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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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 for caesarean section; however, it is associated with dangerous adverse effects on both mother and fetus, this includes: spinal anesthesia induced shivering and hypotension. Previous studies suggest serotonin may have a role in hypotension, bradycardia, and shivering occurrence perioeratively. In this prospective double-blind randomized control trial study, we evaluated the efficacy of the ondansetron, a serotonin receptor antagonist, on the incidence of spinal anesthesia-induced shivering, hypotension, nausea, vomiting and other possible complications in elective caesarean sections. This study conducted in Palestine, West Bank, Nablus city in the caesarean section operation rooms, and post-anesthesia care unit at Rafidia governmental hospital. Eighty full-term elective caesarean section parturient (Age 18-50 years) with ASA 1 or 2 classification were recruited and randomly allocated into two groups: prophylactic IV ondansetron treatment group and placebo 0.9% saline control group. The

primary outcomes were the incidence of spinal anesthesia-induced shivering and hypotension, while secondary outcomes were perioperative bradycardia, nausea, vomiting, headache, pain, pruritus, dizziness and respiratory depression and parturient satisfaction.

Results: Incidence of intraoperative hypotension and dizziness in the ondansetron group was significantly lower than which occurred in the control group (22.5% vs. 62.5% respectively; $P < 0.001$), the incidences and intensity of intraoperative shivering in the ondansetron group was lower than the control group (12.5 % vs. 32.5 % respectively; $P = 0.032$), Intraoperative nausea intensity in the ondansetron group was lower than control group ($P = 0.049$). Postoperatively, the incidence of postoperative dizziness in the ondansetron group was lower than the control group (5% vs. 37.5 % respectively; $P = 0.001$), the incidence and intensity of postoperative shivering in the ondansetron group was lower than the control group (12.5% vs. 37.5 % respectively; $P = 0.01$). Incidence and intensity of postoperative nausea in the ondansetron group was lower than the control group (17.5% vs. 40 % respectively; $P = 0.026$), the incidence of postoperative vomiting in the ondansetron group was lower than the control group (25.5% vs. 2.5 % respectively; $P = 0.014$).

Conclusion: Prophylactic 4 mg IV ondansetron can significantly attenuate the incidences of spinal anesthesia-induced shivering and hypotension, dizziness, nausea, and vomiting occurrence and increase parturient satisfaction scale for parturient who undergo caesarean section.

1. Introduction

Spinal anesthesia is often used in cesarean section delivery due to its rapid onset, definite motor and sensory blockade, and low risk of local anesthetic systemic toxicity. Furthermore, it offers diverse benefits for both mothers and their developing infant's outcomes, i.e., better oxygenation and acid-base balance, despite of that, it is not free of risks

(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 have harmful effects on the fetus and the delivering mother, including reduced utero placental perfusion, impaired fetal perfusion and gas exchange, fetal acidemia, serious maternal complications, e.g., reduced cardiac output and diminished cerebral perfusion (Limongi & Lins, 2011), altered level of consciousness, nausea, and vomiting (Lee, George, & Habib, 2017).

Hypotension can lead to nausea, vomiting, altered consciousness, an increased risk of aspiration, and reduced 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 are involved in these changes, including the 5-HT3 receptor. In human studies, 5-HT3 receptor antagonists have been evaluated for their efficacy to prevent spinal anesthesia-induced hypotension, but the results are 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). Furthermore, it leads to hypercarbia, hypoxemia, lactic acidosis, and worsening pain sensation (Begum et al., 2008). In addition to that, shivering prolongs hospital stay, may lead to surgical wound infection, decreases immunity, causes coagulopathy, and increases the incidence of cardiac morbidity (Kim et al., 2014; Reynolds et al., 2008). All of this burdens health care facilities and put the patient's overall health status at risk.

It is worth to mention that, until now there is no consensus regarding the efficacy of ondansetron on the reduction of spinal anesthesia-induced shivering and hypotension.

This study primarily carried out to evaluate the efficacy of prophylactic 4mg intravenous ondansetron on the reduction of spinal anesthesia-induced shivering and hypotension in an obstetric population that undergoes elective cesarean section.

1.1 Problem statement

Spinal anesthesia is often complicated by postoperative hypotension and shivering. Hypotension affects approximately 50% of the obstetric population (Klöhr et al., 2010). A drop in arterial blood pressure can lead to nausea and vomiting, altered consciousness, an increased risk of aspiration, and reduced uterine-fetal blood flow. The mechanisms that cause hypotension during spinal anesthesia include sympatholysis, which induces a decrease in systemic vascular resistance (Langesæter et al., 2008), as well as the Bezold-Jarisch reflex. The latter phenomenon leads to vasodilation, bradycardia, and hypotension (Warltier et al., 2003). Several receptors are involved in these changes, including the 5-HT3 receptor. Antagonists for this receptor can block the Bezold-Jarisch reflex in animal models (Yamano et al., 1995). In human studies, 5-HT3 receptor antagonists have been evaluated for their efficacy to prevent spinal-anesthesia-related hypotension, but the results are inconsistent (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 excited muscular activity compromises myocardial function and worsens morbidity rates, especially when the patient has preexisting diminished myocardial oxygen flow, e.g. arteriosclerosis (Alfonsi, 2001; Ciofolo et al., 1989). These conditions will affect uteroplacental blood flow. Some of used drugs for treating post-anesthesia shivering are meperidine, tramadol, and clonidine, but all of these have adverse effects, including sedative effects, nausea, vomiting, bradycardia, and hypotension. Postoperative shivering prolongs hospital stays, may lead to surgical wound infection, decreases immunity, causes coagulopathy, and increases the incidence of cardiac morbidity (Kim et al., 2014; Reynolds et al., 2008). These morbidities burden health care facilities and put the patient's overall health status at risk.

1.2 Study objectives

This study was conducted to achieve the following objectives:

a) Primarily, to determine the efficacy of prophylactic intravenous ondansetron on the reduction of spinal-anesthesia-induced shivering and hypotension in an obstetric population that undergoes elective caesarean sections.

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

1.3 Significance of the Study

Spinal-anesthesia-induced shivering and hypotension have significant negative consequences on the mother and infant during cesarean section. These factors can increase the length of a

hospital stay and cause financial and other burdens to health services. Conducting this study will help to whether ondansetron can reduce these complications. Moreover, earlier studies suggest that avoiding shivering will provide valuable benefits in patients and promote a superior prognosis (Kurz et al., 1996). *Notably, this study is the first of its kind in Palestine*. The results should provide benefits to our patients and their relatives by decreasing their preventable suffering and to our hospitals by decreasing patients' hospitalization and, consequently, the economic burden on these health care facilities.

1.4 Study methodology

Study design

The study was conducted as a prospective, cohort, randomized, double-blinded, placebo-controlled trial (RCT). This design was adopted due the strength of the hierarchy of scientific evidence, namely, reduced bias and more accurate results.

Clinical Trial Registration

This clinical trial registered at Thai Clinical Trials Registry (TCTR) on 22/08/2020 with registration ID: TCTR20200825001.

Participants

The target population was a cohort of full-term obstetrics participants with an ASA I or II classification who planned for elective caesarean section at Rafidia Governmental Surgical Hospital.

Eligibility (inclusion and exclusion criteria)

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

Sample size calculation

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

- 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.

According to this tool and these assumptions, we decided to increase the sample size to 40 patients per group (a total of 80 participants) who met the inclusion criteria.

Randomization

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

Blinding

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

Measured Outcomes:

Primarily, the outcomes were to determine the efficacy of prophylactic intravenous ondansetron on the incidence of spinal anaesthesia-induced shivering and hypotension in an obstetric population that undergoes elective caesarean section; secondarily, to determine the effect of ondansetron on the prevention of postoperative spinal anaesthesia complications, including bradycardia, nausea, vomiting, headache, pain, pruritus, dizziness, respiratory depression, and on overall participants satisfaction score.

Measurement and data collection procedure

Study observations and hemodynamic parameters were measured preoperatively (baseline), intraoperatively, and postoperatively. For both groups, study observations were recorded every 3 min until the end of the operation and every 5 min (for 15 min total) in the post-anaesthesia care unit (PACU), which is the total time participant stayed in PACU at the Rafedia hospital. These observations included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and those measured non-invasively, heart rate (HR), respiratory rate (RR) via cardiac monitor with chest leads, peripheral capillary oxygen concentration (SpO2) via pulse oximeter, and Axillary temperature (T) via digital thermometer. Intraoperative and postoperative shivering incidence and severity, hypotension incidence, nausea and vomiting incidence and severity, incidence of used meperidine to treat shivering, the incidence of the use of hypotension rescue medications (ephedrine, phenylephrine) and the participants overall satisfaction level of 0-4 likert type scale. 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= sever, and this scale 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 min was considered a positive shivering sign. 31 A positive shivering sign and low-grade shivering were annoying for the participants and managed with intravenous 0.5 mg/kg meperidine.

Anaesthesia protocol

A physical assessment was performed by 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 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) 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 dermatomes levels after administering subarachnoid block every minute using alcohol-soaked swap authorization only given for the surgeon only when the level of block reached T5. Supplemental oxygen (5 L/min) via a simple face mask was provided until the end of delivery. Vital signs changes and adverse spinal anesthesia effects were recorded periodically as prescribed.

Data Analysis

The data were analysed with SPSS version 22 for Windows (IBM Corp., Armonk, NY, USA). Data normality was tested using Kolmogorov–Smirnov test. The data were not normally distributed. Thus, nonparametric statistics tests were used. The Scale data are 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 have been used. A P value ≤ 0.05 was considered to indicate a statistically significant difference.

Declarations

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.

Consent for publication

Not applicable

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.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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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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2. Results

Ninety women were assessed for eligibility; 10 did not meet the inclusion criteria, were contraindicated for spinal anesthesia, and converted to general anesthesia. The remaining 80 women were enrolled and randomized into the treatment or control group, Consort diagram (Fig. 1). There were no differences in demographic data between the groups, 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: incidence of intraoperative hypotension and dizziness; there were 25/40 cases (62.5%) in the control group vs. 9/40 cases (22.5%) in ondansetron group ($P < 0.001$), incidences and intensity of intraoperative shivering there were 13/40 cases (32.5 %) in control group vs. 5/40 cases (12.5 %) in ondansetron group ($P = 0.032$). Intraoperative nausea intensity was lower in the ondansetron group ($P = 0.049$).

Postoperatively, incidence of dizziness where 15/40 cases (37.5 %) in the control group vs. 2/40 cases (5 %) in the ondansetron group ($P = 0.001$), incidence and intensity of postoperative shivering where 15/40 cases (37.5 %) in control group vs. only 5/40 cases (12.5 %) in ondansetron group ($P = 0.010$). Incidence and intensity of postoperative nausea where 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 where 9/40 cases (25.5 %) in control group vs. only 1/40 cases (2.5 %) in ondansetron group ($P = 0.014$).

Table (2): Demographic data of Participants

VARIABLE	Ondansetron	Control	P value
Age (years)	29.5 [27 - 32.7]	28 [25.2-30]	0.154
Weight (kg)	83.5 [78.2 - 96.5]	80.5 [73 - 86.7]	0.052
Parity	3 [1.25 - 4]	3 [2 - 4]	0.670
Gravidity	3 [2 - 4]	3 [2 - 5]	0.122
Gestational age (weeks)	40 [40 - 40]	39 [38 - 40]	0.637
History of cesarean section	2 [1-3]	2 [1 - 3]	0.323
Time of delivery	11 [10-12]	11 [9.2 - 12]	0.723

CONSORT Flow Diagram (Fig. 1)

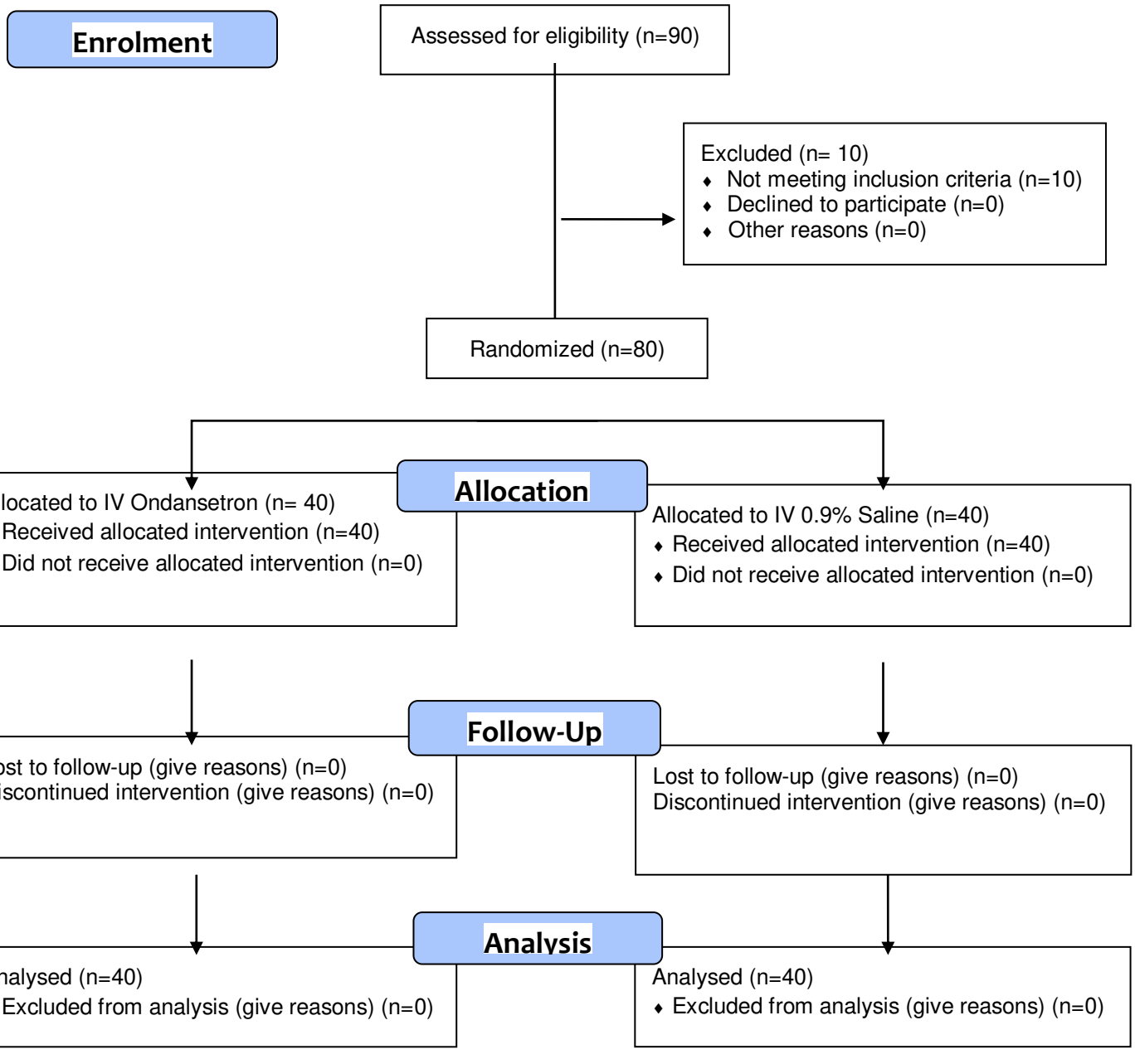

Table 3: Intraoperative hemodynamics

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]	0.250
Baseline temperature	37 [36.8-37.1]	36.9 [36.8 -37.1]	0.200
Induction Systolic blood pressure	122 [109 -129]	101 [90-115]	<O.OO1*
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]	0.330
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*
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 hemodynamics (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) hemodynamics

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]	0.170
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]	<. OO1*
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.OO1*
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.OO1*
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.OO1*
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*

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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%)	1.000
	NO	68 (85%)	34 (85%)	34 (85%)	
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%)	
Post-operative 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*

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3. Discussion

To our knowledge, this study is the first performed in Palestine to assess the effects of the 5HT3 antagonist ondansetron on the incidence of hypotension and shivering after administration of spinal anesthesia. Ninety women were assessed for eligibility, but 10 were excluded and switched to general anesthesia because spinal anesthesia was contraindicated. The remaining 80 women were enrolled in the study and randomly allocated into two groups: intravenous 4 mg ondansetron or intravenous 0.9% saline; each treatment was administered prior to spinal anesthesia induction (Fig. 1). There were no demographic differences between the groups ($P > 0.05$; Table 2). Numerous hemodynamic parameters and other observations were recorded every 3 min during the intraoperative period and every 5 min in the PACU.

1- The effect of ondansetron on spinal anesthesia-induced shivering

Ondansetron has 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 antishivering worldwide 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 controls there 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, ondansetron reduced the shivering incidence by 67%. In addition to that, He et al. in 2016 carried out a meta-analysis that used PubMed, Embase, and Cochrane library databases, where total 8 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 parturient underwent C/S, 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 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).

2- 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 compared to the control group (30 and 58%, respectively). In that study, arterial pressure was higher at spinal anesthesia induction and 30 min post- 58 induction (P = 0.006), data that are in agreement with the present study. Gao 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 into 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 hemodynamic 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 parturient who underwent spinal anesthesia with bupivacaine and fentanyl for elective cesarean delivery (Ortiz-Gomez et al., 2014).

3- 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 works. 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 parturient 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) suggested that prophylactic ondansetron reduces the incidence of bradycardia.

4- 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, they 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).

5- 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.

4. Recommendations

In clinical practice, it is recommended to administer 4 mg 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.

5. Conclusions

In the current study, 4 mg ondansetron administration in parturient who underwent elective cesarean section significantly and effectively decreased intraoperative and postoperative spinal anesthesia-induced hypotension and vasopressor use, reduced intraoperative and postoperative spinal anesthesia-induced shivering (incidence and severity) and meperidine use, decreased intraoperative nausea (severity), postoperative nausea (incidence and severity), postoperative vomiting, and intraoperative and postoperative dizziness compared to saline. On the other hand, ondansetron was not effective in the prevention of the following: intraoperative and postoperative bradycardia, intraoperative and postoperative headache,

intraoperative and postoperative pain (incidence and intensity), intraoperative and postoperative pruritus, intraoperative nausea (incidence), intraoperative vomiting and intraoperative and postoperative respiratory depression. Finally, the participant's satisfaction rating was higher in the ondansetron group compared to the control group.

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Figures

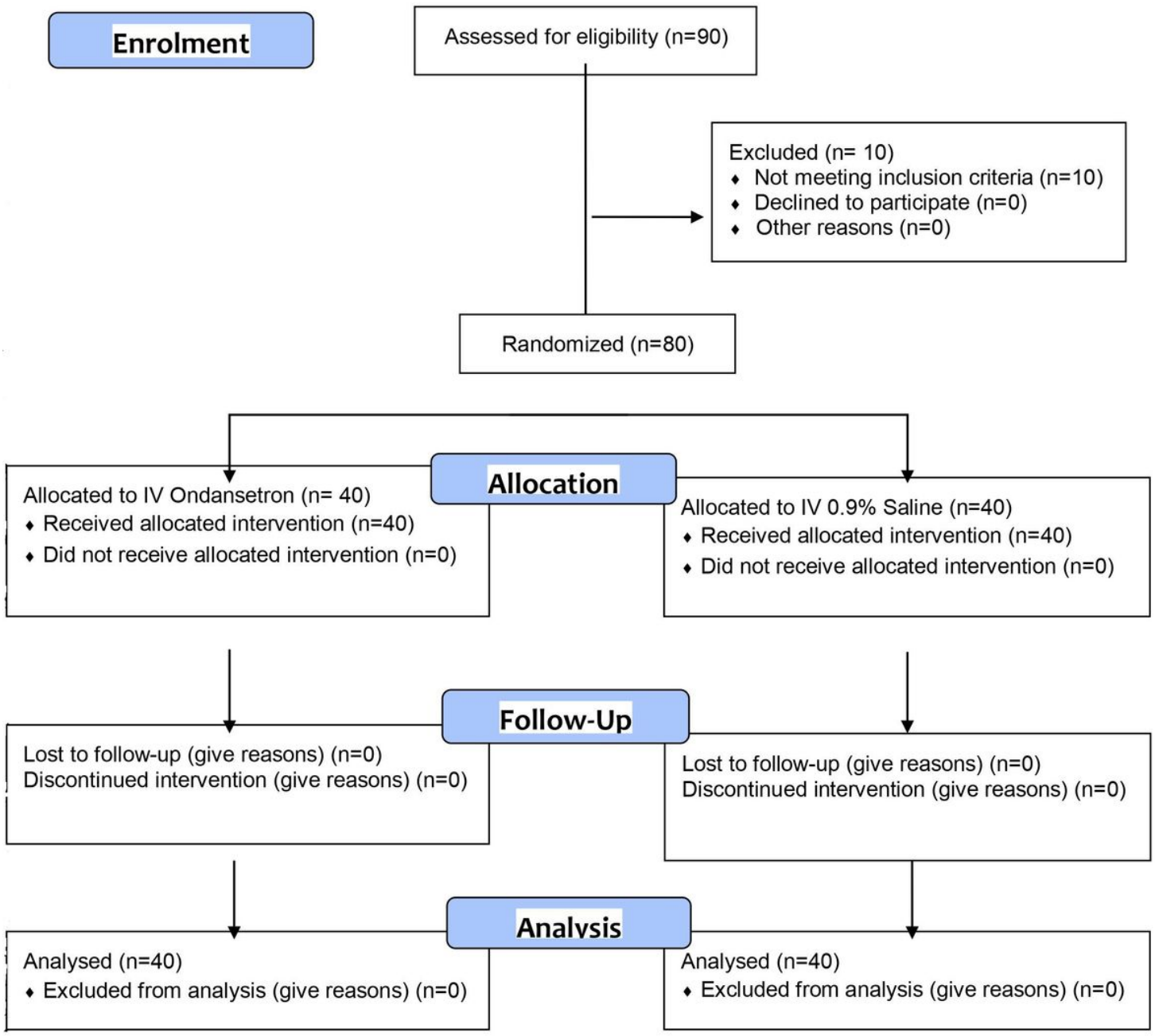

Figure 1

CONSORT Flow Diagram