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Two Prophylactic Bolus Doses of Phenylephrine Coadministered With Oxytocin to Prevent Hypotension During Elective Cesarean Section: A Single-Center Randomized Controlled Trial

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Abstract

Background

Intravenous oxytocin at delivery lowers systemic vascular resistance and worsens subarachnoid block-induced hypotension. Prophylactic phenylephrine coadministered with the oxytocin bolus is a rational strategy, but the optimal dose has not been settled.

Objective

To determine whether, compared with a 75 µg bolus, a 100 µg bolus of phenylephrine coadministered with oxytocin at cord clamping reduces the incidence of maternal hypotension in parturients undergoing elective lower segment (low transverse) cesarean section under spinal anesthesia at a tertiary teaching hospital in Puducherry, India, from September 2024 to December 2025.

Methods

In a prospective, single-center, double-blinded, randomized trial, 80 parturients with American Society of Anesthesiologists physical status (ASA-PS) II scheduled for elective cesarean section under spinal anesthesia were randomly allocated in a 1:1 ratio to phenylephrine 75 µg (group A) or 100 µg (group B), coadministered with oxytocin 3 IU at cord clamping. The primary outcome was the incidence of hypotension, defined as a systolic blood pressure (SBP) below 90 mm Hg or a fall of 20% or more from the baseline SBP, within six hours after the subarachnoid block.

Results

Hypotension occurred in 10 of 40 women (25.0%) in group A and three of 40 women (7.5%) in group B (risk difference = 17.5 percentage points, odds ratio = 4.04, exact 95% confidence interval (CI) = 0.93 to 24.90, Fisher exact p = 0.066), so the pre-specified primary comparison did not reach statistical significance. Hypotensive episodes and rescue phenylephrine were fewer in group B (mean rescue dose = 17.5 µg versus 5.0 µg, Mann-Whitney U p = 0.035). Serial hemodynamics were similar at all 12 time points. No bradycardia or reactive hypertension occurred.

Conclusion

Compared with a 75 µg bolus, a 100 µg prophylactic phenylephrine bolus coadministered with oxytocin at cord clamping was associated with a lower incidence of maternal hypotension, but the difference was not statistically significant on the pre-specified Fisher's exact test. Compared with 75 µg, the 100 µg dose required less rescue phenylephrine, and no bradycardia or reactive hypertension occurred with either dose. An adequately powered trial is needed before a preferred dose can be recommended.

Categories: Therapeutics, Obstetrics/Gynecology, Anesthesiology
Keywords: caesarean section, hypotension, oxytocin, phenylephrine, spinal anaesthesia, vasopressor

Introduction

Hemorrhage is a leading cause of maternal death worldwide [1]. Intravenous oxytocin is given at the delivery of the fetus to promote uterine contraction, but the bolus itself has immediate hemodynamic effects. In healthy parturients monitored with an arterial line, an oxytocin 5 IU bolus increased cardiac output by a mean maximum of 94% and changed systolic arterial pressure by a mean maximum of 31% [2], and bolus doses produced marked changes in heart rate and mean arterial pressure that were not seen with a continuous infusion [3]. In a trial of oxytocin 3 IU, peak changes in blood pressure and heart rate were

measured within the first 150 seconds after the injection [4].

This oxytocin effect additionally worsens the hypotension associated with the sympathetic block of subarachnoid anesthesia. Pregnancy itself lowers systemic vascular resistance and raises cardiac output [5,6]. This pregnancy-induced vasodilation is mediated by endothelium-derived vasodilators and by hormones such as relaxin, which interacts with angiotensin II pathways to dilate blood vessels [7]. A further fall in vascular resistance, such as that caused by spinal anesthesia and oxytocin, therefore readily produces hypotension. Spinal-induced hypotension can cause nausea, vomiting, dizziness, reduced cardiac output, and impaired uteroplacental perfusion [8]. Vasopressors are therefore given prophylactically, and the international consensus statement recommends alpha-1 agonists such as phenylephrine as the first-line drugs during cesarean section under spinal anesthesia [9].

Phenylephrine, a selective alpha-1 agonist, has largely replaced ephedrine as the first-line drug because it restores blood pressure with less maternal tachycardia and less fetal acidemia [10-12]. Contemporary Indian obstetric anesthesia opinion mirrors this shift [13]. Bayesian network meta-analyses have since compared ephedrine, phenylephrine, and norepinephrine for the prevention and management of neuraxial hypotension, with differing rankings for efficacy and for fetal acid-base outcomes [14,15].

The bolus regimen given together with oxytocin has attracted specific attention because the two drugs act on the vascular tree within the same short window. Rumboll and colleagues found that a 50 µg phenylephrine bolus given immediately before 3 IU oxytocin did not prevent hypotension and tachycardia in 40 women, although the mean fall in mean arterial pressure over the following 150 seconds was smaller than with saline [4]. Gangadharaiah and colleagues randomized 90 parturients to oxytocin with phenylephrine 50 µg, phenylephrine 75 µg, or saline and reported hypotension in 90%, 10%, and 98%, respectively [16]. To our knowledge, no randomized trial has compared 75 µg with 100 µg coadministered with oxytocin, and the most effective coadministered dose has not been established.

We designed the present trial to test whether a 100 µg prophylactic bolus of phenylephrine coadministered with 3 IU oxytocin at cord clamping reduces the incidence of maternal hypotension compared with a 75 µg bolus in parturients with American Society of Anesthesiologists physical status (ASA-PS) II undergoing elective cesarean section under spinal anesthesia. Secondary objectives were to compare the number of hypotensive episodes, the total rescue phenylephrine dose, serial hemodynamic variables up to six hours after the subarachnoid block, and adverse events between the two doses. We hypothesized that the higher dose would lower the incidence of hypotension and the rescue vasopressor requirement without a proportionate increase in bradycardia or reactive hypertension.

Materials And Methods

Study design

This was a prospective, single-center, parallel-group, double-blind, randomized controlled trial. Reporting followed the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [17]. The trial was conducted in accordance with the Declaration of Helsinki. Data were extracted directly from the anesthesia records and entered into a case-record form on the same day.

Setting

The trial was conducted at a tertiary teaching hospital in Puducherry, India, from September 2024 to December 2025.

Study population and sampling strategy

We recruited women aged 18 to 40 years, with ASA-PS II, scheduled for elective cesarean section under subarachnoid block. We excluded women with ASA-PS III or higher, uncontrolled hypertension, pre-eclampsia, cardiovascular or renal disease, a body mass index above 35 kg/m², multiple gestation, placenta previa, known fetal anomaly, contraindication to spinal anesthesia, and known allergy to phenylephrine or oxytocin.

Sample size was determined a priori, assuming a hypotension incidence of 45% with the lower dose and 15% with the higher dose, which were the investigators' a priori estimates stated in the dissertation protocol. To detect this 30 percentage-point difference with a two-sided alpha of 0.05 and 80% power, 35 women per group were required, and 40 per group were recruited to allow for attrition of up to 12.5%. No participant was lost to follow-up, and all 80 were analyzed in the groups to which they were randomized.

Eighty eligible women were randomized in a one-to-one ratio to group A (phenylephrine 75 µg) or group B (phenylephrine 100 µg) with a computer-generated randomization sequence and sequentially numbered opaque sealed envelopes. The study drug was drawn and diluted to the allocated dose by an anesthesiology resident who did not participate in outcome assessment. The attending anesthesiologist who managed the airway and monitored hemodynamics, the outcome assessor at the postoperative visit, and the data analyst

were blinded to allocation. Participants were blinded to their allocation.

Intervention

Participants were fasted for six hours for solids and two hours for clear liquids. On arrival in the operating room, standard monitoring was applied with a multiparameter patient monitor (IntelliVue MP30, Philips Healthcare, Eindhoven, Netherlands), comprising three-lead electrocardiography, non-invasive blood pressure, and pulse oximetry. Baseline heart rate, systolic and diastolic blood pressures, mean arterial pressure, and peripheral oxygen saturation were recorded before subarachnoid block. A 250 mL Ringer lactate co-load was started with the block. Subarachnoid block was performed by same anesthesiologist having 20 plus years of experience for all 80 patients, at the L3 to L4 interspace in the sitting position with a 25-gauge Quincke spinal needle (Spinocan, B. Braun Melsungen AG, Melsungen, Germany) and 2 mL of hyperbaric bupivacaine 0.5% (Anawin Heavy, Neon Laboratories Ltd, Mumbai, India) with fentanyl 15 µg (Fentanyl Citrate, Verve Human Care Laboratories, Haridwar, India). The parturient was placed supine with 15 degrees of left uterine displacement immediately after the block.

At clamping of the umbilical cord, oxytocin 3 IU (Evatocin, Neon Laboratories Ltd., Mumbai, India) was given as a slow intravenous bolus over five minutes together with the allocated phenylephrine bolus (phenylephrine hydrochloride, 75 µg for group A and 100 µg for group B, Phenpres, Neon Laboratories Ltd., Mumbai, India). A continuation oxytocin infusion of 10 IU in 500 mL of Ringer lactate was then administered over four hours. Rescue phenylephrine 50 µg was administered by intravenous bolus for each qualifying hypotensive episode. Bradycardia below 60 beats per minute was treated with intravenous atropine 0.4 mg. Nausea or vomiting was managed with intravenous ondansetron 4 mg once the blood pressure had been restored.

Data collection

The primary outcome was the incidence of any hypotension episode within six hours after subarachnoid block. Hypotension was defined a priori as systolic blood pressure (SBP) below 90 mm Hg or a fall of 20% or more from the baseline SBP value, whichever occurred first. Secondary outcomes were the number of recurrent hypotensive episodes per participant; the total rescue phenylephrine dose; and heart rate, SBP, diastolic blood pressure, mean arterial pressure, and peripheral oxygen saturation recorded at baseline and at 2, 4, 6, 8, 10, 15, and 30 minutes and 1, 2, 4, and 6 hours after subarachnoid block. These variables were measured with the multiparameter monitor at each of these time points, and hypotension was assessed at every measurement. Adverse events consisted of bradycardia (heart rate below 60 beats per minute), reactive hypertension (SBP above 140 mm Hg), and nausea or vomiting. These outcomes correspond to the outcomes registered with the Clinical Trials Registry of India (CTRI/2024/08/073061), where the primary outcome was the comparison of the effects of phenylephrine coadministered with oxytocin and the secondary outcomes were the need for rescue vasopressors and the incidence of side effects.

Data analysis

The statistical analysis was performed with Graipe Stats X version 6.2 (DTRAS Global, Chennai, India). Distribution was assessed for every continuous variable with the Shapiro-Wilk test. Variables that were normally distributed in both groups were compared with the Welch t-test, and variables that were non-normally distributed in either group with the Mann-Whitney U test. Continuous variables are presented as mean ± standard deviation (SD), with the median and interquartile range (IQR) added for the highly skewed rescue dose. Categorical variables were compared with Fisher's exact test as the primary analysis, with the uncorrected Pearson chi-square statistic reported as a sensitivity analysis. The test statistic is reported with each p-value.

For the primary outcome, we report the incidence in each group with a Wilson score 95% confidence interval (CI), the risk difference with a Newcombe hybrid score 95% CI, the relative risk with a Katz log 95% CI, the conditional maximum likelihood odds ratio with its exact 95% CI, which corresponds to the Fisher exact test, and the number needed to treat as the reciprocal of the risk difference and of its CI limits. The number of hypotensive episodes per woman was compared with the Mann-Whitney U test, and the rate ratio of episodes was estimated with Poisson regression. A two-sided p-value below 0.05 was considered statistically significant. Secondary outcomes were not adjusted for multiple comparisons and are interpreted as exploratory.

Ethical considerations and trial registration

The trial was approved by the Institutional Ethics Committee (Human Studies) of Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry (reference number: 64/SVMCH/IEC-Cert/February 24; dated: 7 February 2024), after review at its meeting on 20 January 2024. Written informed consent was obtained from every participant. The trial complied with the Declaration of Helsinki as revised in 2013. The trial was registered prospectively with the Clinical Trials Registry of India (CTRI/2024/08/073061, registered on 29 August 2024).

Results

Of 96 women assessed for eligibility during the recruitment period, 16 were excluded (10 did not meet the inclusion criteria, four declined consent, and two were withdrawn for administrative reasons). Eighty women were randomized, 40 to each group. No participant was lost to follow-up, and none discontinued the intervention. The CONSORT flow of participants is shown in Figure *1*.

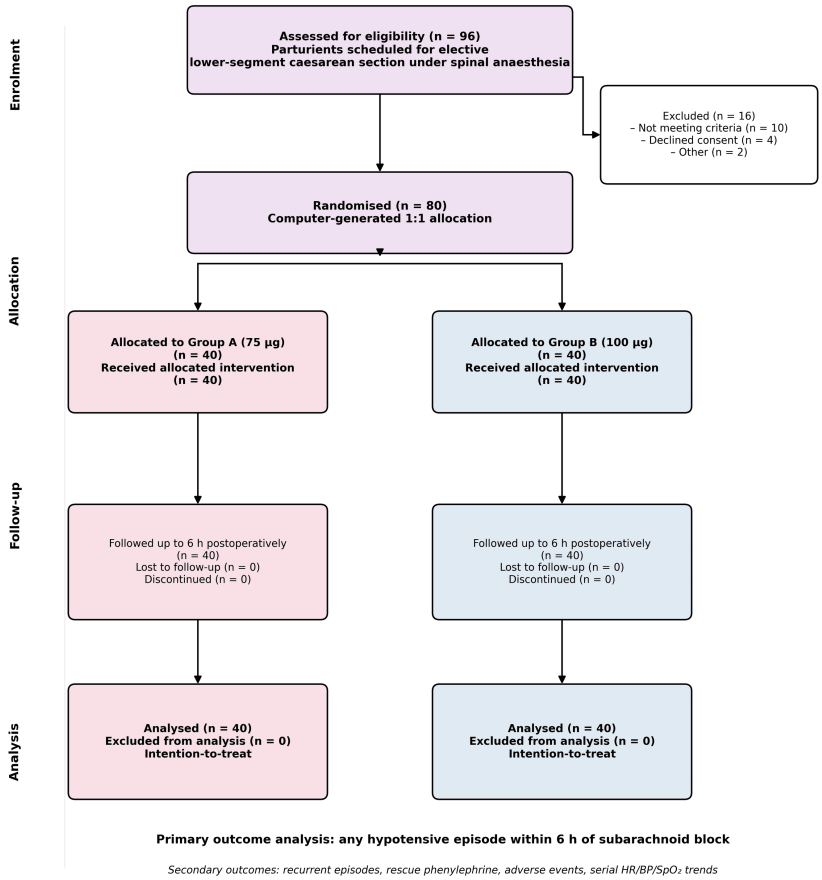


FIGURE 1: CONSORT 2010 flow of participants.

Ninety-six women were assessed for eligibility during the recruitment period. Sixteen were excluded (10 did not meet the inclusion criteria, four declined consent, and two were withdrawn for administrative reasons). Eighty women were randomized, 40 to each group. All 80 participants received the allocated intervention, completed follow-up to six hours after the subarachnoid block, and were analyzed by intention-to-treat.

CONSORT: Consolidated Standards of Reporting Trials.

Baseline characteristics

Age, height, weight, and body mass index were comparable between the two groups (Table *1*). Baseline heart rate, systolic and diastolic blood pressures, mean arterial pressure, and peripheral oxygen saturation were also comparable (Table *2*). The mean baseline body mass index in group A was 25.90 ± 2.89 kg/m² and in group B was 25.05 ± 2.79 kg/m² (p = 0.186).

Variable	Group A (75 µg, n = 40)	Group B (100 µg, n = 40)	Statistical test	Test statistic	p-value
Age, mean ± SD, years	28.68 ± 4.39	27.45 ± 4.90	Welch t test	t = 1.18 (df = 77.1)	0.243
Height, mean ± SD, cm	156.62 ± 4.25	156.65 ± 3.25	Mann-Whitney U test	U = 829.5	0.779
Weight, mean ± SD, kg	63.42 ± 6.52	61.40 ± 6.31	Mann-Whitney U test	U = 960.5	0.123
Body mass index, mean ± SD, kg/m²	25.90 ± 2.89	25.05 ± 2.79	Welch t test	t = 1.33 (df = 77.9)	0.186
Sex, female, n (%)	40 (100.0)	40 (100.0)	Not tested (identical in both groups by inclusion criteria)	Not applicable	Not tested
ASA-PS II, n (%)	40 (100.0)	40 (100.0)	Not tested (identical in both groups by inclusion criteria)	Not applicable	Not tested
Type of cesarean section (elective), n (%)	40 (100.0)	40 (100.0)	Not tested (identical in both groups by inclusion criteria)	Not applicable	Not tested

TABLE 1: Baseline demographic and clinical characteristics.

Values are mean ± SD or n (%). Group A received phenylephrine 75 micrograms, and group B received phenylephrine 100 micrograms, both coadministered with intravenous oxytocin 3 IU at cord clamping. Distribution of continuous variables was assessed with the Shapiro-Wilk test. Welch t-test was applied to normally distributed variables and the Mann-Whitney U test to non-normal variables. Sex, ASA-PS, and type of cesarean section were identical in both groups by the inclusion criteria and were not tested. No between-group difference reached the pre-specified significance threshold of p = 0.05.

ASA-PS: American Society of Anesthesiologists physical status; SD: standard deviation; t: Welch t statistic; df: degrees of freedom; U: Mann-Whitney U statistic.

Time	HR A	HR B	SBP A	SBP B	DBP A	DBP B	MAP A	MAP B	SpO2 A	SpO2 B
Baseline	91.7 ± 8.1	90.4 ± 7.6	110.3 ± 8.7	111.7 ± 8.5	73.6 ± 9.1	71.4 ± 8.5	85.8 ± 8.9	84.9 ± 8.2	99.1 ± 0.8	99.2 ± 0.9
2 min	92.2 ± 8.5	91.2 ± 7.6	110.9 ± 8.7	112.3 ± 8.2	72.4 ± 9.9	74.8 ± 8.9	85.2 ± 9.2	87.3 ± 8.4	99.1 ± 0.8	98.8 ± 0.9
4 min	92.1 ± 8.3	91.0 ± 8.0	110.2 ± 10.7	113.0 ± 8.5	74.3 ± 11.9	75.1 ± 9.2	86.2 ± 11.2	87.7 ± 8.7	99.0 ± 0.8	98.9 ± 0.8
6 min	92.0 ± 8.3	90.4 ± 8.0	107.7 ± 13.8	110.0 ± 8.8	70.0 ± 14.4	71.8 ± 10.6	82.5 ± 14.0	84.5 ± 9.6	99.2 ± 0.8	99.0 ± 0.8
8 min	91.8 ± 8.3	90.7 ± 7.9	109.2 ± 10.6	112.2 ± 8.9	71.5 ± 11.6	73.9 ± 10.6	84.0 ± 11.0	86.6 ± 9.6	99.0 ± 0.8	99.2 ± 0.9
10 min	92.0 ± 8.6	90.7 ± 7.9	110.6 ± 10.6	112.1 ± 8.8	73.5 ± 13.7	74.6 ± 8.9	85.8 ± 12.5	87.1 ± 8.5	99.1 ± 0.8	99.0 ± 0.8
15 min	92.0 ± 8.2	91.0 ± 7.8	109.1 ± 12.0	111.8 ± 9.2	72.7 ± 12.5	74.7 ± 10.2	84.9 ± 12.2	87.1 ± 9.4	99.1 ± 0.9	99.0 ± 0.8
30 min	92.3 ± 8.2	90.4 ± 7.3	110.9 ± 8.9	112.0 ± 8.6	72.7 ± 9.9	75.0 ± 8.8	85.4 ± 9.3	87.5 ± 8.2	98.8 ± 0.9	99.0 ± 0.9
1 h	90.2 ± 8.1	89.1 ± 8.0	110.8 ± 9.4	112.7 ± 9.3	73.8 ± 10.1	74.1 ± 9.5	86.1 ± 9.7	87.0 ± 9.1	99.2 ± 0.8	98.9 ± 0.8
2 h	89.9 ± 8.2	88.8 ± 8.2	111.1 ± 9.2	112.0 ± 8.7	75.0 ± 10.2	74.3 ± 9.4	87.0 ± 9.7	86.8 ± 8.8	98.9 ± 0.8	99.0 ± 0.8
4 h	90.4 ± 8.1	89.3 ± 7.5	110.7 ± 9.1	112.5 ± 9.0	73.3 ± 9.5	74.2 ± 9.6	85.8 ± 9.2	87.0 ± 9.1	98.7 ± 0.8	99.0 ± 0.9
6 h	90.1 ± 8.4	89.1 ± 7.3	111.1 ± 9.1	112.0 ± 8.8	73.4 ± 10.3	73.0 ± 8.6	86.0 ± 9.6	86.0 ± 8.2	99.0 ± 0.8	99.1 ± 0.8

TABLE 2: Serial hemodynamic parameters at 12 pre-specified time points (mean ± SD).

Values are mean ± SD. All five parameters were recorded at every time point in every participant (n = 40 per group, 100% complete data). Group comparisons at each time point used the Welch t-test or the Mann-Whitney U test as indicated by the Shapiro-Wilk normality assessment. The between-group p-value did not fall below the pre-specified significance threshold of 0.05 at any individual time point for any of the five parameters. Baseline (row 1) is the pre-block measurement. Subsequent time points refer to elapsed time after the subarachnoid block.

A: Group A; B: Group B; DBP: diastolic blood pressure; HR: heart rate; MAP: mean arterial pressure; SBP: systolic blood pressure; SD: standard deviation; SpO2: peripheral oxygen saturation.

Primary outcome

Hypotension occurred in 10 of 40 women (25.0%, 95% CI: 14.2 to 40.2) in group A and three of 40 women (7.5%, 95% CI: 2.6 to 19.9) in group B (Fisher exact p = 0.066), so the pre-specified primary comparison did not reach statistical significance. The risk difference was 17.5 percentage points (95% CI: 1.1 to 33.5 by the Newcombe hybrid score method, an asymptotic interval that, unlike the exact test, excludes a zero difference), the relative risk was 3.33 (95% CI: 0.99 to 11.22), and the odds ratio was 4.04 (exact 95% CI: 0.93 to 24.90). The uncorrected Pearson chi-square statistic was 4.50 with p = 0.034, reported as a sensitivity analysis only (Table *3* and Figure *2*).

Measure	Group A (75 µg, n = 40)	Group B (100 µg, n = 40)	Effect estimate (95% CI)	Statistical test	Test statistic	p-value
Hypotension, n (%)	10 (25.0)	3 (7.5)	NA	Fisher exact test (primary analysis)	NA (exact test)	0.066
Hypotension incidence, 95% CI, %	14.2 to 40.2	2.6 to 19.9	NA	Wilson score method	NA	NA
Risk difference, percentage points	NA	NA	17.5 (1.1 to 33.5)	Newcombe hybrid score method	NA	NA
Odds ratio, conditional maximum likelihood	NA	NA	4.04 (0.93 to 24.90)	Exact CI (corresponds to the Fisher exact test)	NA	NA
Relative risk	NA	NA	3.33 (0.99 to 11.22)	Katz (log) method	NA	NA
Number needed to treat	NA	NA	6 (3 to 93)	Reciprocal of the Newcombe risk difference CI	NA	NA
Hypotension, sensitivity analysis, n (%)	10 (25.0)	3 (7.5)	NA	Pearson chi-square test, uncorrected	$\chi^2 = 4.50$ (df = 1)	0.034
Women with no hypotensive episode, n	30	37	NA	Mann-Whitney U test (episodes per woman)	U = 941.0	0.035
Women with one hypotensive episode, n	6	2	NA	NA	NA	NA
Women with two hypotensive episodes, n	4	1	NA	NA	NA	NA
Total hypotensive episodes, n	14	4	Rate ratio 3.50 (1.15 to 10.63)	Poisson regression	NA	NA

TABLE 3: Primary outcome: Incidence and recurrence of hypotension.

Hypotension was defined a priori as systolic blood pressure below 90 mm Hg or a fall of 20% or more from baseline, whichever occurred first, within six hours of subarachnoid block. The primary comparison was the Fisher exact test between group A and group B, which did not reach statistical significance. The odds ratio is the conditional maximum likelihood estimate with its exact CI, which corresponds to the Fisher's exact test. Wilson score CIs are used for group incidences. The uncorrected Pearson chi-square statistic and the Newcombe risk difference CI are less conservative than the exact test and are reported for completeness. The rate ratio of hypotensive episodes (group A versus group B) and its 95% CI were estimated with Poisson regression.

CI: confidence interval; U: Mann-Whitney U statistic; χ^2: Pearson chi-square statistic; NA: not applicable (the measure is not defined for that cell).

Fisher's exact test has no test statistic.

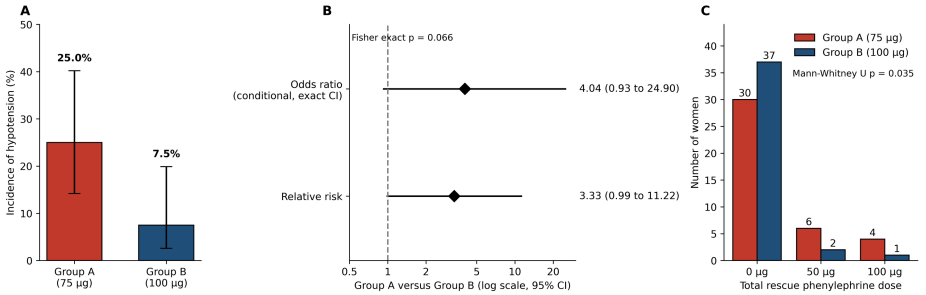


FIGURE 2: Primary outcome: Incidence, effect sizes, and rescue phenylephrine dose.

Panel A shows the incidence of hypotension in each group with Wilson 95% confidence intervals. Panel B shows the relative risk and the odds ratio for group A versus group B on a logarithmic scale. The relative risk interval is the Katz log interval, and the odds ratio is the conditional maximum likelihood estimate with its exact interval, which corresponds to the Fisher exact test (p = 0.066). The dashed vertical line marks no effect (ratio 1). Panel C shows the number of women who received 0, 50, or 100 µg of rescue phenylephrine (Mann-Whitney U, p = 0.035).

Secondary outcomes

Recurrent hypotensive episodes were more frequent in group A. The total number of episodes was 14 in group A and four in group B (rate ratio: 3.50, 95% CI: 1.15 to 10.63, Mann-Whitney U p = 0.035). The distributions are given in Table *3*.

Each rescue bolus was 50 µg given for one hypotensive episode, so the rescue dose in each woman equals 50 µg multiplied by her number of episodes, and the rescue dose comparison is therefore identical to the episode comparison. The mean rescue phenylephrine dose was 17.5 ± 33.1 µg in group A and 5.0 ± 18.9 µg in group B (median = 0 (IQR: 0 to 50) versus 0 (0 to 0), Mann-Whitney U p = 0.035, rank-biserial correlation −0.18). Ten women in group A and three in group B required at least one rescue dose (Table *4*).

Measure	Group A (75 µg, n = 40)	Group B (100 µg, n = 40)	Effect estimate (95% CI)	Statistical test	Test statistic	p-value
Rescue dose, µg, mean ± SD	17.5 ± 33.1	5.0 ± 18.9	NA	NA	NA	NA
Rescue dose, µg, median (IQR)	0 (0 to 50)	0 (0 to 0)	NA	Mann-Whitney U test	U = 941.0	0.035
Rescue dose, rank-biserial correlation	NA	NA	−0.18, favoring group B	Effect size of the Mann-Whitney U test	NA	NA
Participants receiving any rescue bolus, n (%)	10 (25.0)	3 (7.5)	Risk difference 17.5 pp (1.1 to 33.5)	Fisher exact test	Not applicable (exact test)	0.066
Bradycardia (HR below 60 beats/min), n (%)	0 (0.0)	0 (0.0)	Not estimable (no events)	Not tested (no events in either group)	Not applicable	Not tested
Reactive hypertension (SBP above 140 mm Hg), n (%)	0 (0.0)	0 (0.0)	Not estimable (no events)	Not tested (no events in either group)	Not applicable	Not tested
Nausea or vomiting, n (%)	5 (12.5)	2 (5.0)	Relative risk 2.50 (0.52 to 12.14)	Fisher exact test	Not applicable (exact test)	0.432

TABLE 4: Rescue vasopressor use and adverse events.

Rescue phenylephrine was administered as intravenous 50 µg boluses, one for each qualifying hypotensive episode, so the dose per participant was 0, 50, or 100 µg and equaled 50 µg multiplied by the number of episodes. The Hodges-Lehmann estimate is not reported because at least three-quarters of values in both groups were 0. The risk difference CI is the Newcombe hybrid score interval. Bradycardia and reactive hypertension were assessed across all 12 serial time points from baseline to six hours after subarachnoid block. Nausea and vomiting were recorded through six hours.

HR: heart rate; IQR: interquartile range; pp: percentage points; SBP: systolic blood pressure; SD: standard deviation; U: Mann-Whitney U statistic; NA: not applicable (the measure is not defined for that cell).

The Fisher exact test has no test statistic. Bradycardia and reactive hypertension were not tested because no events occurred in either group.

SBP and mean arterial pressure (Figure *3A*) and heart rate and diastolic blood pressure (Figure *3B*) at the 12 pre-specified time points are shown in Table *2*. Between-group differences were small and did not reach statistical significance at any time point after normality-adjusted testing. Both groups maintained clinically acceptable values throughout the observation period.

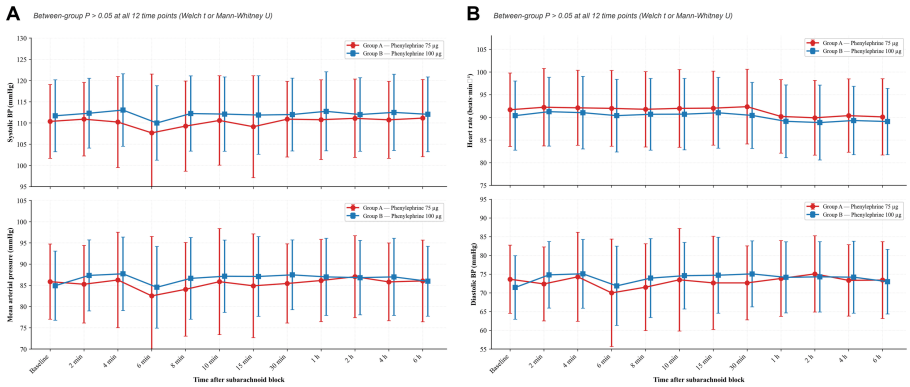


FIGURE 3: Serial maternal hemodynamics at 12 pre-specified time points.

Panel A. Serial systolic blood pressure (top sub-panel) and mean arterial pressure (bottom sub-panel) at 12 pre-specified time points from baseline to six hours after subarachnoid block. Panel B. Serial heart rate (top sub-panel) and diastolic blood pressure (bottom sub-panel) over the same time points. Values are the mean and standard deviation. Red circles denote group A (phenylephrine 75 µg) and blue squares denote group B (phenylephrine 100 µg). Between-group comparisons at each time point used the Welch t-test or the Mann-Whitney U test, as indicated by the Shapiro-Wilk test. No between-group difference reached the pre-specified threshold of p = 0.05 at any time point.

BP: blood pressure.

Adverse events

Nausea or vomiting occurred in five women in group A and two women in group B (Fisher exact p = 0.43, relative risk: 2.50, 95% CI: 0.52 to 12.14). A protocol-defined bradycardia (heart rate below 60 beats per minute) or reactive hypertension (SBP above 140 mm Hg) was not recorded in either group across any of the 12 time points (Table *4*).

Discussion

In healthy parturients undergoing elective cesarean section under subarachnoid block, a 100 µg prophylactic bolus of phenylephrine coadministered with 3 IU oxytocin at cord clamping was associated with a 17.5 percentage-point lower incidence of maternal hypotension than a 75 µg bolus (7.5% versus 25.0%), but the difference did not reach statistical significance on the pre-specified Fisher's exact test (p = 0.066). Hypotensive episodes and the rescue phenylephrine dose were lower with the higher dose (mean = 5.0 versus 17.5 µg, p = 0.035). Serial heart rate, blood pressure, and peripheral oxygen saturation trends were similar in both groups, and neither bradycardia nor reactive hypertension was observed. Nausea and vomiting occurred at low rates and were numerically less common in the higher-dose group.

These findings are consistent with the pharmacology of the two drugs. An oxytocin bolus produces rapid hemodynamic changes, including increases in cardiac output and changes in arterial pressure and heart rate [2,3], which coincide with the sympathectomy of a recent subarachnoid block. Phenylephrine counteracts the fall in systemic vascular resistance through alpha-1-mediated vasoconstriction, and the bradycardia it causes is dose-dependent [14]. Dyer and colleagues showed that coadministration of phenylephrine 80 µg with oxytocin obtunded the oxytocin-induced decrease in systemic vascular resistance and the increases in heart rate and cardiac output [10], whereas Rumboll and colleagues found that a 50 µg bolus given immediately before 3 IU oxytocin did not prevent hypotension and tachycardia [4]. A dose above 50 µg, given together with oxytocin, therefore appears necessary, which is the range examined in our trial.

Gangadharaiah and colleagues, in 90 parturients, coadministered oxytocin with phenylephrine 50 µg or 75 µg over five minutes after delivery and reported hypotension in 90% and 10%, respectively, compared with 98% after oxytocin with saline [16]. Our 75 µg group had a higher incidence of hypotension (25.0%) than their 75 µg group (10%), and our 100 µg group had a similar incidence of hypotension (7.5%) to that of their 75 µg group (10%) (Table *5*). Differences in the speed of administration, which was a bolus over 30 seconds in our trial, and in the definition and observation window of hypotension may account for this. In our trial, mean rescue phenylephrine was 17.5 µg in group A and 5.0 µg in group B.

Author (year)	Sample (n)	Design	Phenylephrine regimen	Hypotension incidence	Key findings
Moran et al. (1991) [18]	60	Randomized double-blind trial	PE 80 µg boluses vs. ephedrine 10 mg boluses to keep SBP above 100 mm Hg	Not reported in the abstract	Umbilical artery pH 7.32 with PE vs. 7.28 with ephedrine. Apgar scores similar.
Ngan Kee et al. (2004) [19]	50	Randomized double-blind trial	PE infusion 100 µg/min vs. PE 100 µg rescue boluses	23% (infusion) vs. 88% (boluses)	Umbilical cord gases and Apgar scores similar.
Dyer et al. (2009) [10]	43	Randomized trial	PE 80 µg vs. ephedrine 10 mg, and oxytocin with or without PE 80 µg in a subgroup of 20	Not reported in the abstract	Co-administered PE obtunded the oxytocin-induced fall in SVR and rise in heart rate and cardiac output.
Bhattarai et al. (2010) [20]	90	Three-arm randomized trial	PE 25 µg vs. ephedrine 5 mg vs. mephentermine 6 mg boluses for established hypotension	Not applicable (treatment of established hypotension)	All three maintained hemodynamics within 20% of baseline. Apgar scores similar.
Bhardwaj et al. (2013) [21]	90	Three-arm randomized trial	PE 30 µg bolus then 15 µg/min infusion vs. metaraminol vs. ephedrine, SBP held at baseline	Not reported in the abstract	Umbilical pH comparable. Reactive hypertension more frequent with metaraminol.
Rumboll et al. (2015) [4]	40	Randomized trial	PE 50 µg bolus immediately before oxytocin 3 U vs. saline	Not reported in the abstract	Did not prevent hypotension or tachycardia. Smaller mean MAP change (−1.5% vs. −6.8%, p = 0.007).
Gangadharaiah et al. (2017) [16]	90	Three-arm double-blind randomized trial	Oxytocin 3 U with PE 50 µg vs. PE 75 µg vs. saline over 5 minutes	90% (50 µg), 10% (75 µg), 98% (saline)	Rescue vasopressor requirement lowest with 75 µg.
Sun et al. (2024) [22]	183 analyzed	Double-blind randomized trial	PE infusion 0.5 µg/kg/min vs. norepinephrine infusion 0.08 µg/kg/min	Not reported in the abstract	Similar changes in fetal heart rate and fetal cardiac output.
Present study (2026)	80	Double-blind randomized trial	PE 75 µg vs. 100 µg bolus with 3 IU oxytocin at cord clamping	25.0% (75 µg) vs. 7.5% (100 µg), p = 0.066	Mean rescue PE: 17.5 vs. 5.0 µg. No bradycardia or reactive hypertension.

TABLE 5: Present study in the context of published randomized trials of phenylephrine during cesarean section under spinal anesthesia, listed in chronological order.

Studies are listed in chronological order, and the final row is the present study. Values for comparator studies are taken from their published abstracts, and all comparator studies are cited in the Discussion.

MAP: mean arterial pressure; PE: phenylephrine; SBP: systolic blood pressure; SVR: systemic vascular resistance.

Earlier randomized trials framed these regimens. Moran and colleagues compared phenylephrine 80 µg boluses with ephedrine 10 mg boluses in 60 women and found phenylephrine to be as effective as ephedrine, with higher umbilical artery pH [18]. Ngan Kee and colleagues showed that a prophylactic phenylephrine infusion of 100 µg per minute reduced the incidence of hypotension from 88% to 23% compared with rescue boluses, with similar umbilical cord gases and Apgar scores [19]. Bhattarai and colleagues found that phenylephrine 25 µg, ephedrine 5 mg, and mephentermine 6 mg boluses all maintained hemodynamics within 20% of baseline in 90 parturients with established hypotension [20], and Bhardwaj and colleagues found comparable umbilical pH with phenylephrine, metaraminol, and ephedrine when systolic pressure was held at 100% of baseline [21].

Our safety findings are consistent with the earlier literature. In a review of phenylephrine administration in women undergoing cesarean delivery under spinal anesthesia, which compared phenylephrine with ephedrine for maternal hemodynamics, nausea and vomiting, uteroplacental perfusion, and neonatal acid-base status, Habib described a low incidence of hypotension and its related side effects with prophylactic phenylephrine regimens [11]. Xue and colleagues found in a network meta-analysis that bradycardia with

phenylephrine was dose-dependent and that doses of 121 to 150 µg carried the highest probability (62%) of reactive hypertension [14]. Neither event occurred with 100 µg in our trial. Kornilov and colleagues observed that regional cerebral oxygen saturation decreased after spinal anesthesia even though a prophylactic phenylephrine infusion kept blood pressure within 20% of baseline [23], a reminder that blood pressure control alone does not guarantee organ perfusion. The international consensus statement recommends alpha-1 agonists such as phenylephrine as first-line vasopressors for hypotension during cesarean section under spinal anesthesia [9].

The choice of vasopressor continues to evolve. Heesen and colleagues found, in eight trials of 712 high-risk patients, no significant difference in fetal acidosis between ephedrine and phenylephrine and insufficient evidence to recommend either [12]. Xue and colleagues ranked ephedrine 21 to 30 mg as the most efficacious prophylactic bolus for preventing hypotension [14], and Singh and colleagues found that norepinephrine and metaraminol were less likely than phenylephrine to be associated with adverse fetal acid-base status [15]. Sun and colleagues reported similar effects of prophylactic phenylephrine and norepinephrine infusions on fetal heart rate and fetal cardiac output [22]. Jain and colleagues found similar fetal acidosis with phenylephrine and ephedrine infusions in emergency cesarean delivery for acute fetal compromise [24]. Sahoo and colleagues found the lowest incidence of hypotension (15.0%) with a prophylactic phenylephrine infusion of 50 µg per minute among four infusion rates [25], and Jeevan and colleagues reported that a preoperative oxytocin infusion reduced hypotension from 59.4% to 8.6% and lowered the phenylephrine requirement [26]. Phenylephrine therefore remains an established option, while the optimal dose coadministered with oxytocin is unresolved.

Strengths and limitations

The trial has three practical strengths. First, the randomization was concealed, and the outcome assessment was blinded, which reduces performance and detection bias. Second, the primary outcome was pre-specified and analyzed with Fisher's exact test as primary, with 95% confidence intervals reported for the risk difference, relative risk, odds ratio, and number needed to treat. Third, the serial hemodynamic data extend to six hours after subarachnoid block, capturing the majority of the postoperative hemodynamic recovery window that matters for maternal safety.

The trial has five limitations. First, it is a single-center and single-country study, and whether the effect extends to parturients with a different baseline hemodynamic profile is untested. Second, umbilical arterial cord blood gases and Apgar scores were not collected, so neonatal acid-base status cannot be assessed directly. Phenylephrine has been associated with better fetal acid-base status than ephedrine in low-risk elective patients [11,12], and a systematic review found that vasoactive drugs, including phenylephrine, did not improve uterine hemodynamics [27], so neonatal safety at the higher dose remains to be measured. Third, hypotension was defined a priori as SBP below 90 mm Hg or a fall of 20% or more from baseline. A more sensitive threshold, such as a 10% fall, would be expected to increase the incidence in both groups. Fourth, the trial was powered for an anticipated incidence of 45% versus 15%. The observed incidences were lower (25.0% and 7.5%); the primary Fisher's exact test did not reach statistical significance ($p = 0.066$), and the confidence intervals for the odds ratio and relative risk include no effect. The chi-square test and the Newcombe interval for the risk difference, which are less conservative than the exact test, excluded no effect, so the result is suggestive rather than conclusive. Approximately 87 women per group would be required to detect the observed difference with 90% power at a two-sided alpha of 0.05. Fifth, secondary outcomes were not adjusted for multiple comparisons and should be interpreted as exploratory.

Implications and recommendations

A 100 µg prophylactic bolus of phenylephrine coadministered with 3 IU oxytocin at cord clamping is a simple modification of existing practice that requires no additional equipment. In this trial, it was associated with fewer hypotensive episodes and a lower rescue requirement without bradycardia or reactive hypertension, but the primary comparison was not statistically significant. There are three priorities for further work. First, an adequately powered multicenter trial with formal neonatal outcome measurement, building on the meta-analysis by Hordofa and colleagues of 19 randomized trials with 2603 participants comparing norepinephrine and phenylephrine [28]. Second, a dose-finding study extending to 125 and 150 µg to define the dose above which reactive hypertension or bradycardia becomes clinically important. Third, extension into parturients with pre-eclampsia and cardiac disease, in whom the balance of benefit and risk is likely to differ.

Conclusions

In ASA-PS II parturients undergoing elective cesarean section under subarachnoid block, a 100 µg prophylactic phenylephrine bolus coadministered with 3 IU oxytocin at cord clamping was associated with a lower incidence of maternal hypotension than a 75 µg bolus (7.5% versus 25.0%), but the difference was not statistically significant on the pre-specified Fisher's exact test ($p = 0.066$). Hypotensive episodes and rescue phenylephrine requirement were lower with the higher dose; serial hemodynamic trajectories were comparable, and no bradycardia or reactive hypertension occurred with either dose. These findings support a larger multicenter trial, with formal neonatal outcome measurement, before a preferred coadministered dose can be recommended.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry issued approval 64/SVMCH/IEC-Cert/February 24. The trial was approved by the Institutional Ethics Committee (Human Studies) of Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry (reference number: 64/SVMCH/IEC-Cert/February 24, dated: 7 February 2024), after review at its meeting on 20 January 2024. Written informed consent was obtained from every participant. The trial complied with the Declaration of Helsinki as revised in 2013. The trial was registered prospectively with the Clinical Trials Registry of India (CTRI/2024/08/073061, registered on 29 August 2024). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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