An-Najah National University

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Effect of Prophylactic Ondansetron on the Incidence of Spinal-anesthesia-induced Shivering and Hypotension in Elective Cesarean Sections: A Prospective, Randomized, Placebo-Controlled, Double-Blind Study

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الإقرار

أنا الموقع أدناه، مقدم الرسالة التي تحمل العنوان:

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أقر بأن ما اشتملت عليه هذه الرسالة أنما هو نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه حيثما ورد، وان هذه الرسالة ككل، أو أي جزء منها لم يقدم من قبل لنيل أيّ درجة أو لقب علميّ لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher`s own work and has not been submitted from anywhere else, for any other degree or qualification.

اسم الطالب: **Student`s name:**

التوقيع **Signature:**

التاريخ: **Date:**

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List of Abbreviations

Abbreviations	Meaning
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	Milliliter
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
AUC	The area under the plasma drug concentration-time curve

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Abstract

Background: Spinal anesthesia is the preferred method of anesthesia for cesarean section, but it is associated with dangerous adverse effects to the mother and fetus, this includes: hypotension and shivering. Studies suggest serotonin may have role in hypotension, bradycardia and shivering occurrence. In this study, we evaluated the efficacy of ondansetron, a serotonin receptor antagonist, on the incidence of spinal-anesthesia-induced shivering, hypotension, nausea, vomiting and other complications in elective cesarean sections.

Methods: this was double blinded RCT, were 80 full-term parturient were randomly allocated into two groups, immediately before induction time, the treatment group received an IV bolus of 4 mg ondansetron and the control group received IV 10 ml of 0.9% saline. Study observations and hemodynamic parameters were recorded pre-, intra-, and postoperatively: every 3 min intraoperatively and every 5 min for 15 min in the post-anesthesia care unit.

Results: there was significant difference between both study groups in regard to: incidences of intraoperative hypotension and dizziness there were 25/40 cases (62.5%) in 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 ondansetron group ($P = 0.049$). Postoperatively, incidences of dizziness where 15/40 cases (37.5 %) in control group vs 2/40 cases (5 %) in ondansetron group ($P =0.001$), incidences and intensity of postoperative shivering where 15/40 cases (37.5 %) in control group vs only 5/40 cases (12.5 %) in ondansetron group ($P = 0.010$). Incidences and intensity of postoperative nausea where 16/40 cases (40 %) in control group vs only 7/40 cases (17.5 %) in ondansetron group ($P = 0.026$), postoperative vomiting, incidences where 9/40 cases (25.5 %) in control group vs only 1/40 cases (2.5 %) in ondansetron group ($P = 0.014$).

Conclusion: prophylactic 4 mg IV ondansetron significantly attenuates the incidence of spinal anesthesia-induced shivering and hypotension, dizziness, nausea and vomiting occurrence.

Key words: Ondansetron, spinal anesthesia, cesarean section, hypotension, shivering, nausea/vomiting

Chapter One
Introduction

1.1 Introduction

1.1.1 Spinal Anesthesia

Spinal anesthesia is often used in cesarean sections deliveries due to its rapid onset, definite motor and sensory blockade, and low risk of local anesthetic systemic toxicity. Further, it offers diverse benefits for both mothers and their developing infant's outcomes i.e. oxygenation and acid-base balance (Smith, Clark & Watson, 1999). It is considered a safe and efficient modality for a wide range of operative procedures, although it is not free of risks (Ghani et al., 2015). Spinal-anesthesia-induced shivering and hypotension frequently occur intra- or postoperatively, 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 uteroplacental perfusion, impaired fetal perfusion and gas exchange, fetal acidemia, serious maternal complications, e.g. reduced cardiac output and diminished cerebral perfusion (Limongi & Lins, 2011), an altered level of consciousness, nausea, and vomiting (Lee, George, & Habib, 2017).

1.1.2 Spinal-anesthesia-induced Shivering

It is estimated that 234.2 million large-scale operative procedures are performed every year throughout the world (Weiser et al., 2008). Perioperative hypothermia is a recurring complication in anesthesia. Some anesthetics suppress the thermoregulation center and lead to shivering (Zhang & Wong, 1999). Indeed, the most effective way to lower human body temperature is to undergo anesthesia (Pickering, 1956).

Perioperative shivering is an unintentional, muscular, and oscillatory contraction that amplifies the metabolic heat yield 6-fold above the baseline metabolic rate (Giesbrecht, Sessler, Mekjavic, Schroeder, & Bristow, 1994). It is clinically associated with different frequencies of tonic or clonic skeletal muscle hyperactivity (Javaherforoosh, Akhondzadeh, Aein, Olapour, & Samimi, 2009). Grades may vary from mild skin eruptions to generalized persistent skeletal muscular contractions, with an incidence up to 50–80% (Begum, Islam, Sarker, Karmakar, & Alam, 2008). This augmented muscular activity increases oxygen consumption by approximately 200–500% (Bay, Nunn, & Prys-Roberts, 1968; Macintyre, Pavlin, & Dwersteg, 1987). Further, hypercarbia, hypoxemia, and lactic acidosis worsen pain sensation (Begum et al., 2008). This excited muscular activity compromises myocardial function and worsens morbidity rates, especially where when a patient has preexisting diminished myocardial oxygen flow, e.g. arteriosclerosis (Alfonsi, 2001; Ciofolo, Clergue, Devilliers, Ben, & Viars, 1989). Postoperative shivering leads to a longer

hospital stay, increased wound sepsis, suppressed immunity, increased coagulopathy, and heightened cardiac morbidity (Kim et al., 2014; Reynolds, Beckmann, & Kurz, 2008). Shivering disturbs care of the operation site, an especially troubling situation when postoperative surgical site immobilization is required (e.g. nerve and vascular surgeries). This outcome threatens the desired surgical goals.

The prevention of post-anesthesia shivering has beneficial outcomes on subjects and markedly improves the prognosis (Kurz, Sessler, & Lenhardt, 1996). Thus, pharmacological and non-pharmacological preventive measures are used. Pharmacological preventive agents are considered to be the backbone of preoperative shivering management. Some researchers have found that while raising the temperature of the surgical theatre and body skin re-warming can prohibit perioperative shivering, these methods are still insufficient (Camus, Delva, Sessler, & Lienhart, 1995; El-Gamal et al., 2000). Warming intravenous fluid have been studied as measure to prevent induced shivering, but it does not reduce spinal-anesthesia-induced shivering (Woolnough, Allam, Hemingway, Cox, & Yentis, 2009; Yokoyama et al., 2009). Another researcher found that non pharmacologic approaches, e.g. maintaining ambient temperature, warming air blankets (Kim et al., 2014), and warming intravenous infusions, are as effective as pharmacologic interventions (Alfonsi, 2003).

The available pharmacological agents used to prevent and manage post-anesthesia shivering include opiates, physostigmine, magnesium sulfate, methylphenidate, alpha2 adrenergic agonists, doxapram, corticosteroids, nefopam, and serotonin 5-HT_3 receptor antagonists, namely ketanserin and ondansetron (Alfonsi, 2001; Kranke, Eberhart, Roewer, & Tramèr, 2003). Meperidine is one opiate that is currently used to treat post-anesthesia shivering, but this medication causes patients somnolence, delayed emergence from anesthesia, nausea, vomiting, and respiratory depression (Anaraki & Mirzaei, 2012; Dabir et al., 2011).

Earlier researchers validated that serotonin (5-HT), which is central nervous system (CNS) biological neurotransmitter, plays a crucial role in perioperative shivering control (Dawson & Malcolm, 1982; Hindle, 1994; Joris, Banache, Bonnet, Sessler, & Lamy, 1993). The exact mechanism by which 5-HT receptor antagonists regulate temperature and prevents perioperative shivering has not been fully elucidated. It is thought to involve abrogation of serotonin re-uptake in the hypothalamus (Alfonsi, 2003; Hammel & Pierce, 1968). Several studies have verified that ondansetron prevents post-anesthesia shivering; however, its safety and efficiency remain controversial (He, Zhao, & Zhou, 2016).

1.1.3 Spinal-anesthesia-induced Hypotension

Spinal anesthesia is considered to be a secure and efficient approach for various operations, although it may cause some adverse effects (Ghani, Varshney, Hasan, Jamil, & Sinha). Hypotension is considered to be a major

disadvantage of spinal block (Sigdel, Shrestha, & Amatya, 2015). There is an incidence of 33% for hypotension and 13% for bradycardia; hypotension is the most common serious adverse effect of spinal block anesthesia (Arndt, Bomer, Krauth, & Marquardt, 1998; Carpenter, Caplan, Brown, Stephenson, & Wu, 1992).

The predominant hypotensive mechanism mediated by spinal anesthesia is a sympatholytic effect that decreases systemic vascular resistance (Langesaeter, Rosseland, & Stubhaug, 2008) as well as activation of the Bezold-Jarisch reflex. This reflex has been proposed to explain perioperative hypotension associated with bradycardia (Kinsella & Tuckey, 2001). Decreased venous return triggers cardiac vagal afferent fibers to elicit this reflex; it promotes paradoxical vasodilatations, reduced heart rate, and low blood pressure (Warltier, Campagna, & Carter, 2003). This phenomenon accompanies the absence of reflex tachycardia despite the presence of hypotension (Dobson, Caldicott, Gerrish, Cole, & Channer, 1994). This circumstance may also be elicited from blockade of the T1–T4 cardio-accelerator sympathetic fibers, and probably the reversal of the Bainbridge reflex (Caplan, Ward, Posner, & Cheney, 1988). Notably, the definition of hypotension during cesarean deliveries varies among researchers. Most studies have adopted changes in systolic blood pressure (SBP): either a proportional decrease of SBP (< 70–80 % of baseline reading) or an absolute SBP reading of ≤ 90–100 mmHg.

The incidence of hypotension after spinal anesthesia has been reported at 50% (Klöhr, Roth, Hofmann, Rossaint, & Heesen, 2010) up to 70–80% in the obstetric population when pharmacological prophylaxis is not administered (Liu & McDonald, 2001). Moreover studies estimated hypotension in 80–100% of clients who undergo cesarean section under spinal anesthesia (Khaw, Kee, & Lee, 2006). A fall in arterial blood pressure can provoke nausea, vomiting, an altered level of consciousness, increased aspiration, and cardiovascular collapse (Limongi & Lins, 2011). It can pose a risk for myocardial and brain ischemia (Juelsgaard et al., 1998).

In an attempt to manage and decrease the incidence of hypotension accompanied with spinal anesthesia during cesarean sections, numerous techniques have been utilized. These include: intravenous fluids, vasoconstriction agents, and lower extremity compression devices. Nevertheless, no technique is sufficient (Critchley & Conway, 1996; Cyna, Andrew, Emmett, Middleton, & Simmons, 2006; Emmett, Cyna, Andrew, & Simmons, 2001; Mitra, Roy, Bhattacharyya, Yunus, & Lyngdoh, 2013; Sharma, Gajraj, & Sidawi, 1997). In addition, a Cochrane review summarized that future studies must focus on the use of combination of hypotension management modalities (Emmett et al., 2001).

The latest research has proposed that ondansetron, which was originally used for prophylaxis and treatment of nausea and vomiting, might be useful to attenuate spinal-anesthesia-related

hemodynamic instabilities (Sahoo, SenDasgupta, Goswami, & Hazra, 2012). In animal models, 5-HT3 receptor antagonists suppress the Bezold-Jarisch reflex (Yamano, Ito, Kamato, & Miyata, 1995). In human studies, 5-HT3 receptor antagonists have been evaluated for their efficacy in order to prevent spinal-anesthesia-related hypotension, but the results are inconsistent (Ortiz-Gómez et al., 2014; Trabelsi et al., 2015).

1.2 Background/Definitions

1.2.1 Cesarean Section Delivery

Cesarean section delivery is defined as the delivery of a fetus through surgical incisions made through the abdominal wall (laparotomy) and the uterine wall (hysterotomy) (Medscape, 2019). This procedure may be elective or emergent due to indications including—but not limited to—a history of cesarean delivery, multifetal pregnancy, a mother with genital herpes or HIV infection, and fetuses with mal-position and mal-presentations (Hannah, 2004).

1.2.2 Regional anesthesia

Regional anesthesia is a type of surgical pain management that numbs and anesthetizes a specific part of the body. The main advantage of this technique is that anesthetic drugs are delivered through an injection or small catheter—a modality that keeps the patient awake during the surgical procedures. Regional anesthesia includes spinal anesthesia, epidural anesthesia, and peripheral nerve block (PNB; Morgan, 2013**)**.

1.2.3 Spinal anesthesia

Spinal anesthesia is a type of regional anesthesia that involves the injection of a local anesthetic through a spinal needle directly between L3–L4 or L4–L5 vertebrae, the needle is placed past the dura mater into the subarachnoid space, in order to reach that space, the needle must pierce through several layers of tissues and ligaments which includes the supraspinous and interspinous ligamentum flavum. Spinal anesthesia is used to block pain in surgeries that involve the lower abdomen, pelvis, genitalia, and lower extremities. The advantages for spinal anesthesia include cost effectiveness, the patient is kept awake and thus their airway is protected, and a reduced risk of aspiration pneumonia. Spinal anesthesia decreases bleeding probabilities and allows early mobilization for patients, a factor that decreases the risk of thrombosis (deep vein thrombosis [DVT] and pulmonary embolisms). The most common disadvantages are hypotension, shivering, and post-dual puncture headache. This modality may be inappropriate for frightened, phobic, or psychogenic patients.

1.2.4 Ondansetron drug

Ondansetron is a potent and highly selective serotonin 5-HT3 receptor-blocking agent, indicated for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, radiotherapy, surgical procedures and anesthetic agents. Dosage are 0.15 mg/kg over 15 min administered 30 min before chemotherapy and prophylaxis 4 mg IV/IM immediately before anesthesia or after procedure. Dose renal

adjustment not necessary, in hepatic impairment dose should not to exceed 8 mg/day, Common side effects of ondansetron include: headache, malaise, fatigue, arrhythmias including supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation, bradycardia, electrocardiographic alterations (including second-degree heart block, QT interval prolongation, and ST segment depression), palpitations. Mechanism of action has not been fully characterized; serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. The released serotonin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex (“Zofran (Ondansetron Hydrochloride Tablets and Solution): Uses, Dosage, Side Effects, Interactions, Warning,” 2017). Ondansetron has been found to cross the placenta during the early stage of pregnancy and can be found in fetal tissue and amniotic fluid. However, Ondansetron does not cause fetal abnormalities. The clearance of ondansetron decreases with age in both pediatric and adult subjects, plasma clearance of ondansetron is significantly reduced in patients with hepatic impairment, leading to an increased AUC and half-life. Metabolism of ondansetron is carried out by multiple liver enzymes, including CYP1A1, CYP1A2, CYP3A and CYP2D6, pertaining drug excretion around 10% of the original dose of ondansetron is excreted unchanged in the urine with a further 34-43% excreted in the urine as metabolites within 24 hours of administration. Pharmacodynamics of Ondansetron as it prevents the binding of serotonin

released from intestinal enterochromaffin cells to 5-HT3 receptors on adjacent vagal afferent nerves. This blockade of 5-HT3 receptors reduces nausea and vomiting by decreasing vagus nerve signaling and the subsequent release of serotonin in the brainstem (Huddart, Altman, & Klein, 2019, p. 96).

1.2.5 Bupivacaine drug

Bupivacaine (trade name: Marcaine spinal 0.5% heavy) is a sterile, hyperbaric solution which is clear, colorless and particle-free, Giving for all ages via the intrathecal route (into subarachnoid) to produce spinal anesthesia for surgeries such urological and lower limb surgery that lasting 2–3 hours and abdominal surgery that lasting 45–60 minutes. Bupivacaine is a long-acting anesthetic agent of the amide type, has a rapid onset of action and long duration, the duration of analgesia in the T10–T12 segments is 2–3 hours. Marcain Heavy produces a moderate muscular relaxation of the lower extremities lasting 2–2.5 hours. The duration of the motor blockade does not exceed the duration of analgesia. There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients. The dose range of 7.5 mg to 10.5 mg (1 mL to 1.4 mL) bupivacaine hydrochloride has been used for Cesarean section under spinal anesthesia. Bupivacaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics,

e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Undesirable effects include hypotension, bradycardia, and post dural puncture headache, nausea, vomiting urinary retention or urinary incontinence. Pharmacodynamic properties of bupivacaine is a long acting local anesthetic agent of the amide type, moderate muscular relaxation of lower extremities, can cause motor blockade of the abdominal muscles, finally, marcain heavy is hyperbaric and its initial spread in the intrathecal space is affected by gravity. Pertaining pharmacokinetic properties it is rapid onset of action and long duration i.e. T10–T12 segments – duration 2–3 hours, muscular relaxation of lower extremities lasts 2–2.5 hours, blockade of the abdominal muscles lasts 45–60 minutes. The duration of motor blockade does not exceed duration of analgesia. In children the pharmacokinetics are similar to that in adults ("Marcain Heavy, 0.5% solution for injection. - Summary of Product Characteristics (SmPC) - (emc)," 2018).

1.2.6 Meperidine drug

Meperidine hydrochloride (trade name: Pethidine) is a narcotic analgesic for the relief of moderate to severe pain, Pethidine is primarily a μ-receptor agonist. Despite its structural dissimilarity to morphine, pethidine shares many similar properties, including antagonism by naloxone. It is extensively metabolized in the liver and the parent drug and metabolites are excreted in the urine. Normeperidine is a pharmacologically active metabolite. It can cause central excitation and, eventually, convulsions, if it

accumulates after prolonged intravenous administration or in renal impairment. Pharmacodynamics: pethidine is a synthetic opioid analgesic similar to morphine although less potent and shorter acting. Its analgesic effect usually lasts for 2 to 4 hours. The analgesic effect occurs after about 10 minutes following parenteral administration. It acts on the CNS system and smooth muscles via the peripheral nervous system. Pethidine causes the release of histamine from mast cells resulting in a number of allergic-type reactions. Like other opioids, pethidine binds to opioid receptors and exerts its principal pharmacological actions on the central nervous system where its analgesic and sedative effects are of particular therapeutic value. Pethidine has atropine-like effects, including dry mouth and blurred vision, regarding the the respiratory depression produced by pethidine can be antagonized by naloxone and nalorphine. Regarding posology, Subcutaneous or intramuscular injection: 25 - 100mg. Intravenous injection: 25 - 50mg. Pharmacokinetic: Pethidine is rapidly absorbed following intramuscular or subcutaneous injection, with a half time of approximately 3 hours, metabolism take place in the liver by hydrolysis, and pethidine is excreted via the urine (70% in 24hrs). Urinary excretion is pH dependent, the lower the pH the greater the clearance. Pethidine crosses the placenta and is excreted in breast milk. Both pethidine and norpethidine cross the blood/brain barrier and are found in the cerebrospinal fluid (“Pethidine Injection BP 50mg/ml - Summary of Product Characteristics (SmPC) - (emc),” 2019).

1.3 Statement of the Problem

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.

1.4 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.

1.5 Aims of the Study

This study was conducted to achieve the following aims:

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 cesarean 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.

1.6 Null Hypotheses

1.6.1 There are no significant differences (at $P < 0.05$) related to the incidence of spinal-anesthesia-induced shivering between the ondansetron and placebo groups in an obstetric population that undergoes elective cesarean section.

1.6.2 There are no significant differences (at $P < 0.05$) related to the incidence of spinal-anesthesia-induced hypotension between the ondansetron and placebo groups in an obstetric population that undergoes elective cesarean section.

1.6.3 There are no significant differences (at $P < 0.05$) related to the incidence of postoperative meperidine use between the ondansetron and placebo groups in an obstetric population that undergoes elective cesarean section.

Chapter 2
Literature Review

2.1 Post-anesthesia Shivering

Shivering can result from thermal deregulation due to surgery and anesthesia. The vasodilatory effect of spinal anesthesia alters the core body temperature and worsens shivering. Ondansetron is one drug that is used to prevent spinal-anesthesia-induced shivering; however, its efficacy is still debated (Li et al., 2016).

2.1.1 Studies that revealed ondansteron is effective in shivering prevention and managment

Tatikonda et al. (2019) conducted a randomized, placebo-controlled trial (RCT) to investigate the effect of intravenous ondansetron (4 mg) on spinal-anesthesia-induced shivering. Of the 140 patients, 17.1% in the control group exhibited shivering while no patients in the ondansetron group presented shivering (P = 0.0001), They concluded that prophylactic ondansetron before spinal anesthesia significantly reduces shivering and the requirement for ephedrine. Varshney et al. (2019) conducted a RCT of 80 parturients to study the role of 0.3 mg ramosetron (another 5-HT3 receptor antagonist) in the reduction of spinal-anesthesia-induced shivering during cesarean sections. This treatment significantly reduced the incidence of shivering and the maximum shivering compared to the control group at all examined time points (P = 0.001). Noaman et al. (2019) carried out a study on 40 patient scheduled for lower abdominal surgery, they studied

the effect of 4 mg ondansetron versus 0.5 mg/kg pethidine for the prevention of postoperative shivering. They concluded that ondansetron is as effective as pethidine for prevention of postoperative shivering. However, postoperative side effects, including nausea and vomiting, were significantly higher in the pethidine group. Badawy and Mokhtar (2017) carried out an RCT for 80 participants underwent C/S, treatment group given 8 mg iv ondansterton vs 4 ml 0.9% saline; the incidences of shivering and total meperidine dose used were lower in the ondansetron compared to the saline group. Nallam, Cherukuru, and Sateesh (2017) carried out an RCT for 80 participants underwent C/S, treatment group given 8 mg iv ondansetron IV 4 ml 0.9% saline, 10% of patients who received ondansetron and 42.5% of patients who received saline reported shivering during the preoperative period (P = 0.001). The shivering was treated with intravenous tramadol. The authors concluded that ondansetron is an effective way to prevent shivering and does not alter the Apgar score.

Two meta-analyses have investigated the potential benefit of ondansetron on post-anesthesia shivering. He et al. (2016) used PubMed, Embase, and Cochrane library databases to search for total 8 RCTs containing 905 subjects that investigated the effectiveness and safety of ondansetron in the prevention of spinal-anesthesia-induced shivering. Compared to 0.9% saline, ondansetron significantly reduced spinal-anesthesia-induced shivering (p=0.0001), and there were no differences detected between ondansetron and pethidine in terms of bradycardia risk. Further, ondansetron was associated with a lower hypotension risk. The

researchers concluded that ondansetron can effectively prevent post-anesthesia shivering and reduce the risk of hypotension. Li et al. (2016) conducted a meta-analysis of 12 RCTs containing 1205 subjects to check the efficacy and safety of ondansetron in preventing post-anesthesia shivering; they used PubMed and Embase databases. Compared with 0.9% saline, ondansetron was associated with a significant reduction of post-anesthesia shivering (relative risk 0.33; 95% confidence interval = 0.21–0.51). There was no significant association of ondansetron with bradycardia in comparison to placebo and meperidine.

2.1.2 Studies that revealed ondansteron is not effective for shivering prevention and managment

Several studies have also reported that ondansetron does not affect the incidence of spinal-anesthesia-induced shivering. Shabana et al. (2018) included 100 participants underwent C/S, found that there were no significant differences in shivering incidence between 4mg ondansetron group (96%) and placebo (100%) groups (P = 0.49). Khouly and Meligyin (2016) revealed that there were no significant differences with regard to shivering between ondansetron (0%) and placebo (4%) treatment (P = 0.49). Suresh, Arora, George, and Vinayak (2013) carried out an RCT for 150 participants; they compared the efficacy and safety of butorphanol, ondansetron 1mg/kg, and tramadol for the control of shivering in patients who underwent surgical procedures with spinal anesthesia. The authors concluded that ondansetron was not very effective for the control of

shivering during regional anesthesia compared to butorphanol and tramadol; 70.6% of the patients who received ondansetron had no relief. Further, Browning et al. (2013) carried out an RCT in 118 women underwent C/S, given 8 mg ondansetron before anesthesia induction, revealed a shivering incidence of 41% in the ondansetron group versus 47% in 0.9% saline group ($P = 0.54$). They concluded that during cesarean section, prophylactic ondansetron does not prevent or even decrease shivering intensity. As shown earlier, there is no consensus on the efficacy of ondansetron on the reduction of spinal-anesthesia-induced shivering. This inconsistency underscores the significance of the study problem statement.

2.2 Spinal-anesthesia-induced Hypotension

Spinal-anesthesia-induced hypotension is a common problem that occurs in patients subjected to spinal anesthesia. The prevention of hypotension might improve the safety of spinal anesthesia and satisfaction for the patient and anesthesia provider. Hypotension can compromise the maternal and neonatal outcomes—including maternal nausea and vomiting and fetal acidosis and cardiovascular collapse—if it is not treated (Limongi & Lins, 2011). Many techniques have been researched and utilized to reduce the occurrence of hypotension: lower extremity elevation, intravenous fluids, and vasopressor drugs. Nevertheless, no single intervention has been deemed entirely successful. The latest research

suggests that ondansetron, a well-known antiemetic drug, has preventative effects on spinal-anesthesia-induced hypotension.

2.2.1 Studies that revealed ondansteron is effective for spinal-anesthesia-induced hypotension prevention

Tatikonda et al. (2019) conducted RCT studt of 140 particpants, treatment group given 4 mg vs 0.9% saline group, they concluded that prophylactic use of ondansetron before spinal anesthesia significantly reduces the requirement of ephedrine. Boyd (2018) examined the literature (CINAHL and PubMed databases) to determine the usefulness of administering intravenous ondansetron prior to spinal anesthesia. While more uniform research should be performed on this topic, the author recommend that intravenous 4 mg ondansetron should be used as an additional tool to help prevent spinal-induced hypotension and minimize adverse outcomes associated with hypotension resulting from spinal anesthesia. Shabana et al. (2018) carried out a study in 100 women underwent elective C/S, given 4 mg ondansetron before anesthesia induction, reported a significantly lower hypotension incidence after ondansetron administration (30%) compared to the control group (70%). Further, ondansetron significantly decreased heart rate (HR) fluctuation and the required vasopressor doses. Badawy and Mokhtar (2017) carried out an RCT in 80 women underwent C/S, given 8 mg ondansetron before anesthesia induction, concluded that ondansetron (8 mg) lowers the incidence of post-spinal hypotension compared to the placebo group.

Khouly and Meligyin (2016, Egypt) conducted an RCT in 100 subjects underwent elective cesarean deliveries; they concluded that prophylactic intravenous ondansetron significantly reduces hypotension and HR fluctuations in patients who undergo elective cesarean deliveries under spinal anesthesia.

Gao et al. (2015) conducted a meta-analysis about the effects of prophylactic ondansetron on spinal-anesthesia-induced hypotension by searching Medline, Embase, and Cochrane Library databases, as well as www.clinicaltrials.gov. 10 RCT consist of 863 participants, they concluded that the incidence of spinal-anesthesia-induced hypotension and vasopressor consumption are reduced when prophylactic ondansetron is used in obstetric and non-obstetric patients. Other complications, including bradycardia, nausea, and vomiting, are also reduced.

2.2.1 Studies revealed ondansteron is not effective for spinal-anesthesia-induced hypotension prevention

Choudhary et al. (2019) conducted a study to evaluate the effects of two 5HT3 receptor antagonists, namely granisetron and palonosetron, on hemodynamics in 126 participants undergoing abdominal hysterectomy. The researchers concluded that administration of granisetron and palonosetron before intrathecal bupivacaine does not attenuate the hemodynamic changes in patients undergoing spinal anesthesia. Oofuvong et al. (2018) performed an RCT in 228 participants undergoing C/S, and concluded that 0.05 or 0.1 mg/kg ondansetron administered before spinal

anesthesia did not reduce the incidence of hypotension. Karacaer et al. (2018) carried out RCT in 108 parturient undergoing elective cesarean delivery, found that 8 mg of prophylactic intravenous ondansetron prior to spinal anesthesia attenuates but does not prevent hypotension in parturients undergoing elective cesarean sections with spinal anesthesia. Further, Terkawi et al. (2016) evaluated the efficacy of ondansetron on spinal induced hypotension. There were no significant differences in the incidence of hypotension between the ondansetron (62%) and 0.9% saline group (61%). Ortiz-Gomez et al. (2014) conducted a RCT in 128 elective C/S, and reported no differences in the number of patients with hypotension in the placebo (43.8%) or 2 mg (53.1%), 4 mg (56.3%), or 8 mg (53.1%) ondansetron groups (P = 0.77). Further, the ephedrine and phenylephrine requirement and the number of patients with adverse effects did not differ among the study groups. The researchers concluded that prophylactic ondansetron has little effect on the incidence of hypotension in healthy parturients who undergo spinal anesthesia with bupivacaine and fentanyl for elective cesarean delivery. Overall, larger studies are required to determine the exact effects of ondansetron in obstetric population

Chapter Three
Methodology

3.1 Study design

The study was conducted as 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.

3.2 Study Site and Setting

This study was conducted at Rafidia Governmental Surgical Hospital (Nablus, Palestine), specifically in cesarean section operation rooms.

3.3 Population

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

3.4 Inclusion criteria and exclusion criteria

Table (1): Inclusion criteria and exclusion criteria

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

3.5 Study variables

3.5.1 Dependent variables

- Spinal-anesthesia-induced shivering.
- Spinal-anesthesia-induced hypotension.

3.5.2 Independent Variables

- Spinal anesthesia.

3.6 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 cesarean 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.

3.7 Pre-enrollment assessment

All recruited participants underwent a complete blood count (CBC) in order to exclude any participants with low hemoglobin or platelet levels (< 100,000 platelet/mm^3). Patients with a low platelet count have an increased risk for bleeding disorders and developing epidural hematomas; spinal anesthesia is contraindicated in those patients.

3.8 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 anesthesiologist assigned for drug administration and both anesthesiologists not involved in data collection procedure.

Table (2): The computerized randomization list

N	Group	N	Group	N	Group	N	Group	N	Group	N	Group	N	Group	N	Group
1	Control	**11**	Ondansetron	**21**	Ondansetron	**31**	Control	**41**	Control	**51**	Ondansetron	**61**	Control	**71**	Control
2	Ondansetron	**12**	Control	**22**	Control	**32**	Ondansetron	**42**	Ondansetron	**52**	Control	**62**	Ondansetron	**72**	Ondansetron
3	Ondansetron	**13**	Control	**23**	Control	**33**	Ondansetron	**43**	Control	**53**	Control	**63**	Ondansetron	**73**	Ondansetron
4	Control	**14**	Ondansetron	**24**	Ondansetron	**34**	Control	**44**	Ondansetron	**54**	Ondansetron	**64**	Control	**74**	Control
5	Ondansetron	**15**	Control	**25**	Control	**35**	Control	**45**	Ondansetron	**55**	Control	**65**	Ondansetron	**75**	Ondansetron
6	Control	**16**	Ondansetron	**26**	Ondansetron	**36**	Ondansetron	**46**	Control	**56**	Ondansetron	**66**	Control	**76**	Control
7	Ondansetron	**17**	Control	**27**	Control	**37**	Ondansetron	**47**	Control	**57**	Ondansetron	**67**	Ondansetron	**77**	Ondansetron
8	Control	**18**	Ondansetron	**28**	Ondansetron	**38**	Control	**48**	Ondansetron	**58**	Control	**68**	Control	**78**	Control
9	Ondansetron	**19**	Control	**29**	Control	**39**	Ondansetron	**49**	Ondansetron	**59**	Control	**69**	Control	**79**	Ondansetron
10	Control	**20**	Ondansetron	**30**	Ondansetron	**40**	Control	**50**	Control	**60**	Ondansetron	**70**	Ondansetron	**80**	Control

3.9 Blinding

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

3.10 Ethical considerations

This study was conducted in adherence to the Declaration of Helsinki Declaration guidelines and with institutional review board (IRB) approval. A Palestinian Ministry of Health facilitation letter allowed data collection from Rafedia Governmental Hospital. Prior to participation, all participants signed a written consent form after the project was thoroughly explained to them.

3.11 Data Collection Procedure

This study was supervised as academic supervision by Dr. Adham Abu Taha (PhD, Pharmacology, An-Najah National University/ College of Medicine and Health Sciences) and clinically by Dr. Nouraldeen Almasri (Anesthesiologist at Rafedia Governmental Hospital). Observations and hemodynamic parameters were measured preoperatively (baseline), intraoperatively, and postoperatively. For both groups, the study observations and hemodynamic parameters were recorded every 3 min until the end of the operation and every 5 min (for 15 min total) in the post-anesthesia care unit (PACU) which is total time the participant stay in PACU at the Rafedia hospital. These observations included systolic blood

pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), peripheral capillary oxygen concentration (SpO_2), and Axillary temperature (T). Intraoperative and postoperative shivering incidence and severity, hypotension incidence, nausea and vomiting incidence and severity, incidence of meperidine use 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 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 measured using the 0-5 numeric rating scale (NRS), where 0= none, 1= anticipated, 2= mild, 3= moderate, 4= great, 5= sever, 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.

A positive shivering sign and low-grade shivering were annoying for the participants and managed with intravenous 0.5 mg/kg meperidine.

3.11.1 Data collection procedure: Anesthesia 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 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 provided until the

end of delivery. Vital signs changes and adverse spinal anesthesia effects were recorded periodically as prescribed above.

3.12 Data Collection plan

Vital sign observations were recorded on data collection sheets; they included: blood pressure, heart rate, SpO_2%, temperature, ECG, and RR, measured every 3 min during surgery until its end and every 5 min (for 15 min total) in the PACU. Other variables recorded were: shivering, hypertension, nausea, vomiting, headache, pain severity on 0-10 NRS, time from spinal blockade until fetal extraction, and dosage of rescue drugs for hypotension and shivering management, if used.

3.13 Data Analysis

The data were analyzed 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, non-parametric 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 analyzed with Chi-square tests have been used. A P value $\leq$ 0.05 was considered to indicate a statistically significant difference.

Chapter Four
Results

Consort diagram (Fig. 1) presents a flow chart of the screening and allocation of the patients. 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. There were no differences in demographic data between the groups ($p > 0.05$; Table 6).

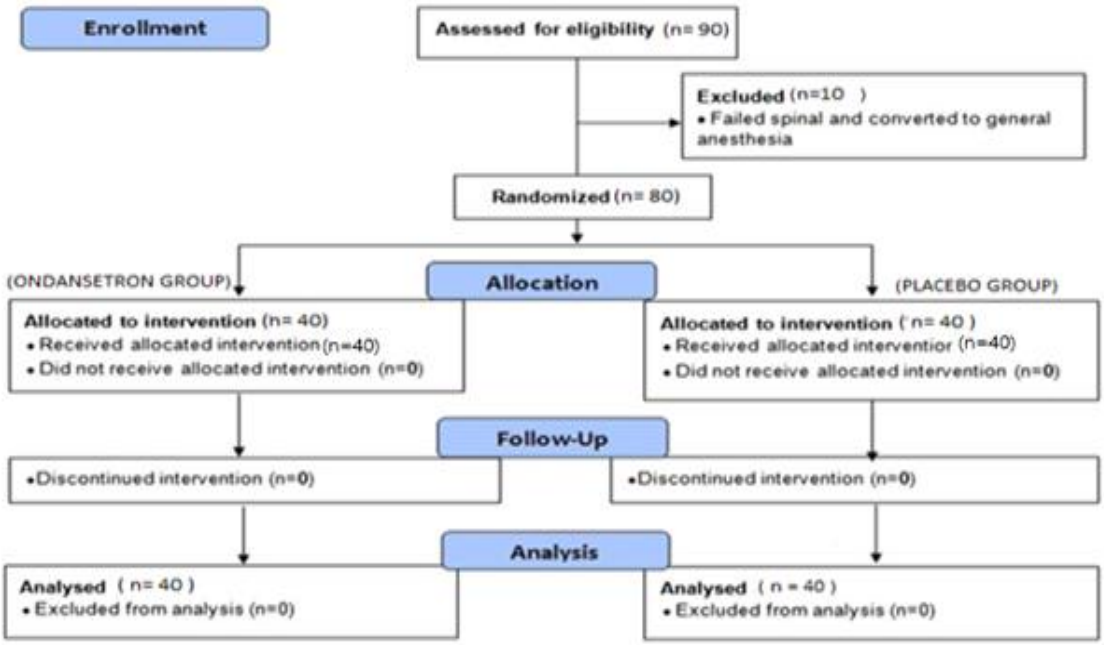

Fig. 1: Consort diagram of patient screening and allocation

Table (3): 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

4.1 Hemodynamic Measurements

4.1.1 SBP

4.1.1.1 Intraoperative SBP

Table (4): Intraoperative Systolic Blood Pressure (SBP)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	121 [119-122]	36.68	121 [120-123]	44.33	0.134
Induction	101 [90-115]	31.11	122 [109-129]	49.89	< 0.001*
3 minute	100 [88 -114]	29.91	118 [110-130]	51.09	< 0.001*
6 minute	111 [103-118]	29.84	122 [113-130]	51.16	< 0.001*
9 minute	117 [111-120]	33.39	120 [114-130]	47.61	0.006 *
12 minute	118 [114 -121]	35.74	120 [116-128]	45.26	0.066
15 minute	120 [116-122]	33.30	121 [121-124]	47.70	0.005 *

SBP hypotension is defined as lower than 100 mmHg (Miller, 2010, p. 2222). At baseline, there were no significant differences in SBP between the groups ($P = 0.134$). Upon spinal anesthesia induction, the control group presented a significant drop in the median SBP, from 121 to 101 mmHg. Further, the lowest reading (100 mmHg) occurred 3 min post-induction. Comparatively, there was SBP stability in the ondansetron group during the

overall intraoperative period (from induction to 15 min). The lowest reading was 118 mmHg at 3 min post-induction. There were significant differences in SBP between the groups at induction, 3 and 6 min (for both $P < 0.001$), 9 ($P = 0.006$), and 15 min ($P = 0.005$) post-induction (Table 7).

4.1.1.2 Postoperative SBP

During the postoperative period, the control group showed a slight drop in the SBP. The lowest median SBP was 116 mmHg at 5 min post-surgery. On the other hand, the ondansetron group showed obvious stability in the SBP during the entire postoperative period. There were significant differences in SBP between the groups at the 1 ($P = 0.032$), 5 ($P = 0.022$), and 15 ($P = 0.010$) min post-surgery (Table 8).

Table (5): Postoperative Systolic Blood Pressure (SBP)

Time	**Control Group**		**Ondansetron Group**		***P* value**
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	118 [111-120]	34.94	121 [112-129]	46.06	0.032*
5 Minute PACU	116 [111-120]	34.55	121 [112 -128]	46.45	0.022*
15 Minute PACU	119 [113 -121]	33.83	122 [115-129]	47.18	0.010*

4.1.2 DBP

4.1.2.1 Intraoperative DBP

A normal DBP range is less than 80 mmHg, and hypotension is defined as a DBP less than 60 mmHg. The baseline DBP was not significantly different between the groups (P = 0.885). At induction, the control group showed a significant drop in the median DBP from 67 to 60 mmHg; the lowest reading (58 mmHg) occurred 3 min post-induction, and it reached 62 mmHg at 6 min post-induction. In the ondansetron group, the DBP was stable during the overall intraoperative period (from induction to 15 min). The lowest DBP was 66 mmHg at induction and 3 and 6 min post-induction. There were significant differences in DBP between the groups at induction (P < 0.091) and 3 (P = 0.001) and 6 min (P = 0.031) post-induction (Table 9).

Table (6): Intraoperative Diastolic Blood Pressure (DBP)

Time	Control Group		Ondansetron Group		P value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	67 [62- 80]	40.88	71 [61 -81]	40.13	0.885
Induction	60 [55 - 63]	34.44	66 [57 -72]	46.56	0.019*
3 Minute	58 [55- 61]	32.0	66 [56 - 74]	49.0	0.001*
6 Minute	62 [60 -65]	34.93	66 [60- 71]	46.08	0.031*
9 Minute	67 [60 -75]	39.86	70 [62 -75]	41.14	0.806
12 Minute	70 [61 -80]	40.13	71 [63 -80]	40.88	0.885
15 Minute	76 [66 -80]	40.21	76 [66 -80]	40.79	0.912

4.1.2.2 Postoperative DBP

During the entire postoperative period, both groups maintained a steady DBP. The lowest median DBP in both groups was 66 mmHg. There were no significant differences in DBP between the groups during the overall postoperative period (*P* > 0.05; Table 10).

Table (7): Postoperative Diastolic Blood Pressure (DBP)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	66 [61- 78]	44.06	66 [58 -74]	36.94	0.170
5 Minute PACU	66 [60 - 78]	40.86	67 [61 -74]	40.14	0.889
15 Minute PACU	68 [61- 77]	40.88	67 [61 - 77]	40.13	0.885

4.1.3 MAP

4.1.3.1 Intraoperative MAP

A normal MAP is 60–100 mmHg. At baseline, there were no significant differences between the groups with regard to MAP (*P* = 0.053). At induction, there was a significant drop in the median MAP of the control group (from 80 to 70 mmHg). The lowest reading was 69 mmHg at 3 min post-induction, and it remained low at the 6 and 9 min time points. On the other hand, the ondansetron group MAP was higher at all time points. The lowest reading was 81 mmHg at induction. Overall, there were significant differences in MAP between the groups during the entire intraoperative period (from induction to 15 min; p < 0.005; Table 11).

Table (8): Intraoperative Mean Arterial Pressure (MAP)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	80 [78 -81]	35.51	81 [79-84]	45.49	0.053
Induction	70 [67-80]	31.78	81 [74-88]	49.23	0.001*
3 Minute	69 [67 -77]	30.33	85 [73 -90]	50.68	< 0.001*
6 Minute	77 [72 - 80]	29.50	85 [78 - 88]	51.50	< 0.001*
9 Minute	78 [75 -80]	31.21	84 [77 -91]	49.79	< 0.001*
12 Minute	80[78 -81]	33.14	82 [79 -89]	47.86	0.004*
15 Minute	80 [78 -81]	32.83	82 [79 -88]	48.18	0.003*

4.1.3.2 Postoperative MAP

During the postoperative period, the control median MAP dropped slightly, with the lowest value of 77 mmHg at 15 min post-surgery. The ondansetron group showed higher MAP values at all time points; the lowest median MAP was 81 mmHg at 15 min post-surgery. Overall, there were significant differences in MAP during the entire postoperative period (*P* > 0.005; Table 12).

Table (9): Postoperative Mean Arterial Pressure (MAP)

Time	Control Group		Ondansetron Group		P value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	78 [75 -81]	31.93	82 [87-89]	49.08	0.001*
5 Minute PACU	78 [74-80]	31.09	85 [78-89]	49.91	< 0.001*
15 Minute PACU	77 [74 -80]	30.10	81 [79 -89]	50.90	< 0.001*

4.1.4 HR

4.1.4.1 Intraoperative HR

A normal HR is 60–100 beats per minute (bpm). The baseline HR was not different between the groups (P = 0.062). Upon induction, HR slightly decreased in the control group: The control group median HR dropped from 81 to 77 bpm and the ondansetron group dropped from 81 to 80 bpm (P =0.171). The lowest median HR for the control group was 73 bpm at 3 min post-induction, and it remained reduced at the 6, 9, 12, and 15 min time points. On the other hand, the ondansetron group showed obvious stability on the HR during the entire intraoperative period (from induction to 15 min), with the lowest value (80 mmHg) at induction time. Overall, there were significant differences in HR between the groups at 3, 6, 9, 12, and 15 min post-induction (P < 0.005; Table 13).

Table (10): Intraoperative Heart Rate (HR)

Time	Control Group		Ondansetron Group		P value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	81[75-90]	39.23	81[78 -90]	41.78	0.622
Induction	77[71-82]	36.95	80[75-89]	44.05	0.171
3 Minute	73[70 - 81]	33.00	80[75- 88]	48.00	0.004*
6 Minute	75[72- 80]	33.03	80[75 - 87]	47.98	0.004*
9 Minute	78[70 -81]	33.61	81[78 -88]	47.39	0.008*
12 Minute	77[69 -81]	32.15	80[78 -86]	48.85	0.001*
15 Minute	77[69-82]	34.85	81[78 -87]	46.15	0.029*

4.1.4.2 Postoperative HR

During the postoperative period, the control group HR dropped slightly, with the lowest median HR (78 bpm) at 5 min post-induction. On the other hand, the ondansetron group showed HR stability during the postoperative period; the lowest median HR was 81 bpm. Overall, there were significant differences in HR at 5 and 15 min post-surgery ($P \leq 0.05$; Table 14).

Table (11): Postoperative Heart Rate (HR)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	80 [76-84]	38.24	81 [78 -89]	42.76	0.381
5 Minute PACU	78 [72-82]	34.58	81 [78-87]	46.43	0.022*
15 Minute PACU	80 [72 - 82]	35.43	81 [78- 88]	45.58	0.05*

4.1.5 RR

4.1.5.1 Intraoperative RR

A normal RR is 12–20 breathes per minute (bpm). At baseline, the RR was not different between the groups ($P = 0.085$). Both groups presented a steady RR during the entire intraoperative period, with the lowest RR of 15 bpm. Overall, there were no significant differences in RR between the groups at any time ($P > 0.05$; Table 15).

Table (12): Intraoperative Respiratory Rate (RR)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	18 [15 - 19]	41.13	18 [15 -20]	39.88	0.805
Induction	16 [14- 18]	37.03	18 [14 - 19]	43.98	0.176
3 Minute	16 [14 - 18]	37.03	17 [14 - 19]	43.98	0.178
6 Minute	16 [13 -19]	36.99	18 [14 -19]	44.01	0.174
9 Minute	15 [12 -18]	36.95	18 [14 -19]	44.05	0.168
12 Minute	15 [12 -18]	36.31	17 [14 -19]	44.69	0.104
15 Minute	15 [12 -18]	37.90	15 [14 -18]	43.10	0.313

4.1.5.2 Postoperative RR

The control group showed a slight decline in RR during the postoperative period; the lowest RR was 15 bpm. Comparatively, the ondansetron group showed no decline in RR. Overall, there was only a significant difference between the groups at 15 min post-surgery (p= 0.003; Table 16).

Table (13): Postoperative Respiratory Rate (RR)

Time	Control Group		Ondansetron Group		***P* value**
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	18 [14 - 19]	38.44	18 [14 -20]	42.56	0.413
5 Minute PACU	18 [14- 18]	36.95	18 [15 - 19]	44.05	0.165
15 Minute PACU	15 [14 - 18]	32.80	18 [16 - 19]	48.20	0.003*

4.1.6 SpO_2%

4.1.6.1 Intraoperative SpO_2%

A normal SpO2% is 96–99%. At baseline, there were no significant differences in SpO_2% between the groups (P = 0.25). Both groups showed a steady SpO_2% during the intraoperative period. In control patients, the lowest SpO_2% was 98%, while in the ondansetron group it was 99%. There were significant differences in SpO2% at the induction and 6 min post-induction (P < 0.05; Table 17).

Table (14): Intraoperative Peripheral Capillary Oxygen Saturation (SpO2%)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	100 [99 -100]	38.43	100 [100 - 100]	42.58	0.250
Induction	98 [98 -99]	35.70	99 [98 -99]	45.30	0.050*
3 Minute	99 [98- 99]	38.20	99 [99 - 99]	42.80	0.330
6 Minute	99 [98 -99]	35.60	99 [99 -99]	45.40	0.038*
9 Minute	99 [98 -100]	35.86	99 [99 -100]	45.14	0.055
12 Minute	99 [98-99]	37.39	99 [99 -99]	43.61	0.196
15 Minute	99 [98 -99]	39.35	99 [99 -99]	41.65	0.624

4.1.6.2 Postoperative SpO_2%

During the postoperative period, the control group showed a slight decline in SpO_2%, with the lowest reading of 98%. In the ondansetron group, the lowest SpO_2% was 99%. Overall, there were significant differences between the groups during the entire postoperative period *(*P < 0.05; Table 18).

Table (15): Postoperative Peripheral Capillary Oxygen Saturation (SpO2%)

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	98 [98 -99]	30.45	99 [99 - 100]	50.55	< 0.001*
5 Minute PACU	98 [97 -99]	31.49	99 [98 -100]	49.51	< 0.001*
15 Minute PACU	99 [98- 99]	34.93	99 [99 - 100]	46.08	0.022*

4.1.7 Temperature

4.1.7.1 Intraoperative Temperature

The normal temperature range is 36.4–37.5°C (measured axillary). The baseline temperature was not significantly different between the groups (P = 0.20). The control group showed a continuous decrease in temperature during the intraoperative period, with the lowest value (36°C) at 15 min post-induction. In the ondansetron group, the temperature remained steady, with the lowest temperature (36.7°C) at 15 min post-induction. There were significant differences in temperature between the groups during the entire intraoperative period ($P < 0.05$), except at 9 and 12 min post-induction (Table 19).

Table (16): Intraoperative Temperature

Time	Control Group		Ondansetron Group		*P* value
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
Baseline	36.9 [36.8 - 37.1]	37.21	37 [36.8-37.1]	43.79	0.200
Induction	36.8 [36.6 -37.1]	35.38	37 [36.8 - 37.1]	45.63	0.047*
3 Minute	36.5 [35.8- 37.1]	34.85	36.9 [36.7-37.1]	46.15	0.029*
6 Minute	36.3 [35.6 -37.1]	34.75	36.9 [36.6-37.1]	46.25	0.026*
9 Minute	36.5 [35.4 -37.2]	35.83	36.9 [36.8-37.1]	45.18	0.071
12 Minute	36.5 [35.6 -37.2]	36.28	36.9 [36.8-37.2]	44.73	0.103
15 Minute	36 [35.4 -37.1]	34.88	36.7 [36.7-37.1]	46.13	0.030*

4.1.7.2 Postoperative Temperature

During the postoperative period, the control group temperature declined slightly, with the lowest reading at 36.2°C. Comparatively, the ondansetron group temperature was steady at 36.9°C during the entire postoperative period. There were significant differences between the groups at all postoperative time points ($P < 0.05$; Table 20).

Table (17): Postoperative Temperature

Time	Control Group		Ondansetron Grou		***P* value**
	Median [Q1-Q3]	Mean rank	Median [Q1-Q3]	Mean rank	
1 Minute PACU	36.4 [35.8 - 37.0]	33.05	36.9 [36.8-37.1]	47.95	0.004*
5 Minute PACU	36.2 [35.6 - 37.1]	33.35	36.9 [36.7 -37.1]	47.65	0.006*
15 Minute PACU	36.5 [35.6- 37.1]	33.85	36.9 [36.7- 37.2]	47.15	0.010*

4.2 Complications

4.2.1 Bradycardia

4.2.1.1 Intraoperative Bradycardia

In control group 3 cases out of 40 (7.5% of participants) were complicated by intraoperative bradycardia, while there was no (0/40) bradycardia in the ondansetron group. However, there were no significant differences between the groups ($P = 0.241$; Table 21).

4.2.1.2 Postoperative Bradycardia

There were no cases complicated with bradycardia during the postoperative period, and thus there was no difference between the groups *(*$P > 0.999$; Table 22).

4.2.2 Hypotension

4.2.2.1 Intraoperative hypotension

There was 25 cases out of 40 (62.5%) in the control group were complicated with intraoperative hypotension, while only 9 out of 40 cases (22.5 %) complicated with hypotension in the ondansetron group. There was a significant difference between the groups ($P < 0.001$; Table 21), [relative risk (RR) = 0.36, 95% confidence interval (CI) = 0.193 to 0.671) and NNT (Benefit) = 2.5].

4.2.2.2 Postoperative hypotension

During the postoperative period, 6/40 control cases (15%) and 3 / 40 ondansetron cases (7.5%) were complicated with hypotension. There was no significant differences between the groups (P = 0.481; Table 22), that not significant differences explained by the given intravenous fluids intraoperatively to treat induced hypotension, for that all participant postoperatively did not have significant difference regard hypotension incidence.

4.2.3 Headache

4.2.3.1 Intraoperative headache

During the intraoperative period, 11 out of 40 control cases (27.5%) and 5 out of 40 ondansetron cases (12.5%) were complicated with headache. There was no difference between the groups (P = 0.094; Table 21).

4.2.3.2 Postoperative headache

During the postoperative period, 6 out of 40 cases (15%) in both groups were complicated by headache (P = 1.00; Table 22).

4.2.4 Pain

4.2.4.1 Intraoperative Pain (Incidence and Intensity)

Perioperative pain measured using the numerical pain rating scale (NPRS) which validated via (Ferreira-Valente, Pais-Ribeiro and Jensen, 2011). During the intraoperative period, 17 out of 40 control cases (42.5%) and 10 out of 40 ondansetron cases (25%) were complicated with pain; there was no difference between the groups (P = 0.098; Table 21). There was no difference in pain intensity between the groups (P = 0.107; Table 21). Thus, ondansetron did not affect pain management (incidence or intensity).

4.2.4.2 Postoperative pain (Incidence and Intensity)

During the postoperative period, 8 out of 40 control cases (20%) and 6 out of 40 ondansetron cases (15%) were complicated by pain; there was no difference between the groups (P = 0.556). Pain intensity was not different between the groups, both study groups have pain intensity 0.00 on 0-10 NRS pain scale (P = 0.537; Table 22). Thus, ondansetron did not affect postoperative pain management (incidence and intensity).

4.2.5 Pruritus

4.2.5.1 Intraoperative Pruritus

During the intraoperative, 19 out of 40 control cases (47.5 %) and 11 out of 40 ondansetron cases (27.5%) were complicated with pruritus. There was

no significant difference between the groups (*P* = 0.065; Table 21); hence, ondansetron did not affect intraoperative pruritus management.

4.2.5.2 Postoperative pruritus

During the postoperative period, 5 out of 40 control cases (12.5 %) and 2 out of 40 ondansetron cases (5%) were complicated by pruritus. There was no significant difference between the groups (*P* = 0.432; Table 22); hence, ondansetron did not affect postoperative pruritus management.

4.2.6 Shivering

4.2.6.1 Intraoperative Shivering (Incidence and Intensity)

During the intraoperative period, 13 out of 40 control cases (32.5 %) and only 5 out of 40 ondansetron cases (12.5%) were complicated by shivering (*P* = 0.032). The control group had more intense shivering compared to the ondansetron group (*P* =0.010; Table 21), [relative risk (RR) = 0.384, 95% confidence interval (CI) = 0.151 to 0.978) and NNT (Benefit) = 5]. Thus, ondansetron reduced the intraoperative shivering incidence and intensity.

4.2.6.2 Postoperative Shivering (Incidence and Intensity)

During the postoperative period, 15 out of 40 control cases (37.5 %) and only 5 out of 40 ondansetron cases (12.5%) were complicated by shivering (*P* = 0.010). The control group had more intense postoperative shivering compared to those taking ondansetron (*P* = 0.003; Table 22).

[relative risk (RR) = 0.333, 95% confidence interval (CI) = 0.133 to 0.830) and NNT (Benefit) = 4]. Thus, ondansetron reduced both incidence and intensity of postoperative shivering.

4.2.7 Nausea

4.2.7.1 Intraoperative Nausea (Incidence and Intensity)

During the intraoperative period, 16 out of 40 control cases (40 %) and only 10 out of 40 ondansetron cases (25%) were complicated with nausea (*P* = 0.152). The control group had more intense intraoperative nausea compared to those taking ondansetron (*P* =0.049; Table 21). Ondansetron reduced the intraoperative nausea intensity but not incidence.

4.2.7.2 Postoperative Nausea (Incidence and Intensity)

During the postoperative period, 16 out of 40 control cases (40%) and only 7 out of 40 ondansetron cases (17.5%) were complicated with nausea (*P* = 0.026). The control group had more intense postoperative nausea compared to those taking ondansetron (*P* =0.008; Table 22). Overall, ondansetron reduced the postoperative nausea incidence and intensity.

4.2.8 Vomiting

4.2.8.1 Intraoperative vomiting

During the intraoperative period, 5 out of 40 control cases (12.5 %) and only 1 out of 40 ondansetron cases (2.5 %) were complicated with

vomiting (*P* = 0.201; Table 21). Ondansetron did not prevent intraoperative vomiting.

4.2.8.2 Postoperative vomiting

During the postoperative period, 9 out of 40 control cases (22.5 %) and only 1 out of 40 ondansetron cases (2.5%) presented vomiting (*P* = 0.014; Table 22). Notably, ondansetron effectively prevented postoperative vomiting.

4.2.9 Respiratory Depression

4.2.9.1 Intraoperative Respiratory Depression

During the intraoperative period, 4 out of 40 control cases (10 %) and no ondansetron cases (0%) were complicated with respiratory depression (less than 12 bpm). Nevertheless, there was no significant difference between the groups (*P* = 0.116; Table 21). Thus, ondansetron did not prevent intraoperative respiratory depression.

4.2.9.2 Postoperative Respiratory Depression

During the postoperative respiratory, only 1 out of 40 control cases (2.5%) and no ondansetron cases were complicated with respiratory depression. There was no significant difference between the groups (*P* = 0.317; Table 22), and thus ondansetron did not prevent postoperative respiratory depression.

4.2.10 Dizziness

4.2.10.1 Intraoperative dizziness

There is a significant difference regarding intraoperative dizziness between control group 25/40 case (62.5%) compared to ondansetron group only 9/40 (22.5%), (*P*= < 0.001; Table 21).

4.2.10.2 Postoperative dizziness

There is a significant difference regarding intraoperative dizziness between control group 15/40 case (37.5%) compared to ondansetron group only 2/40 (5%), (*P*= 0.001; Table 22).

4.2.11 Client Satisfaction

After surgery, the patients were asked to rate their satisfaction on a 4-point Likert scale. The median satisfaction in the control group was 3 (“satisfied”), while the median satisfaction in the ondansetron group was 4 (“very satisfied”). This result indicates higher satisfaction and better comfort felt by participants in ondansetron group throughout the cesarean section surgery (Table 22).

Table (18): Intraoperative complications

Variable		Total n (%)	Ondansetron n (%)	Control n (%)	
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 (19): 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 :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 liker scale	4.0 [3.0 - 4.0]		3.0 [1.25-4.0]		<0.001*

Chapter 5
Discussion

Spinal anesthesia is often used in cesarean section deliveries due to its rapid onset, definitive motor and sensory blockade, and low risk of local anesthetic systemic toxicity, as well as diverse benefits for both mothers and their developing infants (Smith, Clark & Watson, 1999). It is considered safe and efficient for a wide range of operative procedures, but it is not free of risks (Ghani et al., 2015). Spinal-anesthesia-induced shivering and hypotension are frequent complications during the intraoperative and postoperative periods, 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 uteroplacental perfusion reduction, impairment of fetal perfusion and gas exchange, fetal acidemia, serious maternal complications (reduced cardiac output and in turn diminished cerebral perfusion; Limongi & Lins, 2011), altered level of consciousness, and nausea and vomiting (Lee, George, & Habib, 2017).

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 1). Numerous hemodynamic parameters and other observations were recorded every 3 min during the intraoperative period and every 5 min in the PACU.

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

Some studies showed ondansetron has anti-shivering effect following both general and spinal anesthesia (Tie et al., 2014). It has a potential advantage in the obstetric anesthesia, because of its very low incidence of sedation, hypotension, bradycardia, or risk to the neonate, The mechanism of action of Ondansetron as anti-shivering 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 divided into two groups: intravenous onansetron (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 the meperidine

requirement. Moreover, the results are consistent with an Indian study from Nallam et al. (2017) where they carried out an RCT for 80 participants 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, where 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 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 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).

5.2 The Effect of Ondansetron on Spinal-anesthesia-induced Hypotension

Studies suggest that in the presence of decreased blood volume induced by vasodilatory effect of spinal anesthesia, 5-HT (a serotonin receptor) may be an important factor inducing the Bezold Jarisch reflex via 5-HT3 receptors located in intracardiac vagal nerve endings, for that ondansetron as a 5-HT3 receptor antagonist it is hypothesized to have a role to blunt this reflex (Sahoo, SenDasgupta, Goswami, & Hazra, 2012).

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), where intravenous onansetron (4 mg) significantly reduced hypotension and the 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 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-

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 on 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 study groups with regard to SBP, DBP, MAP, and phenylephrine requirements. The incidence of hypotension was 62% for the ondansetron group and 61% for the saline

group (*P* = 1.00). A Spanish RCT conducted to study the efficacy of iv ondansetron on participants hemodynamic during elective caesarean sections 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). Further, 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).

5.3 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 antagonists 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 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 regards 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 al. (2015) suggested that prophylactic ondansetron reduces the incidence of bradycardia.

5.4 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 with regard to 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).

5.5 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.

5.6 Limitations

One of the limitations of this study is the relatively small sample size. A larger sample might allow for a more accurate assessment of bradycardia differences. Further, larger groups size are required to determine the potential effect of ondansetron on the incidence of bradycardia. In the hospital-as-research setting, there is no specified protocol or guideline to standardize and guide operation rooms'

temperature. This deficit may have affected the temperature (use of air conditioning or warming devices and blankets) and created patient-patient and time-time variations. This phenomenon increases the risk for temperature difference biases.

5.7 Recommendations

For clinical practice, it is recommended to administer 4 mg ondansetron intravenously prior to spinal anesthesia induction in clinical areas in our hospital for women who will undergo a cesarean section. This administration should attenuate the incidence of spinal-anesthesia-induced shivering and hypotension. Further, 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 efficiency of ondansetron on the attenuation of spinal-anesthesia-induced shivering and hypotension for women who undergo a cesarean section.

5.8 Conclusions

In the current study, 4 mg ondansetron administration in parturients who underwent elective cesarean sections 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 compared to the control group.

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Appendices

1. Data Collection Sheet

2. Consent Form

3. The Thesis profesional proofreading checkup certifcate

4. IRB acceptance letter

Appendices 1

Data collection Sheet

Data Collection Sheet

AN-NAJAH NATIONAL UNIVERSITY

MASTER OF ANESTHESIOLOGY

RESEARCHER: AHMAD SALAHAT

Group? : Ondansetron / Placebo

Date and time: _____

Participant # ON LIST: ----------

1. Patient profile (Demographic data)	
Age (years)	
Weight (Kg)	
Parity	
Gravida	
Gestational age	
ASA	
History of spinal C/S	

- **Time from spinal blockade –removal of baby : _____ min**

2. Intraoperative hemodynamic						
Time	**BP+(MAP)**	**HR**	**RR**	**SPO_2**	**ECG**	**T°-q15-**
Baseline V/S	/ ( )					
Induction time	/ ( )					
3 min after	/ ( )					
6 min after	/ ( )					
9 min after	/ ( )					
12 min after	/ ( )					
15 min after	/ ( )					
18 min after	/ ( )					
21 min after	/ ( )					
24 min after	/ ( )					
27 min after	/ ( )					
30 min after	/ ( )					

3. Intraoperative Side effect table

Parameter	yes	No	Frequency or value	Required treatment
Bradycardia heart rate <60				
Hypotension SBP <100mm Hg				
Headache				
Pain scale (0-10)				
Pruritus				
Shivering (0-4) *0= no, 1* =piloerection or peripheral *vasoconstriction but no visible* *2* = one muscle, *3 = >2 muscle but not generalized, 4 = generalized*				
Use of IV meperidineto treat PAS				
Nausea				
Vomiting				
Respiratory depression, respiratory rate < 10.				
Dizziness				
Need of intravenous fluids				

PACU v/s	BP+(MAP)	HR	RR	SPO2	ECG	TEMP
1 min	/ ( )					
5 min	/ ( )					
15 min	/ ( )					
20 min	/ ( )					

4. Post-operative Side effect: In PACU

Parameter	Yes	No	Frequency or value	Required treatment
Bradycardia heart rate <60				
Hypotension SBP<100				
Headache				
Pain scale (0-10)				
Pruritus				
Shivering (0-4) *0= no, 1* =pilo-erection or peripheral *vasoconstriction* *2* = one muscle, *3 = >2 muscle but not generalized, 4 = generalized*				
Use of IV meperidineto treat PAS				
Severity of Nausea				
Vomiting				
Respiratory Depression, RR < 10.				
Dizziness				
Satisfaction: liker-type scale (0-4) 0:Very unsatisfied _ 4: Very satisfied				
Need of Post op. intravenous fluids				

Appendices 2

Consent form

نموذج طلب موافقة على المشاركة في بحث علمي

عنوان الدراسة: فعالية دواء الأوندانسيترون على نسبة حدوث هبوط ضغط الدم وحدوث الإرتعاش الملازمان للتخدير النصفي (النخاعي) عند النساء الخاضعات لعمليات الولادة القيصرية الإختيارية.

اسم الباحث الرئيسي: أحمد صلاحات

المشرفين على البحث: د.أدهم ابو طه (مشرفاً اكاديمياً) د. نورالدين المصري (مشرفاً سريرياً).

ملخص البحث: نقوم بهذه الدراسة استيفاءاً لمتطلبات التخرج من برنامج ماجستير تخدير التمريض في جامعة النجاح الوطنية وهي دراسة سريرية لمعرفة فعالية دواء الأوندانسيترون على نسبة حدوث هبوط ضغط الدم والإرتعاش الملازمان للتخدير النصفي (النخاعي) عند النساء الخاضعات لعمليات الولادة القيصرية الأختيارية. وسوف يتم اعطاء النساء الحوامل اللاتي يوافقن على المشاركة بالدراسة دواء الاوندانسيترون وريديا قبل البدأ بالعملية القيصرية ومراقبة فعالية الدواء على نسبة حدوث هبوط ضغط الدم والارتعاش.

معلومات عن العينة المنتقاة والفترة الزمنية المقدرة لاستكمال المقابلة أو الاستبيان:

تم اختيار فئة النساء الخاضعات للعمليات القيصرية الاختيارية لإجراء هذا البحث العلمي عليهم لما فيه من نتائج ايجابية متوقعة على كل من الأم والجنين على حد سواء، وستبدأ الدراسة من لحظة دخول المشاركة لغرفة العمليات وصولا الى غرفة الأفاقة.

المخاطر المتوقعة والخصوصية:

ليست هنالك اي مخاطر للدراسة سواء نفسية ام جسدية. سيتم حفظ خصوصويتك كمشاركة بالدراسة وسوف يتم التكتم على هويتك وسيبقى اسمك طي الكتمان والمكان الوحيد الذي سيتم ذكر اسمك فيه هو نموذج الموافقة على المشاركة في الدراسة. سيتم التعامل مع المعلومات الخاصة بك بطريقة الترميز، لك حق الانسحاب من المشاركة في البحث في اي وقت دون وجود اي تَبِعات قد تأثر ذلك عليك او على الرعاية الطبية التي سوف تتلقينها.

المنافع المتوقعة:

تتطلع هذه الدراسة للوصول الى دراسة علاج يُحد من نسب حدوث هبوط ضغط الدم والارتعاش عند النساء الخاضعات لعمليات الولادة القيصرية الأختيارية التي تجرى تحت تأثير التخدير النصفي النخاعي وسيكون لهذا إنعكاساً ايجابا على صحة الأم والطفل على حد سواء.

طريقة التواصل مع الباحث:

إذا كانت لديك اي سؤال او استسفار عن الدراسةيمكنك التواصل مع الباحث (احمد صلاحات) بكل رحابة وفي اي وقت عن طريق (الهاتف0598557748) أو البريدالإلكتروني (Rn.Salahat@hotmail.com).

توقيع المشاركة في البحث:

لقد حصلت على شرح مفصل عن الدراسة وأهدافها وإجراءاتها، ومنافعها، والمخاطر المحتملة. ولقد فهمت كافة المعلومات التي قدمت لي وتمت الإجابة كل أسئلتي. لذا فأنني أوافق وبمحض ارادتي على ألمشاركة في هذه الدراسة.

الاسم:.....

التوقيع:.....

التاريخ:.....

Appendices 3

The Thesis professional proofreading checkup certificate

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PhD theses, journal papers, books and other professional documents

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26 February 2020

To whom it may concern,

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Document title: Effect of Prophylactic Ondansetron on the Incidence of Spinal-anesthesia-induced Shivering and Hypotension in Elective Cesarean Sections: A Prospective, Randomized, Controlled, Double-Blind Study

Author(s): **Ahmad salahat**

Format: **American English**

Style guide: **APA at http://www.apa.org/pubs/authors/instructions.aspx**

Appendices 4

IRB acceptance letter

An-Najah
National University
Health Faculty of medicine&
Sciences
IRB

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

IRB Approval Letter

Study Title: "Effect of prophylactic ondansetron on the incidence of spinal anesthesia-induced shivering and hypotension in elective cesarean sections"

Submitted By:
Ahmad Salahat

Supervisor:
Dr. Adham Abu Taha, Dr. Nouraldin Almasri

Date Reviewed:
15th April 2019

Date Approved:
21th April 2019

Your Study titled **"Effect of prophylactic ondansetron on the incidence of spinal anesthesia-induced shivering and hypotension in elective cesarean sections"** with archived number (7) April 2019 was reviewed by An-Najah National University IRB committee and was approved on **21th April 2019**

Hasan Fitian, MD
IRB Committee Chairman
An-Najah National University

IRB

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جـامــعة الــنجاح الــوطــنية

كليـــة الدراســات العليـا

فعالية دواء الأوندانسيترون على نسبة حدوث هبوط ضغط الدم وحدوث الإرتعاش الملازمان للتخدير النصفي (النخاعي) عند النساء الخاضعات لعمليات الولادة القيصرية الإختيارية

إعداد

أحمد مطلق صلاحات

إشراف

د. أدهم أبو طه

د. نور الدين المصري

قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في تمريض التخدير، بكلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس- فلسطين.

2020

فعالية دواء الأوندانسيترون على نسبة حدوث هبوط ضغط الدم وحدوث الإرتعاش الملازمان للتخدير النصفي (النخاعي) عند النساء الخاضعات لعمليات الولادة القيصرية الإختيارية

إعداد

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الملخص

الخلفية: التخدير النخاعي هو طريقة التخدير المفضلة لعمليات الولادة القيصرية، لكنه يرتبط بآثار ضارة خطيرة على الأم والجنين، وهذا يشمل: انخفاض ضغط الدم والارتعاش. تشير الدراسات انه قد يكون للسيروتونين دورا في حدوث كل من هبوط ضغط الدم، تباطئ نبضات القلب والإرتجاف. في هذه الدراسة، قمنا بتقييم فعالية دواء الأوندانسيترون، وهو مضاد لمستقبلات السيروتونين، على حدوث الارتعاش، انخفاض ضغط الدم، الغثيان، التقيؤ والمضاعفات الأخرى الناجمة عن التخدير النصفي (النخاعي) في العمليات القيصرية الاختيارية.

الطريقة: هذه الدراسة مزدوجة التعمية، وتم توزيع 80 مشترك بشكل عشوائي في مجموعتين، المجموعة الأولى تلقت جرعة 4 ملغرام من دواء الأوندانسيترون وريدا قبل البدء بالتخدير النصفي، والمجموعة الثانية تلقت 10 مليميترات من المحلول الملحي تركيز 0.9% وريديا قبل البدا بالتخدير النصفي ايضا، تم تسجيل ملاحظات الدراسة والعلامات الحيوية قبل، اثناء وبعد عملية الولادة القيصرية التي اجريت تحت التخدير النصفي، تم التسجيل كل 3 دقائق أثناء العملية الجراحية وكل 5 دقائق لمدة 15 دقيقة في وحدة (العناية ما بعد التخدير).

النتائج: استطاع دواء الأوندانسيترون بفرق إحصائي واضح من تخفيض نسبة حدوث كل من هبوط ضغط الدم خلال وبعد العمليات القيصرية، حدوث وشدة الارتعاش خلال وبعد العمليات القيصرية، تقليل شدة الغثيان خلال العملية، تقليل تكرار وشدة حدوث الغثيان بعد العملية، حدوث التقيؤ بعد العملية، حدوث الدوار خلال وبعد العملية مقارنة مع مجموعة المحلول الملحي.

الخلاصة: يقلل الاستخدام الوقائي لدواء الاوندانسيترون الوريدي بدلالة احصائية واضحة من نسبه حدوث هبوط ضغط الدم، الارتعاش، الدوار، الغثيان والقيء الناجمة لدى النساء الخاضعات للعمليات القيصرية تحت تأثير التخدير النصفي النخاعي.

الكلمات المفتاحية: أوندانسيترون، التخدير النخاعي، العملية القيصرية، انخفاض ضغط الدم، الارتعاش، الغثيان، القيء.