ORIGINAL ARTICLE

Ondansetron versus Ephedrine for prophylaxis of Subarachnoid Block-Induced Hypotension in Pregnant Women

Chikamnario Josiah, Benjamin Olusomi Bolaji, Majeed Babajide Adegboye, Israel Kayode Kolawole

Department of Anaesthesia, University of Ilorin Teaching Hospital, Ilorin, Nigeria.

ABSTRACT

Background: Hypotension is the most frequent adverse effect of subarachnoid block (SAB) in patients undergoing elective caesarean section (C/S), presenting a significant challenge to both maternal and foetal safety. It is believed that the Bezold-Jarisch reflex (BJR), triggered by serotonin-mediated stimulation of 5-hydroxy-triptamine-3 (5-HT3) receptors in cardiac chambers, could be a contributor to the mechanism of SAB-induced hypotension. Therefore, the use of ondansetron, a 5-HT3 receptor antagonist, holds promise in mitigating this type of hypotension.

Objective: The aim of this study was to compare the efficacy of prophylactic intravenous 4 mg ondansetron versus intravenous 15 mg ephedrine in reducing the incidence of SAB-induced hypotension in patients scheduled for elective caesarean section at the University of Ilorin Teaching Hospital.

Methodology: This randomised controlled trial included 80 ASA 2 patients, between 18 and 40 years, who were scheduled for elective C/S under SAB. Participants were allocated to 2 groups of 40: Group OS received 4 mg intravenous ondansetron 10 minutes before SAB, and Group ES received 15 mg intravenous ephedrine immediately after SAB. The primary outcome measure was the incidence of hypotension while secondary outcome measures were quantity of phenylephrine and atropine consumption, incidence of post-spinal spinal shivering, and study drug side effects: hiccups, skin flushing, and headaches.

Data Analysis: Statistical analysis was conducted using the Statistical Product and Service Solutions SPSS Statistic 20 (IBM Corp., Armonk, NY, USA), employing Chi-square test/ Fisher's exact test) or independent student's t-test as appropriate. P <0.05 was considered statistically significant.

Results: The demographic characteristics and baseline haemodynamic parameters were similar across both groups. Although the incidence of hypotension recorded in the ephedrine group was 12.5% lower than that recorded in the ondansetron group, this was not statistically significant (60% in OS vs 47.5% in ES, 95% confidence interval [CI] = -0.03 - 0.28, P = 0.37). Notably, the mean systolic blood pressure (SBP) was significantly higher in the

Corresponding author:
Chikamnario Josiah
Department of Anaesthesia, University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Keywords: Bradycardia, ephedrine, hypotension, ondansetron, pethidine, phenylephrine, shivering, subarachnoid block.

This article is available online at: http://www.mjz.co.zm, http://ajol.info/index.php/mjz, doi: https://doi.org/10.55320/mjz.52.2.620

The Medical Journal of Zambia, ISSN 0047-651X, is published by the Zambia Medical Association

ephedrine group (P < 0.05) at six critical time points. The mean DBP values were similar in both groups. Apart from the 4th minute, where the mean arterial blood pressure (MAP) value was significantly higher in the ephedrine group (82.73 ± 14.37 in ES vs 74.65 ± 15.17 in OS, 95% CI = -14.65 - -1.49, p = 0.02), the values were comparable at other times. The mean heart rate (HR) values were significantly elevated (P < 0.05) in the ephedrine group at nearly all-time intervals, barring the second minute. One patient in the ondansetron group experienced bradycardia, which was treated with 0.6 mg atropine, whereas none in the ephedrine had bradycardia. The mean consumption of phenylephrine (in µg) was lower in the ES group by 25 µg (77.50 ± 96.71 in group ES versus 102.50 ± 110.33 in group OS, 95% CI = -21.18 - 71.18, P = 0.28) but was not statistically significant. Interestingly, the percentage of participants in group OS who experienced shivering was 17.5% lower compared to the percentage in the ephedrine group (5% in group OS vs 22.5% in group ES, 95% CI = 0.03 - 0.32, P = 0.023). No significant differences in the incidences of study drug side effects were noted between the groups.

Conclusion: Our findings suggest that prophylactic use of 4 mg intravenous ondansetron has a comparable efficacy to 15 mg intravenous ephedrine in preventing SAB-induced hypotension in pregnant women. However, patients pretreated with ondansetron before SAB had a significantly lower incidence of post-spinal shivering, indicating its potential value in enhancing maternal comfort and safety during caesarean sections.

INTRODUCTION

Hypotension is the most common adverse effect associated with subarachnoid block in obstetric patients, with reported incidences ranging from 15.8% to an alarming 91.4%.[1] When not treated promptly, it can lead to serious foeto-maternal complications, including loss of consciousness and cardiac arrest, particularly when accompanied by bradycardia.[2,3] SAB-induced hypotension is commonly defined as a drop in maternal systolic blood pressure below 90-100 mmHg or a decrease by more than 20-30% from baseline.

The mechanisms underlying SAB-induced hypotension largely involve sympathetic blockade, which causes peripheral vasodilation and a reduction in systemic vascular resistance.[4] Additionally, the Bezold-Jarisch reflex (BJR), a cardiac inhibitory reflex, plays a role in triggering bradycardia and hypotension after SAB through serotonin-mediated activation of 5-hydroxytryptamine-3 (5-HT3) receptors found in cardiac chambers.[5] While the extent of BJR's contribution to post-spinal hypotension remains unclear, significant involvement could make ondansetron, as a 5-HT3 receptor antagonist, a valuable adjunctive therapy to reduce hypotensive episodes during a subarachnoid block.

There are various available methods for reducing the occurrence of SAB-induced hypotension, but none is completely reliable when used alone. Ondansetron is a relatively cheap and widely available drug used commonly for the prevention and treatment of nausea and vomiting. It may improve maternal comfort and safety in the perioperative period by reducing the incidence of post-spinal shivering and SAB-induced hypotension. Previous studies have demonstrated the efficacy of ondansetron in attenuating SAB-induced hypotension in the obstetric population; however, most of these studies compared ondansetron to placebo as against a standard vasopressor such as ephedrine.[6]

Ephedrine, a mixed sympathomimetic drug with both alpha and beta-agonist activity, is one of the mainstay vasopressors, alongside phenylephrine, used in treating SAB-induced hypotension in the obstetric population. Studies by Simon et al. and Iqbal et al. demonstrated that an intravenous dose of 15 mg ephedrine significantly reduced maternal incidence of hypotension without causing significant tachycardia.[7] However, ephedrine has been associated with foetal acidosis, prompting a shift of attention to other agents.[8] Ondansetron which

possesses anti-emetic and anti-shivering properties could be a worthy alternative if proven to be efficacious.

This study aimed to compare the efficacy of ondansetron to ephedrine in maintaining maternal haemodynamic stability during elective caesarean sections. It was hypothesised that there would be no difference between intravenous ondansetron and ephedrine in preventing maternal SAB-induced hypotension.

METHODS

Study Setting: The study took place at the University of Ilorin Teaching Hospital, located at Ilorin East Local Government Area, Kwara State, Nigeria

Study Population: Subjects recruited into this study were pregnant women with American Society of Anaesthesiologists (ASA) physical status class II, aged between 18 and 40 years, scheduled for elective caesarean section under subarachnoid block.

Inclusion Criteria: All consenting pregnant women between the ages of 18 and 40 years with American Society of Anaesthesiologists (ASA) classification II, scheduled for elective lower segment caesarean section under subarachnoid block.

Exclusion Criteria:

- Patients who refused to participate in the study.
- Patients with unstable haemodynamics.
- Patients with coagulation abnormality.
- Patients with known allergies to ondansetron or local anaesthetic agents.
- Patients with chronic hypertension or hypertensive disorders of pregnancy.
- Patients with body mass index (BMI) greater than 35 kg/m^2

Study Design: This study was a randomised, double-blind study that involved patients scheduled for elective caesarean section under subarachnoid block.

Study Duration: The study took place between August 2022 and March 2023.

Sample Size Determination: The sample size was calculated using the formula for comparing two proportions.

$$n = [A + B]^2 \times [(P_1 \times (1-P_1)) + (P_2 \times (1-P_2))] / (P_1-P_2)^2$$

n = Sample size

A = Significance level set at 5% (0.05) with value at 1.96

B = Power of the study = 80%, with value corresponding to 0.84

P1= the first proportion

P2 = the second proportion

P1= P2 - Difference in proportion of clinical importance which can be a decrease or increase.

Based on the previous work done by Trabelsi et al, the incidence of hypotension in the placebo group was 77.5%.

To achieve a reduction in the incidence of hypotension to 47.5%, the sample size was calculated as follows:

$$n = [1.96 + 0.84]^2 \times [(0.775 \times (1-0.775)) + (0.45 \times (1-0.45))] / 0.3^2$$

$$n = 7.84 \times 0.423 / 0.09$$

$$n = 36$$

Assuming attrition of 10%,

$$n = 36 + 3.6$$

$$n = 39.6$$

Therefore, 40 patients were recruited in each group

Sampling Technique: Patients were randomised into two groups, OS (Ondansetron group) and ES (Ephedrine group) using simple random techniques. The randomisation was done by allocation concealment, with patients picking from a sealed envelope containing the groups. The research assistant made the sealed envelope available on the morning of surgery.

Blinding Technique: It was a double-blind study: both the researchers and the patients were blinded to the group to which the patient belonged. For each

patient, the research assistant prepared two transparent syringes containing colourless solutions and labelled syringe 1 and syringe 2. One solution was administered 10 minutes before SAB, while the other was administered immediately after SAB. Only the research assistant knew the contents of these syringes, which were either ondansetron and saline or ephedrine and saline. Patients in the ondansetron group received 4 mg (diluted to 10 ml colourless solution) intravenous ondansetron (Swiss parenteral LTD, Gujarat India) 10 minutes before SAB and 10 ml of saline (placebo) immediately after SAB. Patients in the ephedrine group received 10 ml of saline (placebo) 10 minutes before SAB and 15 mg intravenous ephedrine (Martindale Pharma, Buckinghamshire, UK, diluted to 10 ml colourless solution) immediately after SAB. The research assistant administered the study drugs.

Ethical Consideration

Ethical approval was obtained from the University of Ilorin Teaching Hospital Ethics Review Board **b**efore the commencement of the proposed study. The Ethics Review Board assigned number was NHREC 02/02/2010. Oral and written informed consent, signed and dated, was obtained from all patients following the investigator's comprehensive explanation of the procedure. The data obtained were kept confidential during and after the study period.

Pre-Operative Assessment and Preparation

Patients were reviewed on the ward a day before their elective caesarean section, and relevant investigations were obtained. Blood was grouped and cross-matched as required for the surgery. Informed consent for the study and SAB was obtained from the patients after a detailed explanation. Patients fasted for at least 6-8 hours before surgery.

On the morning of surgery, patients were randomised into two groups (OS or ES) by the research assistant using a sealed envelope containing the groupings.

Procedure

On arrival at the operating suite, a pre-anaesthesia equipment check was carried out to ensure their optimum functioning. Appropriate equipment and drugs for resuscitation were made available. Probes for peripheral oxygen saturation (SpO_2) and temperature were attached to the finger and the axilla, respectively, while an appropriate-sized cuff for non-invasive blood pressure (NIBP) measurement was attached to the arm and connected to the pressure tubing. Baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate (PR), peripheral arterial oxygen saturation (SpO_2), temperature and electrocardiogram (ECG) were obtained using a multi-parameter patient monitor (B105 Patient Monitor, GE Medical systems information technologies Inc. 8200W. Tower Ave Milwaukee, Wisconsin USA). Intravenous access was secured with a size 16-G intravenous cannula using a prominent forearm vein under an aseptic technique. All the patients in both groups were preloaded with 15 ml/kg of normal saline administered over 15-20 minutes.

The study drugs (4 mg of ondansetron and 15 mg of ephedrine) were prepared by the research assistant, and both the researchers and the patients were blinded to the study drugs as previously described in the blinding section. Patients in the ondansetron group were given intravenous ondansetron 4 mg about 10 minutes before SAB and 10 ml of normal saline immediately after SAB. The patients in the ephedrine group were given 10 ml of normal saline about 10 minutes before SAB and 15 mg of intravenous ephedrine immediately after SAB. The research assistant injected the study drugs slowly over two minutes. The patient was placed in the sitting position, and routine cleaning and draping of the block site were carried out to ensure strict asepsis. The skin and deeper tissues were infiltrated with 2 ml of 1% lidocaine to prevent procedural pain. Spinal anaesthesia was performed in the midline at the L3-4 interspace with a 26-G Quincke needle. Hyperbaric bupivacaine 0.5%

(Rotexmedica GMBH Arzneimittelwerk, Bunsenstrasse4.22946 Trittau. Germany) 2.5 ml was administered after confirmation of free flow of cerebrospinal fluid through the spinal needle. The spinal needle was removed from the back of the patient, and thereafter, the patient was positioned supine with 15^0 left lateral tilt using a wedge applied under the right buttock to prevent supine hypotension syndrome. The patient's head and shoulders were supported on a pillow to prevent the rostral spread of the local anaesthetic agent. Sensory block height was assessed using a loss of sensation to temperature with the methylated spirit-soaked swab and motor block using the Bromage scale. Surgery commenced once the sensory blockade was up to the T6 dermatome.

Haemodynamic variables (HR, SBP, DBP and MAP) were measured every two minutes after SAB until 20 minutes, and every 5 minutes thereafter until the end of surgery. The attending anaesthetist maintained constant communication with the patient to record complaints of hiccups, headaches, and skin flushing. Hypotension (a reduction of 20% or more in baseline systolic blood pressure) was treated with fluids and 50 micrograms of intravenous phenylephrine. In contrast, bradycardia (HR<50 bpm) was treated with 10 µg/kg of intravenous atropine. Episodes of shivering, nausea and vomiting were treated with 25 mg of intravenous pethidine and 10 mg of intravenous metoclopramide, respectively. Blood loss was monitored closely, and blood transfusion was initiated if the patient's blood loss exceeded the calculated allowable blood loss. Crystalloids were given for fluid deficit, maintenance and ongoing losses. All patients received 15 mg/kg of paracetamol just before the skin incision at the commencement of surgery. Five international units (5 IU) of bolus intravenous oxytocin were given immediately after delivery of the foetus followed by an infusion of 40 IU in 1 L of normal saline to run at 100 ml/hour. APGAR scores were recorded at 1 and 5 minutes, respectively.

At the end of data collection for each patient, the attending anaesthetist handed over the data collection sheet of each patient to the research assistant, who indicated the group of the patient on the sheet. The proformas were kept safe and confidential in a large envelope. Patients were transferred to the recovery room and observed for about one hour while monitoring and fluid therapy continued. Pain was assessed in the recovery room using the numeric rating scale, and patients with pain scores greater than 3 were given 50 mg of intravenous pethidine. Patients were transferred to the ward after an hour, having satisfied the departmental criteria for discharge to the ward.

Primary Outcome Measure:

- Incidence of hypotension: defined as more than 20% decline in SBP from baseline

Secondary Outcome Measure

- Quantity of Phenylephrine and atropine consumption in both groups
- Incidence of post-spinal shivering
- Side effects of study drugs: hiccups, skin flushing and headaches.

Data Analysis

Statistical analysis was conducted using Statistical Product and Service Solutions (SPSS Statistic 20 IBM Corp. Armonk, NY, USA). Nominal variables (such as incidence of hypotension, post-spinal shivering, side effects- headache, hiccups, skin flushing) were presented as percentages and proportions and analysed using the Chi-square test or Fisher's exact test as appropriate. Continuous variables were presented as means and standard deviations and analysed using the student's t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of eighty (80) pregnant women, 40 in each group, were recruited into the study (as shown in Figure 1), between August 2022 and March 2023. All the recruited patients were in the ASA II physical status category, and all completed the study.

The demographic characteristics of the patients were similar in both groups as shown in Table I.

Table I: Demographic Characteristics of Patients in Both Groups

VARIABLES	GROUP OS (N=40)	GROUP ES (N=40)	P-VALUE
Age (Years)	30.93 (4.22)	30.73 (3.82)	0.83
Gestational Age (Weeks)	37.75 (1.08)	38.05 (1.55)	0.32
Weight (Kg)	73.63 (11.58)	75.95 (9.72)	0.33
Height(M)	1.59 (0.07)	1.59 (0.07)	0.75
BMI (Kg/M2)	29.18 (3.71)	30.05 (3.40)	0.28

Mean (Standard deviation)

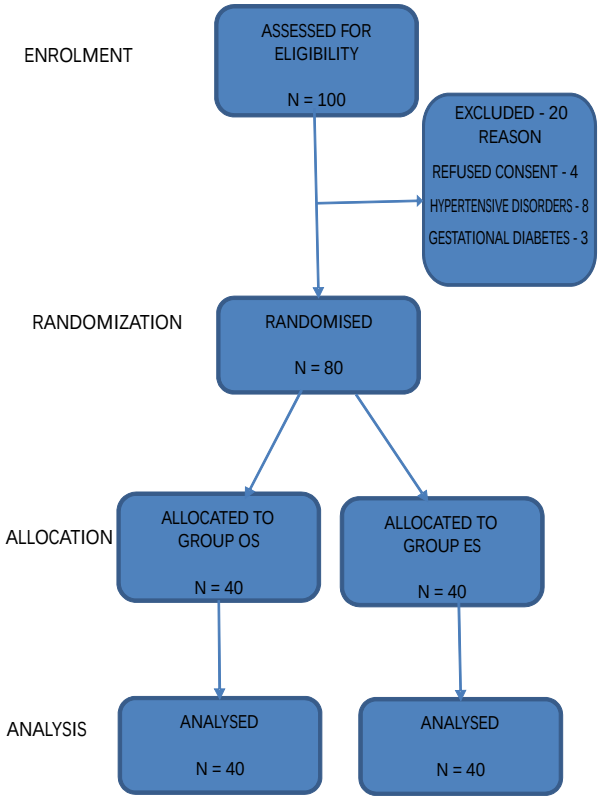

Figure 1- CONSORT FLOW DIAGRAM

The indications for surgery were similar in both groups (P = 0.58). The commonest indication for surgery in both groups was a previous scar, which was the reason for surgery in 27 of the patients in the OS group (67.5%) and 28 of the patients in group ES (70%). While a contracted pelvis was the least indication for surgery in the OS group (1/40, 2.5%), breech presentation accounted for the least indication for surgery in the ES group (4/40, 10%).

There was no difference in both groups in terms of intraoperative characteristics as shown in Table II.

Table II: Intraoperative Characteristics

VARIABLE	GROUP OS (N=40)	GROUP ES (N=40)	P-VALUE
SA-SI Time (Minutes)	14.23 (4.44)	14.95 (5.129)	0.50
SI-DT(Minutes)	18.75 (10.372)	22.23 (12.392)	0.17
Surgery Duration (Minutes)	85.50 (23.201)	86.45 (26.422)	0.86
Blood loss (Ml)	548.79 (196.820)	583.75 (299.052)	0.51
Fluid Requirement (L)	2.437 (0.5714)	2.40 (0.5139)	0.78
Episodes of Hypotension	1.78 (2.057)	1.43 (2.011)	0.44

Mean (Standard deviation), SA-SI Time: Spinal anaesthesia to skin incision Time, SI-DT: Skin incision to Delivery time

The baseline haemodynamic variables were comparable in both groups with no statistically significant difference. The mean baseline HR was 91.67 ± 13.28 beats/minute in the OS group vs 91.68 ± 12.90 beats/minute in the ES group (P-value =1). The mean baseline SBP was 119.95 ± 10.84 mm Hg in the OS group and 121.85 ± 10.66 mm Hg in the ephedrine group, with a P-value of 0.43. The mean baseline DBP was 74.03 ± 7.59 mm Hg and 73.45 ± 9.35 mm Hg in groups OS and ES respectively (P-value = 0.76). The mean baseline MAP in the OS group was 90.05 ± 9.10 mm Hg vs. 90.33 ± 8.71 mm Hg in the ES group, with P-value = 0.89.

Of the 40 patients recruited into the OS group, 24 had hypotension (60%), while 19 out of the 40 patients in group ES had hypotension (47.5%). The difference was insignificant (95% CI = -0.03-0.28, P-value = 0.37). The mean number of episodes of hypotension was similar in both groups: 1.78 ± 2.057 in group OS and 1.43 ± 2.011 in group ES, 95% CI = -0.55 - 1.25, P-value = 0.44.

The mean HR values were significantly higher in the ES group (P-value < 0.05) than in the OS at all the time points during the study period except in the 2nd minute (see Table III). The mean maximum decline in the HR values (baseline HR – lowest HR during the study period) in the OS group was significantly higher than in the ES group, 21.03 ± 13.63 vs 12.68 ± 9.41, 95% CI = 3.13-13.56, P-value = 0.002.

The mean SBP values in the ES group, when compared to the OS group, were higher at all the time points during the study period but were only significant at the 2nd, 4th, 6th, 20th, 25th, and 40th minutes. This is shown in Figure 2. The mean maximum decline in the SBP (baseline SBP – lowest SBP value) was higher in the OS group than in the ES group, but the difference was not statistically significant (30.38 ± 16.69 vs 26.75 ± 16.57, 95% CI = -3.77-11.02, P-value = 0.33).

Table III: Mean Heart Rate of Patients (Beats/Minute)

		Group ES (N=40)	
Time (Minutes)	**Group OS (N=40) Mean (SD)**	**Mean (SD)**	**P Value**
0 (Baseline)	91.68 (13.28)	91.68 (12.90)	1
2	94.18 (18.34)	100.63 (21.83)	0.16
4	91.83 (21.99)	101.90 (21.13)	0.04
6	89.35 (20.70)	101.00 (21.52)	0.016
8	85.4 (20.27)	97.65 (20.26)	0.008
10	84.73 (16.44)	97.73 (17.52)	0.001
12	86.03 (16.79))	96.58 (17.51)	0.007
14	86.63 (16.30)	94.20 (17.45)	0.048
16	85.55 (16.76)	97.58 (16.61)	0.002
18	83.70 (16.01)	93.65 (16.04)	0.007
20	82.03 (17.50)	91.23 (16.41)	0.018
25	84.03 (16.32)	92.13 (15.59)	0.026
30	83.28 (15.99)	92.78 (13.47)	0.005
35	84.43 (14.56)	90.70 (15.35)	0.064
40	84.28 (13.26)	93.05 (17.93)	0.015

Mean (Standard deviation)

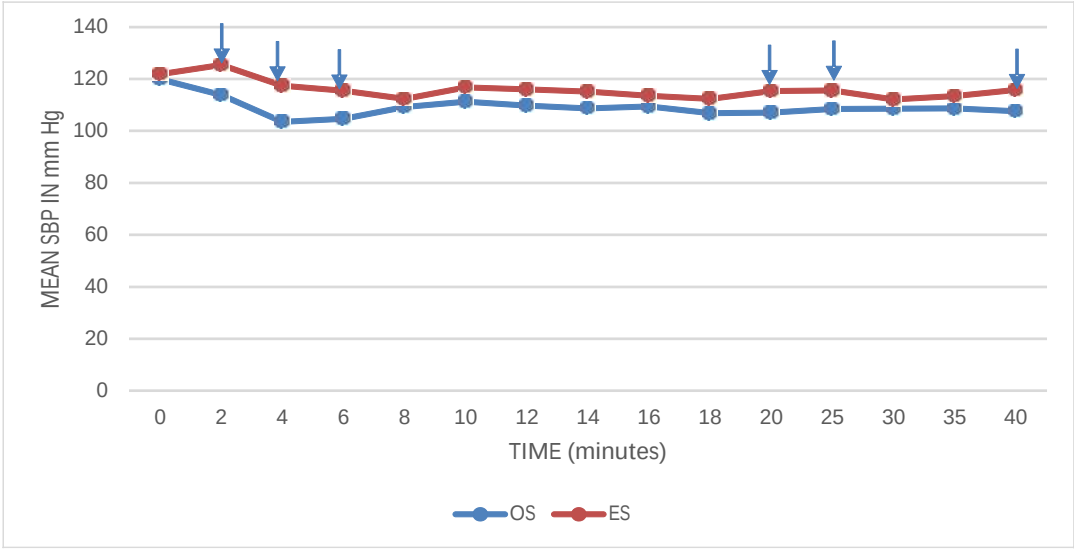

Figure 2: Trends in Mean Systolic Blood Pressure of Patients in mm Hg

↓- Indicates time points of significant difference

The mean DBP values were comparable in both groups throughout the study period (P-value > 0.05) as shown in Figure 3. The mean maximum decline in DBP was comparable in both groups: 24.33 ± 12.82 in the OS group vs 23.85 ± 9.50 in the ES group, 95% CI = -4.55 - 5.50, P-value = 0.851.

Apart from the 4th minute in which the mean MAP in the ES group was significantly higher, it was comparable in both groups at all the other time points during the study period (Figure 4.) There was no significant difference between the two groups regarding the mean maximum decline in MAP values (baseline MAP – lowest MAP value during the study period). The value in the OS group was 25.08 ± 12.69, while the value in the ES group was 23.58 ± 11.26, 95% CI = -3.92 - 6.91, with a P-value of 0.58.

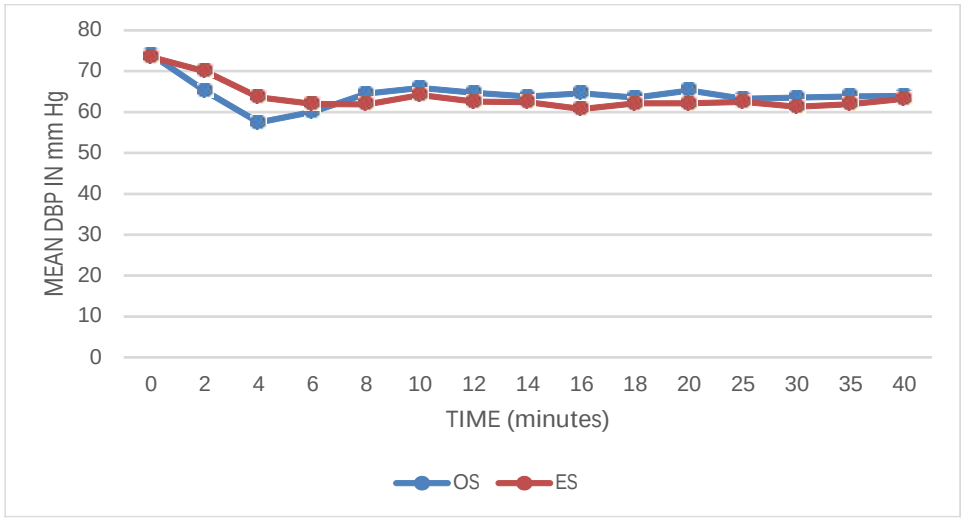

Figure 3: Trends in Mean Diastolic Blood Pressure of Patients in mm Hg

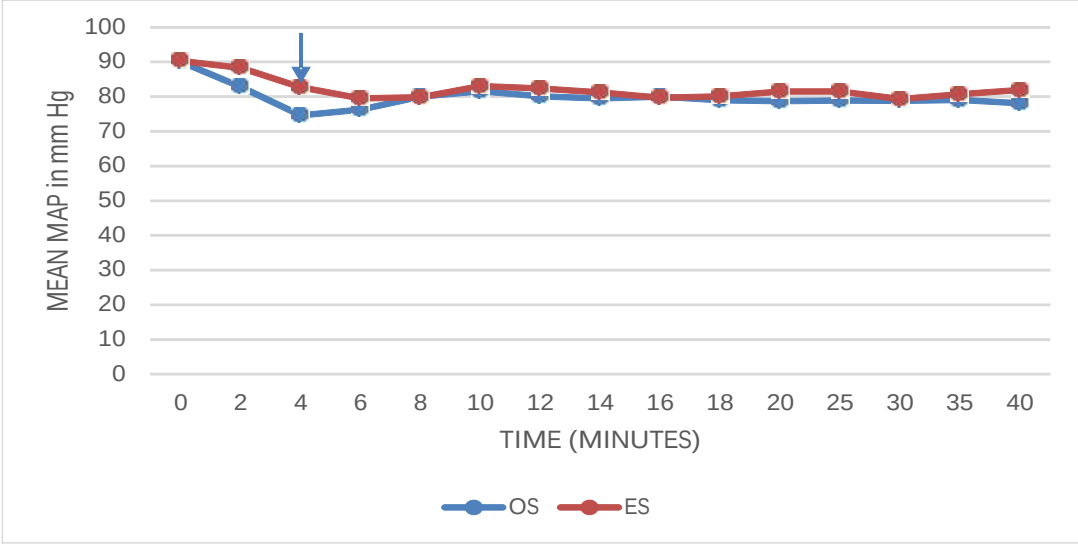

Figure 4: Trends in Mean MAP of Patients in mm Hg

↓ - **Indicates the point of significant difference**

The mean phenylephrine consumption was lower in the ES group than in the OS group (77.50 ± 96.71 vs 102.50 ± 110.33), but the difference was not statistically significant (95% CI = -21.18 – 71.18, P-value = 0.284). Only one patient in the OS group required atropine treatment, while no patient in the ES group required atropine treatment (P-value = 0.32.).

The incidences of side effects are summarised in table IV below.

Table IV: Incidence of Side Effects

SIDE EFFECTS	Group OS(N=40)	Group ES(N=40)	95% CI	P-VALUE
Headache	4 (10%)	5 (12.5%)	-	1
Skin Flushing	0	0	-	
Hiccups	0	0	-	
Shivering	2 (5%)	9 (22.5%)	0.03-028	0.023

DISCUSSION

This randomised double-blind study demonstrates that there is no significant difference in the incidence of hypotension and phenylephrine/atropine consumption in patients who were pretreated with 4 mg intravenous ondansetron 10 minutes before SAB compared to patients who received bolus 15 mg intravenous ephedrine immediately after SAB for elective caesarean sections. Notably, we also found a significantly lower incidence of post-spinal shivering in the ondansetron group, highlighting its potential added benefit.

The results of this study add to several other studies examining whether prophylactic intravenous ondansetron is effective in attenuating SAB-induced hypotension in patients undergoing elective caesarean sections. Most of the previous studies compared intravenous ondansetron with a placebo, while just a few studies[-] compared it with a vasopressor such as ephedrine. Our results suggest that prophylactic intravenous ondansetron is as effective as prophylactic intravenous ephedrine in reducing the incidence of SAB-induced hypotension despite more patients in the ondansetron group experiencing hypotension. This effect is thought to occur due to ondansetron's ability to inhibit the Bezold-Jarisch reflex (BJR), which is mediated by serotonin stimulation of 5-HT_3 receptors in the cardiac chambers.

Studies by Khamis *et al.*[19] and Nasr *et al.*[20] demonstrated that ondansetron and ephedrine had comparable effects on the incidence of SAB-induced hypotension in women undergoing elective C/S. Their observation is like our findings, suggesting that the BJR, which is inhibited by ondansetron, may be a significant contributor to the mechanism of SAB-induced hypotension in term pregnant women. However, comparing the figures for the incidence of hypotension in the two previous studies with our study, the incidence of hypotension recorded in theirs was much lower in both the ondansetron and the ephedrine groups and significantly lower when compared to the placebo group in their studies. Khamis *et al*. reported a hypotension incidence of 16.7% in the ondansetron group and 19% in the ephedrine group, while Nasr *et al*. reported that the incidence of hypotension was 16.7% in the ondansetron group and 20% in the ephedrine group. The lower incidence of hypotension in their study compared to ours could be due to some differences in the study methodology and the definition of hypotension employed. For instance, Nasr *et al*. used a higher dose of ephedrine (25 mg), which was administered intramuscularly, and this might have ensured a gradual, steady release of ephedrine into the bloodstream over a longer period. The different doses of local anaesthetic used for the procedure might also have contributed to some differences. In our study, 2.5 ml of 0.5% heavy bupivacaine was used for all the patients. Nasr *et al*. used a dose of 2 ml of 0.5% heavy bupivacaine plus 25 µg of fentanyl, while Khamis *et al* used just 2 ml of 0.5% heavy bupivacaine. Another important difference is in the definition of hypotension employed. Nasr *et al* utilised a drop in MAP by > 20% or a fall in SBP < 90 mm Hg as their definition of hypotension, while the definition used in the present study was a drop in SBP by > 20% from the baseline.

Although ondansetron was not found by Ortiz-Gomez *et al.* to influence the number of patients who developed SAB-induced hypotension when compared to the placebo control group, their study demonstrated the ability of ondansetron to reduce the severity of hypotension experienced by each patient. The mean episodes of hypotensive events in their study were 1.4 ± 2.2 in the ondansetron group and 2.9 ± 4.0 in the placebo control group, P = 0.011. They concluded that ondansetron reduced the severity of SAB-induced hypotension in patients undergoing elective caesarean sections. This is partially like our findings; the mean episodes of hypotension in the ondansetron group were 1.78 ± 2.06 vs 1.43 ± 2.01 in the ephedrine group with a P value = 0.44. Our study also did not find any significant difference between ondansetron and ephedrine in terms of maximum decline in systolic,

diastolic, and mean arterial pressures, further strengthening the assertion by Ortiz-Gomez that ondansetron reduces the severity of hypotension.

Phenylephrine (50 µg) was used as a rescue vasopressor to treat each episode of hypotension. Although the mean phenylephrine consumption was higher in the ondansetron group (102.50 ± 110.33) compared to the ephedrine group (77.50 ± 96.71), the difference between the two groups was not statistically significant. This finding reflects the similarity in the mean episodes of hypotensive events observed across the two study groups (1.78 ± 2.057 in the ondansetron group vs 1.42 ± 2.011in the ephedrine group). In a similar study by Khalifa *et al*, they observed that while patients in the ondansetron and ephedrine groups had a significantly lower need for vasopressor than patients in the placebo group, the need for vasopressor was similar in both the ondansetron and ephedrine groups. This is also supported by the findings of Nivatpumin *et al* who demonstrated that there was no significant difference in the number of patients requiring ephedrine and or norepinephrine in both the ephedrine and ondansetron groups. Fodiel *et al*. also reported in their study that there was no difference in vasopressor requirement (10 mg ephedrine) between patients in the ephedrine group and patients in the ondansetron group.

Shivering is another frequent complication that obstetric patients undergoing elective C/S under SAB could encounter, with a reported incidence of up to 55%. It can cause significant maternal discomfort and interference with patient monitoring such as electrocardiogram, pulse oximetry and blood pressure measurement. Pethidine, clonidine and tramadol are drugs that are commonly employed in the control of post-spinal shivering. However, their administration before delivery could lead to neonatal central nervous system depression and, subsequently, poor APGAR scores. Our study has further corroborated the efficacy of ondansetron in mitigating post-spinal PSS, making it a safer alternative to the traditional medications used in managing PSS in the obstetric population. This aligns with the results of studies and meta-analysis that have demonstrated the ability of prophylactic intravenous ondansetron to alleviate post-spinal shivering in pregnant women. This finding also suggests the added advantage the perioperative use of ondansetron possesses over standard vasopressors used in managing SAB-induced hypotension. Therefore, based on its anti-emetic and anti-shivering properties and its ability to attenuate SAB-induced hypotension, routine ondansetron premedication of obstetric patients scheduled for elective C/S would potentially not only improve maternal safety and comfort but may also reduce the cost of patient care.

Although the anti-shivering mechanism of ondansetron is not clearly understood, it is believed to interfere with serotonin reuptake at the pre-optic anterior hypothalamic region, thereby obtunding the response of the temperature-regulating centre to hypothermia. Badawy *et al*. observed that compared to the placebo group, patients pretreated with 8 mg intravenous ondansetron before SAB had a significantly lower incidence of PSS. Similar to the result of our study, Marashi *et al.* also demonstrated in their study that patients in the ondansetron group had a significantly lower incidence of shivering than those who had a placebo. The efficacy of ondansetron in mitigating PSS is further supported by the study done by Nnacheta *et al*, who observed that pregnant women pretreated with ondansetron had a significantly lower incidence of shivering (5.9%) compared to women who received 50 mg tramadol (39.4%) and women who received placebo (48.5%). In a study done by Sadeghi *et al*, ondansetron was found to be as effective as dexamethasone in reducing the incidence of postoperative shivering in women who underwent elective C/S under SAB. Hasan *et al*. demonstrated the comparable efficacy of intravenous ondansetron to intrathecal fentanyl in reducing the incidence of PSS in women undergoing elective C/S under SAB.

The result of our study contrasts with the findings of Khalifa *et al*. who reported that there was no difference in the incidence of shivering in pregnant women pretreated with 4 mg intravenous ondansetron and those pretreated with 10 mg intravenous ephedrine. The difference could be due to the possible anti-shivering effect of low-dose ephedrine, as observed by El-Deeb *et al* who reported in their study that 6 mg ephedrine had a comparable anti-shivering effect with 15 mg pethidine. We administered a higher dose of ephedrine (15 mg) in our study, and it is not clear if it could have a similar anti-shivering effect as low-dose ephedrine. The incidence of shivering in the current study was 22.5% and this is lower than the reported incidence of up to 55% when no prophylaxis is applied.[26]

LIMITATION

Ondansetron was found to significantly reduce the incidence of PSS; however, this finding was limited to the period of their stay in the recovery room. The patients were discharged to the ward after being observed in the recovery room for an hour and were not followed up in the ward to know if any of them had shivering. It is unclear if the anti-shivering effects extend beyond one hour of the postoperative period.

Although our study suggests that ondansetron has a comparable efficacy with ephedrine in mitigating SAB-induced hypotension, it may be that the power of our study was not sufficient to detect a difference between the two groups. A study with a larger sample size may be required to further compare the efficacy of ondansetron vs ephedrine in reducing SAB-induced hypotension.

Also, it is unclear whether the combination of ondansetron and ephedrine is synergistic compared to ondansetron and ephedrine alone when used prophylactically. Further study comparing the ondansetron-ephedrine combination versus ondansetron versus ephedrine may give some clarity. Despite the above limitations, we consider our results valid based on strict adherence to the well-outlined study protocol.

CONCLUSION

This study has demonstrated that ondansetron has comparable efficacy to ephedrine in attenuating SAB-induced hypotension; however, it is superior to ephedrine in preventing PSS, an unpleasant complication of SAB. It is therefore recommended that obstetric patients scheduled for elective caesarean section should be routinely premedicated with intravenous ondansetron because of its ability to attenuate PSS and SAB-induced hypotension, which are all common complications this group of patients encounters under spinal anaesthesia.

What is already known about this topic:

- Bezold-Jarisch Reflex worsens SAB-induced hypotension
- Effectiveness of ondansetron in attenuating SAB-induced hypotension when compared to placebo in pregnant women.
- Ephedrine and phenylephrine are both effective for prevention and treatment of SAB-induced hypotension.

What is not known:

- To what extent does Bezold Jarisch reflex contribute to SAB-induced hypotension in pregnant women. It is not fully known whether the contribution is significant or not.
- Whether ondansetron could be as effective as vasopressors in the prophylaxis of SAB-induced hypotension

ACKNOWLEDGEMENT

All thanks to the almighty God for the strength and wisdom to carry out this research work.

Thanks to all the anaesthesia residents at the University of Ilorin Teaching Hospital who assisted in one way or another.

Special thanks to all the consultant anaesthetists at the University of Ilorin Teaching Hospital, Ilorin: Prof Z.A Suleiman, Dr. O.O. Oyedepo, Dr. O.A. Ige, Dr. O.J. Oni, Dr. C. I Oyewopo, Dr. A.M. Adewumi, and Dr. K.A. Adegboye for their immense contributions. Appreciation also goes to Prof A.A. Nasir, a consultant paediatric surgeon, for his assistance in data analysis.

The members of the Department of Obstetrics and Gynaecology of the University of Ilorin Teaching Hospital deserve praise for their cooperation during the period of recruiting patients and obtaining data.

FUNDING

The study was funded by the researchers.

CONFLICT OF INTEREST

The researchers had no conflict of interest to declare.

REFERENCES

1. Zwane SF, Bishop DG, Rodseth RN, Group F. Hypotension during spinal anaesthesia for Caesarean section in a resource-limited setting? towards a consensus definition. *South Afr J Anaesth Analg*. 2019;25(1):1–5.
2. Shitemaw T, Jemal B, Mamo T, Akalu L. Incidence and associated factors for hypotension after spinal anaesthesia during caesarean section at Gandhi Memorial Hospital Addis Ababa, Ethiopia. *PLoS One*. 2020;15:1–11.
3. Bower JR, Kinsella SM. Preventing and treating hypotension during spinal anaesthesia for caesarean section. *BJA Educ*. 2020;20(11):360–361.
4. Šklebar I, Bujas T, Habek D. Spinal anaesthesia-induced hypotension in obstetrics: Prevention and therapy. *Acta Clin Croat*. 2019;58(1):90–95.
5. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev. 2006;(4):81–153.
6. Medonca FT, Crepaldi Junior LC, Gersanti RC, Christian de Araujo K. Effect of ondansetron on spinal anaesthesia-induced hypotension in non-obstetric surgeries? a randomised, double-blind and placebo-controlled trial. *Braz. J. Anesthesiol*. 2021;71(3):233–240.
7. Loubert C. Fluid and vasopressor management for Caesarean delivery under spinal anaesthesia?: Continuing Professional Development. *Can. J. Anaesthesia*. 2012;59(6):604–619.
8. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszułowicz R, Dylczyk-Sommer A, et al. Ondansetron Given Intravenously Attenuates Arterial Blood Pressure Drop Due to Spinal Anaesthesia: A Double-Blind, Placebo-Controlled Study. *Reg Anesth Pain Med*. 2008;33(4):332–339.
9. Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME. Ondansetron Does Not Attenuate Hemodynamic Changes in Patients Undergoing Elective Caesarean Delivery Using Subarachnoid Anaesthesia: A Double-Blind, Placebo-Controlled, Randomized Trial. *Reg Anesth Pain Med*. 2015;40(4):344–348.
10. Trabelsi W, Romdhani C, Elaskri H, Sammoud W, Bensalah M, Labbene I, et al. Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anaesthesia for elective caesarean section: A prospective, randomized, controlled, double-blind study. *Anesthesiol Res Pract*. 2015;2015:1–7.
11. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study. *Int. J. Obstet. Anesth*. 2012;21(1):24–8.
12. Simon L, Provenchere S, Blanquat LS, Boulay G, Hamza J. Dose of Prophylactic Intravenous

Ephedrine During Spinal Anaesthesia for Caesarean Section. *J. Clin. Anesth.* 2001;13(01):366–369.

13. Iqbal MS, Ishaq M, Masood A, Khan MZ. Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during caesarean section. *Anaesth Pain Intensive Care.* 2010;14(2):71–75.
14. Ngan Kee WD, Khaw KS,Tan EP,Ng FF,Karmaker MK. Placental Transfer and Foetal Metabolic Effects of Phenylephrine and Ephedrine during Spinal Anaesthesia for Caesarean Delivery. *Anaesthesiology*. 2009;(3):506–512.
15. Bland J, Butland B, Peacock J, Poloniecki J, Reid F, Sedgwick P. *Statistical Guide for Research Grant Application,* London: St George's University of London. 2012; 42–44.
16. Ortiz-Gómez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-Jiménez A, Bermejo-Albares ML. The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: A double-blind, randomised, placebo-controlled trial. *Int. J. Obs. Anesth.* 2014;23(2):138–143.
17. Shabana AA, Elkholy NI, Mohamed MA, Abdel-Hamid MI. Effect of ondansetron on hypotension and bradycardia associated with spinal anaesthesia during caesarean section. *Menouflia Med. J.* 2018;31:12–17.
18. Nivatpumin P, Thamvittayakul V. Ephedrine versus ondansetron in the prevention of hypotension during caesarean delivery: a randomized, double blind, placebo-controlled trial. *IJOA.* 2016;27:25–31.
19. Khamis AM, Abd El-Aziz A, Mostapha HR, Noser M. Ephedrine Versus Ondansetron in the Prevention of Hypotension During Caesarean Section: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Cell. Mol. Anesth.* 2022;7(3):168–174.
20. Nasr N, Mahdy ME. Comparative Study Between Ondansetron And Ephedrine For Prophylaxis Of Spinal Anaesthesia-Induced Hypotension During Caesarean Section . *AAMJ.* 2015;13(3):464–472.
21. Marashi SM, Soltani-omid S, Mohammadi SS, Movafegh A. Comparing Two Different Doses of Intravenous Ondansetron With Placebo on Attenuation of Spinal-induced Hypotension and Shivering. *Anesth. Pain Med.* 2014;4(2):2–6.
22. Hou X, Chen Y, Lai L, Liu K, Shen Q. Ondansetron Reduces the Incidence of Hypotension after Spinal Anaesthesia: A Systematic Review and Meta-Analysis. *Pharmaceuticals.* 2022;15(1588):1–16.
23. Ortiz-Gomez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz L, Lorenzo-Jimenez A, Bermejo-Albares ML. Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anaesthesia: Effect of prophylactic ondansetron and / or continuous infusion of phenylephrine-a double-blind, randomized , placebo-controlled trial. *Saudi J. Anaesth.* 2017;11:408–414.
24. Khalifa OSM. A comparative study of prophylactic intravenous granisetron, ondansetron, and ephedrine in attenuating hypotension and its effect on motor and sensory block in elective caesarean section under spinal anaesthesia. *Ain-Shams J. Anesth.* 2015;3:166–172.
25. Fodiel MMA, Elfeky MA, Mostafa S, Hameed SM. Comparative Study between Intramuscular Ephedrine Versus Intravenous Ondansetron Versus Intravenous Dexamethasone for Prevention of Spinal Anaesthesia-Induced Hypotension in Parturients Undergoing Caesarean Section. *Med. J. Cairo Univ.* 2022;90(2):609–617.
26. Brull R, Macfarlane AJR, Chan VWS. Spinal, Epidural, and Caudal Anaesthesia. in Miller's Anaesthesia. 9th edition. Philadelphia: Elsevier Inc.; 2020. p. 1444.
27. Badawy AA, Mokhtar AM. The role of ondansetron in prevention of post-spinal shivering (PSS) in obstetric patients: A double-

blind randomized controlled trial. *Egypt J. Anaesth*. 2017;33(1):29–33.

28. Nnacheta TE, Onyekulu FA, Amucheazi AO. Prevention of postanaesthetic shivering under subarachnoid block for caesarean section: A randomized, controlled study comparing tramadol versus ondansetron. *Niger J Clin Pr.* 2020;23(5):619–25.
29. Li M, Hu X, Tan Y, Yang B, Li K, Tang Z. Meta-analysis of randomized controlled trials on the efficacy and safety of ondansetron in preventing postanesthesia shivering. *IJS.* 2016;35:34–43.
30. Shen QH, Li HF, Zhou X, Lu Y, Yuan XZ. 5-HT3 receptor antagonists for the prevention of perioperative shivering undergoing spinal anaesthesia: A systematic review and meta-Analysis of randomised controlled trials. *BMJ Open*. 2020;10(10):e038293
31. Nallam S, Cherukuru K, Sateesh G. Efficacy of intravenous ondansetron for prevention of postspinal shivering during lower segment caesarean section: A double-blinded randomized trial. *Anesth Essays Res*. 2017;11(2):508.
32. Sadeghi MS, Razlighi VN, Razlighi HV. Comparison of the Effect of Ondansetron and Dexamethasone on Postoperative Shivering After Caesarean Section in Patients Undergoing Spinal Anaesthesia. *EJMED*. 2024;6(1):53–7.
33. Hasan SH, Qadir HR, Mohammed HN. Fentanyl Versus Ondansetron for Shivering Prevention in Caesarean Section: A Comparative Study. *Cureus*. 2023;15(10):2–7.
34. El-Deeb A, Barakat R. Could ephedrine replace meperidine for prevention of shivering in women undergoing Caesarean Section under spinal anaesthesia? A randomized study. *Egypt J Anaesth*. 2012;28(4):237–41.