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CLINICAL TRIAL REPORT

Vasopressor Regimens and Maternal Core Temperature During Cesarean Delivery: A Randomized, Double-blind, Non-inferiority Trial

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Background: Norepinephrine (NE), a vasopressor commonly used during cesarean section, avoids the phenylephrine (PE)-induced decreases in heart rate and cardiac output. Conversely, PE reduces the incidence and severity of maternal shivering and hypothermia during cesarean section. Therefore, before recommending NE as a complete replacement for PE, their effects on maternal core temperature must be compared. This study aimed to determine whether prophylactic infusion of NE is non-inferior to PE in maintaining maternal core temperature.

Materials and Methods: One hundred and forty eligible women scheduled for cesarean section under spinal or combined spinal-epidural anaesthesia were randomly assigned to either the NE or PE group. All participants, caregivers, and outcome assessors were blinded. NE (8 μg/mL) or PE (100 μg/mL) was administered intravenously at a fixed rate of 15 mL/h (equivalent to NE 2 μg/min or PE 25 μg/min), starting concurrently with the subarachnoid injection, and continuing until the end of surgery. The primary outcome was postoperative maternal core temperature, with a non-inferiority margin set at 0.2°C.

Results: Postoperative maternal core temperature was non-inferior in the NE group (mean, 36.35°C; 95% confidence interval [CI], 36.28–36.42) compared to the PE group (mean, 36.41°C; 95% CI, 36.34–36.49). The mean difference between the two groups was −0.06°C (95% CI, - 0.16 to 0.04), meeting the criterion for non-inferiority (one-sided $p = 0.008$). The incidence of bradycardia was significantly lower in the NE group than in the PE group (7.4% vs. 33.8%; $p < 0.001$). No significant differences were found between the groups in the incidence or severity of shivering, the incidence of hypothermia, or the thermal comfort score.

Conclusion: NE was not inferior to PE regarding its effect on maternal core temperature, providing a rationale for its use during cesarean sections.

Keywords: norepinephrine, phenylephrine, body temperature, cesarean section, spinal anaesthesia

Introduction

Spinal anaesthesia (SA) induces systemic vasodilation and redistribution of blood from the core to the periphery, leading to a decrease in maternal temperature and, in some cases, resulting in hypothermia.[1,2] These thermal disturbances can prolong clotting time, delay wound healing, and increase susceptibility to infection.[3–5] Vasoconstrictor drugs can mitigate this core-to-peripheral blood redistribution, thereby helping to maintain maternal body temperature. Additionally, intraoperative hypotension is associated with increased postoperative complication rates.[6] Norepinephrine (NE) and phenylephrine (PE) are the two vasopressors most frequently compared for managing hypotension in this context.

Prophylactic infusion of equivalent doses of PE or NE has shown no differential effects on fetal heart rate, cardiac output, or prognosis.[7] Moreover, PE infusion has been demonstrated to improve the management of maternal hypothermia and reduce the incidence of shivering.[8,9] However, a key disadvantage of PE is its tendency to trigger baroreceptor-

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mediated reflex bradycardia and reduce maternal cardiac output,[10–12] potentially limiting its use in parturients with pre-existing cardiac insufficiency or fetal compromise. In contrast, NE is a potent α-agonist with additional weak β-adrenergic activity,[13] a pharmacological profile that distinguishes it from the pure α-agonist PE. This characteristic suggests that NE may be superior for maintaining cardiac output during cesarean delivery under spinal or combined spinal-epidural anaesthesia. Given PE's beneficial effects on temperature regulation alongside its potential hemodynamic drawbacks, a direct comparison of their impact on maternal core temperature is warranted to inform clinical choice.

A continuous prophylactic infusion of PE is more effective than rescue boluses for maintaining circulatory stability.[14] Similarly, a fixed-rate NE infusion is as effective as a PE infusion in treating hypotension.[15–17] Based on these protocols, we conducted this randomized controlled trial to compare the effect of a fixed-rate prophylactic infusion of NE versus PE on maternal core temperature during cesarean section under spinal or combined spinal-epidural anaesthesia. We hypothesized that the core temperature of women receiving NE would be non-inferior to that of women receiving PE.

Methods

We conducted a randomized, double-blind, non-inferiority clinical trial. The study enrolled women undergoing elective cesarean section under spinal or combined spinal-epidural anaesthesia at the Second People's Hospital of Hefei between September 5, 2025 and January 18, 2026. The protocol was approved by the Institutional Ethics Committee of the Second People's Hospital of Hefei and was registered prospectively on ClinicalTrials.gov (Identifier: ChiCTR2500105375). The trial was conducted in accordance with the Declaration of Helsinki and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[18] Patients were screened during the preoperative visit. After providing written informed consent, 140 American Society of Anesthesiologists (ASA) physical status II women with term, uncomplicated, normotensive pregnancies were enrolled.

Exclusion criteria included: age < 18 years, known allergy to PE or NE, fetal malformations, preoperative fever (axillary temperature > 37.5°C), or the presence of shivering. Participants could withdraw at any time. The attending anesthesiologist and obstetrician were responsible for assessing and managing any perioperative adverse events and deciding on study discontinuation if necessary. Participants were randomly allocated in a 1:1 ratio to the PE or the NE group by an external statistician who had no role in patient enrollment or the administration of interventions. A computer-generated randomisation sequence was created using SPSS software (version V.16.0) with variable block sizes. The allocation was concealed using sequentially numbered, opaque, sealed envelopes. Patients, caregivers (anesthesiologists, surgeons, nurses), and outcome assessors were all blinded to group assignment.

Study drug preparation: a nurse not involved in patient care or outcome assessment prepared identical 50 mL syringes containing either NE (8 μg/mL) or PE (100 μg/mL) in a 5% dextrose solution. Syringes were labelled only with "Study Solution" and a randomisation code. Anesthetic and study protocol: Upon arrival in the operating room (ambient temperature set at 22–24°C), an 18-gauge intravenous catheter was placed. All patients received a preload of lactated Ringer's solution at 5 mL/kg over 15 minutes, followed by a maintenance infusion at 6 mL/kg/h. After urinary catheterization, a rectal temperature probe (XC-TS-T, XIAO CHUANG Medical, China) was inserted and connected to a monitor (Bene Vision M15, Mindray, China) for continuous core temperature measurement. Preoperative core temperature was defined as the value recorded just before intrathecal injection (after at least 5 minutes of stabilization). Postoperative core temperature was defined as the value recorded immediately after skin closure, before the patient left the operating room.

With the patient in the lateral decubitus position, anaesthesia was administered at the L_2-L_3 or L_3-L_4 interspace. In this study, spinal anaesthesia was performed by intrathecal injection of 1.5 mL of 1.0% hyperbaric ropivacaine hydrochloride via a 25-gauge needle. For the combined spinal-epidural technique, an 18-gauge Tuohy needle was used to locate the epidural space. A 25-gauge spinal needle was then passed through the Tuohy needle into the subarachnoid space. After confirming free cerebrospinal fluid flow, the same dose of ropivacaine was injected. An epidural catheter was then inserted 3–5 cm into the epidural space and secured. No epidural medications were administered to any patient during surgery. Concurrently with the intrathecal injection, the blinded "Study Solution" infusion was initiated at a fixed rate of 15 mL/h and maintained until the end of surgery. The patient was then repositioned supine with left uterine

displacement. Sensory block level was assessed using a blunt-tipped needle at the midline; surgery was permitted to begin only upon confirmation that the blockade had reached the T_4 dermatome.

The study drug infusion rate was titrated to maintain systolic blood pressure (SBP) within 80–120% of baseline value. The protocol was: If SBP > 120% of baseline, reduce infusion rate to 7.5 mL/h. If SBP > 130% of baseline, stop the infusion. If SBP < 80% of baseline, increase the infusion rate to 30 mL/h. The infusion was also stopped if Heart Rate (HR) was < 60 bpm while SBP remained within the target range (80–120% of baseline). If HR was < 55 bpm with concurrent SBP < 80% of baseline, or if the absolute HR was < 50 bpm, intravenous atropine (0.5 mg) was administered.

The primary outcome was postoperative maternal rectal temperature. "Shivering" was assessed perioperatively and defined as visible muscle contractions of the face, neck, chest, or limbs lasting ≥ 15 seconds. Its severity was graded as: 1 = None; 2 = Mild (facial/neck muscles only); 3 = Moderate (involving trunk); 4 = Severe (generalized).[19] For severe shivering, 25 mg intravenous pethidine was administered as rescue therapy. Thermal comfort was assessed postoperatively using a 100-mm visual analogue scale (VAS), where 0 mm represented "unbearably cold", 50 mm "thermoneutral", and 100 mm "unbearably hot".[20] A fresh, unmarked scale was used for each assessment. The participants were instructed to use these VASs immediately before the commencement of this operation.

Data Collection

Preoperative collected data included maternal age, weight, height, gestation, baseline SBP and diastolic blood pressure (DBP), HR and maternal rectal temperature. Intraoperative and postoperative data included the total fluid volume, duration of surgery, postoperative maternal rectal temperature, incidence of shivering and hypothermia (core temperature < 36.0°C), and VAS score for thermal comfort.

Statistical Analysis

The primary analysis followed the per-protocol principle. The non-inferiority margin (Δ) for the difference in mean postoperative core temperature (NE minus PE) was set at −0.2°C, a value considered clinically insignificant. Non-inferiority would be concluded if the lower limit of the two-sided 95% confidence interval (CI) for the between-group difference was greater than −0.2°C. The sample size was calculated for the non-inferiority test. Based on preliminary data (SD = 0.336°C), 61 participants per group were required to achieve 90% power at a one-sided 2.5% significance level, with a non-inferiority margin of 0.2°C. To account for a 10% dropout rate, 70 participants per group (total N = 140) were enrolled.

Data were analyzed using SPSS 16.0 and GraphPad Prism 8.0.2. Normality was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous data are presented as mean ± SD and compared using Student's *t*-test; non-normally distributed data as median (IQR) and compared using the Mann–Whitney *U*-test. Categorical data are presented as n (%) and compared using the Chi-squared test. A one-sided p-value for non-inferiority was calculated using the method described by Mascha and Sessler.[21] A p-value < 0.025 was considered statistically significant for the primary non-inferiority hypothesis.

Result

A total of 140 eligible women were enrolled and randomly assigned to the PE (n = 70) or NE (n = 70) group. Four patients (two per group) who required epidural supplementation due to failed spinal anesthesia were excluded from the per-protocol analysis. The participant flow diagram is shown in Figure 1. As shown in Table 1, the groups were comparable in all demographic parameters, baseline core temperatures, hemodynamics, and surgical duration. Additionally, no significant differences were found in the incidence of shivering, hypotension, hypothermia, or reactive hypertension, nor in the thermal comfort VAS scores or shivering severity (Table 2). The incidence of hypothermia (core temperature < 36.0°C) was 5.9% (4/68) in the PE group and 8.8% (6/68) in the NE group, with no significant difference between the groups (p = 0.744).

The incidence of bradycardia was significantly lower in the NE group (7.4%) than in the PE group (33.8%) (RR 0.217, 95% CI 0.089 to 0.512; p < 0.001). Regarding the primary outcome, the mean postoperative core temperature did not differ significantly between the NE and PE groups [36.35°C ± 0.31 vs. 36.41°C ± 0.29; p = 0.218] (Table 2). The distributions of preoperative and postoperative temperatures are shown in Figure 2. The mean between-group difference

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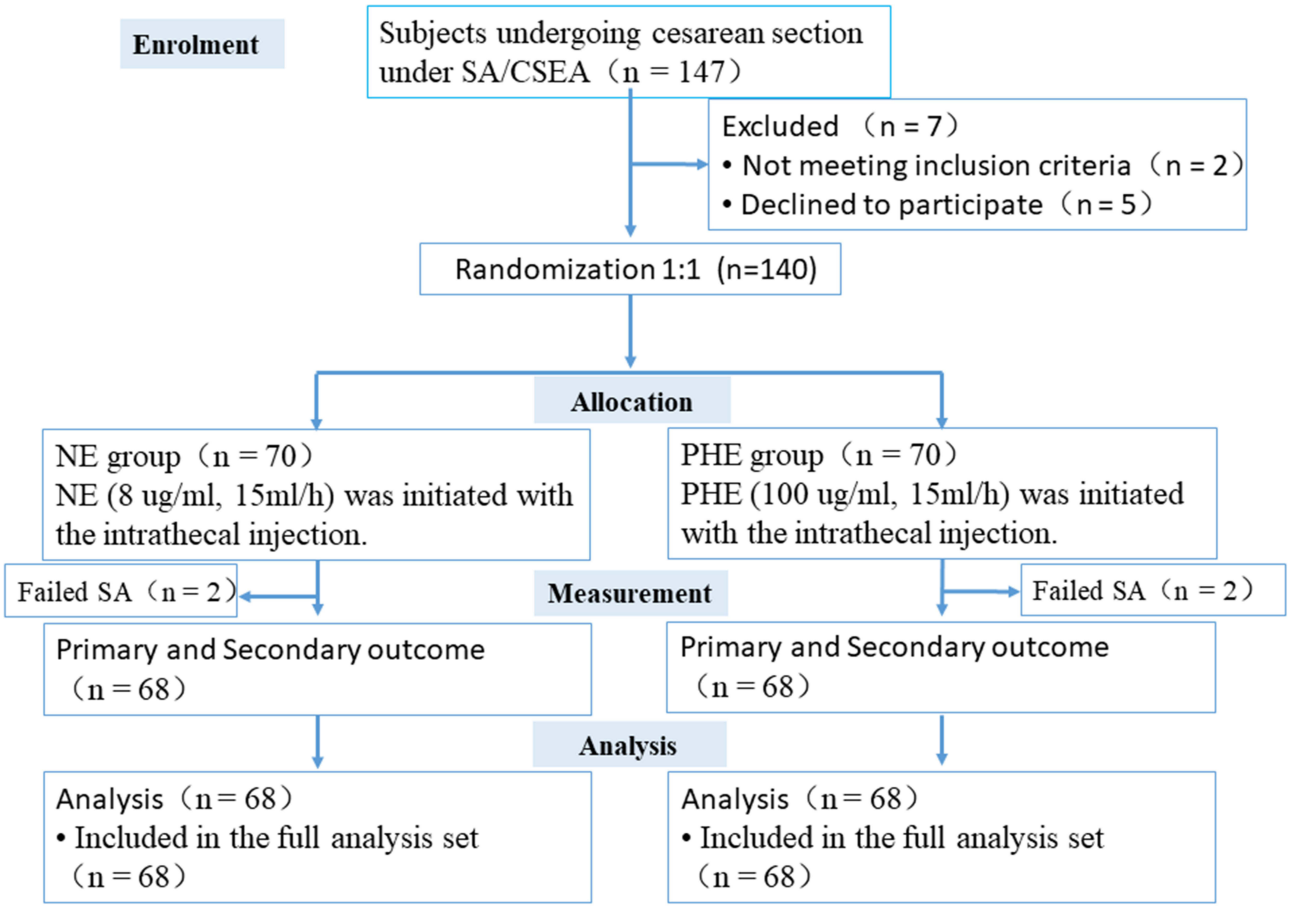

Figure 1 CONSORT flow diagram.
Abbreviation: SA, spinal anaesthesia.

in postoperative core temperature was -0.06°C (95% CI, −0.16 to 0.04). Since the lower limit of the 95% CI (−0.16°C) was greater than the pre-specified non-inferiority margin of −0.2°C, the non-inferiority of NE to PE was established (one-sided non-inferiority $p = 0.008$) (Figure 3).

Table 1 Parturient Demographic Characteristics and Intraoperative Data

Parameters	PE (n = 68)	NE (n = 68)	*p*-value
Age (yr)	31.9 [22–39]	31.1 [21–38]	0.946
Weight (kg)	71.7 ± 8.2	71.9 ± 8.7	0.867
Height (cm)	160.4 ± 4.2	159.8 ± 4.4	0.382
Gestational (weeks)	38.9 (38.3–39.1)	38.7 (38.1–39.1)	0.655
Ambient temperature (°C)	23.0 (23–23)	23.0 (23–24)	0.334
Duration of surgery (min)	58.4 ± 12.9	57.5 ± 14.3	0.692
Fluid administered (mL)	854.2 ± 166.4	838.6 ± 160.0	0.579
Baseline SAP (mmHg)	113.4 ± 9.4	114.5 ± 9.4	0.473
Baseline DAP (mmHg)	69.0 ± 7.1	70.5 ± 7.8	0.273
Baseline HR (bpm)	86.0 ± 11.2	83.5 ± 10.2	0.174

Notes: Values are shown as mean ± standard deviation, mean [range], or median (interquartile range). Continuous variables with normal distribution were compared using Student's *t*-test (presented as mean ± SD); non-normally distributed continuous variables were compared using the Mann-Whitney *U*-test (presented as median [IQR]). Categorical variables were compared using the chi-square test (presented as n [%]).

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Table 2 Intra-Operative Core Body Temperature, Shivering, Hypothermia and VAS Score for Thermal Comfort

Parameters	PE (n = 68)	NE (n = 68)	*p*-value
Core body temperature			
Pre-operative (°C)	37.0 (36.7–37.2)	36.9 (36.7–37.1)	0.311
Post-operative (°C)	36.4 ± 0.31	36.4 ± 0.29	0.218
Incidence of shivering	15 (22.1%)	17 (25.0%)	0.840
Severity of shivering (None/mild/moderate/severe)	53/4/11/0	51/6/11/0	0.803
Incidence of bradycardia (< 60bpm), n/N (%)	23/68 (33.8%)	5/68 (7.4%)	**<0.001**
Incidence of hypotension, n/N (%)	9/68 (13.2%)	10/68 (14.7%)	0.805
Reactive hypertension, n/N (%)	8/68 (11.8%)	6/68 (8.8%)	0.572
Incidence of hypothermia (< 36°C)	4 (5.9%)	6 (8.8%)	0.744
Thermal comfort score (0–100)	50 (40–50)	48 (40–50)	0.369

Notes: Bold text indicates a statistically significant difference ($p < 0.001$). Continuous variables with normal distribution were compared using Student's *t*-test (presented as mean ± SD); non-normally distributed continuous variables were compared using the Mann–Whitney *U*-test (presented as median [IQR]). Categorical variables were compared using the chi-square test (presented as n [%]).

Discussion

This randomized, double-blind, non-inferiority trial demonstrates that a prophylactic fixed-rate infusion of norepinephrine is not inferior to phenylephrine in maintaining maternal core temperature at the end of cesarean delivery under spinal or combined spinal-epidural anaesthesia. This finding is significant because it addresses a key uncertainty surrounding the use of NE as an alternative to PE.

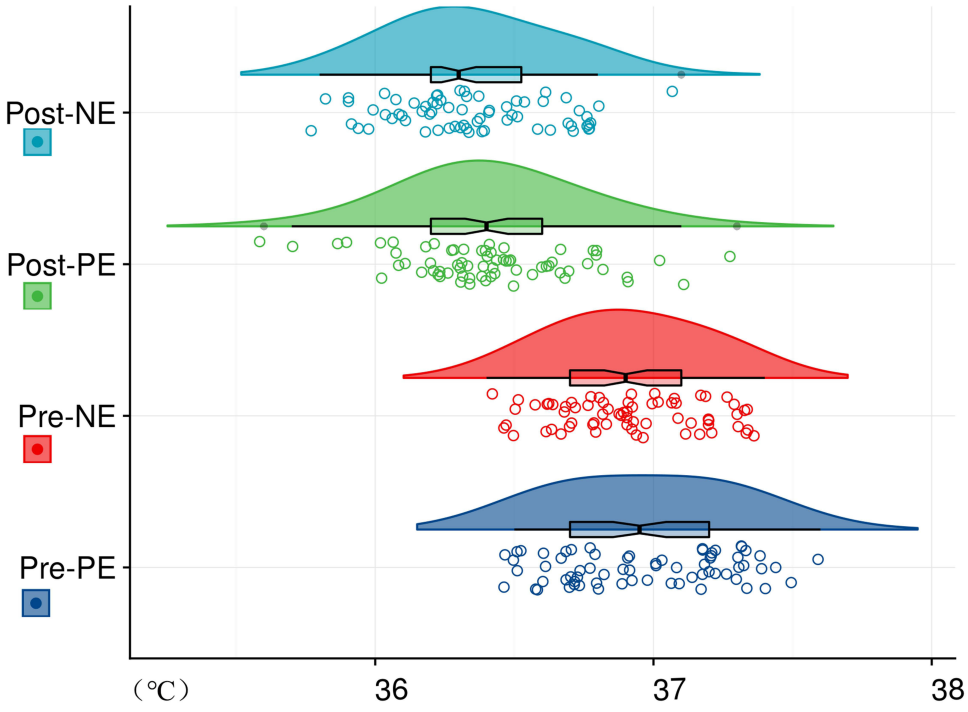

Figure 2 Preoperative and postoperative maternal core body temperatures were totalled for each group. Box plots median and interquartile ranges of 25% and 75%. Raincloud plots show the distribution of maternal core body temperature.

Abbreviations: Pre-PE, preoperative temperature in the PE group; Pre-NE, preoperative temperature in the NE group; Post-PE, postoperative temperature in the PE group; Post-NE, postoperative temperature in the NE group.

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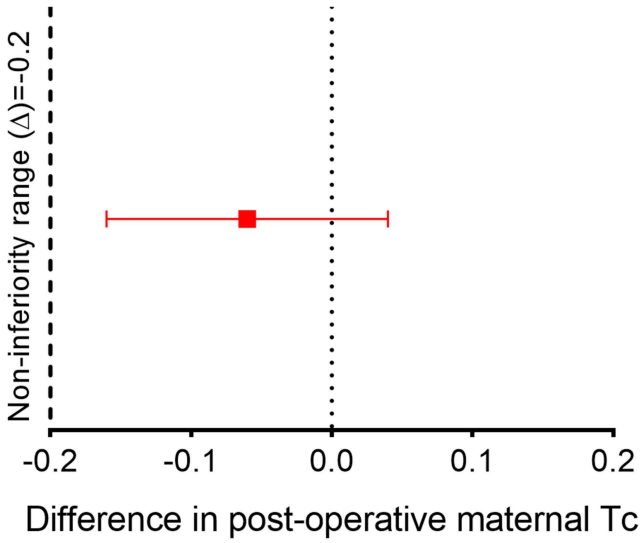

Figure 3 Differences in core body temperature between the two groups. The CI for the difference in core temperature between the two groups did not cross the non-inferiority margin (- 0.2°C), suggesting that NE is non-inferior to PE. Mean and 95% CI.

PE is a commonly used vasopressor for spinal or combined spinal-epidural anaesthesia during cesarean section. NE has been shown to be equally effective as PE for circulatory stabilization,[15,22] neonatal outcome,[17] while avoiding the PE-associated reflex bradycardia.[23] However, prophylactic PE infusion has also been demonstrated to significantly reduce shivering and hypothermia in this setting.[8,9] The effect of NE on maternal core temperature remained unclear, potentially limiting its adoption as a full PE alternative. Our findings directly address this gap by demonstrating that prophylactic NE infusion is non-inferior to PE in maintaining maternal core temperature at the end of surgery. This evidence supports clinicians' confidence in choosing NE, particularly when aiming to maintain stable hemodynamics without compromising maternal thermal regulation.

The margin of inferiority represents the greatest degree of reduction in effectiveness that an individual is willing to accept while still considering the treatment to be equal. There are many methods to determine the non-inferiority margin.[24] Margins should be established in a manner that ensures their suitability for clinical practice, while also being set at a level that is sufficiently elevated to guarantee their efficacy in comparison to a placebo.[25] Studies of clinical practice consider the clinical significance of observed outcomes. In studies comparing core temperatures, a mean difference $\geq$ 0.2°C is generally considered clinically significant.[1,8,26,27] Therefore, to claim non-inferiority, we aimed to confine any potential temperature difference to within this margin. Considering the precision (± 0.1°C) of our monitoring equipment, a margin of 0.2°C was deemed appropriate. This margin also approximates half of the standard deviation observed in our pilot data, aligning with empirical recommendations for continuous outcomes while ensuring a clinically relevant threshold.[24] Although conservative, this margin strengthens the robustness of our non-inferiority conclusion.

The incidence of hypothermia and shivering following cesarean section under spinal anaesthesia is high, with prevalence rates of 82.7% and 53.3%, respectively.[8] In contrast, the incidence of hypothermia in our study was 5.9% in the PE group and 8.8% in the NE group, substantially lower than the previously reported rate. This discrepancy may be attributed to differences in temperature measurement sites (rectal vs. nasopharyngeal) and perioperative warming protocols. To prevent hypothermia, various techniques are employed, including forced-air heating, intravenous fluid warming, and elevation of the operating theatre temperature.[28] However, even when fluid and active air warming are used during cesarean section, the average body temperature at the end of the procedure does not exceed 36°C.[29] This can be attributed to the brief duration of the surgical procedure, the limited efficacy of active warming techniques, and considerable heat loss. Consequently, the minimization of perioperative heat loss represents a crucial aspect of thermoprotection.

PE and NE both act as alpha-adrenergic receptor agonists, which reduce vasodilation and may improve the accelerated heat loss due to blood redistribution from the center to the periphery following spinal anaesthesia, which is the theoretical basis for their ability to improve maternal hypothermia. It is also important to note that vasoconstrictors have the potential to induce non-shivering thermogenesis in skeletal muscle.[30] The relative potency ratio of NE and PE is approximately 13:1[31,32] and pumping equivalent doses of NE and PE did not differ in blood pressure, although there was a difference in the effect on heart rate.[15] In this study, the fixed-rate infusion of PE and NE was utilised instead of a weight-based dosing regimen. Hasanin et al and Kinsella et al concluded that the fixed-rate infusion of PE to prevent maternal hypotension reduced the necessity for physician interventions and unnecessary calculations during cesarean section[14,33] and facilitated both simplification of the infusion protocol and blinding. In a recent study, the ED 90 of PE and NE for effective control of spinal anaesthesia-induced hypotension during cesarean delivery was calculated to be 0.6 μg/kg/min and 0.05 μg/kg/min, respectively.[34] The infusion doses set for PE and NE in this study were also analogous to the doses set in the above study at an average maternal weight of 70 kg.

It is noteworthy that the incidence of maternal shivering was similar in the present study compared to previous findings,[8] whereas the incidence of hypothermia was significantly lower. The discrepancy may be attributed to the monitoring of maternal rectal temperature as the core body temperature in this trial, as opposed to the measurement of nasopharyngeal temperature. The principal benefit of this approach was that it minimizes the stimulation of the awake patient, thereby enhancing comfort, and circumvents alterations and inaccuracies in values resulting from air movement caused by maternal respiration. Additionally, rectal temperatures are inherently higher and more stable than nasopharyngeal temperatures. Consequently, the time required for a temperature to decline to meet the criteria for hypothermia will be longer.

At the same time, factors such as the duration of the operation and the volume of fluids given also affect the maternal core temperature at the end of the operation. In our study, these factors were balanced between groups, minimizing their potential confounding effect. It must be acknowledged that this study has several limitations. Active warming devices (eg, forced-air warmers, intravenous fluid warmers) were not used in this study due to equipment and procedural constraints. If such devices had been applied, they might have raised maternal core temperature in both groups and potentially diminished the absolute temperature difference between NE and PE. Nevertheless, given that NE was non-inferior to PE without active warming, it is reasonable to hypothesize that non-inferiority would be maintained—or even strengthened—under active warming conditions, as both groups would benefit from additional heat preservation. Future studies incorporating active warming are encouraged to validate the external validity of our results. In addition, anxiety may affect maternal shivering,[35] and we tried to reassure women as much as possible to reduce their anxiety. Fortunately, the use of a randomized controlled trial in this study may have reduced the impact of reduced anxiety on the study outcome, as evidenced by the similar incidence of shivering in the two groups.

Conclusion

In summary, this study demonstrates that prophylactic NE infusion is non-inferior to PE for preserving maternal core temperature during spinal or combined spinal-epidural anaesthesia for cesarean delivery. Combined with its more favourable heart rate profile, these findings support NE as a viable and potentially advantageous vasopressor for use in this context. Future studies incorporating active warming measures (eg, forced-air warmers or intravenous fluid warmers) are warranted to determine whether the non-inferiority of NE to PE remains consistent under standard thermoprotective conditions.

Abbreviations

BP, blood pressure; ASA, American Society of Anesthesiologists physical status; MAP, mean arterial pressure; HR, heart rate; SA, spinal anaesthesia; NE, Norepinephrine; PE, phenylephrine.

Data Sharing Statement

Individual deidentified raw data, study protocol, and statistical analysis plan will be made available to qualified researchers upon reasonable request to the corresponding author Dr Xianwen Hu (efy110302@fy.ahmu.edu.cn). Data and documents will be available beginning 6 months after article publication and ending 36 months thereafter.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Ethics Committee of the Second People's Hospital of Hefei (ID:2025-089), registered at ClinicalTrials.gov (trial registration number ChiCTR2500105375). Informed written consents were obtained from all subjects. We confirm our study complies with the Declaration of Helsinki.

Consent for Publication

All authors have read and approved the manuscript and agreed to submit to your journal.

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Disclosure

The authors have no conflicts of interest related to this work.

References

1. Yang C, Cheng Y, Liu S, Huang S, Yu X. Effect of preoperative oral carbohydrate loading on body temperature during combined spinal-epidural anesthesia for elective cesarean delivery. *Anesthesia Analg*. 2021;133(3):731–738. doi:10.1213/ANE.0000000000005447
2. Yu L, Zhang Z, Li L, et al. The effect of preventive administration of metaraminol on hypothermia and shivering in cesarean section patients randomized clinical trial –a randomized controlled study. *Front Pharmacol*. 2025;16:1631503. doi:10.3389/fphar.2025.1631503
3. Link T. Guidelines in practice: hypothermia prevention. *AORN J*. 2020;111(6):653–666. doi:10.1002/aorn.13038
4. van Veelen MJ, Brodmann Maeder M. Hypothermia in Trauma. *Int J Environ Res Public Health*. 2021;18(16):8719. doi:10.3390/ijerph18168719
5. Chen J, Zhan Y, Zhao X, Huang W. Improving perioperative normothermia: insights from clinical practice. *Anesthesiol Perioperat Sci*. 2025;3 (2):20. doi:10.1007/s44254-025-00098-2
6. Legrand M, Kothari R, Fong N, et al. Norepinephrine versus phenylephrine for treating hypotension during general anaesthesia in adult patients undergoing major noncardiac surgery: a multicentre, open-label, cluster-randomised, crossover, feasibility, and pilot trial. *Br J Anaesth*. 2023;130 (5):519–527. doi:10.1016/j.bja.2023.02.004
7. Sun L, Tang Y, Guo F, et al. Norepinephrine or phenylephrine for the prevention of post-spinal hypotension after caesarean section: a double-blinded, randomized, controlled study of fetal heart rate and fetal cardiac output. *J Clin Anesth*. 2024;97:111533. doi:10.1016/j.jclinane.2024.111533
8. Palanisamy S, Rudingwa P, Panneerselvam S, Satyaprakash MVS, Kuberan A, Amala R. Effect of low dose phenylephrine infusion on shivering and hypothermia in patients undergoing cesarean section under spinal anesthesia: a randomized clinical trial. *Int J Obstet Anesth*. 2022;50:103542. doi:10.1016/j.ijoa.2022.103542
9. Tan Sook Kuan J, Musthafa QA, Abdullah FH, Sayed Masri SNN. Intraoperative phenylephrine infusion to reduce perioperative shivering in lower segment caesarean section: a randomised controlled study. *Medicine*. 2023;102(19):e33721. doi:10.1097/MD.0000000000033721
10. Pan ZB, Sheng ZM, Zhu M, et al. Randomized double-blinded comparison of intermittent boluses phenylephrine and norepinephrine for the treatment of postspinal hypotension in patients with severe pre-eclampsia during cesarean section. *Drug Des Devel Ther*. 2024;18:639–650. doi:10.2147/DDDT.S446657
11. Du W, Song Y, Li J, Zhou X, Xu Z, Liu Z. Comparison of prophylactic norepinephrine and phenylephrine infusions during spinal anaesthesia for primary caesarean delivery in twin pregnancies: a randomized double-blinded clinical study. *Drug Des Devel Ther*. 2022;16:789–798. doi:10.2147/DDDT.S357507

12. Belin O, Casteres C, Alouini S, Le Pape M, Dupont A, Boulain T. Manually controlled, continuous infusion of phenylephrine or norepinephrine for maintenance of blood pressure and cardiac output during spinal anesthesia for cesarean delivery: a double-blinded randomized study. *Anesthesia Analg*. 2023;136(3):540–550. doi:10.1213/ANE.0000000000006244
13. Chen Y, Xiong X, Qin R, Guo L, Shi Y, Ni X. Up-and-down determination of different crystalloid coload volumes on the ED 90 of prophylactic norepinephrine infusion for preventing postspinal anesthesia hypotension during cesarean section. *Drug Des Devel Ther*. 2024;18:2609–2616. doi:10.2147/DDDT.S460436
14. 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(1):71–92. doi:10.1111/anae.14080
15. Theodoraki K, Hadzilia S, Valsamidis D, Stamatakis E. Prevention of hypotension during elective cesarean section with a fixed-rate norepinephrine infusion versus a fixed-rate phenylephrine infusion. A double-blinded randomized controlled trial. *Int J Surg*. 2020;84:41–49. doi:10.1016/j.ijsu.2020.10.006
16. Ravichandrane B, Subramaniam R, Muthiah T, Talawar P, Ramadurai R. Comparison of prophylactic infusion of phenylephrine versus norepinephrine for the prevention of post spinal hypotension in parturients undergoing elective caesarean section-a randomized, double-blinded, non-inferiority trial. *Turk J Anaesthesiol Reanim*. 2023;51(3):213–218. doi:10.4274/TJAR.2022.22909
17. Tao W, Bao J, Wang Q, et al. Effects of prophylactic constant-rate infusion of norepinephrine or phenylephrine on neonatal outcomes during caesarean section. *Eur J Med Res*. 2026;31(1):188. doi:10.1186/s40001-025-03761-3
18. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ*. 2025;389:e081123.
19. Vanderstappen I, Vandermeersch E, Vanacker B, Mattheussen M, Herijgers P, Van Aken H. The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study. *Anaesthesia*. 1996;51(4):351–355. doi:10.1111/j.1365-2044.1996.tb07747.x
20. Horn EP, Schroeder F, Gottschalk A, et al. Active warming during cesarean delivery. *Anesthesia Analg*. 2002;94(2):409–414. doi:10.1213/00000539-200202000-00034
21. Mascha EJ, Sessler DI. Equivalence and noninferiority testing in regression models and repeated-measures designs. *Anesthesia Analg*. 2011;112(3):678–687. doi:10.1213/ANE.0b013e318206f872
22. Mujahid OM, Sinha M, Kumar M, Singha SK, Khetarpal M, Dubey R. A comparison of phenylephrine and norepinephrine infusions in preventing hypotension after subarachnoid block in caesarean section: a randomized, double-blind study. *Cureus*. 2025;17(4):e82176. doi:10.7759/cureus.82176
23. Guo L, Qin R, Ren X, et al. Prophylactic norepinephrine or phenylephrine infusion for bradycardia and post-spinal anaesthesia hypotension in patients with preeclampsia during Caesarean delivery: a randomised controlled trial. *Br J Anaesth*. 2022;128(5):e305–e307. doi:10.1016/j.bja.2022.01.027
24. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. 2011;12:106. doi:10.1186/1745-6215-12-106
25. Walker J. Non-inferiority statistics and equivalence studies. *BJA Educ*. 2019;19(8):267–271. doi:10.1016/j.bjae.2019.03.004
26. Hamamoto H, Yamamoto M, Masubuchi S, et al. The impact of preoperative carbohydrate loading on intraoperative body temperature: a randomized controlled clinical trial. *Surg Endosc*. 2018;32(11):4393–4401. doi:10.1007/s00464-018-6273-2
27. Thorburn PT, Monteiro R, Chakladar A, Cochrane A, Roberts J, Mark Harper C. Maternal temperature in emergency caesarean section (MATES): an observational multicentre study. *Int J Obstet Anesth*. 2021;46:102963. doi:10.1016/j.ijoa.2021.102963
28. Caughey AB, Wood SL, Macones GA, et al. Guidelines for intraoperative care in cesarean delivery: enhanced recovery after surgery society recommendations (Part 2). *Am J Clin Exp Obstet Gynecol*. 2018;219(6):533–544. doi:10.1016/j.ajog.2018.08.006
29. Cobb B, Cho Y, Hilton G, Ting V, Carvalho B. Active warming utilizing combined IV fluid and forced-air warming decreases hypothermia and improves maternal comfort during cesarean delivery: a randomized control trial. *Anesthesia Analg*. 2016;122(5):1490–1497. doi:10.1213/ANE.0000000000001181
30. Tong AC, Rattigan S, Dora KA, Clark MG. Vasoconstrictor-mediated increase in muscle resting thermogenesis is inhibited by membrane-stabilizing agents. *Can J Physiol Pharmacol*. 1997;75(7):763–771. doi:10.1139/y97-090
31. 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(6):934–941. doi:10.1097/ALN.0000000000001880
32. Guo L, Xu X, Qin R, et al. Prophylactic norepinephrine and phenylephrine boluses to prevent postspinal anesthesia hypotension during cesarean section: a randomized sequential allocation dose-finding study. *Drug Des Devel Ther*. 2023;17:1547–1555. doi:10.2147/DDDT.S406671
33. Hasanin A, Habib S, Abdelwahab Y, et al. Variable versus fixed-rate infusion of phenylephrine during cesarean delivery: a randomized controlled trial. *BMC Anesthesiol*. 2019;19(1):197. doi:10.1186/s12871-019-0879-3
34. Tan H, Chen Y, Jiang Y, et al. Determination of ED90s of phenylephrine and norepinephrine infusion for prevention of spinal anesthesia-induced hypotension in patients with preeclampsia during cesarean delivery. *Drug Des Devel Ther*. 2024;18:2813–2821. doi:10.2147/DDDT.S467072
35. Wódarski B, Chutkowski R, Banasiewicz J, et al. Risk factors for shivering during caesarean section under spinal anaesthesia. A prospective observational study. *Acta anaesthesiologica Scandinavica*. 2020;64(1):112–116. doi:10.1111/aas.13462