

Timing of Ondansetron Administration for the Prevention of Spinal Hypotension in Nonobese Parturients Undergoing Elective Cesarean Section: A Prospective Cohort Study

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Abstract

Background: Ondansetron has been proposed as an adjunct to phenylephrine for prophylactic spinal hypotension (SH) during cesarean section (C-section). However, the optimal timing of administration is unclear.

Objectives: To evaluate the timing of prophylactic ondansetron administration and other factors associated with SH in nonobese parturients undergoing elective C-section.

Methods: This prospective cohort study enrolled 154 nonobese term parturients receiving elective C-section under spinal anesthesia (SA) with standardized prophylaxis, including phenylephrine, crystalloid coload, and left uterine displacement. All patients received 4 mg of intravenous ondansetron at least 10 minutes before SA. The primary outcome was SH, defined as systolic blood pressure < 90% of baseline. Associations between ondansetron timing, perioperative variables, and SH were evaluated using multivariable logistic regression.

Results: The incidence of SH was 62.3% (95% CI, 54.6%-70.1%). Extending the interval between ondansetron administration and SA beyond 10-20 minutes was not associated with a reduced risk of SH in either univariate or multivariable analyses. In contrast, a longer interval from SA to delivery independently predicted SH (adjusted odds ratio [OR], 1.61; 95% CI 1.27-2.05; $P < .001$). Neonatal outcomes were uniformly reassuring, with normal Apgar scores across all groups.

Conclusions: Administering ondansetron approximately 10 minutes before SA appears sufficient for SH prophylaxis, with no additional benefit from prolonging the interval between ondansetron administration and SA. A shorter SA-to-delivery interval was associated with improved maternal hemodynamic stability. However, this association should not be interpreted as evidence of a causal relationship.

Keywords: Cesarean section, Hypotension, Ondansetron, Prophylactic phenylephrine, Spinal anesthesia

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Introduction

The international consensus statement on the management of hypotension with vasopressors during cesarean section (C-section) under spinal anesthesia (SA)¹ and the recent consensus on the Southeast Asian management of spinal hypotension (SH) using vasopressors and adjunct modalities² strongly recommend a proactive approach to the management of SH, consistently designating phenylephrine as the first-line vasopressor

for prophylactic use during C-section. Despite these recommendations, SH remains highly prevalent; a recent randomized controlled trial (RCT) in Thailand reported incidence rates of 83.9% and 61.3% with prophylactic phenylephrine doses of 50 µg and 100 µg, respectively.³

Given this persistently high incidence, the need for highly effective prophylactic strategies is paramount. Consequently, adjunctive approaches have been explored, including ondansetron, a 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist primarily indicated for the prevention of nausea and vomiting. Its proposed antihypotensive effect is mediated through inhibition of the Bezold-Jarisch reflex via blockade of left ventricular 5-HT₃ receptors. Previous studies demonstrated that ondansetron could reduce the incidence of SH and decrease vasopressor requirements in both obstetric and nonobstetric surgeries,⁴⁻⁶ and might also attenuate maternal bradycardia,^{7, 8} with different dose and timing regimens of ondansetron administration. A prior RCT demonstrated that administration of 4 mg ondansetron at least 10 minutes before SA, in combination with slow intravenous injection of 100 µg of phenylephrine, was clinically effective in reducing SH in nonobese parturients undergoing C-section, with an incidence of 34.4% in the ondansetron-phenylephrine group compared with 45.9% in the phenylephrine-only control group. Importantly, the study reported a favorable safety profile, with no episodes of maternal bradycardia and normal Apgar scores in both groups.⁹

However, the optimal timing of ondansetron administration beyond a 10-minute prespinal interval has not been established, and the duration required to achieve maximal prophylactic efficacy remains unknown. Establishing an evidence-based prophylactic strategy that optimally integrates ondansetron with established preventive measures — including prophylactic phenylephrine, crystalloid coload, and left uterine displacement — is therefore essential for clinical practice to maximize the prevention of SH. This clinically relevant knowledge gap directly motivated the present study, which was rigorously designed with an a priori sample size calculation to evaluate the association between the timing of ondansetron administration and SH. This study aimed to determine the timing of prophylactic ondansetron administration and to evaluate factors associated with SH in nonobese patients undergoing C-section.

Methods

Study Design, Setting, and Participants

A prospective cohort study was conducted at Chaophrayayommarat Hospital. A total of 154 patients with a body mass index (BMI) less than 30 kg/m² undergoing elective C-sections from April 2025 to January 2026 were recruited to study the optimal timing of ondansetron administration and factors associated with SH. Data collection was conducted after obtaining approval from the research ethics committee of Chaophrayayommarat Hospital, registration with the Thai Clinical Trials Registry, and written informed consent from the participants. The inclusion criteria were American Society of Anesthesiologists (ASA) physical status classification II or III, age of at least 18 years, singleton pregnancy, and term pregnancy (gestational age [GA] of at least 37 weeks). The exclusion criteria were high blood pressure (BP) (chronic hypertension, gestational hypertension, and preeclampsia), cerebrovascular disease, complicated pregnancy (abruptio placenta and placenta previa totalis), fetal abnormalities, a history of maternal use of monoamine oxidase inhibitor or drug-induced bradycardia, and the use of drugs other than except spinal bupivacaine and morphine administration after SA and before baby delivery.

Interventions and Methods of Analysis

Preoperative demographic data, including age, body weight, height, BMI, GA, ASA physical status, indication for C-section, and underlying diseases, were recorded. Baseline values for average BP and heart rate (HR) were calculated from previous records in the obstetric ward. The calculation included all individual recorded values along with their corresponding time points, with each participant having between 3 and 6 records. A total of 3 anesthesiologists participated in this study, with 16, 3, and 2 years of clinical experience, respectively. In the operating room, monitoring and routine SA were performed in accordance with standard guidelines. Elastic bandaging or lower-limb compression devices were not used before SA. At least 10 minutes before starting SA, 4 mg of ondansetron (Emistop, Baxter Pharmaceuticals India Private Limited, India) in 2 mL was administered. The actual interval varied due to routine operating room workflow, including operating room availability, delays from preceding cases, and emergency case prioritization, rather than predetermined allocation to different timing groups. All patients received a standardized fluid coload of 0.9% sodium chloride solution at 10 mL/kg intravenously during the SA procedure. The patient was positioned on the left side, and anesthesia was administered using a 27-gauge Quincke spinal needle at the L2-L3 or L3-L4 vertebral interspace. Once free flow of cerebrospinal fluid was confirmed, 2.2 mL of 0.5% hyperbaric bupivacaine and 0.2 mg of preservative-free morphine were injected intrathecally. Following the injection, the patient was placed in the supine position with left uterine displacement at a 15° angle, achieved by using a champagne-shaped pillow under the right hip. After completing SA, the patients received prophylactic slow intravenous injections of phenylephrine at a dose of 100 µg over 30 seconds by anesthesiologists, as they needed to be well-trained in this specific injection technique (by opening 3 ports of a 3-way stopcock to imitate the function of a smart pump).^{3, 9, 10} Patients with a HR below 60 beats per minute (bpm) before phenylephrine administration were to be excluded. One-minute automatic interval noninvasive BP, HR, and oxygen saturation monitoring commenced immediately after the completion of the spinal medication injection (referred to as Time 0). It continued until the delivery of the baby. The dermatomal level of anesthesia was assessed by evaluating the loss of cold-sensation discrimination at the 1st and 5th minutes following the completion of SA. An adequate sensory block extending to the T5 level was considered sufficient for C-section.

SH was defined as a systolic blood pressure (SBP) less than 90% of the baseline value with a HR greater than 60 bpm. Each SBP measurement below the predefined threshold was recorded as one episode of SH and was treated with an intravenous injection of 100 µg of phenylephrine. If SH occurred with an associated HR between 50 and 60 bpm, a rescue dose of 6 mg of ephedrine was administered intravenously. Additional doses of phenylephrine and ephedrine were administered every 2 minutes if SH persisted. For the primary analysis, participants were classified as having SH if at least one episode occurred during the observation period. SH with HR < 50 bpm was treated with 0.6 mg of atropine. Other side effects were also documented. The assessment of SH was performed from the initiation of SA until baby delivery. Reactive hypertension was defined as a SBP exceeding 110% of the baseline value following vasopressor administration. It was evaluated as a secondary hemodynamic outcome to assess the safety and overall hemodynamic effects of prophylactic vasopressor administration. The following timestamps were recorded: completion of SA, skin incision, uterine incision, and baby delivery. Nausea was evaluated using a 4-point ordinal scale: 0, no nausea; 1, mild nausea not requiring pharmacological intervention;

2, nausea requiring pharmacological intervention; and 3, nausea resistant to pharmacological treatment. For vomiting, the scale was as follows: 0, no vomiting; 1, single vomiting event; 2, repeated vomiting events requiring pharmacological intervention; and 3, vomiting resistant to pharmacological treatment. These symptoms were recorded and managed with an antiemetic drug, typically 10 mg of metoclopramide administered intravenously. Oxytocin, at a concentration of 20 units, was diluted in 1000 mL of 0.9% sodium chloride solution and administered to the patient. The Apgar scores for the baby were recorded at the 1st and 5th minutes after birth.

Statistical Analysis

The sample size was calculated based on the findings of a prior study,⁹ which reported an incidence of SH of 34.4% in the group receiving 4 mg of ondansetron at least 10 minutes before SA, and the number of predictor parameters included in the regression analysis. All predictor parameters were selected based on previous studies and incorporated into the sample size calculation. These factors included the ondansetron administration interval (4 factors) including the time from ondansetron administration-to-SA induction, categorized into 4 intervals: 10-20 minutes, 21-30 minutes, 31-40 minutes, and 41-50 minutes.¹⁰ Sensory block level at 5 minutes (2 factors), including sensory block height at 5 minutes post-SA, was categorized into 2 levels: T12-T5 and T4-T1 (excluding C-level and above).¹¹ Indication for C-section (4 factors) included categorical surgical indications, including cephalopelvic disproportion, previous C-section, oligohydramnios/premature rupture of the membranes, and breech presentation.¹¹ This design accounted for a total of 10 relevant factors. Following the recommendation that a minimum of 5 subjects per factor is required for reliable regression analysis, the target number of patients experiencing the event (SH) was set at $10 \times 5 = 50$. Based on the expected SH incidence of 34.4%, the required sample size was calculated as target event count/expected event rate = $50/0.344$, approximately 145.35 patients. Therefore, the minimum required sample size of 146 patients was initially calculated. To account for potential dropouts or incomplete data, an additional 10% was added, resulting in a final target sample size of at least 161 patients. Phenylephrine reportedly ceased importation into Thailand in mid-2025. The drug's regulatory status in Thailand was canceled because the manufacturer voluntarily requested withdrawal of the drug formulation, effective 8 May 2025, resulting in a critical shortage in the management of SH.¹² Therefore, the actual sample size of this study was 154. Although phenylephrine registration was canceled during the study period, sufficient institutional stock remained available to maintain the standardized prophylactic phenylephrine protocol until January 2026.

Continuous variables were presented as means (SD) and compared between groups using the independent-samples *t* test. Categorical variables were reported as frequencies and percentages and analyzed using the chi-square test or Fisher exact test, as appropriate. The clinically relevant variable (time from ondansetron administration-to-SA completion), along with variables with a *P* value < .05 from the initial comparisons, was subsequently included in univariate binary logistic regression to assess the association between each independent variable — weight, BMI, time from SA to skin incision, time from SA to uterine incision, and time from SA to delivery — and the primary binary outcome (SH: yes/no). Univariate results were reported as crude odds ratios (ORs) with 95% CIs, and *P* values.

Variables with a *P* value < .20 in the univariate analysis — weight, BMI, time from SA to skin incision, time from SA to uterine incision, and time from SA to delivery — along with the absence of multicollinearity and clinical relevance, were used as the 3 primary criteria

for variable selection. Multicollinearity was identified between weight and BMI, as well as between time from ondansetron to SA completion and both time from SA to skin incision and time from SA to uterine incision. Consequently, BMI and time from SA to delivery were selected from the correlated sets, and time from ondansetron to SA completion was retained based on clinical relevance.

The multivariable logistic regression model was initially constructed using the Enter method. Model reduction was subsequently performed by removing variables with P values $> .05$. BMI was excluded during this process, resulting in a final model in which all remaining predictors had P values $< .05$, namely time from SA to delivery (minutes) and the clinically relevant variable. Multivariable results were reported as adjusted ORs with 95% CIs and P values.

Data were analyzed using SPSS, version 22.0 (IBM Corp). A P value $< .05$ was considered statistically significant.

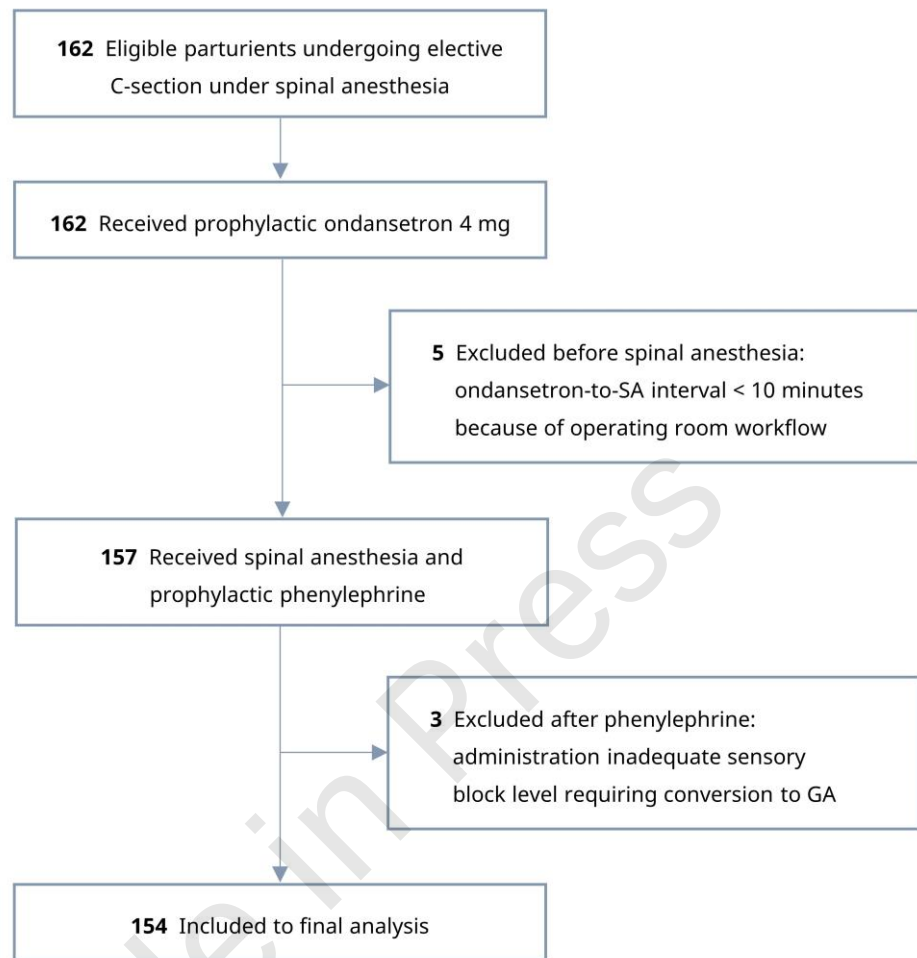
Results

A total of 162 parturients were assessed for eligibility. Five participants were excluded before SA because the interval between ondansetron administration and SA completion was less than 10 minutes due to operating room workflow. Three participants were excluded after phenylephrine administration because of an inadequate sensory block requiring conversion to general anesthesia. Finally, 154 participants were included in the final analysis (Figure 1).

The incidence of SH was 62.3% (95% CI, 54.6%-70.1%). Weight and BMI differed significantly between the groups, while no statistically significant differences were observed for the other variables. Although the study eligibility criteria included patients with ASA physical status II or III, all enrolled participants were classified as ASA II; therefore, no ASA III patients were included in the final analysis (Table 1).

Analysis of intraoperative data and anesthetic outcomes showed that statistically significant differences were observed between the groups in the time from SA completion to skin incision, uterine incision, and delivery. No statistically significant differences were observed in any other variables. All neonates had normal Apgar scores (Table 2).

The associations of the timing of ondansetron administration and other perioperative factors with SH were evaluated. The timing of ondansetron administration was not significantly associated with SH in either the univariate or multivariable analyses. Compared with the reference interval (10-20 minutes), administration at 21-30 minutes (adjusted OR, 1.26; 95% CI, 0.50-3.15; $P = .62$) and > 30 minutes (adjusted OR, 0.93; 95% CI, 0.41-2.14; $P = .87$) showed no significant differences. After adjustment for BMI, only the time from SA to delivery remained an independent predictor of SH (adjusted OR, 1.61; 95% CI, 1.27-2.05; $P < .001$), indicating that a longer interval between SA and delivery was associated with a higher likelihood of SH (Table 3).

Figure 1. Flow of the Study

Abbreviations: C-section, cesarean section; GA, gestational age; SA, spinal anesthesia.

Table 1. Baseline Characteristics and Demographic Data

Characteristic	No. (%)		P Value
	Non-SH (n = 58)	SH (n = 96)	
Age, mean (SD), y	29.7 (6.1)	29.8 (5.7)	.85 ^a
Weight, mean (SD), kg	64.2 (8.3)	67.3 (7.3)	.02 ^a
Height, mean (SD), cm	160.5 (5.5)	160.2 (5.7)	.76 ^a
GA, mean (SD), wk	38.1 (0.5)	38.1 (0.7)	.68 ^a
Baseline SBP, mean (SD), mmHg	119.6 (9.7)	119.3 (9.7)	.87 ^a
Baseline MAP, mean (SD), mmHg	88.9 (7.9)	87.7 (7.6)	.35 ^a
Baseline HR, mean (SD), bpm	81.3 (8.5)	83.0 (8.1)	.24 ^a
BMI, mean (SD), kg/m ²	24.8 (2.9)	26.1 (2.3)	.004 ^a
ASA class II	58 (100.0)	96 (100.0)	NA

Table 1. Baseline Characteristics and Demographic Data (Continued)

Characteristic	No. (%)		P Value
	Non-SH (n = 58)	SH (n = 96)	
Indication for surgery			
Cephalopelvic disproportion	25 (43.1)	40 (41.7)	.11 ^b
Oligohydramnios	9 (15.5)	5 (5.2)	
Previous C-section	16 (27.6)	40 (41.7)	
Breech	4 (6.9)	8 (8.3)	
Premature rupture of the membranes	3 (5.2)	2 (2.1)	
Placenta previa	1 (1.7)	0	
Twins	0	1 (1.0)	
Comorbidity			
Diabetes	9 (15.5)	17 (17.7)	.75 ^b
Asthma	1 (1.7)	1 (1.0)	
Thalassemia trait	1 (1.7)	0	
Hepatitis B infection	0	1 (1.0)	
None	47 (81.0)	77 (80.2)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; C-section, cesarean section; HR, heart rate; GA, gestational age; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure; SH, spinal hypotension.

^a Independent *t* test.

^b Fisher exact test.

Table 2. Intraoperative Data and Anesthetic Outcomes

Characteristic	No. (%)		P Value
	Non-SH (n = 58)	SH (n = 96)	
Time from ondansetron to SA completion, min			
10-20	32 (55.2)	50 (52.1)	.90 ^b
21-30	11 (19.0)	18 (18.8)	
> 30	15 (25.9)	28 (29.2)	
Anesthesia level at minute 1			
L1-T11	14 (24.1)	24 (25.0)	.73 ^b
T10-T5	41 (70.7)	64 (66.7)	
T4-T1	3 (5.2)	8 (8.3)	
Anesthesia level at minute 5			
T10-T5	25 (43.1)	30 (31.3)	.08 ^c
T4-T1	32 (55.2)	66 (68.8)	
C level	1 (1.7)	0	
Cardiac arrhythmia (PVC)	1 (1.7)	1 (1.0)	> .99 ^b
Number of SH episodes			
0	58 (100.0)	0	NA
1	0	76 (79.2)	
2	0	18 (18.8)	
3	0	1 (1.0)	
4	0	1 (1.0)	

Table 2. Intraoperative Data and Anesthetic Outcomes (Continued)

Characteristic	No. (%)		P Value
	Non-SH (n = 58)	SH (n = 96)	
Number of reactive hypertension episodes (SBP > 110% of baseline)			
0	38 (65.5)	72 (75.0)	.03 ^c
1	8 (13.8)	17 (17.7)	
2	4 (6.9)	5 (5.2)	
3	7 (12.1)	1 (1.0)	
4	1 (1.7)	1 (1.0)	
Apgar score at 1st min			
8	1 (1.7)	0	.38 ^c
9	57 (98.3)	96 (100.0)	
Apgar score at 5th min			
8	1 (1.7)	0	.38 ^c
10	57 (98.3)	96 (100.0)	
Total phenylephrine dose, µg			
0	58 (100.0)	3 (3.1)	NA
100	0	76 (79.2)	
200	0	16 (16.7)	
400	0	1 (1.0)	
Total ephedrine dose, mg			
6	0	2 (50)	NA
12	0	2 (50)	
Atropine	1 (1.7)	6 (6.3)	.26 ^c
HR before phenylephrine, mean (SD), bpm	92.3 (14.7)	92.4 (12.5)	.97 ^a
Time from SA to skin incision, mean (SD), min	3.4 (1.0)	4.0 (1.1)	.002 ^a
Time from SA to uterine incision, mean (SD), min	5.6 (1.5)	6.7 (1.8)	< .001 ^a
Time from SA to delivery, mean (SD), min	6.7 (1.5)	8.0 (1.8)	< .001 ^a

Abbreviations: HR, heart rate; NA, not applicable; PCV, premature ventricular contraction; SA, spinal anesthesia; SBP, systolic blood pressure; SH, spinal hypotension.

^a Independent *t* test.

^b Chi-square test.

^c Fisher exact test.

Table 3. Timing of Ondansetron Administration and Other Factors Associated With Spinal Hypotension

Factor	Crude OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Weight, kg	1.06	1.01-1.10	.02	NA	NA	NA
BMI, kg/m ²	1.21	1.06-1.38	.05	NA	NA	NA
Time from ondansetron to SA completion, min						
10-20	1 [Reference]	NA	NA	1 [Reference]	NA	NA
21-30	1.05	0.44-2.50	.92	1.26	0.50-3.15	.62
> 30	1.20	0.55-2.58	.65	0.93	0.41-2.14	.87
Time from SA to skin incision, min	1.69	1.20-2.37	.003	NA	NA	NA
Time from SA to uterine incision, min	1.52	1.21-1.92	< .001	NA	NA	NA
Time from SA to delivery, min	1.60	1.26-2.01	< .001	1.61	1.27-2.05	< .001

Abbreviations: BMI, body mass index; NA, not applicable; SA, spinal anesthesia.

Discussion

In this prospective cohort of nonobese parturients undergoing elective C-section under SA with prophylactic phenylephrine, the incidence of SH remained high at 62.3%, despite standardized hemodynamic management. However, this finding should be interpreted with caution. Since all participants received prophylactic ondansetron and phenylephrine, the present study was not designed to determine the efficacy of ondansetron in preventing SH. Rather, it evaluated whether different timing intervals of ondansetron administration were associated with SH occurrence. Therefore, differences in study design, patient characteristics, and individual hemodynamic responses to SA and prophylactic vasopressor administration may partly account for the observed differences in the incidence of SH.⁹ The findings suggest that SH remains a multifactorial complication despite standardized prophylactic strategies. Previous randomized evidence has shown that even with prophylactic phenylephrine at varying doses (100-200 µg), SH and bradycardia could still occur, highlighting the persistent challenge of achieving optimal hemodynamic stability during C-section.¹⁰ This relatively high incidence might be partly explained by the definition of SH used in the present study, in which a SBP below 90% of baseline was considered SH. Such a threshold is commonly adopted in obstetric anesthesia research because even modest reductions in maternal BP could compromise uteroplacental perfusion and increase the risk of maternal symptoms such as nausea and vomiting.¹

Ondansetron has been studied as a potential adjunctive prophylaxis for SH based on its antagonism of 5-HT₃ receptors and hypothesized inhibition of the Bezold-Jarisch reflex, which might contribute to hypotension and bradycardia after spinal blockade. Recent evidence from systematic reviews and RCTs suggests that prophylactic 5-HT₃ receptor antagonists, including ondansetron, could reduce the incidence of hypotension and associated vasopressor requirements following SA, although the effect size and clinical significance varied across patient populations and study designs.⁷ The reason for not evaluating administration within 10 minutes before SA was that ondansetron may require sufficient time to exert its pharmacodynamic effect through blockade of 5-HT₃ receptors involved in the Bezold-Jarisch reflex. Although intravenous ondansetron has a rapid onset of action, the optimal interval for attenuation of SH has not been established. Previous studies have used administration times ranging from 5 to 20 minutes before SA, reflecting the absence of consensus regarding the ideal timing.^{9, 13} A RCT conducted in Thai nonobese parturients demonstrated that prophylactic administration of 4 mg ondansetron at least 10 minutes before SA, combined with phenylephrine, significantly reduced the incidence of SH and vasopressor consumption while maintaining favorable maternal and neonatal safety outcomes.⁹ Nevertheless, ondansetron did not completely eliminate SA-induced bradycardia. In this study, SH accompanied by mild bradycardia (HR 50-60 bpm) was managed with ephedrine according to the predefined protocol, whereas atropine was reserved for HR < 50 bpm. Although no clinically significant bradycardia was reported in the previous randomized trial,⁹ the present findings indicated that bradycardia might still occur in some patients despite prophylactic ondansetron, suggesting that its protective effect is not absolute. Because the efficacy of prophylactic ondansetron has already been demonstrated in RCTs, the present study was not designed to compare ondansetron with placebo or no prophylaxis. Instead, it focused on whether different timing intervals for prophylactic ondansetron administration were associated with the occurrence of SH under a standardized prophylactic protocol.

The variability in the interval between ondansetron administration and SA primarily reflected routine operating room workflow rather than deliberate clinical decision-making.

Although the timing was not randomized, it was determined by logistical factors such as operating room availability, delays from preceding cases, and emergency case prioritization. Nevertheless, residual confounding from unmeasured procedural factors cannot be completely excluded. In this study, prolonging the interval between ondansetron administration and SA beyond 10-20 minutes did not confer additional protection against SH, as demonstrated in both univariate and multivariable analyses. Administration at 21-30 minutes or more than 30 minutes before SA was not associated with a significant reduction in the odds of SH compared with the reference interval. These findings were consistent with prior literature indicating that the hemodynamic effects of ondansetron are heterogeneous and might depend on multiple factors, including patient characteristics, anesthetic technique, and concomitant prophylactic measures, rather than on the timing of ondansetron administration alone.¹⁴ Although the final sample size ($N = 154$) was slightly lower than the planned target ($N = 161$), the observed incidence of SH (62.3%) was substantially higher than anticipated (34.4%).⁹ Consequently, the number of observed SH events exceeded the prespecified requirement for the planned multivariable analysis, suggesting that the study retained adequate statistical power for the primary analysis. Nevertheless, the study may have had limited power to detect smaller differences between individual timing subgroups. Therefore, the absence of a significant association between longer ondansetron administration intervals and SH should be interpreted as a lack of evidence for additional benefit rather than definitive evidence of equivalence.

Although a previous RCT demonstrated that prophylactic ondansetron administered at least 10 minutes before SA reduced the incidence of SH, it remained uncertain whether extending the administration-to-SA interval beyond this duration would provide additional hemodynamic benefit. From a clinical standpoint, the present results support the pragmatic use of ondansetron approximately 10 minutes before SA as part of a multimodal strategy for the prevention of SH, aligning with prior randomized findings demonstrating clinically meaningful reductions in hypotension with this timing strategy.⁹ These findings further suggest that prolonging the interval beyond approximately 10 minutes does not provide additional protection against SH. Importantly, extending the preoperative waiting period solely to lengthen the ondansetron administration interval appears unwarranted and might counterproductive, as prolonged time in the operating room could compromise optimal fetal surveillance, which is generally better achieved in the labor or obstetric ward.

By contrast, the interval between SA and baby delivery emerged as an independent predictor of SH after adjustment for confounders, with longer durations being associated with increased odds of SH. Prolonged intervals following SA likely allowed progressive sympathetic blockade, reduced venous return, and sustained aortocaval compression, all of which could exacerbate maternal hypotension, suggesting that procedural timing might exert a stronger influence on hemodynamic stability than discrete pharmacologic timing variables when an effective prophylactic regimen was already implemented.

Although the SH group had longer intervals from SA to skin incision, uterine incision, and delivery, the absolute differences were modest (0.6, 1.1, and 1.3 minutes, respectively) and remained within the range of routine elective C-section practice. Nevertheless, the SA-to-delivery interval remained independently associated with SH after adjustment for confounders. The absolute difference in the mean SA-to-delivery interval between groups was modest (1.3 minutes); each additional minute was independently associated with a 61% increase in the odds of SH (adjusted OR, 1.61; 95% CI, 1.27-2.05). These findings suggest that even relatively small differences in procedural timing may warrant clinical attention.

However, because this was an observational study, the observed association should not be interpreted as evidence of a causal relationship. Furthermore, the SA-to-delivery interval may have been influenced by unmeasured procedural factors, such as variations in anesthesia and surgical workflow, which were not evaluated in the present study. Recent meta-analyses have demonstrated that ondansetron has a moderate effect on reducing the incidence of SH following SA overall, but with significant heterogeneity across studies, underscoring the multifactorial nature of SH.¹³ These findings aligned with previous research showing that prolonged intervals from SA to delivery were correlated with adverse physiological changes, including lower umbilical arterial pH and an increased risk of neonatal acidosis, suggesting that longer operative timing might compound the hemodynamic effects of SA beyond maternal BP changes alone.¹⁵ Although higher body weight and BMI were associated with SH in univariate analyses, these associations did not persist in the multivariable model, indicating that anthropometric characteristics were less predictive of SH than intraoperative timing dynamics in nonobese parturients managed under standardized anesthetic protocols.

Interestingly, reactive hypertension occurred less frequently in the SH group despite both groups receiving prophylactic phenylephrine. This finding may reflect differences in individual hemodynamic responses to SA and prophylactic vasopressor administration rather than differences in phenylephrine exposure. Patients who developed SH may have had greater reductions in vascular tone and/or different cardiovascular responses, resulting in fewer subsequent increases in SBP above baseline. In contrast, patients without SH may have maintained higher baseline vascular tone, increasing the likelihood of transient SBP elevation after phenylephrine administration. Although ondansetron may influence hemodynamic responses after SA by modulating the Bezold-Jarisch reflex, the present study was not designed to evaluate its specific effect on reactive hypertension. However, no patients in either group developed a hypertensive crisis or clinically significant adverse events.

Importantly, neonatal outcomes were reassuring, with normal Apgar scores observed across all groups. However, Apgar scores have limited sensitivity for detecting mild neonatal physiological disturbances; therefore, normal Apgar values cannot completely exclude subtle neonatal acid-base abnormalities. Previous RCTs demonstrated no significant differences in Apgar scores or umbilical artery pH between ondansetron and control groups during cesarean delivery under SA, supporting the neonatal safety profile of prophylactic ondansetron.^{16, 17} From a clinical perspective, these data reinforce the use of ondansetron as part of a multimodal prophylactic strategy for SH without compromising early neonatal well-being.

This prospective study evaluated the clinical relevance of ondansetron timing within a standardized hemodynamic protocol — including prophylactic phenylephrine, fluid coload, and left uterine displacement — thereby reflecting contemporary obstetric anesthesia practice. The use of multivariable modeling strengthened the robustness of the findings by accounting for perioperative confounders, while the relatively homogeneous cohort of nonobese parturients reduced physiologic variability and allowed a more precise assessment of procedural timing factors.

This study encountered several limitations. The single-center design may affect generalizability, although it ensured protocol consistency. Furthermore, the association between a longer SA-to-delivery interval and SH may be subject to temporal ambiguity and reverse causation. Although a prolonged interval after SA may contribute to hypotension,

early hemodynamic changes or intraoperative factors could also influence the timing of subsequent procedures. Therefore, causality cannot be established from the present observational data. Additionally, because the population was restricted to nonobese patients undergoing elective cesarean delivery, extrapolation to higher-risk obstetric groups should be undertaken with appropriate clinical judgment.

Conclusions

In nonobese parturients undergoing elective cesarean delivery under SA with standardized prophylaxis, ondansetron administration approximately 10 minutes before SA appeared sufficient for the prevention of SH. Extending the administration-to-spinal interval beyond this timeframe was not associated with additional hemodynamic benefit. Conversely, a longer interval between SA and delivery was independently associated with an increased risk of hypotension, although this observational finding should not be interpreted as evidence of a causal relationship. Neonatal outcomes remained reassuring across all groups.

Additional Information

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