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Effect of Prophylactic Ondansetron on the Incidence of Spinal Anesthesia-Induced Shivering and Hypotension in Elective Cesarean Sections: Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Spinal anesthesia is the preferred method of anesthesia during cesarean section; nonetheless, it is associated with serious side effects both on mother and fetus, including spinal anesthesia-induced shivering and hypotension. Previous research suggests that serotonin may have a role in the occurrence of hypotension, bradycardia, and shivering perioperatively. We investigated the efficacy of ondansetron, a serotonin receptor antagonist, on the incidence of spinal anesthesia-induced shivering, hypotension, nausea, vomiting, and other potential problems in elective cesarean sections in this prospective double-blind randomized control trial research. This study was carried out in Palestine, West Bank, Nablus city, at the cesarean section surgery rooms and post-anesthesia care unit at Rafidia governmental hospital.

Eighty full-term elective cesarean section parturients (Age 18-50 years) with ASA 1 or 2 were recruited and randomly assigned to one of two groups: prophylactic IV ondansetron group and placebo 0.9 % saline control. The incidence of spinal anesthesia-induced shivering and hypotension were the primary outcomes, whereas the secondary outcomes were perioperative bradycardia, nausea, vomiting, headache, pain, pruritus, dizziness, respiratory depression, and parturient satisfaction.

Results: Intraoperatively, the incidence of intraoperative hypotension and dizziness was significantly lower in the ondansetron group than in the control group (22.5 % vs. 62.5 %, respectively; P< 0.001), as were the incidences and intensity of intraoperative shivering was lower than the control group (12.5 % vs. 32.5 %, respectively; P = 0.032). The intensity of intraoperative nausea was lower in the ondansetron group than in the control group (P = 0.049).

Postoperatively, the incidence of postoperative dizziness was lower in the ondansetron group than in the control group (5 % vs. 37.5 %, respectively; P = 0.001), as did the incidence and intensity of postoperative shivering (12.5 % vs. 37.5 %, respectively; P = 0.01). The incidence and severity of postoperative nausea were lower in the ondansetron group than in the control group (17.5 % vs. 40 %, respectively; P = 0.026), as did the incidence of postoperative vomiting (25.5 % vs. 2.5 %, respectively; P = 0.014).

Conclusion: Prophylactic 4 mg IV ondansetron can considerably reduce the occurrence of spinal anesthesia-induced shivering and hypotension, dizziness, nausea, and vomiting, and enhance the parturient favorable rating in cesarean section clients.

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Keywords: Ondansetron; spinal anesthesia; Hypotension; Bradycardia; cesarean sections.

List of Abbreviations

ASA: American Society of Anesthesiologists; SAIH: Spinal Anesthesia-Induced Hypotension; BP: Blood Pressure; SA: Spinal Anesthesia; GA: General Anesthesia; PAS: Post Anesthesia Shivering; CBC: Complete Blood Count; PT: Prothrombin Time; APTT: Activated Partial Prothrombin Time; INR: International Normalized Ratio; HR: Heart Rate; MAP: Mean Arterial Pressure; CS: Cesarean Section; C/D: Cesarean Delivery; RCT: Random Control Trial; Pt: Patient; V/S: Vital signs; T: Temperature; Ml: Millilitre; Mg: Milligram; Mcg: Microgram; IV: Intravenous; IM: Intramuscular; SC: Subcutaneous; vs.: versus; Cm: Centimeter; ECG: Electrocardiogram; Kg: kilogram; Min: minute; Spo2: peripheral capillary oxygen saturation; UOP: Urine output; PNB: Peripheral nerve blocks; DVT: Deep Vein Thrombosis; NPRS: Numerical Pain Rating Scale

Introduction

Because of its rapid onset, definite motor and sensory blockage, and low risk of systemic anesthetic toxicity, spinal anesthesia is frequently utilized in cesarean section deliveries. Furthermore, it provides a variety of benefits for both mothers and their developing infants, including as improved oxygenation and acid-base balance; nonetheless, it is not free of risk (Ghani et al., 2015). Spinal-anesthesia-induced shivering and hypotension frequently occur perioperatively, with an incidence of 80% and 60%, respectively (Habib, 2012; Tie et al., 2014). These complications are harmful for both fetus and the delivering mother, and include reduced uteroplacental perfusion, impaired fetal perfusion and gas exchange, fetal acidemia, and serious maternal consequences such as decreased cardiac output and altered cerebral perfusion. (Limongi & Lins, 2011), altered level of consciousness, nausea, and vomiting (Lee, George, & Habib, 2017).

Hypotension can cause nausea, vomiting, altered consciousness, an increased risk of aspiration, and impaired uterine-fetal blood flow. The mechanisms that cause hypotension during spinal anesthesia are sympatholysis, where systemic vascular resistance is induced (Langesæter et al., 2008), as well as the activation of Bezold-Jarisch reflex which leads to vasodilatation, bradycardia, and hypotension (Warltier et al., 2003). Several receptors, notably the 5-HT3 receptor, are involved in these alterations. Human studies have been conducted to assess the effectiveness of 5-HT3 receptor antagonists in preventing spinal anesthesia-induced hypotension, but the findings have been inconsistent (Ortiz-Gómez et al., 2014; Trabelsi et al., 2015).

Perioperative shivering amplifies the metabolic heat yield up to 6-fold above the baseline metabolic rate (Giesbrecht et al., 1994); increasing the oxygen consumption approximately 200–500% (Bay, Nunn, & Prys-Roberts, 1968; Macintyre, Pavlin, & Dwersteg, 1987). It also causes hypercarbia, hypoxemia, lactic acidosis, and worsening pain sensation (Begum et al., 2008). Furthermore, shivering lengthens hospital stays, increases the risk of surgical wound infection, lowers immunity, induces coagulopathy, and raises the risk of cardiac morbidity (Kim et al., 2014; Reynolds et al., 2008), All of this places a burden on health-care facilities and endangers the patient's overall health.

It is worth noting that there is currently no final consensus on the effectiveness of ondansetron in reducing spinal anesthesia-induced shivering and hypotension. The purpose of this research was to evaluate the effectiveness of prophylactic 4mg intravenous ondansetron in reducing spinal anesthesia-induced shivering and hypotension in an obstetric population undergoing elective cesarean section.

Problem statement

Postoperative hypotension and shivering are common complications of spinal anesthesia. Hypotension affects almost half of the obstetric population (Klöhr et al., 2010). A fall in arterial blood pressure can cause nausea and vomiting, altered consciousness, a higher risk of aspiration, and decreased uterine-fetal blood flow. Sympatholysis, which causes a reduction in systemic vascular resistance, is one of the mechanisms that causes hypotension during spinal anesthesia (Langesæter et al., 2008), Additionally, the Bezold-Jarisch reflex, a phenomenon, causes vasodilation, bradycardia, and hypotension (Warltier et al., 2003). Several receptors, notably the 5-HT3 receptor, are implicated in these alterations, In animal studies, antagonists for this receptor can inhibit the Bezold-Jarisch reflex (Yamano et al., 1995). Meanwhile, 5-HT3 receptor antagonists have been investigated in human research for their usefulness in preventing spinal-anesthesia-related hypotension, however the findings have been inconclusive (Ortiz-Gómez et al., 2014; Trabelsi et al., 2015).

Preoperative shivering amplifies the metabolic heat yield up to 6-fold above the baseline metabolic rate (Giesbrecht et al., 1994); it is clinically associated with different frequencies of tonic or clonic skeletal muscular hyperactivity (Javaherforoosh et al., 2009).This augmented muscular activity increases oxygen consumption approximately 200–500% (Bay, Nunn, & Prys-Roberts, 1968; Macintyre, Pavlin, & Dwersteg, 1987). Further, it leads to hypercarbia, hypoxemia, and lactic acidosis, all of which worsen pain sensations (Begum et al., 2008). This accelerated muscle activity impairs myocardial function and worsens morbidity rates, especially if the patient already has a reduced myocardial oxygen flow, such as arteriosclerosis which

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Salahat AM et al., Obstet Gynecol Res 2022
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may affect uteroplacental blood flow in turn (Alfonsi, 2001; Ciofolo et al., 1989). Meperidine, tramadol, and clonidine are some of the medications used to treat post-anesthesia shivering, however all of them have side effects such as sedation, nausea, vomiting, bradycardia, and hypotension. Shivering after surgery prolongs hospital stays, increases surgical wound infection risk, suppresses immunity, induces coagulopathy, and raises the risk of cardiac morbidity, All of these morbidities place a burden on health-care facilities and jeopardize the patient's overall health (Kim et al., 2014; Reynolds et al., 2008).

Study objectives

The following goals were pursued by this study:

a) Primarily, to investigate the effectiveness of prophylactic intravenous ondansetron in reducing spinal-anesthesia-induced shivering and hypotension in an obstetric population undergoing elective caesarean sections.

b) Secondarily, to investigate the efficacy of ondansetron on the prevention of postoperative spinal anesthesia complications including bradycardia, nausea, vomiting, headache, pain, pruritus, dizziness, and respiratory depression.

Significance of the Study

Shivering and hypotension caused by spinal anesthesia have serious effects for the mother and newborn after cesarean delivery. These variables can prolong a hospital stay and impose financial demands on health-care systems. The results of this trial will help determine if ondansetron can decrease these problems. Furthermore, previous research suggests that minimizing shivering would bring substantial advantages to patients and promote a better prognosis (Kurz et al., 1996). Notably, this is the first research in this topic in Palestine. The outcomes should help our patients and their families by reducing avoidable suffer, as well as our hospitals by reducing patient hospitalization and, as a result, the financial load on these health care institutions.

Study Methodology

Study design

This research was carried out as a prospective, cohort, randomized, double-blind, placebo-controlled trial (RCT). Because of the strength of the scientific evidence hierarchy, this approach was chosen, resulting in less bias and more accurate outcomes.

Participants

The study group consisted of a cohort of full-term obstetrics participants with an ASA I or II classification who were scheduled for an elective caesarean section at Rafidia Governmental Surgical Hospital

Eligibility (inclusion and exclusion criteria)

S.No	Inclusion criteria	S. No	Exclusion criteria
1.	Patients undergoing elective caesarean sections surgery	1.	Pre-existing or gestational hypertension
		2.	History of allergy to ondansetron drug
2.	18–50 years old	3.	Cardiovascular or cerebrovascular diseases
		4.	Urgent caesarean sections
3.	American Society of Anesthesiologists (ASA) I or II classification	5.	Mothers with suspected deteriorated foetuses
		6.	Contraindications for spinal block
		7.	Thyroid disorders
4.	No major systemic diseases	8.	Participant temperature > 38°C or <36.5°C
		9.	Patients likely to receive intraoperative blood transfusion

Table 1: Inclusion criteria and exclusion criteria

Sample size calculation

The sample size was calculated using the tools available at https://clincalc.com/stats/samplesize.aspx, which provides evidence-based clinical decision support tools and calculators for medical professionals. The sample size was calculated using the following assumptions:

- The accepted alpha is 5% and beta is 20%.
- The median incidence of spinal-anesthesia-induced shivering in a review of 21 studies is 55%. It is expected to go down to 22.5% with ondansetron treatment. A sample size of 34 subjects in each group would be required to detect this difference.
- The incidence of spinal hypotension during caesarean delivery is 77%, which would be expected to decrease to 45% with ondansetron treatment. A sample size of 35 subjects in each group would be required to detect this difference.

We opted to raise the sample size to 40 patients each group (for a total of 80 participants) based on this tool and these assumptions.

Randomization

Participants who met the inclusion criteria and according to the randomization list prepared by www.randomization.com, they were randomly assigned to one of two groups: the treatment group received intravenous ondansetron (4 mg diluted in 10 ml 0.9 % saline) prior to spinal anesthesia induction, whereas the control group got intravenous placebo (10 ml of 0.9 % saline). There were two anesthesiologists, the first for drug preparation and dilution in indistinguishable syringes, the second for drug administration, and both were not involved in the data collection procedure.

Salahat AM et al., Obstet Gynecol Res 2022
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Blinding

This study was double blinded: the participants, and the data recorder were blinded in the study, whereas the anesthesiologists who prepared and administered the study drugs were not blinded.

Measured Outcomes:

The primary goals were to assess the efficacy of prophylactic intravenous ondansetron on the incidence of spinal anaesthesia-induced shivering and hypotension in an obstetric population undergoing elective caesarean section; and secondarily, to assess the effect of ondansetron on the prevention of postoperative spinal anaesthesia complications such as bradycardia, nausea, vomiting, headache, pain, pruritus, dizziness, respiratory depression, and overall participants satisfaction score.

Measurement and data collection procedure

Preoperative (baseline), intraoperative, and postoperative observations and hemodynamic data were recorded. The study observations for both groups were collected every 3 minutes till the end of the surgery and every 5 minutes (for a total of 15 minutes) in the post-anaesthesia care unit (PACU), which is the entire time participant remained in the PACU at the Rafedia hospital. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) assessed non-invasively, heart rate (HR), respiratory rate (RR) via cardiac monitor with chest leads, pulse oximeter, and axillary temperature (T) via digital thermometer also assessed. Intraoperative and postoperative shivering incidence and severity, hypotension, nausea and vomiting incidence and severity, meperidine use to treat shivering, hypotension rescue medications use (ephedrine, phenylephrine), and the participants' overall satisfaction level on a 0–4 Likert type scale also recorded.

Perioperative pain and headache were measured using the numerical rating scale (NRS), which is a subjective measure in which individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 to 10, where NRS scores ≤ 5 correspond to mild, scores of 6–7 to moderate, and scores ≥8 to severe pain in terms of pain-related interference with functioning and 10 is worst imaginable pain (Boonstra et al., 2016), this scale validated by (Ferreira-Valente, Pais-Ribeiro and Jensen, 2011). Nausea and vomiting severity were measured using the 0–5 numeric rating scale (NRS), where 0 = none, 1 = anticipated, 2 = mild, 3 = moderate, 4 = great, 5 = severe, and this scale was validated by (Halpin, Huckabay, Kozuki and Forsythe, 2010). Shivering was graded using the previously validated 5-item scale (Crossley & Mahajan, 1994; Tsai & Chu, 2001), where 0 = no shivering; 1 = peripheral vasoconstriction or piloerection but not visible shivering; 2 = shivering in one muscle group only, 3 = shivering in ≥ 1 muscle group but not generalized shivering; and 4 = generalized shivering. Grade 3 or 4 shivering for at least 3 minutes was considered a positive shivering sign. A positive shivering sign and low-grade shivering were annoying for the participants were managed with intravenous 0.5 mg/kg meperidine.

Anesthesia protocol

A physical assessment was performed by the anesthesiologist, and CBC platelet tests were assessed for all participants. The anesthesia machine, anesthesia equipment, and spinal anesthesia drugs were checked for proper functioning. Standard monitoring precautions and guidelines from the American Surgical Association (ASA) were followed, including continuous electrocardiography (ECG), non-invasive BP measurement, and pulse oximeter (asahq.org, 2020). The operating rooms were maintained at 24°C by air conditioning. An intravenous cannula (18–20 Fr) was inserted; 500 mL of 0.9% saline solution was given to all patients before the spinal injection per the targeted hospital protocol. An anesthesiologist performed the spinal puncture by pencil point spinal needle (27 Fr) between the L3–L4 or L4–L5 vertebrae with the participant in a sitting position on the side of the operation table. The participants were given 7.5 mg (1.5 ml) of Marcaine Heavy 0.5% (bupivacaine) mixed with 20 µg fentanyl and 200 µg morphine into the subarachnoid space. The patients were placed in the supine position immediately after the spinal anesthesia injection. The anesthesiologists assessed dermatome levels after administering subarachnoid block every minute using alcohol-soaked swap, authorization for incision only given when the level of block reaches T5. Supplemental oxygen (5 L/min) via a simple face mask was provided until the end of delivery. Vital sign changes and adverse spinal anesthesia effects were recorded periodically as prescribed.

Data Analysis

The data was analysed with SPSS version 22 for Windows (IBM Corp., Armonk, NY, USA). Data normality was tested using the Kolmogorov–Smirnov test. The data was not normally distributed. Thus, nonparametric statistical tests were used. The scale data is expressed as the median (quartile 1 [Q1]–quartile 3 [Q3]). The groups were compared with the Mann-Whitney U Test. Categorical variables (YES/NO questions) were statistically analysed with Chi-square tests. A P value ≤ 0.05 was considered to indicate a statistically significant difference.

Results

Ninety women were assessed for eligibility; 10 did not meet the inclusion criteria, were contraindicated for spinal anesthesia, and were converted to general anesthesia. The remaining 80 women were enrolled and randomized into the treatment or control group, as shown in the consort diagram

Salahat AM et al., Obstet Gynecol Res 2022
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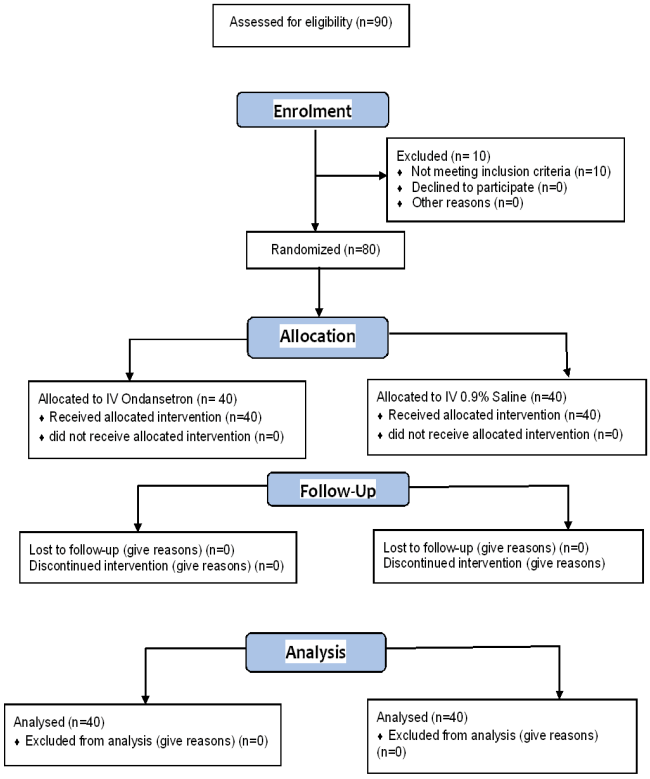
(Figure 1). There were no differences in demographic data between the groups; the p value was > 0.05 (Table 2).

As tables (3, 4, 5, and 6) show, between both study groups, there was a significant difference regarding the following: In the control group, there were 25/40 cases (62.5%) of intraoperative hypotension and dizziness, compared to 9/40 cases (22.5%) in the ondansetron group (P = <0.001), incidence and intensity of intraoperative shivering In total, there were 13/40 cases (32.5 %) in the control group vs. 5/40 cases (12.5%) in the ondansetron group (P = 0.032), Finally, Intraoperative nausea intensity was lower in the ondansetron group (P = 0.049).

Postoperatively, the incidence of dizziness was 15/40 cases (37.5%) in the control group vs. 2/40 cases (5 %) in the ondansetron group (P = 0.001). The incidence and intensity of postoperative shivering were 15/40 cases (37.5%) in the control group vs. only 5/40 cases (12.5%) in the ondansetron group (P = 0.010). Incidence and intensity of postoperative nausea: 16/40 cases (40%) in the control group vs. only 7/40 cases (17.5 %) in the ondansetron group (P = 0.026); postoperative vomiting, incidence of 9/40 cases (25.5%) in the control group vs. only 1/40 cases (2.5%) in the ondansetron group (P = 0.014).



Consort Flow Diagram (Figure 1)

Table 2: Intraoperative hemodynamic

VARIABLE	Ondansetron Median [Q1-Q3]	Control Median [Q1-Q3]	P value
Baseline systolic blood pressure	121 [120-123]	121 [119-122]	0.134
Baseline diastolic blood pressure	71 [61 -81]	67 [62- 80]	0.885
Baseline mean arterial pressure	81 [79-84]	80 [78 -81]	0.053
Baseline heart rate	81 [78 -90]	81 [75-90]	0.622
Baseline respiratory rate	18 [15 -20]	18 [15 - 19]	0.805
Baseline peripheral capillary oxygen saturation	100 [100 - 100]	100 [99 -100]	0.25
Baseline temperature	37 [36.8-37.1]	36.9 [36.8 -37.1]	0.2
Induction Systolic blood pressure	122 [109 -129]	101 [90-115]	<0.001*
Induction diastolic blood pressure	66 [57 -72]	60 [55 - 63]	0.019*
Induction mean arterial pressure	81 [74-88]	70 [67-80]	0.001*
Induction heart rate	80 [75-89]	77 [71-82]	0.171
Induction respiratory rate	18 [14 - 19]	16 [14- 18]	0.176
Induction peripheral capillary oxygen saturation	99 [98 -99]	98 [98 -99]	0.050*
Induction temperature	37 [36.8 -37.1]	36.8 [36.6 -37.1]	0.047*
3-minute Systolic blood pressure	118 [110-130]	100 [88 -114]	<O.OO1*
3-minute diastolic blood pressure	66 [56 - 74]	58 [55- 61]	0.001*
3-minute mean arterial pressure	85 [73 -90]	69 [67 -77]	<.001*
3-minute heart rate	80 [75- 88]	73 [70 - 81]	0.004*
3-minute respiratory rate	17 [14 - 19]	16 [14 - 18]	0.178
3-minute peripheral capillary oxygen saturation	99 [99 - 99]	99 [98- 99]	0.33
3-minute temperature	36.9 [36.7- 37.1]	36.5[35.8- 37.1]	0.029*
6-minute Systolic blood pressure	122 [113-130]	111 [103-118]	<0.001*

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Salahat AM et al., Obstet Gynecol Res 2022
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6-minute diastolic blood pressure	66 [60- 71]	62 [60 -65]	0.031*
6-minute mean arterial pressure	85 [78 - 88]	77 [72 - 80]	<0.001*
6-minute heart rate	80 [75 - 87]	75 [72- 80]	0.004*
6-minute respiratory rate	18 [14 -19]	16 [13 -19]	0.174
6-minute peripheral capillary oxygen saturation	99 [99 -99]	99 [98 -99]	0.038*
6-minute temperature	36.9 [36.6 37.1-]	36.3 [35.6 -37.1]	0.026*
9-minute Systolic blood pressure	120 [114 -130]	117 [111 -120]	0.006*
9-minute diastolic blood pressure	70 [62 -75]	67 [60 -75]	0.806
9-minute mean arterial pressure	84 [77 -91]	78 [75 -80]	<0.001*
9-minute heart rate	81 [78 -88]	78 [70 -81]	0.008*
9-minute respiratory rate	18 [14 -19]	15 [12 -18]	0.168
9-minute peripheral capillary oxygen saturation	99 [99 -100]	99 [98 -100]	0.055
9-minute temperature	36.9 [36.8 -37.1]	36.5 [35.4 -37.2]	0.071

Table 3: Intraoperative hemodynamic (continued)

VARIABLE	Ondansetron Median [Q1-Q3]	Control Median [Q1-Q3]	P value
12-minute Systolic blood pressure	120 [116 -128]	118 [114 -121]	0.066
12-minute diastolic blood pressure	71 [63 -80]	70 [61 -80]	0.885
12-minute mean arterial pressure	82 [79 -89]	80 [78 -81]	0.004*
12-minute heart rate	80 [78 -86]	77 [69 -81]	0.001*
12-minute respiratory rate	17 [14 -19]	15 [12 -18]	0.104
12-minute peripheral capillary oxygen saturation	99 [99 -99]	99 [98-99]	0.196
12-minute temperature	36.9 [36.8 -37.2]	36.5 [35.6 -37.2]	0.103
15-minute Systolic blood pressure	121 [121 -124]	120 [116 -122]	0.005*
15-minute diastolic blood pressure	76 [66 -80]	76 [66 -80]	0.912
15-minute mean arterial pressure	82 [79 -88]	80 [78 -81]	0.003*
15-minute heart rate	81 [78 -87]	77 [69-82]	0.029*
15-minute respiratory rate	15 [14 -18]	15 [12 -18]	0.313
15-minute peripheral capillary oxygen saturation	99 [99 -99]	99 [98 -99]	0.624
15-minute temperature	36.7 [36.7 -37.1]	36 [35.4 -37.1]	0.030*

Table 4: Post anesthesia care unit (PACU) hemodynamic

VARIABLE	Ondansetron Median [Q1-Q3]	Control Median [Q1-Q3]	P value
PACU 1-minute systolic blood pressure	121 [112-129]	118 [111-120]	0.032
PACU 1-minute diastolic blood pressure	66 [58 -74]	66 [61- 78]	0.17
PACU 1 minute mean arterial pressure	82 [87-89]	78 [75 -81]	0.001*
PACU 1 minute heart rate	81 [78 -89]	80 [76-84]	0.381
PACU 1-minute respiratory rate	18 [14 -20]	18 [14 - 19]	0.413
PACU 1-minute peripheral capillary oxygen saturation	99 [99 - 100]	98 [98 -99]	<.001*
PACU 1 minute temperature	36.9 [36.8-37.1]	36.4 [35.8 -37.0]	0.004*
PACU 5-minute systolic blood pressure	121 [112 -128]	116 [111-120]	0.022*
PACU 5-minute diastolic blood pressure	67 [61 -74]	66 [60 - 78]	0.889
PACU 5 mean arterial pressure	85 [78-89]	78 [74-80]	<0.001*
PACU 5-minute heart rate	81 [78-87]	78 [72-82]	0.022*
PACU 5-minute respiratory rate	18 [15 - 19]	18[14- 18]	0.165
PACU 5-minute peripheral capillary oxygen saturation	99 [98 -100]	98 [97 -99]	<0.001*

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Salahat AM et al., Obstet Gynecol Res 2022
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PACU 5-minute temperature	36.9 [36.7 -37.1]	36.2 [35.6 -37.1]	0.006*
PACU 15-minute systolic blood pressure	122 [115-129]	119 [113 -121]	0.010*
PACU 15-minute diastolic blood pressure	67 [61 - 77]	68 [61- 77]	0.885
PACU 15 mean arterial pressure	81 [79 -89]	77 [74 -80]	<0.001*
PACU 15-minute heart rate	81 [78- 88]	80 [72 - 82]	0.050*
PACU 15-minute respiratory rate	18 [16 - 19]	15 [14 - 18]	0.003*
PACU 15-minute peripheral capillary oxygen saturation	99 [99 - 100]	99 [98- 99]	0.022*
PACU 15-minute temperature	36.9 [36.7- 37.2]	36.5[35.6- 37.1]	0.010*

Table 5: Intraoperative complications

Variable		Total n(%)	Ondansetron n (%)	Control n (%)	P value
Intraoperative Bradycardia	Yes	3 (3.8%)	0 (0.0%)	3 (7.5%)	0.241
	No	77 (96.3%)	40 (100%)	37 (92.5%)	
Intraoperative Hypotension	Yes	34 (42.5%)	9 (22.5%)	25 (62.5%)	<0.001*
	No	46 (57.5 %)	31 (77.5%)	15 (37.5%)	
Intraoperative Headache	Yes	16 (20 %)	5 (12.5 %)	11 (27.5 %)	0.094
	No	64 (80 %)	35 (87.5 %)	29 (72.5 %)	
Intraoperative Pain	Yes	27 (33.8 %)	10 (25 %)	17 (42.5 %)	0.098
	No	53 (66.3 %)	30 (75 %)	23 (57.5 %)	
Intraoperative Pruritus	Yes	30 (37.5 %)	11 (27.5 %)	19 (47.5 %)	0.065
	No	50 (62.5 %)	29 (72.5 %)	21 (52.5 %)	
Intraoperative shivering	Yes	18 (22.5 %)	5 (12.5%)	13 (32.5 %)	0.032*
	No	62 (77.5 %)	35 (87.5 %)	27 (67.5 %)	
Intraoperative Nausea	Yes	26 (32.5 %)	10 (25%)	16 (40%)	0.152
	No	45 (67.5 %)	30 (75 %)	24 (60%)	
Intraoperative Vomiting	Yes	6 (7.5%)	1 (2.5%)	5 (12.5%)	0.201
	No	74 (92.5%)	39 (97.5%)	35 (87.5%)	
Intraoperative respiratory depression	Yes	4 (5%)	0 (0%)	4 (10%)	0.116
	No	76 (95%)	40 (100%)	36 (90%)	
Intraoperative Dizziness	Yes	34 (42.5%)	9 (22.5%)	25 (62.5%)	<0.001*
	No	46 (57.5%)	31 (77.5%)	15 (37.5%)	
	Ondansetron Median [Q1-Q3]		**Control Median [Q1-Q3]**		**P value**
Intraoperative pain (0–10 NPRS scale)	0.00 [0.00-1.0]		0.00 [0.00-3.0]		0.107
Intraoperative shivering (0–4 scale)	0.00 [0.00- 0.00]		0.00 [0.00-1.0]		0.010*
Intraoperative nausea (0–6 scale)	0.00 [0.00- 0.75]		0.00 [0.00-0.30]		0.049*

Table 6: Postoperative complication

Variable		Total: n (%)	Ondansetron: n (%)	Control: n (%)	P value
Post-operative Bradycardia	Yes	0 (0%)	0 (0%)	0 (0%)	> 0.999
	No	80 (100%)	40 (100%)	40 (100%)	
Post-operative Hypotension	Yes	9 (11.3%)	3 (7.5)	6 (15%)	0.481
	No	71 (88.8)	37 (92.5)	34 (85%)	
Post-operative headache	Yes	12 (15%)	6 (15%)	6 (15%)	1
	No	68 (85%)	34 (85%)	34 (85%)	

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Salahat AM et al., Obstet Gynecol Res 2022
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Post-operative pain	Yes	14 (17.5%)	6 (15%)	8 (20%)	0.556
	No	66 (82.5%)	34 (85%)	32 (80%)	
Post-operative pruritus	Yes	7 (8.8%)	2 (5%)	5 (12.5%)	0.432
	No	77 (91.3%)	38 (95%)	35 (87.5%)	
Postoperative shivering	Yes	20 (25%)	5 (12.5%)	15 (37.5%)	0.010*
	No	60 (75%)	35 (87.5%)	25 (62.5%)	
Post-operative nausea	Yes	23 (28.8%)	7 (17.5%)	16 (40%)	0.026*
	No	57 (71.3%)	33 (82.5%)	24 (60%)	
Post-operative vomiting	Yes	10 (12.5%)	1 (2.5%)	9 (22.5%)	0.014*
	No	70 (87.5%)	39 (97.5%)	31 (77.5%)	
Respiratory depression	Yes	1 (1.25%)	0 (0%)	1 (2.5%)	0.317
	No	79 (98.75%)	40 (100%)	39 (97.5%)	
Post-operative dizziness	Yes	17 (21.3%)	2 (5%)	15 (37.5%)	0.001*
	No	63 (78.8 %)	38 (95%)	25 (62.5%)	
	Ondansetron group Median [Q1-Q3]		**Control Median [Q1-Q3]**		**P value**
PACU pain 0-10 scale	0.00 [0.00 - 0.00]		0.00 [0.00 - 0.00]		0.537
PACU shivering 0-4 scale	0.00 [0.00 - 0.00]		0.00 [0.00-4.00]		0.003*
PACU nausea 0-6 scale	0.00 [0.00 – 0.00]		0.00 [0.00 -3.0]		0.008*
Satisfaction 0-4 Likert scale	4.0 [3.0 - 4.0]		3.0 [1.25-4.0]		<0.001*

Discussion

To the best of our knowledge, this is the first study in Palestine to assess the effects of the 5HT3 antagonist ondansetron on the incidence of hypotension and shivering after spinal anesthesia administration. Ninety women were evaluated for eligibility, but ten were excluded and turned to undergo general anesthesia because spinal anesthesia was contraindicated. The remaining 80 women were randomly assigned to one of two groups: intravenous 4 mg ondansetron or intravenous 0.9 % saline; each treatment was given prior to spinal anesthesia induction (Fig. 1). There were no differences in demographics between the groups (P > 0.05; Table 2). All needed hemodynamic parameters and observations were recorded every 3 minutes during the surgery and every 5 minutes in the recovery room.

The effect of ondansetron on spinal anesthesia-induced shivering

Ondansetron has an antishivering effect following both general and spinal anesthesia (Tie et al., 2014). It has a potential advantage in obstetric anesthesia because of its very low incidence of sedation, hypotension, bradycardia, or risk to the neonate. The mechanism of action of Ondansetron as an antishivering agent is still not clear, and it is proposed to act centrally at the level of the pre-optic anterior hypothalamic region by inhibition of serotonin reuptake and control of the temperature set point (kelsaka et al., 2006). In our study, there was a significant decrease in the incidence and severity of intraoperative shivering in the ondansetron group. This finding is consistent with Tatikonda et al. (2019). An Indian RCT that involved 140 patients was divided into two groups: intravenous ondansetron (4 mg) and placebo (0.9% saline). In that study, the shivering incidence was 17.1% in the saline group versus 0% in the ondansetron group (P = 0.0001). The current findings also agree with Badawy and Mokhtar (2017), who conducted a double-blind RCT study in Egypt that showed ondansetron effectively reduced post-spinal shivering and decreased meperidine requirement. Moreover, the results are consistent with an Indian study by Nallam et al. (2017) where they carried out an RCT for 80 participants who underwent C/S, The shivering incidence in the 8 mg ondansetron group was 10% versus 42.5% in the 0.9% saline group (P = 0.001). Furthermore, the results are in agreement with Lie et al. (2016) from China, who found that ondansetron reduced the shivering incidence by 67%. In addition to that, He et al. (2016) carried out a meta-analysis that used PubMed, Embase, and Cochrane library databases, where a total of eight RCTs containing 905 subjects were included, The analysis showed that ondansetron effectively decreases spinal anesthesia-induced shivering (He et al., 2016). Finally, Tie et al. (2014) showed a shivering incidence of 49.3% in the control group and 23.4% in the ondansetron group. On the contrary, the current study is inconsistent with Shabana et al. (2018). This Egyptian study examined 100 parturients who underwent C/S and found no significant differences regarding shivering incidence: 96% for the ondansetron group and 100% for the 0.9% saline group (P = 0.49). Khouly and Meligy (2016), also in Egypt, revealed

Salahat AM et al., Obstet Gynecol Res 2022
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no significant differences regarding shivering between the two groups: ondansetron (0%) and placebo (4%). An Australian RCT of 118 women reported a similar incidence of severe shivering in the ondansetron (32%) and 0.9% saline (33%) groups (P = 0.79; Browning et al., 2013). Finally, an Indian study reported that ondansetron failed to efficiently manage regional anesthesia-induced shivering, where 70.6% of ondansetron participants complained of shivering (Suresh et al., 2013).

The Effect of Ondansetron on Spinal-anesthesia-induced Hypotension

Our results showed a significant decrease in the incidence of intraoperative and postoperative hypotension in the ondansetron group. These results are consistent with Tatikonda et al. (2019), intravenous ondansetron (4 mg) significantly reduced hypotension and ephedrine requirement compared to placebo (0.9% saline). Boyd (2018) concluded that intravenous ondansetron can be used as an additional tool to help prevent spinal anesthesia-induced hypotension. In addition, Shabana et al. (2018) revealed a significantly reduced incidence of hypotension in the ondansetron compared to the control group (30 vs. 70%, respectively) and a significant decrease in vasopressor doses. Badawy and Mokhtar (2017) also reported a lower incidence of spinal anesthesia-induced hypotension in a double-blind RCT. Furthermore, Kholy and Meligyin (2016) reported a significantly lower incidence of hypotension in the ondansetron group compared to the control group (30 and 58%, respectively). In that study, arterial pressure was higher during spinal anesthesia induction and 30 minutes after induction (P = 0.006), which is consistent with the current study. al. (2015) conducted a meta-analysis and concluded that prophylactic ondansetron can lower the occurrence of both hypotension and vasopressor requirements in spinal anesthesia practice. Lastly, the current study is in line with Trabelsi et al. (2015), in which 80 participants were randomized into two groups (4 mg ondansetron or 10 ml of saline). Overall, 37.5% of patients in the ondansetron group experienced hypotension, compared to 77.5% in the saline group ($P < 0.001$). The current study is inconsistent with several reports regarding the effect of ondansetron on spinal anesthesia-induced hypotension. Choudhary et al. (2019) concluded that intravenous 5-HT3 serotonin receptor antagonist administration prior to spinal anesthesia does not attenuate hemodynamic changes. Moreover, a Thai RCT randomized 228 participants to 0.9% saline, 0.05 mg/kg ondansetron, or 0.1 mg/kg ondansetron. There was no difference in hypotension among the groups: saline = 81.9%, ondansetron (0.05 mg) = 84.5%, and ondansetron (0.1 mg) = 73.6% (P = 0.23; Oofuvong et al., 2018). In addition, Karacaer et al. (2018) found no significant differences in hypotension incidence (P = 0.76). Terkawi et al. (2016) also presented results that are contradictory to the current findings. They found no differences between the study groups regarding SBP, DBP, MAP, and phenylephrine requirements. The incidence of hypotension was 62% for the ondansetron group and 61% for the saline 59 group (P=1.00). A Spanish RCT conducted to study the efficacy of IV ondansetron on participants' hemodynamics during elective caesarean section under spinal anesthesia, concluded that there were no differences in the number of patients with hypotension in the placebo (43.8%) or 2 mg (53.1%), 4 mg (56.3%), and 8 mg (53.1%) ondansetron groups (P = 0.77). Furthermore, ephedrine and phenylephrine requirements and the number of patients with adverse effects did not differ among the study groups. In their study, they concluded that prophylactic ondansetron had little effect on the incidence of hypotension in healthy parturients who underwent spinal anesthesia with bupivacaine and fentanyl for elective cesarean delivery (Ortiz-Gomez et al., 2014).

The Effect of Ondansetron on Bradycardia

The current study results showed no significant differences regarding the incidence of intraoperative and postoperative bradycardia (HR<50 bpm). Our results are consistent with several studies. Choudhary et al. (2019) concluded that intravenous 5-HT3 serotonin receptor antagonist before spinal anesthesia does not affect HR changes. Tatikonda et al. (2019) found that 5.7% of patients in the ondansetron group and no patients (0%) in the placebo group exhibited bradycardia that required atropine (P=0.120). In addition, Karacaer et al. (2018) showed no significant differences in the incidence of bradycardia between the study groups. Oofuvong et al. (2018) randomly allocated 228 participants into one of three groups: 0.9% saline, 0.05 mg/kg ondansetron, or 0.1 mg/kg ondansetron. The measured HR did not differ among the study groups during the overall operation period. Potdar et al. (2017) conducted a RCT in India with 180 parturients randomly divided into three groups: 0.9% saline, 4 mg ondansetron, and 8 mg ondansetron. HR did not significantly differ among the groups. Terkawi et al. (2016) also did not find differences between the two groups regarding HR (P=0.18).

On the contrary, the current study is inconsistent with several studies. Shabana et al. (2018) reported that ondansetron decreases the occurrence of spinal anesthesia-induced bradycardia. Moreover, a meta-analysis result conducted by Gao et al. (2015) suggests that prophylactic ondansetron reduces the incidence of bradycardia.

The Effect of Ondansetron on Pruritus

The present study showed no significant differences regarding the incidence of intraoperative and postoperative pruritus. These findings are consistent with Terkawi et al. (2016). In this study, 86 subjects underwent elective cesarean section, they were randomly allocated AND were anesthetized using a mixture of 15 mg of 0.75% bupivacaine, 20 mcg of

fentanyl, and 100 mcg of preservative-free morphine. The occurrence of pruritus was not statistically different between the ondansetron (63%) and placebo (56%) groups (P = 0.59). Moreover, the study results are in line with Ortiz-Gomez et al. (2014). This RCT with 128 participants— randomly divided into placebo or intravenous ondansetron (2, 4, or 8 mg)—revealed no statistical differences among the groups regarding pruritus incidence (P =0.77). Our study is inconsistent with the results of Yeh et al. (2000), in which 60 participants were randomly divided into 0.9% saline, diphenhydramine, and ondansetron groups. The ondansetron group showed a significantly lower pruritus incidence (25%) compared to the other groups. They concluded that prophylactic ondansetron can statistically reduce the incidence of pruritus (Yeh et al., 2000).

The Effect of Ondansetron on Pain and Headache

There were no significant differences between the groups regarding the incidence of intraoperative and postoperative pain and headache. The results are consistent with Yeh et al. (2000), where 60 participants were randomly divided into 0.9% saline, diphenhydramine, and ondansetron groups. The postoperative pain score and headache among all study groups did not statistically differ in that study.

Recommendations

In clinical practice, it is recommended to administer 4 mg of ondansetron intravenously prior to spinal anesthesia induction for women who will undergo a cesarean section. This administration should attenuate the incidence of spinal anesthesia-induced shivering and hypotension. Furthermore, ondansetron is a category A drug and is thus safe to use during pregnancy. It also has well-known antiemetic and anti-nausea effects. Larger sample sizes are required to detect the exact effectiveness of ondansetron on the attenuation of spinal anesthesia-induced shivering and hypotension in women who undergo a cesarean section.

Conclusions

In the current study, 4 mg of ondansetron administration significantly and effectively reduced intraoperative and postoperative spinal anesthesia-induced hypotension and shivering; meperidine vasopressor use; decreased intraoperative nausea (severity); postoperative nausea (incidence and severity); postoperative vomiting; and intraoperative and postoperative dizziness, Finally, the participant's satisfaction rating was higher in the ondansetron group compared to the control group. On the other hand, there was no difference in the following prevention between two study group: perioperative bradycardia; perioperative headache; perioperative pain (incidence and intensity), perioperative pruritus, intraoperative nausea (incidence), intraoperative vomiting, and perioperative respiratory depression.

Declarations

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Conflict of interest

The authors have no conflicts of interest to disclose.

Ethical approval and consent to participate

This study was conducted in adherence to the Helsinki declaration guidelines and institutional review board (IRB) approval taken from An-Najah National University IRB board. A Palestinian Ministry of Health facilitation letter allowing data collection in Rafedia Governmental Hospital also have been taken. Prior to participation, all participants signed a thoroughly explained informed consent form.

Availability of data and materials

Data used to support the findings of this study are available from the corresponding author (Ahmad M Salahat, E-mail: Ahmad.salahatt@gmail.com) upon reasonable request.

Consent for Publication

Not applicable.

Code availability

Not applicable.

Authors' contributions

1. Ahmad Salahat (The Corresponding author): planned and conceived the study i.e., do the study design and study implementation, research writing, results' SPSS analysis.
2. Dr. Adham Abu Taha: The study Academic supervisor
3. Dr. Nouraldin Almasri: The study Clinical supervisor-Rafidia governmental hospital
4. Mr. Essa Sweity: Assisted in both SPSS analysis and study writing process.

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Salahat AM et al., Obstet Gynecol Res 2022
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