Original Article

Ephedrine Versus Ondansetron in the Prevention of Hypotension During Cesarean Section: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Common side effects of spinal anesthesia for cesarean section (C.S.) include hypotension and bradycardia. Ondansetron, a 5HT3 receptor antagonist, has been suggested for prophylactic prevention of spinal induced hypotension (SIH) in elective cesarean section. This study compared a traditional vasopressor "ephedrine" with two doses of 5-HT3 receptor antagonist "ondansetron" to prevent SIH during cesarean section.

Materials and Methods: A total of 168 full-term parturients undergoing C.S. under spinal anesthesia were included. Patients were divided randomly into four groups (ephedrine, 4 mg ondansetron (O4), 8 mg ondansetron (O8), and control group). All patients were monitored for mean blood pressure, heart rate, vasopressor requirement, and side effects. The primary outcome of this study was the incidence of SIH in all four groups during the first 60 minutes after spinal anesthesia.

Results: The incidence of SIH was significantly higher in the control group (45.2%) compared to the ephedrine, O4, and O8 groups (19%, 16.7%, and 11.9%, respectively). There were significant differences between the four groups regarding maternal mean arterial pressures during the 1st 60 minutes after spinal anesthesia. No side effects were recorded.

Conclusion: Prophylactic intravenous ondansetron (at a dose of 4mg or 8mg) could be an effective/non-inferior alternative to ephedrine in reducing the incidence of SIH and the requirement of vasopressors in parturients undergoing C.S.

Keywords: Bezold-Jarisch reflex, Cesarean section, Ephedrine, Ondansetron, Spinal induced hypotension

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Introduction

Regional anesthesia has been recognized as the best option for elective cesarean section due to its avoidance of airway instrumentation, less risk of aspiration, and ease of performance (1). Still, unfortunately, spinal-induced hypotension (SIH) is a common complication with an incidence of 55% to 90% if left untreated (2). SIH usually decreases maternal cardiac output and uteroplacental flow, which may induce fetal and maternal morbidity and mortality

(2). Therefore, it is crucial to prevent and treat it quickly and effectively (3). Multiple modalities have been tested, for example, fluid preloading or the use of drugs like ephedrine and phenylephrine.

Ephedrine was regarded as the first-choice drug to treat SIH by maintaining maternal blood pressure. Its sympathomimetic stimulant activity on α and β adrenergic receptors causes positive inotropic and chronotropic effects, but repeated administration diminishes its vasoconstrictive effect through tachyphylaxis (4).

The Bezold-Jarisch reflex (BJR) has been suggested as an additional cause of SIH in parturients. This chemical reflex is mediated through serotonin receptors (5-HT3 subtype) located on the vagus nerve and within the wall of the cardiac ventricles. Serotonin receptors are activated by serotonin released in response to systemic hypotension and lead to an increase in efferent vagal signaling with the subsequent triad of bradycardia, hypotension, and apnea (5). Ondansetron modulates 5-HT3 receptors leading to Bezold-Jarisch reflex (BJR) antagonism (6).

The study aimed to evaluate the effectiveness and safety of different doses of ondansetron versus ephedrine to prevent or minimize SIH. We hypothesize that ondansetron is non-inferior to ephedrine in attenuating spinal-induced hypotension in parturients undergoing C.S.

Methods

Ethics: The study was a prospective randomized parallel-group, nonfunded**,** single-center study. The Ethics committee approved the work of the university hospital (FMASU R 04/ 2022) on 9/1/2022. It also was registered at Clinical Trial Registry ClinicalTrials.gov Identifier: NCT05127876. Written informed consent was obtained from all patients. This trial followed the CONSORT statement.

Study population: Inclusion criteria were age 18-40 years; American Society of Anesthesiologists physical status II; term; elective cesarean section. Exclusion criteria were contraindication to spinal anesthesia, preeclampsia, and morbid obesity.

Study groups: According to the prophylactic intravenous medication used, patients were randomly assigned to one of four groups – according to the syringe's content- using a computer-generated sequence and opaque envelopes. Syringes were identical in volume (10 mL), color, viscosity, and odor.

- Group C: 10 mL 0.9% saline
- Group E: 10mg ephedrine diluted in 0.9% saline
- Group O4: 4 mg ondansetron diluted in 0.9% saline
- Group O8: 8 mg ondansetron diluted in 0.9% saline

The previous doses were according to earlier guidelines (7, 8).

Anesthesia: Standard monitoring was established on arrival at the operating room, and an intravenous infusion of 500 mL crystalloid was started. 5 minutes before spinal anesthesia, study medication was injected over 1 minute by a nurse anesthesiologist who had no further study involvement

Under aseptic precautions, spinal anesthesia was administered in the sitting position at L2–3 or L3–4 with a 25-gauge Whitacre spinal needle. When the free-flow cerebrospinal fluid was observed, 0.5% hyperbaric bupivacaine 2 mL was injected intrathecally (9).

The patient was then positioned supine on the operating table with left uterine displacement. A second anesthesiologist, blinded to the study solution, measured hemodynamic parameters at specific time points. Sensory block was examined by loss of sensation to pinprick at particular time points during the 1st 15 minutes. The surgeon could start surgery when the sensory block level was established at T6. Patients who failed to reach this level were excluded from the study, and general anesthesia was initiated. The time of intrathecal injection was considered as 0 min. Hypotension was defined as a decrease in MBP >20% of baseline. If hypotension developed, ephedrine 10 mg was given intravenously (9). Heart rate <50 beats/min was treated with intravenous atropine 0.3 mg (10).

Sample size: By using the PASS 11 program for sample size calculation, setting the confidence level at 90%, the margin of error ± 0.15, and after reviewing previous study results (11), demonstrating the incidence of maternal hypotension among pregnant females that underwent cesarean section was 31.25% in ondansetron (4mg) versus 16% in those took ondansetron (8mg); so, a sample size of at least 168 pregnant females undergoing cesarean section divided into 4 groups (42 pregnant females in each group)

would be sufficient to achieve study objective.

Statistical analysis: Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges. The following tests were done: A one-way analysis of variance (ANOVA), a Post Hoc test: Tukey's test, Chi-square test, and Fisher's exact test.

Results

All 168 patients completed the study. All spinal blocks were successful with a satisfactory level of anesthesia. There was no significant difference in demographic data (Table 1). Duration of surgery, blood loss, and APGAR score at 1 min and 5 min were also comparable between the four groups.

The incidence of hypotension was higher in the Control group (45.2%) than in other groups (P = 0.002). The least incidence of hypotension was noticed in the O8 group (Table 2). Additionally, the number of patients who needed ephedrine or atropine was significantly higher in the control group (Table 3). It is noted that clinically more patients in the ephedrine group needed vasopressor rescue doses than in the two ondansetron groups.

From the 10th to 60th min, the mean MBP was significantly lower in group C compared with the other three groups. On the other hand, from the 10th to 60th min, the mean H.R. was remarkably stable (with lesser fluctuation) in group O8 compared with the other three groups who showed different degrees of significantly lowered heart rate. (Fig 1&2). No side effects were recorded during the first six postoperative hours (flushing, ECG changes).

Discussion

Phenylephrine is the first-line choice for treating and preventing SIH (12). But since phenylephrine was not regularly available in Egypt when the study was conceived, we used ephedrine instead. Ephedrine has previously been the gold standard vasopressor, but its position has been challenged because of potential complications. It is safe, available, and familiar to most anesthesiologists. However, adverse effects must be

Table 1: Comparison between groups according to demographic data.

Demographic data	Control Group (n=42)	Ephedrine Group (n=42)	Ondansetron 4mg Group (n=42)	Ondansetron 8mg Group (n=42)	Test value	p-value
Age (years)						
Mean±SD	27.52±3.58	28.17±3.39	27.90±3.34	28.31±4.51	0.359	0.783
Range	20-36	20-37	20-36	20-39		
Height (cm)						
Mean±SD	160.17±5.55	158.24±3.48	158.40±3.46	158.38±2.46	2.309	0.078
Range	150-175	150-167	152-170	151-166		
Weight (kg)						
Mean±SD	81.71±4.15	82.10±3.09	80.48.48±3.29	82.24±3.38	2.196	0.091
Range	72-90	75-90	72-89	72-89		
Gestational age (wk)						
Mean±SD	37.74±0.59	37.56±0.48	37.69±0.47	37.72±0.51	1.040	0.376
Range	37-39	37-38	37-38	37-38		
Dur oper (min)						
Mean±SD	39.52±4.25	40.00±3.49	40.00±3.31	40.00±3.66	0.174	0.914
Range	35-45	35-45	35-45	35-45		
Blood Loss (ml)						
Mean±SD	690.48±158.97	690.48±146.19	738.10±122.88	676.19±146.19	1.478	0.222
Range	500-900	500-900	500-900	500-900		

Using: F-One Way Analysis of Variance; x^2: Chi-square test, p-value >0.05 NS

Table 2: Comparison between groups according to incidence of hypotension.

Incidence of hypotension	Control Group (n=42)	Ephedrine Group (n=42)	Ondansetron 4mg Group (n=42)	Ondansetron 8mg Group (n=42)	Test value	p-value
MAP<20% of baseline	19 (45.2%)	8 (19.0%)	7 (16.7%)	5 (11.9%)	15.862	0.002*

x^2: Chi-square test; *p-value <0.05 S

Table 3: Comparison between groups according to number of patients needed ephedrine and atropine.

	Control Group (n=42)	Ephedrine Group (n=42)	Ondansetron 4mg Group (n=42)	Ondansetron 8mg Group (n=42)	Test value	p-value
Ephedrine	14 (33.3%)	7 (16.7%)	3 (7.1%)	4 (9.5%)	12.686	0.005*
Atropine	5 (11.9%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	9.988	0.019*

x^2: Chi-square test; *p-value <0.05 S

considered while administering ephedrine, such as tachyphylaxis, arrhythmia, hypertensive episodes, tachycardia, fetal acidosis, increased myocardial contractility, and oxygen demand (13).

Ondansetron, a 5HT3 receptor antagonist, is a newly introduced medication for attenuating arterial hypotension and bradycardia. It acts by blunting the BJR and reducing the need for vasopressors. In this study, we assessed the effectiveness of ondansetron in preventing SIH in two doses (4 mg and 8 mg) compared to the traditional vasopressor ephedrine. Our general goal is to find a safe, effective alternative to ephedrine - with minimal side effects- to prevent or minimize SIH. Especially, SIH is a daily situation facing anesthetists with variable levels of experience, which necessitates simple and rapid protocols that anesthetists with moderate and low expertise can easily apply.

Regarding ondansetron, the effect of its different doses on the prevention of SIH has been found to vary in various obstetric studies. (7, 10, 11) Sahoo and their colleagues (10), for example, showed a decreased incidence of SIH in the O4 group. The use of vasopressors was also significantly reduced in the

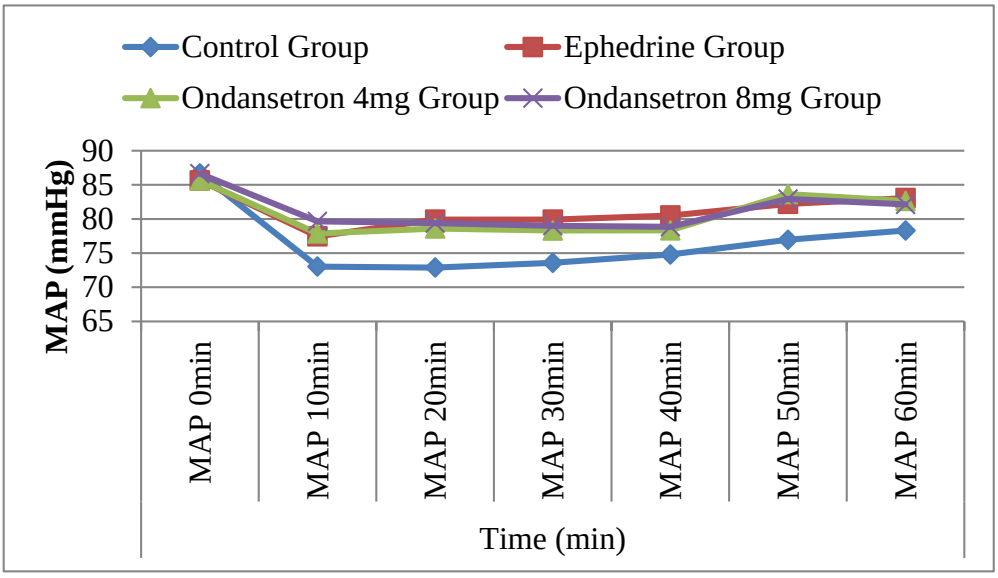

Figure 1. Comparison between groups according to MAP (mmHg).

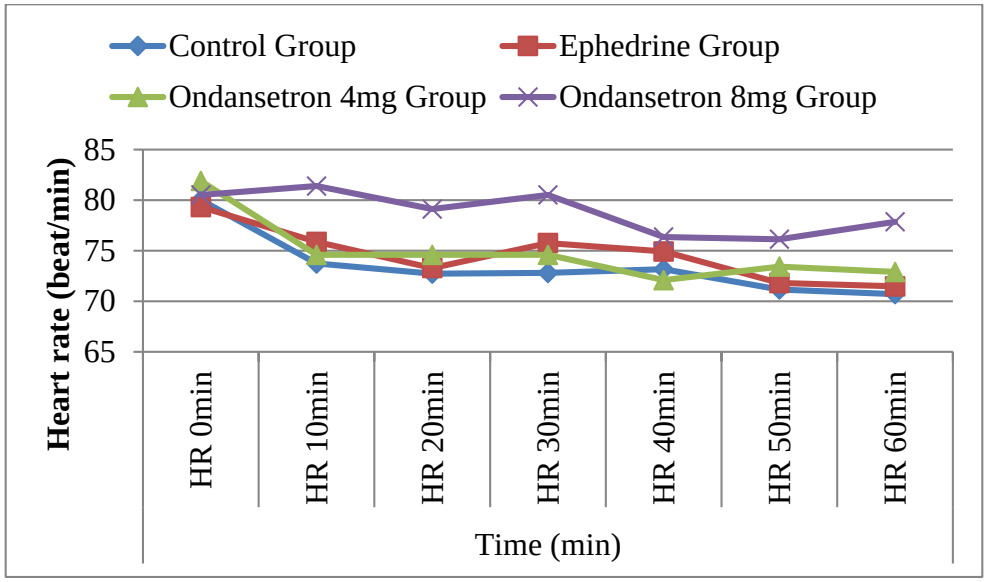

Figure 2. Comparison between groups according to heart rate "beat/min".

O4 group compared to placebo. Additionally, Bhiwal and their colleagues (11) concluded that both 4mg and 8mg ondansetron reduced the incidence of SIH and the requirement of vasopressors in parturients. The incidence of SIH in the control group was 58% compared to the O4 group, 31.25%, and the O8 group, 16%. On the other hand, Ortiz-Gómez and their colleagues (7) found that ondansetron was ineffective in preventing SIH. They found that maternal hypotension in the placebo control group was not significantly different from that in O2, O4, and O8 groups (43.8%,53.1%,56.3%,53.1%, respectively). These contradictory results could be attributed to intrathecal fentanyl added to local anesthetic regarding ondansetron's effectiveness in reducing SIH. Another contributing factor is they defined hypotension differently in their study (systolic blood pressure <75% of baseline), which could affect observed and collected data.

Very few studies compared ephedrine & ondansetron regarding their efficacy in attenuating SIH in obstetric patients (8, 14-16). Interpreted results of our study showed a significant decrease in SIH incidence - during 1st 60 minutes- in the three interventional groups compared to the control group. But, clinically, both 4mg and 8mg ondansetron groups attenuated SIH more than ephedrine. Additionally, a sparse number of patients needed rescue vasopressors in both ondansetron groups compared to the ephedrine. Finally, the 8mg ondansetron showed less heart rate fluctuation when compared to the other three groups. These results suggest the non-inferiority of ondansetron compared to ephedrine in attenuating SIH.

Confirming our results, Khalifa (14) found that the results of all interventional groups were nearly comparable, and all had significantly fewer vasopressor rescue doses. Study medications were intravenously given -diluted- before induction of spinal anesthesia. Her study showed ondansetron's superiority in attenuating SIH compared to ephedrine and granisetron. Also, she found a more stable heart rate in both ondansetron and granisetron groups, which goes with our study.

On the other hand, The Nivatpumin study (8) showed no significant difference in SIH incidence in women administered prophylactic 10mg ephedrine or 8mg ondansetron after spinal anesthesia for cesarean section when compared with placebo (53.6%, 57.1%, 68.5% respectively). It may be attributed to the timing of interventional drug administration. They were given immediately after intrathecal injection (not 5 min before as in our study). Additionally, 200 µg morphine was added to intrathecal bupivacaine, which might have affected the results using a different L.A. regimen.

Also, contradicting our results, Ranjbar and their colleagues (16) concluded that in comparison to intravenous 4mg ondansetron and 500 mL ringer, an

intramuscular dose of 25mg ephedrine 25 minutes before spinal anesthesia had better prevention of blood pressure fluctuations. All interventional medications were given before S.A. Incidence of SIH at the 12th minute after spinal anesthesia was significantly higher in the 4mg ondansetron group (10%) compared to 25mg ephedrine and 500mL ringer groups (0%,0%). But the examination for the rest of the minutes showed no statistically significant difference. Their contradictory results could be attributed to the usage of a higher dose and a different route of ephedrine that was given 25 minutes before S.A. Also, a higher dose of L.A. was given to taller patients

Our study was not without limitations. The first limitation was the failure to record umbilical arterial blood pH. We realized later that recording this item could have added exciting data, especially since Kim and their colleagues (1) suggested that using ephedrine may have a negative effect. Secondly, the placental transfer of ondansetron which is administered just before delivery, and the consequences of fetus exposure to ondansetron at this time are unknown. Additional studies are required to discuss its safety. Finally, postoperative nausea and vomiting, pain, shivering, and analgesic requirement were not recorded, as our primary focus was the effect of interventional medications on maternal hemodynamics.

Conclusion

Prophylactic intravenous ondansetron 4mg or 8mg were non-inferior to ephedrine 10 mg in attenuating SIH and decreasing vasopressors requirement in parturients undergoing C.S.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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