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CLINICAL TRIAL REPORT

# Dose-Response Study of Phenylephrine for Preventing Spinal-Induced Hypotension During Cesarean Delivery with Combined Spinal-Epidural Anesthesia Under the Effect of Prophylactic Intravenous Ondansetron

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**Background:** Ondansetron reduces the median effective dose (ED50) of prophylactic phenylephrine to prevent spinal-induced hypotension (SIH) during cesarean delivery. However, the exact dose response of phenylephrine in combination with prophylactic ondansetron for preventing SIH is unknown. Therefore, this study aimed to determine the dose-response of phenylephrine to prevent SIH in cesarean delivery when 4 mg of ondansetron was used as a preventive method.

**Methods:** A total of 80 parturients were enrolled and divided randomly into four groups (n = 20 in each group) who received either 0.2, 0.3, 0.4, or 0.5 μg/kg/min of prophylactic phenylephrine. Ten minutes before the initiation of spinal induction, 4 mg prophylactic ondansetron was administered. The effective dose of prophylactic phenylephrine was defined as the dose required to prevent hypotension after the period of intrathecal injection and up to neonatal delivery. The ED50 and ED90 of prophylactic phenylephrine and 95% confidence intervals (95% CI) were calculated using probit analysis.

**Results:** The ED50 and ED90 for prophylactic phenylephrine to prevent SIH were 0.25 (95% CI, 0.15 to 0.30), and 0.45 (95% CI, 0.39 to 0.59) μg/kg/min, respectively. No significant differences were observed in the side effects and neonatal outcomes between the four groups.

**Conclusion:** The administration of 4 mg of prophylactic ondansetron was associated with an ED50 of 0.25 (95% CI, 0.15~0.30) and ED90 of 0.45 (95% CI, 0.39~0.59) μg/kg/min for phenylephrine to prevent SIH.

**Keywords:** phenylephrine, ondansetron, dose-response, hypotension, cesarean delivery, spinal

## Introduction

Phenylephrine infusion is an important therapeutic strategy for preventing spinal-induced hypotension (SIH) in cesarean delivery, as it decreases the incidence of hypotension, nausea and vomiting.[1–3] However, infusion high dose of phenylephrine may also result in a reduction in maternal heart rate and subsequently decrease cardiac output in a dose-dependent manner.[4–6] Our previous study showed that prophylactic ondansetron decreased the median effective dose of phenylephrine to prevent SIH, as evaluated by the median effective dose (ED50).[7,8] In theory, a potential clinical benefit may arise from a reduction in the required dosage of phenylephrine through prophylactic administration of ondansetron, as it may inhibit the Bezold-Jarisch reflex by antagonizing the binding of 5-HT3 to receptors in the left ventricle, and subsequently reduce the incidence of SIH.[9,10] However, data on the exact dose–response curve of prophylactic phenylephrine for preventing SIH administered in combination with ondansetron is still unavailable. Since many anesthesiologists prefer to administer phenylephrine at rates closer to the ED90 or ED95, the calculation of 90% or 95% effective doses are more clinically advantageous for the management of SIH

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than of the ED50. Therefore, this study aimed to determine the dose-response of phenylephrine for preventing SIH when prophylactic intravenous ondansetron was administered 10 min prior to combined spinal-epidural anesthesia during cesarean delivery.

## Materials and Methods

This study was approved by the Institutional Review Board of Jiaxing University Affiliated Women and Children's Hospital's Institutional Review Board (IRB 2019–119, date of approval: Nov 6. 2019). The clinical trial was registered at the Chinese Clinical Trials Registry Center (the registration number: ChiCTR2100042453; principal investigator, Xiao-Xia Sun) before enrollment of the parturients. All the patients signed an informed consent form. Patient recruitment was initiated on January 30, 2021, and concluded on August 30, 2021.

The inclusion criteria were a singleton pregnancy at term (≥37 weeks' gestation) and American Society of Anesthesiologists (ASA) physical status of < III, for subjects undergoing elective cesarean delivery. The exclusion criteria were as follows: preeclampsia or preexisting hypertension, preexisting or gestational diabetes, allergy to phenylephrine and local anesthetics, any contraindications to spinal or epidural anesthesia, including a bleeding disorder, local infection or intracranial hypertension, cardiovascular or cerebrovascular disease, ruptured membranes and placenta previa, multiple pregnancies, height <145 or > 175 cm, body weight <50 or >90 kg, and a fetal anomaly.

The patients were instructed to fast without solid food for 8 hours and water for 2 hours before surgery and to take no premedication. After entering the operating room, patients were placed in the supine position with a wedge-shaped thin pillow under the right hip, followed by peripheral IV access using an 18-gauge (G) cannula. All patients slowly received 37°C Ringer's lactate solution without preload with a large quantity of fluid. Oxygen was delivered using a nasal catheter at a rate of 3 L/min, and standard monitoring was applied, including noninvasive blood pressure (NIBP), heart rate, pulse oximetry, and electrocardiography. Baseline values for systolic blood pressure (SBP) and HR were determined by calculating the mean of three consecutive measurements taken at three-minute intervals after the patient was allowed to rest.

A randomized number sheet was produced using an online randomization generator (https://www.random.org/sequences/) that was then placed in sequentially numbered opaque envelopes, with one opened for each enrolled patient by a researcher (Jing-Yue Yang) who was not involved in patient management and data collection. According to the randomized number sheet, the patients were allocated into one of four groups (n = 20 for each group) that received a fixed dose of either a 0.2, 0.3, 0.4, or 0.5 μg/kg/min prophylactic phenylephrine infusion. Phenylephrine diluted to 100 μg/mL was prepared for each patient according to the grouping information by a fixed anesthesia assistant using a uniform 50-mL syringe. Although this assistant was aware of the grouping, he was not involved in managing patient care and data collection. The patients' weights had been measured using a fixed electronic scale before surgery on the day of surgery. The infusion pump rate was set at the start of infusion, and the screen of the infusion pump was covered with opaque paper to ensure that the other investigators were blinded to the patients' grouping.

Ondansetron 4 mg was administered intravenously 10 minutes before the induction of spinal anesthesia. The combined spinal-epidural (CSE) technique was performed with the patient in the left-lateral position. Briefly, the epidural space was located by the loss of resistance in the L3-4 interspace following the injection of < 2 mL saline using an 18-G Tuohy needle. A 25-G Whitacre needle was then inserted intrathecally using the needle-through-needle technique. After confirming the flow of clear cerebrospinal fluid (CSF), a prepared local anesthetic mixture containing 10 mg hyperbaric bupivacaine and 5 μg sufentanil was injected into the subarachnoid space over 15–20 s. Before retreating the Whitacre needle, we gently aspirated the syringe to ensure that the CSF could be withdrawn. The appearance of CSF indicated that it was a successful case; otherwise, the case was regarded as dubious and excluded from the study. After intrathecal injection, a flexible epidural nylon catheter was inserted 3–5 cm into the epidural space and aspirated gently to ensure that there was no blood or CSF.

Immediately after intrathecal injection, prophylactic phenylephrine was infused using an auto injection pump. All patients received 200–300 mL of warmed lactated Ringer's solution within approximately 20 minutes. The primary outcome of the study was the effective dose of prophylactic phenylephrine, which was defined as the absence of hypotension during the study period. Conversely, an ineffective dose of prophylactic phenylephrine was defined as hypotension occurring during the study period. The study period was defined as the duration from intrathecal injection to fetal delivery. Hypotension was defined as a reduction of > 20% of baseline values, absolute value of SBP < 90 mmHg;

and hypertension was defined as absolute value of SBP > 120% of baseline values. Bradycardia was defined as an HR < 50 beats/min. According to the study protocol, 100 μg of phenylephrine was administered when hypotension occurred with an increase in HR; 0.5 mg of atropine and/or 6 mg of ephedrine were administered i.v. for hypotension occurring with bradycardia; while the phenylephrine infusion was discontinued when hypertension occurred and resumed when the SBP returned to < 120% of baseline values.

The level of sensory block was checked by asking the patient about the loss of pain or sharpness experienced from pinprick sensation by an 18-G blunt epidural needle at 5-min intervals during the first 20 min after intrathecal injection. Surgery was not permitted unless the sensory block level was at least at T6.

The following data were recorded during the study: demographic characteristics, including age, height, and weight; duration of surgery; induction of spinal anesthesia to fetal delivery; uterine incision to fetal delivery; number of physician interventions (ie, stopping or restarting the phenylephrine infusion, or injecting phenylephrine or atropine); incidence of side effects, such as hypotension, hypertension, bradycardia, nausea or vomiting, and shivering; and neonatal outcomes, including the 1-min Apgar score and umbilical arterial blood pH.

## Statistical Analysis

The Shapiro–Wilk test was used to test the normality of the distribution of continuous variables. Normally distributed variables, such as demographic characteristics, surgical time, and umbilical arterial blood pH, were expressed as the mean ± standard deviation (SD) and analyzed using one-way analysis of variance, with post–Bonferroni tests for pairwise comparisons. The Levene statistic was employed to examine the homogeneity of the normally distributed variances. Non-normally distributed variables, such as sensory block level and 1-min Apgar score, were expressed as medians and ranges and analyzed using the Kruskal–Wallis test, and the post-Dunns test was applied to analyze pairwise comparisons. Categorical data, such as side effects and the probability of absence of hypotension among the four groups, were expressed as numbers (percentage) and analyzed using the Cochran-Armitage chi-square test for trend. If differences existed between groups, pairwise comparisons were assessed using the chi-square test. Serial changes in BP during the first 15 min after intrathecal injection were evaluated using a summary measurement technique. For each group, the variation in the plotted SBP over time was presented using the area under the curve and calculated using the trapezium rule. One-way ANOVA was used to evaluate the differences between the four groups. The ED50 and ED90 of prophylactic phenylephrine and their 95% confidence intervals (95% CI) were calculated using probit analysis. Analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, California, USA). Statistical significance was defined as a two-sided $P$ value of <0.05. If Bonferroni corrections were used, we calculated the adjusted $P$ values using GraphPad Prism software.

## Sample Size Calculation

The sample size was calculated using the PASS software (version 11.0.7; NCSS, LLC, Kaysville, UT, USA). The calculations were based on the results of early preliminary data that showed that for the four groups receiving intravenous 0.2, 0.3, 0.4 or 0.5 μg/kg/min of phenylephrine, the proportion of patients without hypotension was 0.30, 0.60, 0.75, and 0.90, respectively. A total of 48 subjects (12 in each group) achieved 90% power to detect a linear trend using a two-sided Z test with continuity correction and a significance level of 0.05. To allow for possible dropouts and to increase the power of the study, the sample size was arbitrarily increased to 20 subjects per group (80 subjects in total).

# Results

A total of 94 pregnant patients scheduled for elective cesarean delivery were recruited and assessed for eligibility in the study. Nine patients declined to participate and five patients did not meet the inclusion criteria (Figure 1). No clinically significant differences were observed in patient demographic data, surgical times, or sensory block levels between the four groups (Table 1).

As shown in Figure 2, the probability of patients without hypotension in the four groups in the order of increasing phenylephrine dosage was 35% (7/20), 70% (14/20), 80% (16/20), and 95% (19/20). This difference across the four

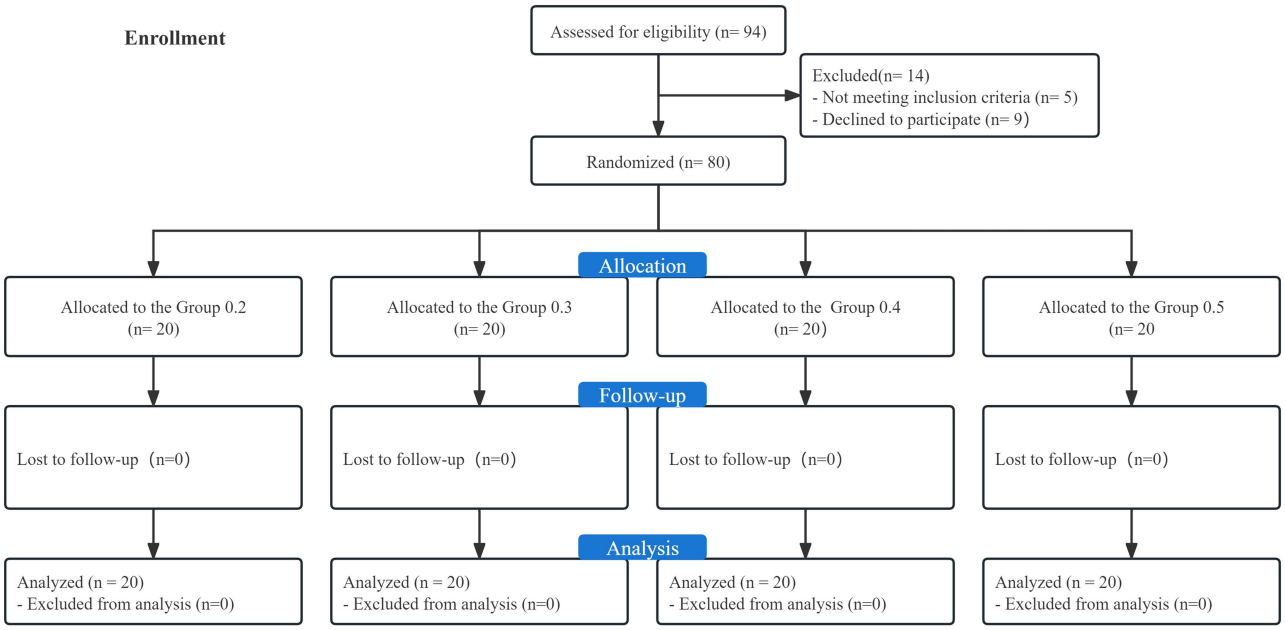


**Figure 1** Consolidated Standards of Reporting Trials diagram showing patient recruitment and flow.

groups was statistically significant ($P<0.001$). The dose–response curve of prophylactic phenylephrine to prevent spinal-induced hypotension, as determined by probit analysis, is shown in Figure 3. The ED50 and ED90 of prophylactic phenylephrine for preventing SIH in patients undergoing a cesarean delivery under CSEA were 0.25 (95% CI, 0.15~0.30) μg/kg/min and 0.45 (95% CI, 0.39~0.59) μg/kg/min, respectively.

The baseline SBP and SBP values in the first 15-min after intrathecal injection in the four groups are shown in Figure 4. There were significant differences in the areas under the curve which were 1724 ± 29, 1649 ± 25, 1600 ± 31, and 1559 ± 30 min·mmHg in the 0.5, 0.4, 0.3, and 0.2 μg/kg/min groups, respectively. A significant linear trend was observed across the four groups ($P < 0.001$).

A total of 13 (65%), 9 (45%), 7 (35%), and 5 (25%) patients required one physician intervention in the groups receiving either 0.2, 0.3, 0.4, and 0.5 μg/kg/min of phenylephrine, respectively. The number of patients who required physician intervention in the 0.2 μg/kg/min phenylephrine group was significantly higher (adjusted $P < 0.05$) than in the other three groups (Table 2).

Side effects and neonatal outcomes are presented in Table 2. Hypotension occurred in 65% (13/20), 30% (6/20), 20% (4/20), and 5% (1/20) of the patients in the four groups in order of increasing phenylephrine dosage, with a significant difference observed between the groups ($P < 0.001$). The incidence of hypotension was significantly higher in the low-dose group than in the high-dose group (adjusted $P < 0.05$). The incidence of reactive hypertension, bradycardia, nausea,

**Table 1** Demographic Data, Surgical Times and Sensory Block Level

| | Group 0.2 (n=20) | Group 0.3 (n=20) | Group 0.4 (n=20) | Group 0.5 (n=20) | *P* value |
|---|---|---|---|---|---|
| Age (yr) | 29.0 ± 4.5 | 31.7 ± 5.3 | 31.0 ± 4.9 | 30.9 ± 3.9 | 0.30 |
| Height (cm) | 160.0 ± 5.2 | 160.7 ± 5.3 | 159.4 ± 4.0 | 160.3 ± 5.2 | 0.87 |
| Weight (kg) | 72.3 ± 10.2 | 72.6 ± 8.7 | 73.0 ± 8.1 | 71.0 ± 10.0 | 0.92 |
| Gestational age (wk) | 39.0 ± 0.6 | 39.0 ± 1.1 | 38.2 ± 0.7 | 39.0 ± 0.9 | 0.06 |
| Induction-delivery interval (min) | 14.0 ± 3.3 | 17.0 ± 4.0 | 16.3 ± 3.3 | 16.8 ± 4.6 | 0.58 |
| Uterine incision delivery interval (s) | 63 ± 17 | 65 ± 19 | 64 ± 20 | 65 ± 20 | 0.62 |
| Sensory block level (dermatome) | T4 (T3-T4) | T4 (T2-T4) | T4 (T2-T4) | T4 (T2-T4) | 0.76 |

**Notes**: Data are mean ± SD or median (range).

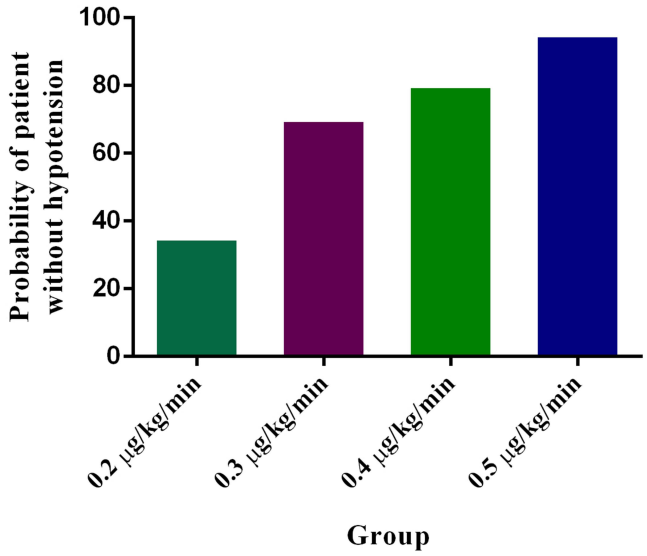


**Figure 2** Comparison of the probability of patients without hypotension among groups.

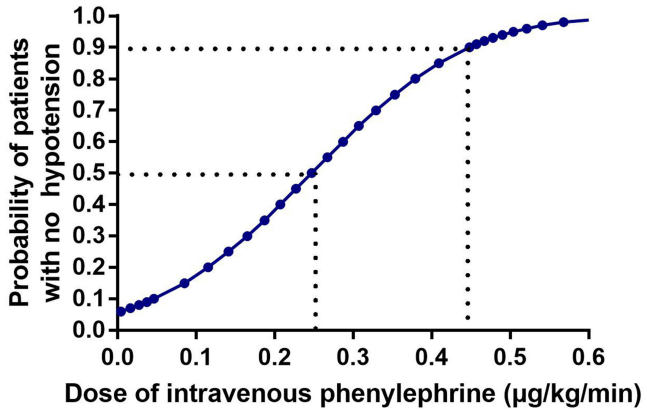


**Figure 3** The dose–response curve of intravenous phenylephrine.

vomiting, and shivering did not differ between the four groups. There was also no difference in Apgar scores or umbilical arterial pH among the four groups.

## Discussion

The data in this study showed that the incidence of SIH decreased with an increase in prophylactic phenylephrine dose. Probit analysis of the logistic regression model showed that the ED50 and ED90 of prophylactic phenylephrine for preventing SIH administered in combination with intravenous administration of 4 mg of prophylactic ondansetron 10-min before spinal induction were 0.25 (95% CI, 0.15~0.30) and 0.45 (95% CI, 0.39~0.59) μg/kg/min, respectively. Our data suggested that 0.45 μg/kg/min of phenylephrine could be a reasonable initial dose for preventing SIH when 4 mg of prophylactic ondansetron was applied 10-min before spinal induction.

The optimal dosage for preventing spinal-induced hypotension (SIH) during cesarean delivery remains controversial. Allen et al[11] conducted a comparative study involving four fixed prophylactic doses of phenylephrine (ranging from 25 to 100 μg/min) to maintain systolic blood pressure (SBP) fluctuations within 80% to 120% of baseline values. Based on considerations, such as the incidence of hypotension and hypertension, physician interventions during the procedure, and SBP variability, they suggested an infusion rate between 25 and 50 μg/min as appropriate. After a careful review of their findings, it was observed that the mean body weights of patients who received phenylephrine infusion at rates of 25 and

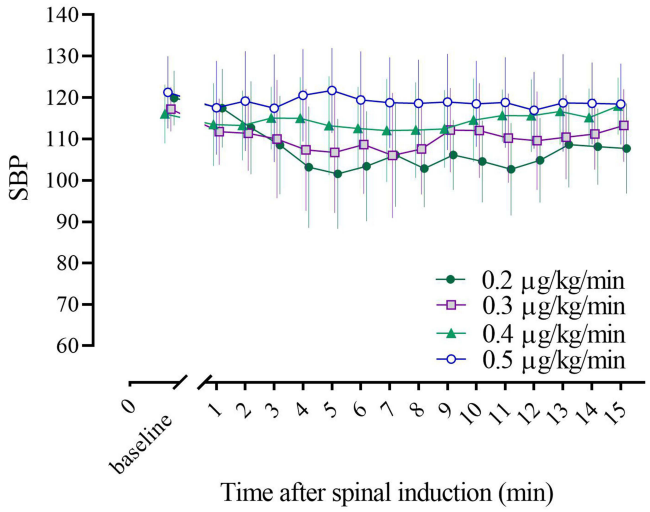


**Figure 4** Systolic blood pressure in the first 15 minutes after spinal anesthesia.

50 μg/min were 90 and 87 kg, respectively. Based on these results, the recommended infusion rate is in the range of 0.28 to 0.57 μg/kg/min. The recommended dose was within the range suggested by Allen et al. In our previous studies employing the same methodology, we conducted a comparative analysis of prophylactic phenylephrine doses (0.25, 0.375, 0.5, and 0.625 μg/kg/min) to maintain systolic blood pressure (SBP) variation within a range of 20% relative to baseline SBP values. Our findings revealed that in the absence of a prophylactic dose of intravenous ondansetron, the effective dose at which 90% of patients responded positively (ED90) was determined as 0.54 μg/kg/min.[12] Although these recommendations exhibit slight variations, it is unnecessary to ascertain the optimal dosage for clinical practice because of individual variability in the phenylephrine response among patients. Consequently, anesthesia care providers should monitor the patient's response and promptly adjust the infusion rate based on changes in blood pressure.

In contrast, in the current study, the ED90 of prophylactic phenylephrine was lower than the value measured in the previous aforementioned studies,[11,12] which revealed that intravenous ondansetron decreased the dose of phenylephrine required to prevent SIH during cesarean delivery.[13,14] Given the side effects of infusion of a relatively high dose of phenylephrine, the results of the current study may provide positive support for the use of ondansetron for preventing

**Table 2** Hemodynamic Changes, Side Effects and Neonatal Outcome

| | Group 0.2 (n=20) | Group 0.3 (n=20) | Group 0.4 (n=20) | Group 0.5 (n=20) | *P*-value |
|---|---|---|---|---|---|
| Hypotension | 13 (65)[a] | 6 (30) | 4 (20) | 1 (5) | 0.0003 |
| Total phenylephrine required | 330 ± 101[b] | 492 ± 167 | 608 ± 130 | 590 ± 211 | < 0.001 |
| Boluses of phenylephrine used in patients with hypotension | 3 (1–6) | 2.5 (1–5) | 2.5 (2–4) | 1 (1–1) | — |
| Reactive hypertension | 0 (0) | 0 (0) | 1 (5) | 2 (10) | 0.282 |
| Bradycardia | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 0.386 |
| Numbers of patients who required a physician intervention | 13 (65) | 9 (45) | 7 (35) | 5 (25) | 0.067 |
| Nausea or vomiting | 2 (15) | 1 (5) | 2 (10) | 1 (5) | 0.721 |
| Shivering | 2 (10) | 1 (5) | 1 (5) | 2 (10) | 0.721 |
| Apgar score | 9 (9–10) | 9 (9–10) | 9 (9–10) | 9 (9–10) | 0.246 |
| Umbilical artery pH | 7.33 ± 0.04 | 7.32 ± 0.04 | 7.33 ± 0.04 | 7.33± 0.03 | 0.586 |

**Notes**: Data are presented as numbers (%), medians (ranges), or means ± SD. Categorical data were analyzed using the Cochran-Armitage chi-square test. Reactive hypertension was defined as a systolic blood pressure > 120% of the baseline value. [a]$P = 0.02$ verse group 0.3; $P = 0.010$ versus group 0.4; $P = 0.0001$ versus group 0.5. [b] $P < 0.001$ vs group 0.3; $P < 0.0001$ verse group 0.4 and group 0.5.

SIH in clinical cesarean delivery; however, there is also literature suggesting that ondansetron does not reduce the dosages of vasopressors required to prevent SIH.[15–17] The strength of the current study is that it provides a lower ED90 value for phenylephrine that decreased by prophylactic ondansetron, which may have a potential advantage in clinical practice, because the use of phenylephrine may be associated with side effects such as bradycardia and reactive hypertension in a dose-dependent manner.

It should be noted that compared with our previous study we showed a reduction in ED90 of phenylephrine administration from 0.54 to 0.45 μg/kg/min, with ondansetron pre-administration, which equates to a reduction of 17%.[12] Additionally, in another study from our center, we showed that prophylactic ondansetron reduces the ED50 of phenylephrine by 26%.[7] The different methodologies used in the two studies (ie, traditional up-and-down design with Dixon and Mood analysis vs randomized dose allocation design with probit analysis) could also account for these differences.

The mechanisms by which ondansetron decreases the incidence of SIH and the required vasopressor dose remain unknown. Some researchers have suggested that the possible mechanism may be that ondansetron inhibits the Bezold-Jarisch reflex by antagonizing the binding of 5-HT3 to receptors in the left ventricle.[9,10] Compared to an earlier study,[7] the current study used ED50 as a comparative value and ED90 as a clinical reference value. In addition, we also provided information on the other values in the dose–response curve, which may be useful for individual care in clinical practice. One patient in the 0.4 μg/kg/min group and two patients in the 0.5 μg/kg/min group experienced reactive hypertension, while one patient in the 0.5 μg/kg/min developed bradycardia. These data also indicate the importance of providing individual care to parturients in clinical practice.

Similar to published literature, our results showed no evidence of a detrimental effect of ondansetron on neonatal outcomes, confirming that it is safe for neonates undergoing cesarean delivery.[17–20] However, the use of ondansetron for preventing SIH in obstetric anesthesia requires careful evaluation due to its off-label status, weighing both patient benefits and potential drawbacks.

It is important to note that the data in the current study did not demonstrate any significant differences in the incidences of reactive hypertension and bradycardia among the four phenylephrine dosing regimens, despite observing a 17% reduction in the effective dose (ED90) of phenylephrine with ondansetron pre-administration. Therefore, further investigations are warranted to validate the clinical significance of employing prophylactic ondansetron in obstetric anesthesia.

This study had several limitations. First, due to strict inclusion and exclusion criteria, some patient populations were not included in this study, such as those with obesity or other specific comorbidities. Therefore, the generalizability of our results is limited. Second, we only used SBP and HR as hemodynamic parameters, whereas other parameters, such as SVR, SV, and CO, were not monitored. Notably, different phenylephrine doses may have different effects on these parameters. Third, the calculation of the required sample size was based only on the primary objective of the study; therefore, the comparison of some secondary outcomes may have lacked statistical power, resulting in inevitable statistical errors. Additionally, the present study did not incorporate an evaluation of HR variability across four distinct groups, which would provide a more comprehensive assessment of the relationship between phenylephrine dosage and baroreflex-induced bradycardia.

In conclusion, under the conditions of this study, the ED50 and ED90 of phenylephrine in preventing SIH were 0.25 (95% CI, 0.15~0.30) and 0.45 (95% CI, 0.39~0.59) μg/kg/min with ondansetron pre-administration.

## Data Sharing Statement

The authors intend to disclose deidentified participant data, including blood pressure, side effects, and demographic data. However, no other documents related to the study will be made accessible. Interested parties can access the data through http://www.chictr.org.cn after a period of 6 months following publication.

## Ethics and Consent Statements

This study was approved by the Institutional Review Board of Jiaxing University Affiliated Women and Children's Hospital's Institutional Review Board (IRB 2019-119, date of approval: Nov 6. 2019).

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients for inclusion in the study.

## Acknowledgments

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## Disclosure

The authors declare no conflicts of interest in this work.

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