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Title Page

Norepinephrine versus phenylephrine during spinal anaesthesia for Caesarean delivery: A randomised double-blinded pragmatic non-inferiority study of neonatal outcome

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Short Running Title:

Neonatal outcome norepinephrine vs phenylephrine

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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. This study aimed to test the hypothesis that umbilical arterial cord pH is at least as good (non-inferior) when norepinephrine is used compared with phenylephrine.

Methods

Six hundred and sixty-eight patients having elective and non-elective Caesarean delivery under spinal or combined spinal-epidural anaesthesia were enrolled in this randomised, double-blinded, two-arm parallel, non-inferiority clinical trial. Blood pressure was maintained using norepinephrine 6 μg ml^{-1} or phenylephrine 100 μg ml^{-1} by the usual practice of the anaesthetist. The primary outcome was umbilical arterial pH with a chosen non-inferiority margin of 0.01 units.

Results

Of 664 patients (531 elective and 133 non-elective) who completed the study, umbilical arterial cord blood was analyzed for 351 samples from 332 patients in the norepinephrine group and 343 samples from 332 patients in the phenylephrine group. Umbilical arterial pH was non-inferior in the

norepinephrine group (mean 7.289 [95% CI 7.284 to 7.294]) versus the phenylephrine group (mean 7.287 [95% CI 7.281 to 7.292]). Subgroup analysis confirmed non-inferiority of norepinephrine for elective cases but was inconclusive for non-elective cases. The risk of intraoperative hypotension (systolic blood pressure < 100 mm Hg) was similar between groups (RR 1.09; 95% CI: 0.95 – 1.24).

Conclusions

Norepinephrine is 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.

Keywords

Caesarean delivery; hypotension; norepinephrine; phenylephrine. spinal anaesthesia

Chinese Clinical Trial Registry registration no. ChiCTR-IPR-15006235.

Introduction

Norepinephrine (noradrenaline) has been investigated recently as a vasopressor for maintaining blood pressure (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 which counteracts the reflexive decreases in heart rate and cardiac output that commonly occur during unopposed stimulation of vascular alpha adrenergic receptors. Consequently, greater maternal haemodynamic stability may be seen with the use of norepinephrine compared with phenylephrine.[4, 7] Accordingly, it has been suggested that norepinephrine may be a superior vasopressor for use in obstetric spinal anaesthesia.[4, 7] However, before norepinephrine can be fully recommended for general clinical use in obstetric anaesthesia, it is important to exclude possible 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 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 generalisability of the results. Umbilical arterial base excess was compared between groups as a secondary outcome.

Methods

Before commencement of the study, 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, the protocol was registered in April 2015 in the Chinese Clinical Trial Registry (registration no. ChiCTR-IPR-15006235) with the title "*Randomized Evaluative Study of Phenylephrine Or Norepinephrine for maintenance of blood pressure during spinal anaesthesia for caesarean Delivery: The RESPOND2 study",* and 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 patients who were scheduled for elective and non-elective Caesarean delivery under spinal or combined spinal-epidural (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 years, 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 patients by a research nurse (FN). For elective cases and other cases transferred from the antenatal ward, consent was obtained in the ward prior to 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.

Patients were randomly assigned in a 1:1 ratio using computer-generated randomisation codes to have their intraoperative BP maintained using either norepinephrine 6 μg ml^{-1} (norepinephrine group) or phenylephrine 100 μg ml^{-1} (phenylephrine group). The randomisation codes were prepared by one of the authors (AL) who had no direct involvement with patient care or data collection and were concealed in consecutively numbered, sealed opaque envelopes. Randomisation was stratified, with separate code sequences generated for patients who had Caesarean delivery for elective or for non-elective indications. . The block size for the randomization was mixed, with randomly permuted blocks of 4, 6 and 8 patients generated using nQuery version 7.0 (Statsols, Cork, Ireland).The randomisation sequences were not revealed until completion of patient 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 labeled 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 μg ml^{-1} which was 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 μg ml^{-1} which was 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 the syringes. The assigned syringes were given to the anaesthetists by the research nurse at the start of each case. Patients and staff caring for the patients were blinded to the patients' 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 and 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 μg ml^{-1} based on the results from our previous work.[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 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, by prehydration and/or cohydration, via a large-bore intravenous cannula placed in an upper limb. Spinal or CSE anaesthesia was administered, using the departmental standard drugs, hyperbaric bupivacaine 0.5%wt/vol and fentanyl, with no restriction on dose. Block height was checked routinely using ice prior to allowing surgery to start.

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 prior to commencement and were instructed to continue their normal practice using the assigned study drug as they would do normally using the standard phenylephrine 100 µg ml^{-1} solution, either prophylactically or therapeutically. They were also at liberty to use other drugs (e.g., phenylephrine, ephedrine, atropine, antiemetics, analgesics) if deemed necessary, at their discretion.

Data collection for the study was continued from induction of anaesthesia until the end of surgery. After delivery, oxytocin 5 IU was routinely given intravenously. Monitoring data were recorded routinely 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 patient demographic details and after each case was completed she recorded details of birthweight, Apgar scores and umbilical cord arterial and venous blood gases (measured routinely from a double-clamped segment of umbilical cord) which were measured and entered routinely in the medical record by the nursing staff. Subsequent to the 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 heart rate <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 of the study and was 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 analyzed umbilical arterial 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 and/or by boluses to maintain BP at a variety of different clinical endpoints. These data showed that the mean UA pH using phenylephrine was 7.291 with standard deviation (SD) 0.042. Using these data, we calculated that a sample size of 303 patients per group would be required to have 90% power with alpha 0.05 to reject the null hypothesis that UA pH would be lower in the norepinephrine group versus the phenylephrine group by 0.01 units or more. To allow for potential dropouts, and to account for anticipated cases where sufficient UA cord blood could not to be obtained for analysis, the sample size was increased by 10% giving a final number of 334 per group. The power calculation was performed using PASS 6.0 (NCSS, LLC, Kaysville, UT, USA). Umbilical arterial base excess (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 analyzed using Student's t-test or the Mann-Whitney U test as appropriate. Categorical data were analyzed using the chi-square 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 were used.

Non-inferiority was assessed by calculating the mean and 95% confidence interval for the difference in UA pH between groups and comparing the limits of the confidence interval 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 confidence interval crossed the non-inferiority margin. We also calculating a one-sided hypothesis non-inferiority *P*-value where a significant value will coincide 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 with a mixture of consultants and residents participated in the study. From a total of 732 patients assessed for eligibility, 668 patients (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 patients were excluded from analysis: one patient allocated to norepinephrine required conversion to general anaesthesia, one patient allocated to phenylephrine required conversion to general anaesthesia, and two patients allocated to phenylephrine received epidural anaesthesia without an intrathecal component during an attempted CSE technique. Of the remaining 664 patients who successfully completed the study, after 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 patients, separated into elective and non-elective cases for clarity, is 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.

Patient characteristics are shown in Table 1. Intraoperative details are summarised in Table 2. Differences between groups were found for median (IQR) 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 to 1.24]). The incidence of bradycardia was lower in the norepinephrine group (83/325 [26%]) versus the phenylephrine group (137/329 [42%]) (RR 0.61

[95% CI 0.49 to 0.77]); however, no patient 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 to 1.50]).

Values for the primary outcome UA pH were: mean 7.289 (95% CI 7.284 to 7.294) in the norepinephrine group and 7.287 (7.281 to 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 confidence interval 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 confidence interval 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 umbilical arterial base excess was not different between the norepinephrine group (mean -4.8, 95% CI -5.0 to -4.5] mmol L^{-1} and the phenylephrine group (-4.9, 95% CI -5.2 to -4.6] mmol L^{-1}, $P = 0.48$), mean difference 0.1 mmol L^{-1}, 95% CI of difference -0.3 to 0.6 mmol L^{-1}.

Discussion

Although phenylephrine is well established as a first-line vasopressor in obstetric anaesthesia, it is known to cause reflexive decreases in heart rate and cardiac output.[12, 13] This has stimulated recent investigation of norepinephrine as an alternative.[1-7, 14-16] A number of studies have been published recently supporting 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 the 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] Of note, in our study design 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 of our study 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 which may be particularly relevant in the context of spinal anaesthesia and use of intraoperative vasopressors. It may be argued that base excess 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 base excess, which is a calculated value and is highly correlated with pH, has any additional prognostic value over

measurement of UA pH.[18] Nonetheless, with respect to this controversy, 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 confidence interval 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. It should be noted that, 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 comparative studies in non-elective and high-risk cases are limited.[19-21]

A number of other studies have previously compared norepinephrine and phenylephrine for maintaining BP during spinal anaesthesia for Caesarean delivery.[4, 7, 14-16, 22-24] However, unlike our current 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 umbilical arterial pH and base excess.[26] However, 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 all 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 delivery. 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 the vasopressors by infusion only. This likely reflects common teaching and sharing of knowledge within the department. In retrospect, 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, 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 also 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 current 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 which 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 versus the norepinephrine which is consistent with findings of previous work.[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 versus 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 prior to 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 the current study, 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.

Following 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 been published which add 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 which are not commonly used in everyday practice.[29] In our current study 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 recently 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, the findings of this study 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

WDNK: Concept, study design, acquisition of data, data analysis, drafting of manuscript, final approval, agreement to be accountable for all aspects of the work.

SWYL: Concept, study design, revising of manuscript, final approval, agreement to be accountable for all aspects of the work.

FFN: Concept, study design, acquisition of data, revising of manuscript, final approval, agreement to be accountable for all aspects of the work.

AL: Concept, study design, data analysis, revising of manuscript, final approval, agreement to be accountable for all aspects of the work.

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Declaration of interests

The authors declare that they have no conflict of interest.

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Table 1. Characteristics of patients who completed the study.

	Norepinephrine Group (*n* = 332)	**Phenylephrine Group (*n* = 332)**
Age (years)	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%)

Values are mean (standard deviation), mean [range], median (interquartile range) or number (%).

Table 2 Intraoperative details.

	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

Haemodynamic data were not available for 10 patients. Hypotension was defined as the occurrence of any systolic blood pressure value < 100 mmHg during the interval from induction of anaesthesia to delivery. Bradycardia was defined as the occurrence of any heart rate 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 gestation. Values are median (interquartile range), mean (standard deviation) or number (%).

Table 3 Neonatal outcome.

	Norepinephrine Group	Phenylephrine Group	*P*-value
Birthweight (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
PCO_2 (kPa)	6.3 (1.0)[c]	6.3 (1.1)[d]	0.95
PO_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

PCO_2 (kPa)	5.4 (0.9)[g]	5.4 (0.9)[h]	0.72
PO_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

Values are mean (standard deviation) or number (%). *GEE model did not converge, *P*- value 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

Legends to Figures.

Figure 1

Patient recruitment and flow.

Figure 2.

Mean and 95% confidence interval for the difference in umbilical arterial pH between patients who had their blood pressure maintained with norepinephrine or phenylephrine. For the primary analysis of all patients (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 versus phenylephrine is demonstrated. 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.

Assessed for eligibility (n=732)

Enrollment

Elective (n=583)

Excluded (n=50)
• Not meeting inclusion criteria (n=16)
• Declined to participate (n=2)
• Other reasons (n=32)

Non-elective (n=149)

Excluded (n=14)
• Not meeting inclusion criteria (n=2)
• Declined to participate (n=0)
• Other reasons (n=12)

Randomised (n=533)

Randomised (n=135)

Allocation

Allocated to receive norepinephrine (n=266)

Allocated to receive phenylephrine (n=267)

Allocated to receive norepinephrine (n=67)

Allocated to receive phenylephrine (n=68)

Follow-Up

Lost to follow-up (n=0)
Discontinued intervention (n=0)

Lost to follow-up (n=0)
Discontinued intervention (n=2)
• Converted to general anaesthesia (n=1)
• Converted to epidural anaesthesia (n=1)

Lost to follow-up (n=0)
Discontinued intervention (n=1)
• Converted to general anaesthesia (n=1)

Lost to follow-up (n=0)
Discontinued intervention (n=1)
• Converted to epidural anaesthesia (n=1)

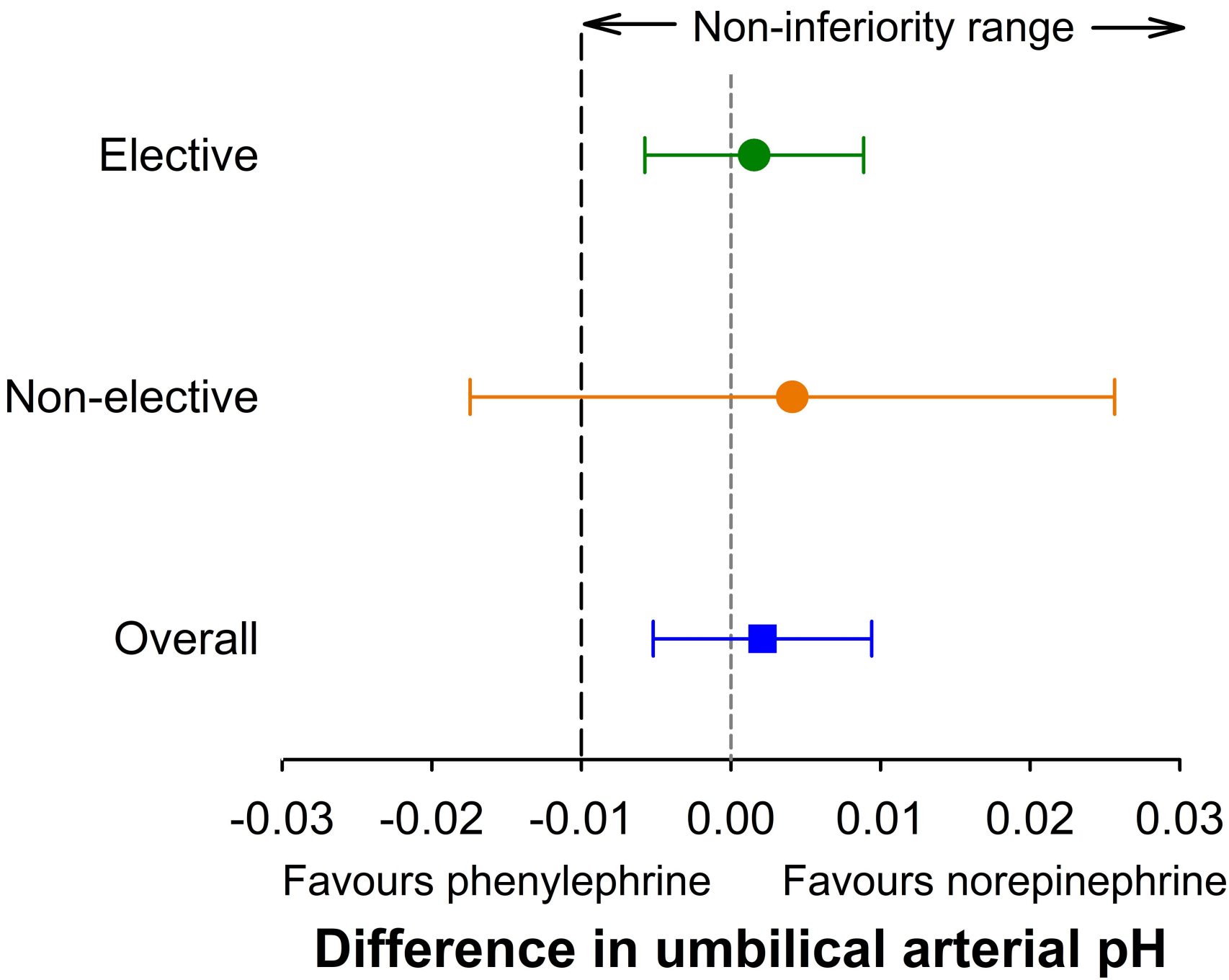
Analysis

Samples analysed for primary outcome (n=287)
Excluded from analysis (n=8)
• No umbilical arterial blood sample (n=8)
Added to analysis (n=29)
• Extra samples from twin birth (n=27)
• Extra samples from triplet birth (n=2)

Samples analysed for primary outcome (n=277)
Excluded from analysis (n=4)
• No umbilical arterial blood sample (n=4)
Added to analysis (n=16)
• Extra samples from twin birth (n=16)

Samples analysed for primary outcome (n=64)
Excluded from analysis (n=4)
• No umbilical arterial blood sample (n=4)
Added to analysis (n=2)
• Extra samples from twin birth (n=2)

Samples analysed for primary outcome (n=66)
Excluded from analysis (n=4)
• No umbilical arterial blood sample (n=4)
Added to analysis (n=3)
• Extra samples from twin birth (n=3)


Non-inferiority range
Elective
Non-elective
Overall
-0.03
-0.02
-0.01
0.00
0.01
0.02
0.03
Favours phenylephrine
Favours norepinephrine
Difference in umbilical arterial pH