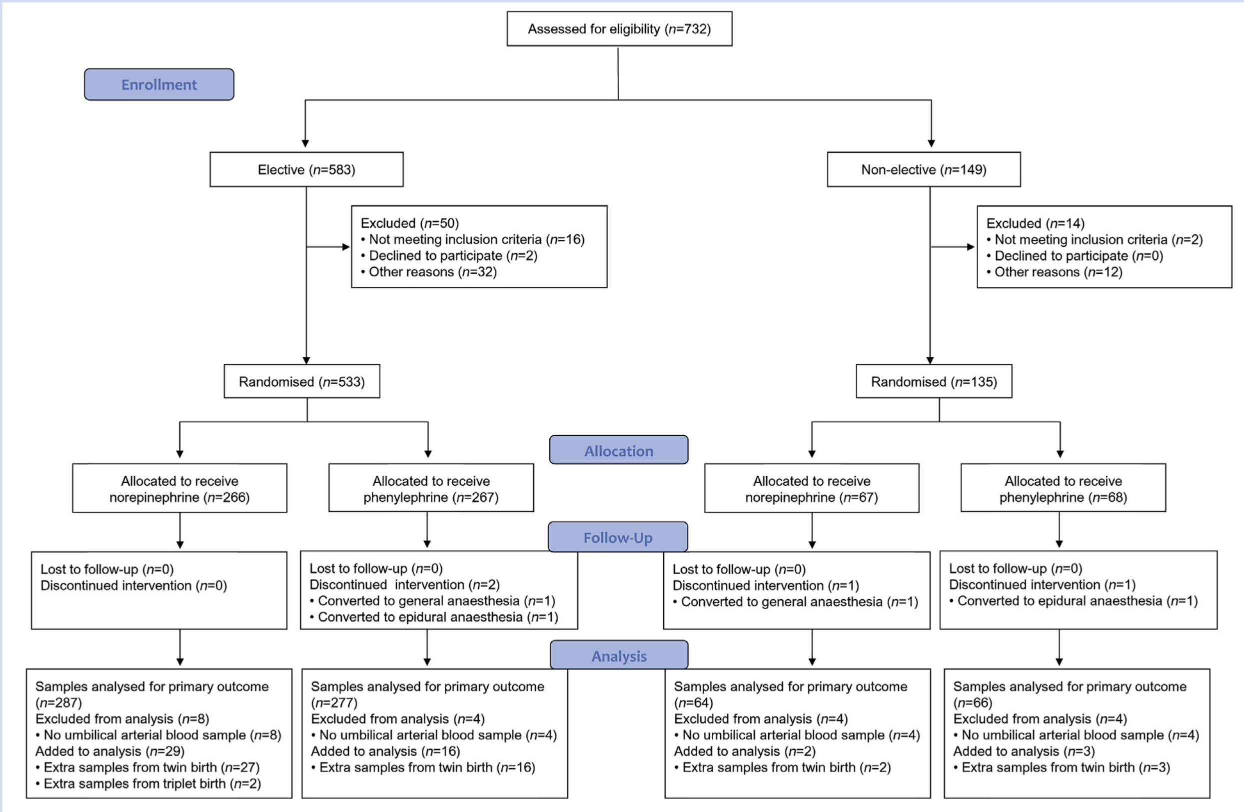

Fig 1. Subject recruitment and flow.

standard unit practice (oral famotidine and oral sodium citrate for elective cases and oral sodium citrate for non-elective cases), had routine monitors applied, and received intravenous crystalloid at the anaesthetist's discretion, as prehydration, cohydration, or both, via a large-bore intravenous cannula placed in an upper limb. Spinal or CSE anaesthesia was administered, using departmental standard drugs, hyperbaric bupivacaine 0.5% (wt/vol), and fentanyl with no restriction on dose. Block height was confirmed using ice before allowing surgery to start.

The normal departmental practice in obstetric anaesthesia was to manage BP using phenylephrine 100 μg ml^{-1} prepared in 25 ml syringes administered by intravenous infusion, intermittent boluses, or both according to individual preference. All participating anaesthetists were given an explanation of the study before commencement and were instructed to continue their usual practice using the assigned study drug as they would do normally using the standard phenylephrine 100 μg ml^{-1} solution, either prophylactically or therapeutically, as an infusion or bolus. They were also at liberty to use other drugs (e.g. vasopressors, atropine, anti-emetics, analgesics) if deemed necessary, at their discretion.

Data collection was continued from induction of anaesthesia until end of surgery. After delivery, oxytocin 5 IU i.v. was routinely given. Monitoring data were recorded on the electronic record and, in addition, the anaesthetists were asked to complete a brief study sheet recording basic case details including indication for surgery, drugs given, block height (assessed using ice), volume of vasopressor and method(s) of administration, and occurrence of nausea or vomiting.

The research nurse collected subject characteristics and after each case recorded details of birth weight, Apgar scores, and umbilical cord arterial and venous blood gases (measured routinely from a double-clamped segment of umbilical cord) that were measured and entered routinely in the medical record by the nursing staff. After completion of the case, one of the investigators extracted haemodynamic data and event times from the electronic anaesthesia record, converted the data to spreadsheet format, and archived these for subsequent analysis. Retrospective assessment of the incidences of hypotension and bradycardia was performed by recording the occurrence of any measurement of systolic BP <100 mm Hg or HR <60 beats min^{-1}, respectively during the period from induction of anaesthesia to delivery of the infant. All patients received routine postoperative review by an anaesthetist.

Statistical analysis

Power analysis was performed *a priori* according to the non-inferiority design and based on the primary endpoint of UA pH. To obtain a representative baseline estimate of mean value and variability for UA pH in routine practice, we analysed UA pH results from 747 patients in our research database who previously had their BP maintained using phenylephrine. This group included patients who had spinal or CSE anaesthesia for elective or non-elective Caesarean delivery, during which phenylephrine was administered by infusion, bolus, or both to maintain BP at a variety of different clinical endpoints. These data showed that the mean UA pH using phenylephrine was 7.291 with a standard deviation (SD) of 0.042. Using these data, we calculated that a sample size of 303 subjects per group would be required for 90% power with alpha 0.05 to reject the null hypothesis that UA pH is lower in the norepinephrine group than in the phenylephrine group by 0.01 units or more. To allow for potential drop-outs, and to account for anticipated cases in which sufficient UA cord blood could not to be obtained for analysis, the sample size was increased by 10% giving 334 subjects per group. The power calculation was performed using PASS 6.0 (NCSS, LLC, Kaysville, UT, USA). UA BE was defined as a secondary outcome of the study.

Continuous data were assessed for normality by visual inspection and Shapiro–Wilk's test and analysed using Student's *t*-test or the Mann–Whitney *U*-test as appropriate. Categorical data were analysed using the χ^2 test. For cases where data were missing for the primary outcome (UA pH), for example because of insufficient sample for measurement, no values were imputed as no assumptions were made of the patterns of missing data. To take correlations into account for cases of multiple gestation, a generalised estimating equation (GEE) model with an exchangeable correlation and robust standard errors was used to compare the groups for all neonatal outcomes. A two-sided 95% confidence interval (95% CI) approach from these models was used.

Non-inferiority was assessed by calculating the mean and 95% CI for the difference in UA pH between groups and comparing the limits of the CI with the predefined non-inferiority margin.[10] The decision to reject the null hypothesis was determined by visual inspection of whether the lower limit of the CI crossed the non-inferiority margin. We also calculated a one-sided hypothesis non-inferiority *P*-value where a significant value coincides with the lower confidence limit being above the specified margin of −0.01 units.[11] Subgroup analysis was planned for elective and non-elective cases. An interaction test was used to assess the subgroup effect on UA pH.

Analyses were performed using IBM SPSS Statistics version 25 (IBM SPSS Inc., Chicago, IL, USA) and Stata version 16.0 (StataCorp, College Station, TX, USA). Values of $P<0.05$ were considered statistically significant.

Results

A total of 47 anaesthetists consisting of a mixture of consultants and residents participated in the care of the subjects enrolled in the study. From a total of 732 patients assessed for eligibility, 668 subjects (533 elective and 135 non-elective) were enrolled in the study of whom 333 were randomised to receive norepinephrine and 335 were randomised to receive phenylephrine. There were no study protocol violations. Four subjects were excluded from analysis: one allocated to norepinephrine required conversion to general anaesthesia, one allocated to phenylephrine required conversion to general anaesthesia, and two allocated to phenylephrine received epidural anaesthesia without an intrathecal component during an attempted CSE technique. Of the remaining 664 subjects who successfully completed the study, taking into account exclusions from insufficient blood samples for analysis and additional samples from multiple gestation deliveries, data were available for final analysis for the primary outcome of UA pH from 351 samples (287 elective and 64 non-elective) in the norepinephrine group and 343 samples (277 elective and 66 non-elective) in the phenylephrine group. The recruitment and flow of subjects, separated into elective and non-elective cases for clarity, are shown in Fig 1. Haemodynamic data were not available for analysis in nine elective cases and one non-elective case because of acquisition failure or corruption of electronic data.

Subject characteristics are shown in Table 1. Intraoperative details are summarised in Table 2. Differences between groups were found for median (inter-quartile range) block height (P=0.038) and total volume of vasopressor given at delivery (P=0.03) and at the end of surgery (P=0.009). The incidence of hypotension was not different between the norepinephrine group (59%) and the phenylephrine group (55%) (relative risk [RR]=1.09; 95% CI, 0.95–1.24). The incidence of bradycardia was lower in the norepinephrine group (83/325; 26%) *vs* the phenylephrine group (137/329; 42%) (RR=0.61; 95% CI, 0.49–0.77); however, no subject received an anticholinergic drug to treat bradycardia. The incidence of nausea or vomiting was not different between the norepinephrine group and the phenylephrine group (RR=1.14; 95% CI, 0.88–1.50).

Values for the primary outcome UA pH were: mean 7.289 (95% CI, 7.284–7.294) in the norepinephrine group and 7.287 (95% CI, 7.281–7.292) in the phenylephrine group (Table 3). The mean difference in UA pH between groups was 0.002 (95% CI, −0.005 to 0.009). The CI did not cross the non-inferiority margin indicating that norepinephrine is non-inferior to phenylephrine (non-inferiority P=0.017) (Fig 2). Results of subgroup analysis for elective and non-elective cases are also shown in Fig 2. The urgency of surgery did not modify the treatment effect on UA pH (P=0.83). For elective cases, the mean difference in UA pH between groups was 0.002 (95% CI, −0.006 to 0.009) and non-inferiority of norepinephrine was confirmed (non-inferiority P=0.012). For non-elective cases, the mean difference in UA pH between groups was 0.004 (95% CI, −0.017 to 0.026); because the CI for the difference in UA pH between drugs crossed the non-inferiority margin, non-inferiority could not be demonstrated (non-inferiority P=0.296).

Other measures of neonatal outcome are shown in Table 3. The defined secondary outcome of UA BE was not different between the norepinephrine group and the phenylephrine group (mean difference, 0.1 mmol L^{-1}; 95% CI of difference, −0.3 to 0.6 mmol L^{-1}).

Table 1 Characteristics of subjects who completed the study. Values are mean (standard deviation), mean [range], median (inter-quartile range) or number (%).

	Norepinephrine group (n=332)	Phenylephrine group (n=332)
Age (yr)	33.4 [20–46]	33.6 [18–45]
Weight (kg)	69.2 (10.5)	67.9 (10.0)
Height (cm)	157 (10)	157 (13)
Gestation (weeks)	38.1 (38.0–38.6)	38.3 (38.0–38.6)
Singleton	296 (89%)	312 (94%)
Twin	35 (11%)	20 (6%)
Triplet	1 (0.3%)	0 (0%)
Elective	266 (80%)	265 (78%)
Non-elective	66 (20%)	67 (20%)

Table 2 Intraoperative details. Haemodynamic data were not available for 10 subjects. Hypotension was defined as any systolic blood pressure value <100 mm Hg during the interval from induction of anaesthesia to delivery. Bradycardia was defined as any HR value <60 beats min^{-1} during the interval from induction of anaesthesia to delivery. Data for induction-to-delivery interval are for the first-born infant in cases of multiple gestations. Values are median (inter-quartile range), mean (standard deviation) or number (%).

	Norepinephrine group (*n*=332)	Phenylephrine group (*n*=332)	*P*-value
Intrathecal bupivacaine dose (mg)	11 (11–11)	11 (11–11)	0.18
Intrathecal fentanyl dose (μg)	15 (15–15)	15 (15–15)	0.08
Block height (dermatome)	T4 [T3/T4–T4/T5]	T4 [T3/T4–T5]	0.038
Induction-to-delivery interval (min)	26.6 (22.7–32.3)	25.8 (21.6–31.3)	0.24
Incidence of hypotension	193/325 (59%)	180/329 (55%)	0.23
Incidence of bradycardia	83/325 (26%)	137/329 (42%)	<0.0001
Intraoperative nausea or vomiting	91/332 (27%)	79/332 (24%)	0.29
Method of vasopressor administration			0.99
Infusion only	238/332 (71.7%)	236/332 (71.1%)	
Boluses only	1/332 (0.3%)	1/332 (0.3%)	
Infusion and boluses	93/332 (28%)	95/332 (28.6%)	
Total volume of vasopressor given at delivery (ml)	11.3 (8.1–15.6)	10.2 (7.4–14.5)	0.026
Total volume of vasopressor given at end of surgery (ml)	18.0 (11.9–26.3)	15.9 (10.6–22.0)	0.009
Additional vasopressor drug given before delivery	8 (2.4%)	6 (1.8%)	0.59

Discussion

Although phenylephrine is well established as a first-line vasopressor in obstetric anaesthesia, it is known to cause reflexive decreases in HR and cardiac output.[12,13] This has stimulated recent investigation of norepinephrine as an alternative.[1–7,14–16] A number of recent studies support the use of norepinephrine as a vasopressor in obstetric anaesthesia. However, an important and necessary step that should precede adoption of norepinephrine in routine clinical practice is demonstration of safety for the fetus and neonate. This concern arises because vasopressors have the potential to cause detrimental effects on uteroplacental blood flow. In this context, the results of our study showing that norepinephrine is non-inferior to phenylephrine for the outcome of UA pH are reassuring given that phenylephrine is widely accepted as a current standard in obstetric anaesthesia.[17] We chose a small effect size of 0.01 pH units to define the non-inferiority margin. Accordingly, our study was powered to detect even minor possible detrimental effects of norepinephrine, the exclusion of which enhances our confidence that norepinephrine does not have a harmful effect on the fetus.

We chose UA pH as the primary outcome because it is a well-established measure of neonatal condition at birth. UA pH reflects both the metabolic and the respiratory components of fetal acidaemia. The latter may occur from carbon dioxide accumulation during acute decreases in uteroplacental perfusion that may be particularly relevant in the context of spinal anaesthesia and use of intraoperative vasopressors. It can be argued that BE is a more appropriate measure of outcome as it reflects the metabolic component of fetal acidaemia resulting from anaerobic metabolism from pronounced hypoxia. However, it has been questioned whether UA BE, which is a calculated value and is highly correlated with pH, has any additional prognostic value over measurement of UA pH.[18] Nonetheless, we performed an additional analysis that compared UA BE between groups as a secondary outcome. Although a non-inferiority analysis was not performed for this outcome, the results showed no difference between groups.

The subgroup analysis did not demonstrate non-inferiority for norepinephrine in non-elective cases; although the mean value of the difference in UA pH was similar to that in elective cases, the CI of the difference was wide, reflecting both the smaller sample size and greater variability of data for non-elective cases compared with elective cases. Although it is not possible to exclude inferiority of norepinephrine based on these findings, it is possible that this result represents a type 2 statistical error related to a lack of power. Further comparative studies of norepinephrine and phenylephrine in non-elective cases with larger numbers of subjects are recommended. Although the results of our study do not provide clear proof of the fetal safety of norepinephrine in non-elective cases, a similar situation exists for phenylephrine for which

Table 3 Neonatal outcome. Values represent the mean (standard deviation) or number (%). [†]GEE model did not converge, *P*-values reported from Fisher's exact test. [‡]Primary outcome. [a]*n*=369; [b]*n*=352; [c]*n*= 351; [d]*n*=343; [e]*n*=291; [f]*n*=294; [g]*n*=354; [h]*n*=340; [i]*n*=350; [j]*n*=335.

	Norepinephrine group	Phenylephrine group	P Value
Birth weight (kg)	3.00 (0.52)[a]	3.02 (0.53)[b]	0.67
Apgar score at 1 min <7	10/369 (27%)	10/352 (28%)	0.73
Apgar score at 5 min <7	4/369 (1%)	0/352 (0%)	0.12[†]
Umbilical arterial blood gases			
pH[‡]	7.289 (0.049)[c]	7.286 (0.048)[d]	0.57
P_{CO_2} (kPa)	6.3 (1.0)[c]	6.3 (1.1)[d]	0.95
P_{O_2} (kPa)	2.2 (0.5)[e]	2.2 (0.7)[f]	0.60
Base excess (mmol L^{-1})	−4.8 (2.7)[c]	−5.0 (2.8)[d]	0.48
Umbilical venous blood gases			
pH	7.338 (0.047)[g]	7.335 (0.044)[h]	0.22
P_{CO_2} (kPa)	5.4 (0.9)[g]	5.4 (0.9)[h]	0.72
P_{O_2} (kPa)	3.3 (0.8)[i]	3.3 (0.8)[j]	0.63
Base excess (mmol L^{-1})	−4.3 (2.7)[g]	−4.5 (2.5)[h]	0.40

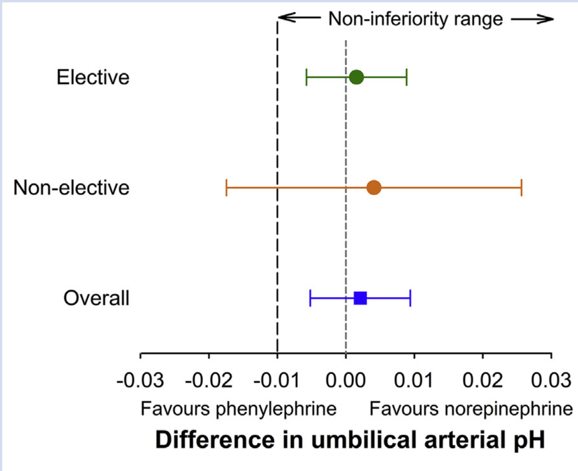

Fig 2. Differences in umbilical arterial pH between subjects who had their BP maintained with norepinephrine or phenylephrine. For the primary analysis of all subjects (blue plot), the confidence interval does not cross the non-inferiority margin, which was set at −0.01 pH units, indicating that norepinephrine is non-inferior to phenylephrine. For the subgroup analysis of elective cases (green plot), non-inferiority of norepinephrine or phenylephrine is shown. For the subgroup analysis of non-elective cases (orange plot), the confidence interval for the difference in umbilical arterial pH crosses the non-inferiority margin; therefore, non-inferiority cannot be concluded. Mean and 95% confidence interval.

comparative studies in non-elective and high-risk cases are limited.[19–21]

A number of other studies have compared norepinephrine and phenylephrine for maintaining BP during spinal anaesthesia for Caesarean delivery.[4,7,14–16,22–24] However, unlike our study, the primary outcomes of previous studies have focused on haemodynamic differences with analysis of fetal outcomes such as umbilical cord blood gases and Apgar scores included only as secondary outcomes. A recent systematic review of studies comparing norepinephrine and phenylephrine found that there was high heterogeneity among studies and too few data to calculate a pooled effect estimate for the outcome of fetal acidosis.[25] A recent network meta-analysis of vasopressors used during neuraxial anaesthesia for Caesarean delivery ranked different agents according to their likelihood of adversely affecting fetal acid–base status and reported that norepinephrine ranked higher (lower probability) than phenylephrine for adversely affecting both UA pH and BE.[26] Because of the imprecision inherent in collating multiple direct and indirect comparisons, the rank orders in that study were considered possibilities rather than absolute ranks. Nevertheless, the findings of that review are generally consistent with the results of our study, which showed no detrimental effect of norepinephrine on fetal outcome when compared directly as a primary outcome with phenylephrine.

Published studies to date on the use of norepinephrine in obstetric anaesthesia have been performed mainly under controlled experimental conditions.[1,4–7,14–16] In contrast, our study utilised a pragmatic study design[9] in which we allowed participating anaesthetists to administer the study vasopressors according to their personal preference with the aim of capturing a wide range of techniques in order to enhance the generalisability of the results to everyday clinical practice. The pragmatic study design probably explains why the overall incidence of hypotension was higher than that which we have reported in previous studies of prophylactic vasopressors,[5,27] because there was no close control of experimental conditions and no requirement for prophylactic vasopressor. Despite the relatively large number of participating anaesthetists, a large degree of homogeneity of practice was observed as evidenced by a large preference for delivering vasopressors by infusion only. This likely reflects common teaching and sharing of knowledge within the department. It is likely that a multicentre trial would have provided greater external validity.

We chose to study norepinephrine at a concentration of 6 μg ml^{-1}, which was estimated to be of equivalent potency to our standard vasopressor solution of phenylephrine 100 μg ml^{-1}. This assumed a potency ratio for norepinephrine/phenylephrine of 16.7:1 based on available information at the time of study design.[4] Subsequent work has suggested that the true potency ratio is probably smaller.[2 15] For example in a recent dose–response comparison of norepinephrine and phenylephrine by intravenous bolus, we calculated a potency ratio of 13.1:1 (norepinephrine 7.6 μg equivalent to phenylephrine 100 μg).[2] Similarly, Mohta and colleagues[15] conducted a comparative dose–response study of norepinephrine and phenylephrine and calculated a potency ratio of 11.3:1 (norepinephrine 8.8 μg equivalent to phenylephrine 100 μg). In our study, the total volume of vasopressor given at delivery and at the end of surgery was greater in the norepinephrine group than in the phenylephrine group, which likely reflects the norepinephrine study solution being less potent than the phenylephrine study solution. Although this represents a potential confounding factor in our study, any effect of this should have been minimised by the study methodology that allowed the anaesthetists to freely titrate the study vasopressors as required. This would explain why there was no difference in the incidence of hypotension between groups.

The incidence of bradycardia was greater in the phenylephrine group than in the norepinephrine group, which is consistent with previous findings.[4 7] However, given that no patient required treatment with an anticholinergic agent, the clinical significance of this is uncertain.

An unexpected finding was a statistically significant difference in block height which was lower in the phenylephrine group. It is possible that this might reflect a greater vasoconstrictor effect on epidural veins in the phenylephrine group related to the use of a higher potency solution compared with norepinephrine, with a consequent effect on lumbosacral cerebrospinal fluid volume as has been described to explain differences in block height observed when phenylephrine is used *vs* ephedrine.[28] However, the magnitude of the difference in block height between groups was small; this was not a predefined secondary outcome of the study, and we made no statistical adjustment for multiple intergroup comparisons. Therefore, this result may simply reflect a type 1 statistical error.

We prepared the vasopressor solutions by adding measured aliquots of norepinephrine and phenylephrine to 100 ml bags of saline before aspirating the solutions into syringes. This introduced potential for inaccuracy of drug concentrations because the commercial saline bags may not have been consistently or precisely filled with the labelled volume. In previous studies, in recognition of this issue, we ensured more precise measurement of the saline diluent by drawing it up into large syringes before adding the vasopressor.[4 5] In keeping with the pragmatic study design, we chose to add the vasopressors directly to the saline bags, which was done in order to maintain consistency with and reflect the prevailing clinical practice in the department. We believe this likely reflects practice in many other institutions.

After our publication of the first randomised comparison of norepinephrine and phenylephrine in obstetric patients in 2015, editorial comment advocated caution with the use of norepinephrine based on a number of issues including the novelty of this application, relative unfamiliarity with use of norepinephrine in the operating room environment, limited availability of research data, and concerns about possible tissue injury from extravasation and local vasoconstriction.[29] These concerns may now largely be allayed by the increasing number of investigations that have added to the body of experience with norepinephrine in obstetric patients. The generalisability of the findings of our earlier study was previously questioned because of our use of computer-controlled vasopressor infusions that are not commonly used in everyday practice.[29] We addressed this concern by ensuring that the vasopressors were delivered by a range of anaesthetists using everyday methods including manually adjusted infusion and intermittent boluses. A large retrospective study found no association between the use of peripheral intravenous norepinephrine infusions and adverse events, which suggests that this practice may be safe for short durations.

In summary, we identified no detrimental effect of norepinephrine on neonatal outcome compared with phenylephrine when used for maintaining BP during spinal and CSE anaesthesia for Caesarean delivery. Our results support a growing body of evidence that suggests that norepinephrine is a suitable agent for use in obstetric anaesthesia.

Authors' contributions

Acquisition of data: WDNK, FFN
Data analysis: WDNK, AL
Drafting of manuscript: WDNK
Revision of manuscript: SWYL, FFN, AL
Final approval: WDNK, FFN, AL
All authors were involved in the concept, study design, and agreed to be accountable for all aspects of the work.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

Departmental and/or institutional funding only.

Acknowledgements

The authors thank all of the staff in the Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, Shatin, Hong Kong, China who participated in this study.

References

1. Hasanin AM, Amin SM, Agiza NA, et al. Norepinephrine infusion for preventing postspinal anesthesia hypotension during cesarean delivery: a randomized dose-finding trial. *Anesthesiology* 2019; **130**: 55–62
2. Ngan Kee WD. A random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology* 2017; **127**: 934–41
3. 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
4. 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
5. Ngan Kee WD, Lee SWY, Ng FF, Khaw KS. Prophylactic norepinephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2018; **126**: 1989–94
6. 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
7. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, Carvalho JCA. Comparison of intermittent intravenous boluses of phenylephrine and norepinephrine to prevent and treat spinal-induced hypotension in cesarean deliveries: randomized controlled trial. *Anesth Analg* 2019; **129**: 1312–8
8. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. *BJOG* 2012; **119**: 824–31
9. Macpherson H. Pragmatic clinical trials. *Complement Ther Med* 2004; **12**: 136–40
10. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; **308**: 2594–604
11. Mascha EJ, Sessler DI. Equivalence and noninferiority testing in regression models and repeated-measures designs. *Anesth Analg* 2011; **112**: 678–87
12. Dyer RA, Reed AR, van Dyk D, et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 2009; **111**: 753–65
13. 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
14. Hasanin A, Amin S, Refaat S, et al. Norepinephrine versus phenylephrine infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery: a randomised controlled trial. *Anaesth Crit Care Pain Med* 2019; **38**: 601–7
15. Mohta M, Dubey M, Malhotra RK, Tyagi A. Comparison of the potency of phenylephrine and norepinephrine bolus doses used to treat post-spinal hypotension during elective caesarean section. *Int J Obstet Anesth* 2019; **38**: 25–31
16. Mohta M, Garg A, Chilkoti GT, Malhotra RK. A randomised controlled trial of phenylephrine and noradrenaline

boluses for treatment of postspinal hypotension during elective caesarean section. *Anaesthesia* 2019; **74**: 850–5
17. Kinsella SM, Carvalho B, Dyer RA, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. *Anaesthesia* 2018; **73**: 71–92
18. Knutzen L, Svirko E, Impey L. The significance of base deficit in acidemic term neonates. *Am J Obstet Gynecol* 2015; **213**: 373. e1–7
19. Dyer RA, Emmanuel A, Adams SC, et al. A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and fetal compromise. *Int J Obstet Anesth* 2018; **33**: 23–31
20. Higgins N, Fitzgerald PC, van Dyk D, et al. The effect of prophylactic phenylephrine and ephedrine infusions on umbilical artery blood pH in women with preeclampsia undergoing cesarean delivery with spinal anesthesia: a randomized, double-blind trial. *Anesth Analg* 2018; **126**: 1999–2006
21. 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
22. Dong L, Dong Q, Song X, Liu Y, Wang Y. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for cesarean section. *Int J Clin Exp Med* 2017; **10**: 12315–21
23. Vallejo MC, Attaallah AF, Elzamzamy OM, et al. 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
24. Wang X, Mao M, Zhang SS, Wang ZH, Xu SQ, Shen XF. Bolus norepinephrine and phenylephrine for maternal hypotension during elective cesarean section with spinal anesthesia: a randomized, double-blinded study. *Chin Med J (Engl)* 2020; **133**: 509–16
25. Heesen M, Hilber N, Rijs K, et al. A systematic review of phenylephrine vs. noradrenaline for the management of hypotension associated with neuraxial anaesthesia in women undergoing caesarean section. *Anaesthesia* 2020. https://doi.org/10.1111/anae.14976 [Epub ahead of print]
26. Singh PM, Singh NP, Reschke M, Ngan Kee WD, Palanisamy A, Monks DT. Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes. *Br J Anaesth* 2020; **124**: e95–107
27. Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. *Anesthesiology* 2005; **103**: 744–50
28. Cooper DW, Jeyaraj L, Hynd R, et al. Evidence that intravenous vasopressors can affect rostral spread of spinal anesthesia in pregnancy. *Anesthesiology* 2004; **101**: 28–33
29. Carvalho B, Dyer RA. Norepinephrine for spinal hypotension during cesarean delivery: another paradigm shift? *Anesthesiology* 2015; **122**: 728–30

Handling editor: Hugh C Hemmings Jr