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A Comparative Study of the Effect of Two Different Doses of Ondansetron on the Reduction of Maternal Hemodynamic Changes in Cesarean Section under Spinal Anesthesia

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ABSTRACT

Background and Objective: Hypotension and bradycardia are among the common side effects of spinal anesthesia. The effect of ondansetron on the reduction of hypotension and bradycardia caused by spinal anesthesia has been studied considering its antagonistic effect on the Bezold–Jarisch reflex. The present study was conducted to determine the effectiveness of two different doses of intravenous ondansetron on the reduction of the incidence of hypotension and bradycardia among candidates for elective caesarean section under spinal anesthesia.

Methods: This double-blind clinical trial was conducted in Shahid Beheshti Hospital in Isfahan in 2020 and included 90 patients aged 18 to 45 years in full-term pregnancy who were candidates for elective caesarean section in three groups of 30. 5 minutes before spinal anesthesia, 6 and 8 mg of ondansetron were injected in the first and second groups, respectively, and normal saline was injected in the third group. Vital signs were examined every 15 minutes during surgery and during recovery, and the incidence of hemodynamic disorders, nausea and vomiting was compared between the three groups.

Findings: There was no significant difference between the three groups in terms of demographic and baseline variables, blood pressure (systolic, diastolic and mean arterial pressure), heart rate, ephedrine intake and incidence of hemodynamic disorders. The frequency of nausea during recovery was significantly different between the three groups (p=0.035); 12 people in the ondansetron 6 mg group, 12 people in the ondansetron 8 mg group and 21 people in the control group had nausea during recovery (40%, 40%, and 70%, respectively). The frequency of vomiting in recovery was significantly different between the three groups (p=0.002); 5 people in the ondansetron 6 mg group, 1 person in the ondansetron 8 mg group, and 12 people in the control group experienced vomiting during recovery (16.7%, 3.3%, and 40%, respectively).

Conclusion: The results of this study showed that administration of ondansetron at 6 and 8 mg doses in caesarean section under spinal anesthesia has no significant effect in reducing the incidence of hypotension, bradycardia, and administration of ephedrine and atropine. However, it is associated with a reduction in the incidence of nausea and vomiting in the recovery room (ondansetron 8 mg is more effective than 6 mg).

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Introduction

In addition to general anesthesia, caesarean section can also be performed with spinal anesthesia (1), which despite problems such as bradycardia, hypotension, headache, nausea and vomiting, is more advantageous due to various benefits such as less pain after surgery and prevention of general anesthesia risks (including tubing and aspiration of gastric contents) (1, 2).

Hypotension is the most common complication after spinal anesthesia in cesarean section. Hypotension occurs in one third of non-pregnant patients and in 70-80% of the obstetric population under spinal anesthesia (3). Maternal hypotension is mainly caused by direct sympathectomy at the level of the block, which causes a decrease in systemic vascular resistance and cardiac output, while the decrease in heart rate is secondary to an increase in the activity of the parasympathetic system or baroreceptors and the activation of Bezold–Jarisch reflex (BJR) (4).

In a study by Carpenter et al., the incidence of bradycardia was reported to be 13% (5). In a study by Somboonviboon et al., the occurrence of bradycardia in pregnant patients was reported in 2.5% of cases (6). Animal studies have shown that Serotonin can trigger Bezold–Jarisch reflex by activating 5HT, which leads to hypotension and bradycardia (6, 7). According to a study on non-pregnant patients by Owczuk et al. and a study by Sahoo et al. on patients undergoing caesarean section, administration of ondansetron before spinal anesthesia reduces hypotension (7, 8).

Other studies also indicate that the BJR is reduced by serotonin antagonists (9, 10). Also, ondansetron improves hypotension by blocking bradycardia caused by serotonin (11). Ondansetron is the first antagonist of HT-3 receptors that is used alone or together with other drugs (12).

Previous studies have shown that ondansetron, primarily an antiemetic, is useful in reducing the incidence of hypotension associated with spinal block in cesarean section. In almost all of these studies, ondansetron was administered 5 minutes before spinal block (13-14).

According to the difference in the results of the effectiveness of ondansetron in previous studies, the present study was conducted to investigate the effect of two different doses of ondansetron on maternal cardiovascular response in cesarean section under spinal anesthesia.

Methods

This prospective randomized double-blind clinical trial was conducted after being approved by the Ethical Committee of Isfahan University of Medical Sciences with the code IR.MUI.MED.REC.1398.446 and registered in the Iranian Registry of Clinical Trials with the code IRCT20191109045371N1. This study was conducted from April to September 2020 on 90 primiparous patients who were candidates for cesarean section in full-term pregnancy (38 weeks or more) referred to Shahid Beheshti Hospital in Isfahan.

Inclusion criteria were 18 to 45 years of age, candidate for elective cesarean section under spinal anesthesia, with class 1 or 2 of the American Society of Anesthesiologists (ASA) and patient consent to participate in the study. Exclusion criteria were women with chronic hypertension or pregnancy-induced hypertension, uncontrolled diabetes, allergy to ondansetron or local anesthetics, prohibition of spinal anesthesia, treated with drugs affecting HT-5 receptors, weight of more than 115 kg and height of less than 152 cm. In case of a change in the anesthesia method (changing to general anesthesia) or surgery (hysterectomy), these were considered as exclusion criteria. The sample size required for the study was estimated to be 30 people in each group using the sample size estimation formula to compare the mean values and 95% confidence level, test power was 80, standard deviation of changes in mean arterial blood pressure during the operation was equal to 1.1 and the minimum significant difference between the groups

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was considered 0.8. In this study, 90 eligible pregnant women were selected and assigned into three groups of 30 people by block randomization method. The method of blinding was such that the patients, the anesthesiologist conducting the study, and the data collector were unaware of the grouping of the patients. The drugs were prepared by an anesthesiologist who was not a member of the research team and based on the categorization of patients, these drugs were provided to the study administrator in syringes with similar appearance and volume. The required information was collected during surgery and during recovery by an observer who was unaware of the drug groups.

Upon entering the operating room, all patients were subjected to electrocardiogram, non-invasive intermittent blood pressure and pulse oximetry monitoring, and hemodynamic variables including heart rate, systolic and diastolic blood pressure, mean arterial pressure and peripheral blood oxygen saturation were measured and recorded as baseline values. Then, the demographic information of the patients, including age, gender, weight and height, was determined and recorded.

For the patients, a green angiocatheter was inserted and 5 ml/kg ringer lactate was infused within 20 minutes. 5 minutes before spinal anesthesia, 6 mg of ondansetron in the patients of the first group, 8 mg of ondansetron (Alborz Pharmaceuticals) in the second group, and normal saline at the same volume were intravenously injected by the study administrator, who was unaware of the contents of the syringes.

The patient was held in a sitting position and after shave prep sterile procedure, underwent spinal anesthesia through injection of 10 mg bupivacaine (ASTRAZENECA, Sweden) in the L3-L4 space with a 25-gauge needle, and the aim was to reach anesthesia up to T4. Then, the patient was placed in a supine position and a pillow was placed under the right side to prevent vena cava syndrome. Sedation in the patients was achieved by 1 mg midazolam plus 25 µg fentanyl. The patient received oxygen at a flow rate of 4 liters per minute through a nasal cannula.

The patient's heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and peripheral blood oxygen saturation were measured and recorded every 15 minutes during surgery for 60 minutes and every 15 minutes during the recovery period for 45 minutes.

In case of any complications, necessary treatment was done and recorded. In case of bradycardia, 0.02 mg/kg atropine was injected, in case of hypotension, serum therapy was administered first, and if no response was observed, ephedrine was injected at a dose of 5 mg. In case of simultaneous occurrence of bradycardia and severe hypotension, 0.02 mg epinephrine (Daru Pakhsh) was injected.

The severity of nausea and vomiting was graded according to the relevant criteria from zero to three. Score 0: absence of nausea and vomiting, score 1: presence of nausea and absence of vomiting, score 2: presence of nausea and vomiting and score 3: occurrence of vomiting more than twice every 30 minutes.

Patients with a score equal to or more than two were injected with intravenous metoclopramide 0.15 mg/kg. Other required information including duration of surgery and length of stay in recovery were determined and recorded.

Finally, the collected data were entered into SPSS software version 23 and analyzed with chi-square statistical tests, one-way analysis of variance and repeated measures ANOVA, and $p<0.05$ was considered significant.

Results

In this study, 90 patients undergoing cesarean section with spinal anesthesia were included in three groups receiving 6 mg ondansetron, 8 mg ondansetron and placebo. During the study period, no patient was excluded from the study due to unwanted complications, and data analysis was performed on 90 patients (Figure 1).

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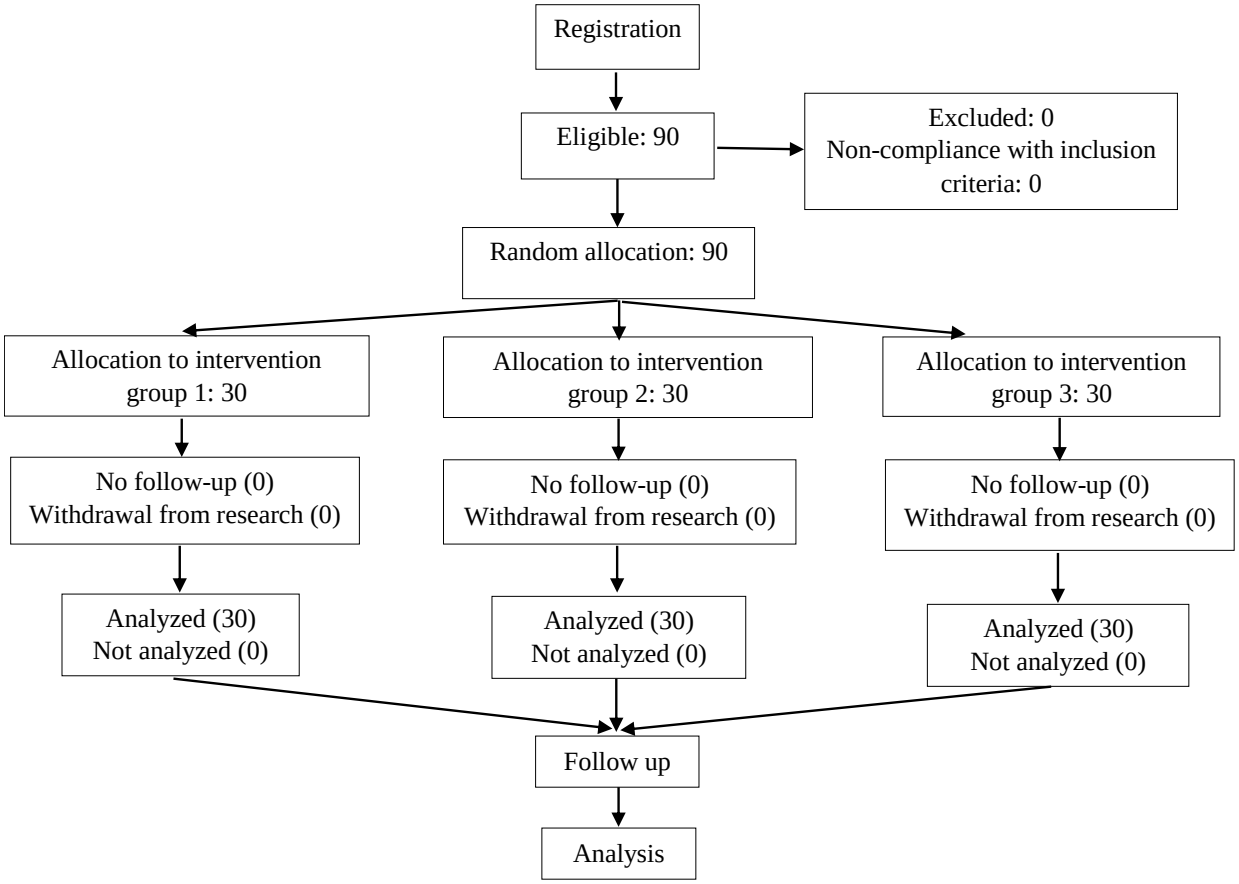

Figure 1. Study procedure algorithm

There was no statistically significant difference between the three groups in terms of mean age, height, weight, BMI, ASA, underlying disease and operation duration (Table 1). There was no significant difference in the mean heart rate and systolic blood pressure before the operation, during the operation and in the recovery between the three groups receiving ondansetron 6 mg, ondansetron 8 mg and placebo. In intra-group studies, heart rate and systolic blood pressure in all three groups showed a significant decrease. Furthermore, in inter-group studies, there was no significant difference in heart rate and systolic blood pressure changes between the three groups (respectively: p=0.51 and p=0.88) (Table 2).

The mean diastolic blood pressure was not significantly different between the three groups at any of the times, but in the intra-group analysis, there was a significant difference in diastolic blood pressure changes in the group receiving 8 mg ondansetron (p=0.013). However, it was not significant in the other two groups. At the same time, in the intergroup analysis, there was no significant difference in diastolic blood pressure changes between the three groups (p=0.62). In the examination of mean arterial pressure, no significant difference was observed between the three groups at any time, but in the intra-group analysis, changes in mean arterial pressure were significant in the 8 mg ondansetron group. However, no significant difference was observed between the three groups in the intergroup analysis (p=0.304).

The percentage of blood oxygen saturation was not significantly different between the three groups at any time, and the intra-group changes were not significant in all three groups. In the intergroup analysis, there was no significant difference in SPO_2 changes between the three groups (p=0.581) (Chart 1).

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Table 1. Distribution of demographic and clinical variables of the three studied groups

Variable	Study groups			p-value
	Ondansetron 6 mg Mean±SD or Number(%)	Ondansetron 8 mg Mean±SD or Number(%)	Normal saline Mean±SD or Number(%)	
Mean age (years)	31.73±4.9	32.57±5.5	30.6±4.9	0.33
Mean weight (kg)	73.1±11.5	77.1±8.3	78.5±9.5	0.092
Mean height (cm)	160.1±6.7	162.2±6.5	163.8±6	0.3
Mean BMI (Kg/m^2)	29.11±3.09	29.22±1.94	29.25±2.83	0.98
ASA 1 2	 22(75.9) 7(24.1)	 15(71.4) 6(286.6)	 19(65.5) 10(34.5)	0.69
Having an underlying disease	9(30)	11(36.7)	4(13.3)	0.11
Mean operation time (minutes)	84.5±24.1	85.5±21.6	87.5 ± 16.8	0.85

ASA= American Society of Anesthesiologists

Table 2. Mean and standard deviation of hemodynamic parameters before and during surgery and recovery in the three groups

Variable and time	Group			p-value[1]
	Ondansetron 6 mg Mean±SD or Number(%)	Ondansetron 8 mg Mean±SD or Number(%)	Normal saline	
Heart rate (per minute)				
before operation	93.5±11.4	94.4±16.8	94.5±12.5	0.42
during operation	94.1±11	88.1±15.7	88.8±10.3	0.324
during recovery	75.4±11.8	78±9	81±9.1	0.24
p-value[2]	<0.001	0.001	<0.001	0.51
Systolic blood pressure (mmHg)				
before operation	126.3±18.3	127.3±17.9	130.5±23.4	0.69
during operation	112.4±13.2	110.9 ± 9	118.8±19.5	0.13
during recovery	112±12.3	114.1±12.1	119.5±12.1	0.061
p-value[2]	<0.001	<0.001	0.002	0.88
Diastolic blood pressure (mmHg)				
before operation	84.4±24.7	78.3±15.3	72.9±18.4	0.092
during operation	66.6±10.9	63.8±8.9	67.9±15.7	0.495
during recovery	70.9±15.1	70.5±10.1	71.3±9.2	0.98
p-value[2]	0.75	0.013	0.053	0.62
Mean arterial pressure (mmHg)				
before operation	95.2±14.3	95.7±20.3	95.3±23.2	0.995
during operation	81.8±10.3	76.7±9.4	87.7±15.4	0.197
during recovery	80.6±7.3	84.8±10.3	87.1±8.5	0.156
p-value[2]	0.056	0.001	0.18	0.304
Arterial oxygen saturation percentage (Spo_2)				
before operation	101.5±13.8	97.6±1.7	96±7	0.22
during operation	97.9±0.98	97.5±1.1	95.3±10.8	0.24
during recovery	97.6±1.24	96.6±1.2	97.3±1.4	0.117
p-value[2]	0.235	0.374	0.165	0.581

p-value[1] (intergroup), p-value[2] (intragroup).

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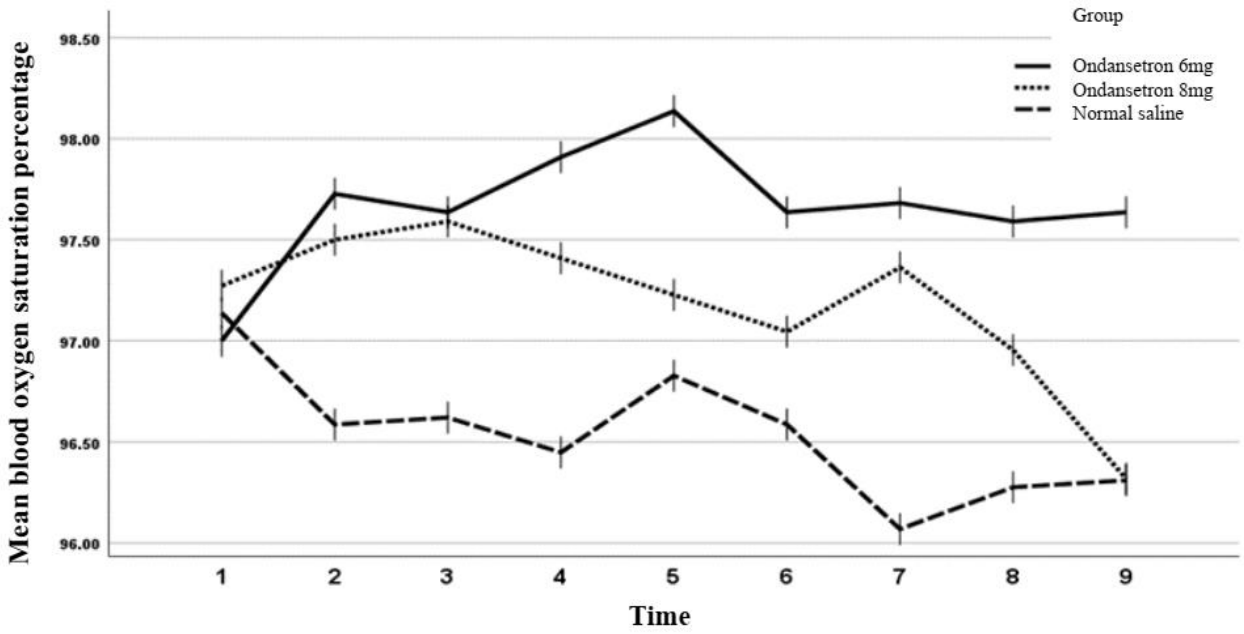

Chart 1. Changes in SPO_2 before surgery and every 15 minutes during surgery and recovery in three groups

There was no significant difference between the three groups in terms of hemodynamic disorder (tachycardia, bradycardia, hypotension and hypertension) (Charts 2-5). During the study, one person (3.3%) from the ondansetron 8 mg group had bradycardia (p=0.99). 6 patients also had tachycardia, 3 of whom were from the ondansetron 6 mg group, 1 from the ondansetron 8 mg group, and 2 from the control group (10%, 3.3%, and 6.7%, respectively) (p=0.87). 5 patients had hypotension: 4 patients (13.3%) were from the ondansetron 8 mg group and 1 patient (3.3%) was from the control group (p=0.12). There were 4 cases of hypertension, of which 2 cases (6.7%) were from the ondansetron 6 mg group and 2 cases (6.7%) were from the ondansetron 8 mg group (p=0.54).

The frequency of nausea during recovery was significantly different between the three groups (p=0.035); 12 people from the ondansetron 6 mg group, 12 people from the ondansetron 8 mg group and 21 people from the control group had nausea during recovery (40 %, 40% and 70%, respectively). The frequency of vomiting in recovery was significantly different between the three groups (p=0.002). 5 people from the ondansetron 6 mg group, 1 person from the ondansetron 8 mg group, and 12 people from the control group experienced vomiting during recovery (16.7%, 3.3%, and 40%, respectively).

4 people (13.3%) from the control group and 1 person (3.3%) from the ondansetron 6 mg group received extra metoclopramide, while in the ondansetron 8 mg group, no patient received an extra dose of antiemetic drug, but the difference was not significant between the three groups.

The mean length of stay in recovery in the three groups of ondansetron 6 mg, ondansetron 8 mg and the control group were 67±14.1, 71.5±17.5, and 72±10.7 minutes, respectively, and no significant difference was seen between the three groups (p=0.34). There was no significant difference between the three groups in terms of the received dose of ephedrine and atropine (Table 3).

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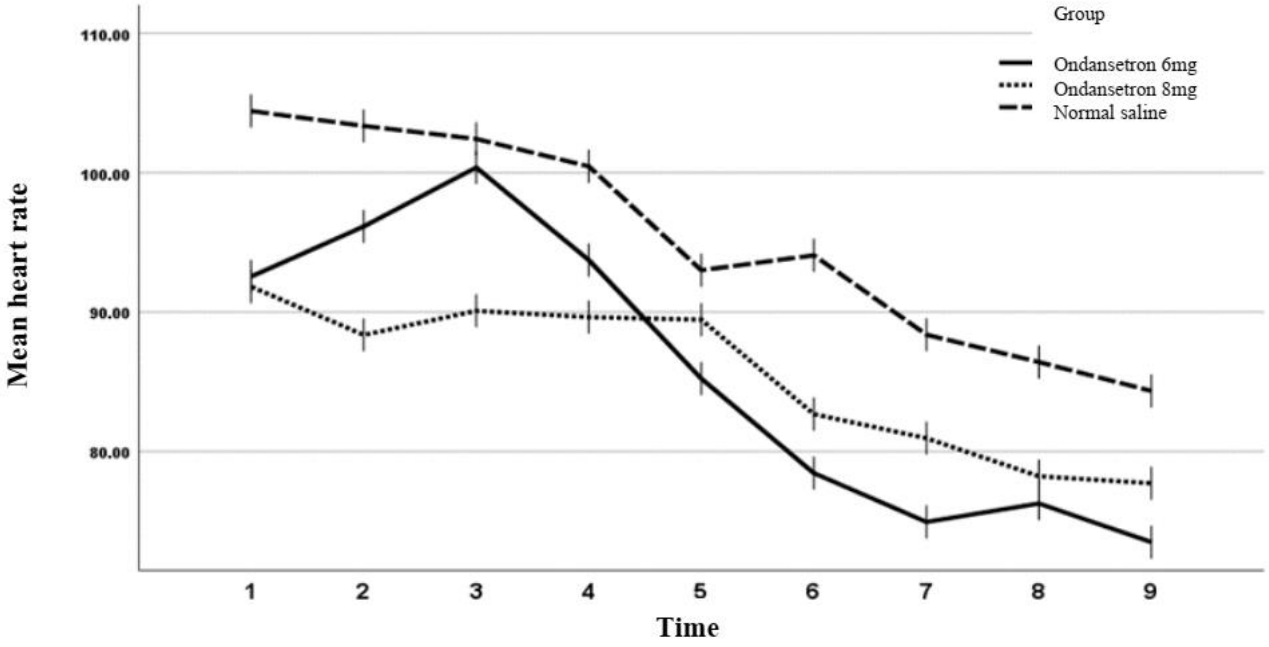

Chart 2. Heart rate changes before surgery and every 15 minutes during surgery and recovery in three groups

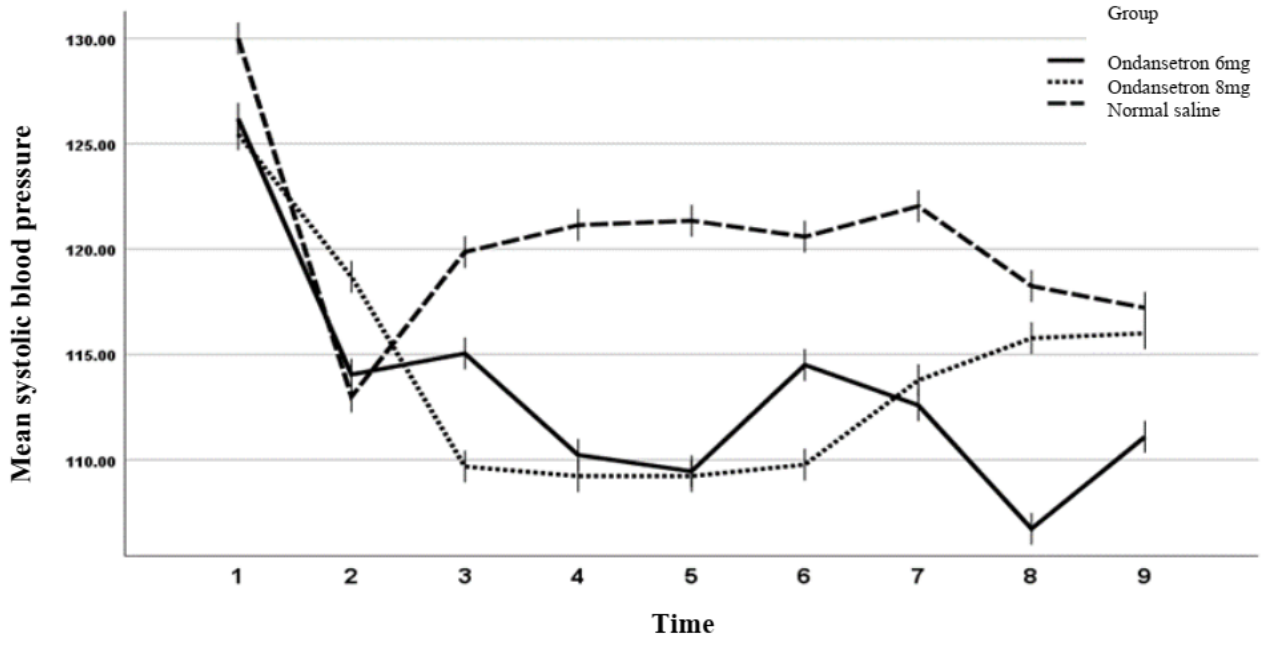

Chart 3. Changes in systolic blood pressure before surgery and every 15 minutes during surgery and recovery in three groups

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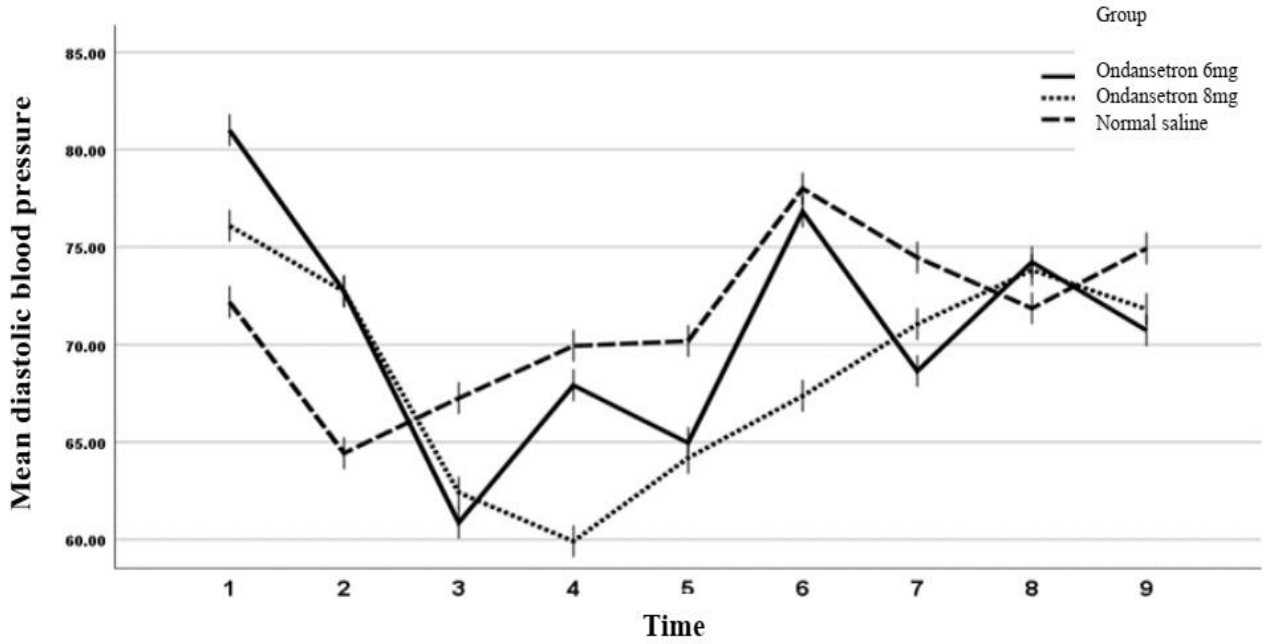

Chart 4. Diastolic blood pressure changes before surgery and every 15 minutes during surgery and recovery in three groups

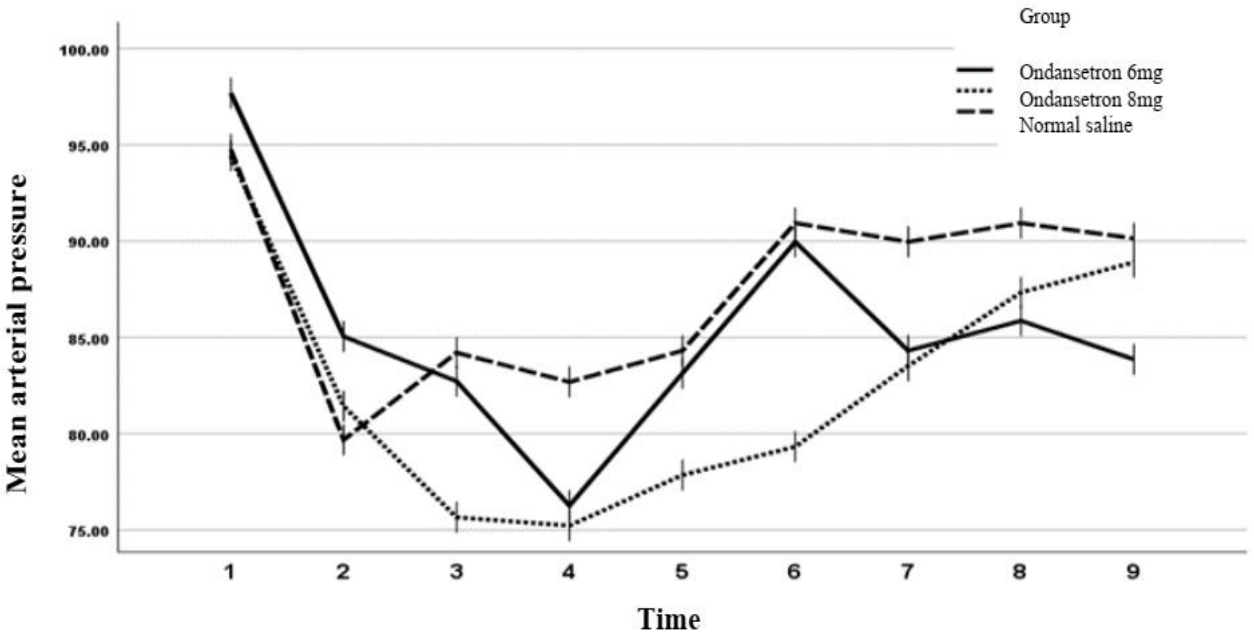

Chart 5. Changes in mean arterial pressure before surgery and every 15 minutes during surgery and recovery in three groups

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Table 3. Frequency distribution of hemodynamic disorder during surgery and complications after surgery and receiving medication in three groups

Variable	Group			p-value*
	Ondansetron 6 mg Mean±SD or Number(%)	Ondansetron 8 mg Mean±SD or Number(%)	Normal saline	
Bradycardia	0(0)	1(3.3)	0(0)	0.99
tachycardia	3(10)	1(3.3)	2(6.7)	0.87
Hypotension	0(0)	4(13.3)	1(3.3)	0.12
Hypertension	2(6.7)	2(6.7)	0(0)	0.54
receiving ephedrine	18(60)	18(60)	22(73.3)	0.49
Dose of ephedrine received (mg)	9.72±4.99	8.89±4.71	9.09±2.94	0.83
nausea	12(40)	12(40)	21(70)	0.035
Vomit	5(16.7)	1(3.3)	12(40)	0.002
receiving metoclopramide	1(3.3)	0(0)	4(13.3)	0.12
Duration of stay in recovery (minutes)	67±14.1	71.5±17.5	72±10.7	0.34
Receiving atropine	4(13.3)	1(3.3)	1(3.3)	0.36
Dose of atropine received (mg)	8.75±4.8	0.5	5	0.399

*p-value (intergroup)

Discussion

According to the results of this study, there was no significant difference between the three groups in terms of cardiovascular response and hemodynamic disorder (tachycardia, bradycardia, hypotension and hypertension) before, during and after the operation. According to the findings of the study, there was no significant difference between the three case groups in terms of distribution of demographic and baseline variables, and no confounding effect of the above factors was observed on the main results.

There was no significant difference in blood oxygen saturation percentage between the three groups at any time. The frequency of nausea in the three groups of ondansetron mg 6, mg 8 and control was 40%, 40%, and 70%, respectively. There was a significant difference between the three groups. The frequency of vomiting in recovery was significantly different between the three groups, and the ondansetron 8 mg group was lower than the other two groups. The incidence of vomiting in the three mentioned groups was 16.7%, 3.3%, and 40%, respectively.

There was no significant difference between the three groups in terms of receiving ephedrine and atropine. The mean duration of operation was not significantly different between the three groups. The mean length of stay in the recovery showed no difference between the three groups of 6 mg ondansetron (67±14.1 minutes), 8 mg ondansetron (71.5±17.5 minutes) and the control group (72±10.7 minutes).

Terkawi et al. observed in a study that ondansetron 8 mg does not reduce hemodynamic changes, vasopressor use, or nausea and vomiting after spinal anesthesia (3). The study of Marciniak et al. did not support the hypothesis of hypotension with 8 mg of ondansetron in spinal anesthesia in cesarean section (13). In the study of Ortiz-Gómez et al., ondansetron at doses of 2, 4, and 8 mg had little effect on the prevention of hypotension during spinal anesthesia with bupivacaine and fentanyl for elective cesarean

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delivery (14). The present study is consistent with the above studies. The study of Sahoo et al. on patients undergoing caesarean section showed that administering ondansetron before spinal anesthesia improves hypotension (8). Marashi et al. concluded that administration of two doses of 6 and 12 mg intravenous ondansetron 5 minutes before spinal anesthesia significantly reduces hypotension, bradycardia, and shivering caused by spinal anesthesia compared to the saline control group (15).

The study of Trabelsi et al. showed that the preventive use of ondansetron has an important effect on the rate of hypotension in spinal anesthesia with bupivacaine and sufentanil for cesarean section (16). In a clinical trial conducted by Owczuk et al., intravenous administration of ondansetron prevented the reduction of systolic blood pressure and mean arterial pressure, but its effect on diastolic blood pressure and heart rate was not significant. At the same time, according to the results of this study, the use of 8 mg dose of ondansetron in cesarean section did not have a significant effect on the occurrence of hemodynamic disorders (7).

In a study among patients under spinal anesthesia, Ranjbar et al. concluded that intramuscular administration of ephedrine causes better prevention of changes in systolic blood pressure compared to intravenous ondansetron and Ringer's solution, while administration of ondansetron and Ringer's solution had the same effects in reducing hemodynamic changes (17). Sayed et al., in a study on caesarean section candidates under spinal anesthesia with 4 mg of ondansetron, 1 mg of granisetron and 10 ml of normal saline, observed that intravenous administration of ondansetron or granisetron can significantly reduce the severity of hypotension caused by spinal anesthesia, nausea, vomiting and chills (18). In their study, Samarah et al. concluded that the administration of 4 and 6 mg ondansetron prophylaxis, 20 minutes before spinal anesthesia in cesarean section, does not prevent the occurrence of hypotension (19). The present study is not consistent with the above studies. The reason for the difference in the results could be the difference in the dose of oxytocin given to the patient, which in the current study groups was prescribed in relatively higher doses of the protocol.

The results of our study show that the use of ondansetron 8 mg has no adverse effect on the hemodynamics of patients, which is in line with the study of Owczuk et al. (7).

The findings of our study showed that the incidence of nausea and vomiting in both doses of 6 and 8 mg of ondansetron is lower than in the control group, and the incidence of vomiting in the 8 mg group was significantly lower than in the 6 mg group. In a study, Sahoo et al. concluded that the use of intravenous ondansetron 4 mg in patients undergoing cesarean section is associated with a significant reduction in the incidence of nausea and vomiting complications compared to the control group (8).

The findings of our study showed that there is no significant difference in the length of stay in recovery and receiving ephedrine and atropine in the three studied groups. Also, there was no significant difference between the three groups in the dose of the mentioned drugs.

The results of the study showed that the administration of ondansetron in doses of 6 and 8 mg in caesarean section under spinal anesthesia has no significant effect on reducing the incidence of hypotension, bradycardia and the use of ephedrine and atropine drugs. However, it was associated with a decrease in the incidence of nausea and vomiting in recovery, and the 8 mg dose of ondansetron was more effective than the 6 mg dose.

Conflict of interest: The authors declare that there is no conflict of interest.

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