JOURNAL OF CURRENT RESEARCH IN SCIENCE
ISSN 2322-5009
CODEN (USA): JCRSDJ
Available at www.jcrs010.com

JCRS
4 (1), 2016: 57-62

Effect of Ondansetron in Prevention of Spinal Anesthesia-Induced Hypotension in Pregnant Women Candidate for Elective Cesarean Section

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Received 8 October, 2015 **Accepted** 21 December, 2015 **Published** 20 February, 2016

K E Y W O R D S: cesarean section, hypotension, Ondansetron, spinal anesthesia

ABSTRACT: Complications such as hypotension and bradycardia may occur during spinal anesthesia for cesarean section. The aim of this study was to determine the effect of Ondansetron on preventing hypotension following spinal anesthesia in pregnant women candidate for elective cesarean delivery. This double blind clinical trial was done on 151 pregnant women with ASA I-II who were randomly divided into two groups. The group O received 4 mg diluted Ondansetron and the group N received placebo before implication of spinal anesthesia with 0.5% hyperbaric bupivacaine. Hemodynamic variables, O2 saturation, nausea, the vomiting episodes, and antiemetic dosage were recorded after spinal anesthesia. Data was analyzed using SPSSv16 and a P< 0.05 was assumed significant. Demographic variables were similar in two groups but mean weight was higher in group O. Mean systolic blood pressure (SBP) was similar in two groups except that group N patients had higher SBP in the 2nd minute after spinal anesthesia. Mean diastolic BP (DBP) and mean arterial pressure (MAP) were lower in group N in 6, 8, 30 and 35 minutes. There was no significant difference in Mean heart rate and O2 saturation, nausea, vomiting and chills between two groups. The 1st minute Apgar score was lower in group O. The attenuating effect of spinal anesthesia on DPB and MAP is significantly decreased by Ondansetron prophylaxy during cesarean section but has no significant effect on SBP, heart rate, chills and nausea, but it can mildly decrease the incidence of vomiting after cesarean section.

Introduction

Cesarean section is a very common practice for the delivery of a baby. Most cesarean sections are done under spinal anesthesia. Since in this practice mother is minimally exposed to anesthetics, the infant is very less prone to depression (Sahoo et al., 2012, Owczuk et al., 2008).

Hypotension is a common complication of spinal anesthesia. The incidence of hypotension and bradycardia in non-obstetric patients has been reported to be 33% and 13%, respectively; whereas, hypotension rate is as high as 50-60% in cesarean patients. As a result, conduction of such studies into the reduction of this complication can play a significant role in clinical outcomes of pregnancy. Several therapeutic measures (including maternal hydration prior to epidural block, administration of vasopressor drugs prior to regional block, and ultimately, administration of intravenous ephedrine in the event of hypotension) have been done to prevent and treat this complication (Owczuk et al., 2008).

Ondansetron hydrochloride is an antiemetic and anti-vertigo drug with higher absorption rate in women (Katzung et al., 2009).

Although animal studies with ondansetron have not shown any side effect on the fetus, it has been classified as a "Pregnancy Category B" drug. Additionally in patients who have not received spinal anesthesia, ondansetron reduces core body temperature and shivering threshold (Katzung et al., 2009).

Ondansetron, as a widely used medication for prevention and treatment of nausea and vomiting, is a 5-HT3 antagonist. Recent animal and human studies have shown that the use of this drug for spinal anesthesia is less associated with hypotension and bradycardia (Wang et al., 2014).

Spinal anesthesia-induced hypotension is mainly due to sympathetic fibers blockade that reduces systemic vascular resistance. Spinal anesthesia-induced bradycardia has several causes including the occurrence of Bezold-Jarisch reflex (BJR). In case of decreased intravascular volume and systemic hypotension, this cardiac reflex occurs due to the stimulation of serotonin receptors in ventricle wall. In such events, serotonin is released and forms a bond with 5-HT3 receptors in heart, leading to higher bradycardia and hypotension by increasing vagal tone (Palmese et al., 2012).

Since the incidence of hypotension and bradycardia is important in Cesarean section patients, conduction of further studies is required. Therefore, this study investigated the role of ondansetron in prevention of spinal anesthesia-induced hypotension in pregnant women candidate for elective Cesarean section.

Materials And Methods

The research was first approved by the Research and Ethics Committee of Hormozgan University of Medical Sciences. This was a prospective clinical trial performed on 170 pregnant women with ASA 1 and 2, admitted to Shariati Hospital in Bandar abbas for elective Cesarean section. All patients were examined by an anesthesiologist the day before the surgery and then the written informed consents of patients were obtained. Emergency patients, patients with history of sensitivity to ondansetron or local anesthetics, hypertensive or cardiovascular disorders in pregnancy, patients under treatment with serotonin reuptake inhibitors or migraine medications, and patients with coagulation disorders or hemodynamic instability, surgery complications, and incomplete-block, in need of supplementary drugs, were excluded from the study.

All patients received 500ml ringer lactate before surgery. After transfer to the operating room, standard monitoring systems including NIBP, ECG, and pulse oximetry were applied and initial vital signs of all patients were measured and recorded. Then, they were randomly placed into one of the following groups: The first group (O group) of patients received 4mg ondansetron diluted in 10ml solution in one minute; whereas, the second group (N group) of patients received 10ml normal saline in one minute. After about 5 minutes, an experienced anesthesiologist performed spinal anesthesia in the sitting position at L3–L4 interspace using a 25-G Quincke spinal needle, and injected 2ml of 0.5% hyperbaric bupivacaine after locating the subarachnoid space and cerebrospinal fluid (CSF) aspiration. Patients were immediately put in supine position and with 15º right tilt. After that, the systolic and diastolic blood pressure, mean arterial pressure, mean heart rate and saturation of peripheral oxygen (SpO2) of all patients were measured in following time points: Immediately after the completion of block, every 2 minutes for 10 minutes, and then every 5 minutes until the end of surgery. These parameters were also measured and recorded during recovery phase.

In addition, information regarding the incidence of nausea and vomiting, and the use of anti-emetic agents was recorded in a special form. The sensory level was also assessed and the surgical procedure was allowed at T4-6 spinal level. The systolic blood pressure<90mmHg or blood pressure drop>20%, relative the initial blood pressure, was regarded as hypotension and treated with intravenous ephedrine. The symptomatic bradycardia (HR<60 bpm) or heart rate<50 bpm was treated with intravenous atropine. The information regarding the incidence of shivering and the need for its treatment, as well as hypotension and bradycardia cases were also recorded.

After the collection of required samples and information, data was analyzed with chi-square (X2) and t-test, using SPSS and a P value < 0.05 was considered significant.

Results and Discussion

In this clinical trial, a total of 170 patients were included, among which 3 and 16 patients from O and N groups were removed for having such post-operative complications as bleeding and/or incomplete block, and the need for supplementary drugs such as ketamine and fentanyl. As a result, the role of ondansetron in preventing spinal anesthesia-induced hypertension in 151 pregnant women candidate for elective Cesarean section was studied. The O-group and N-group included 82 (54.3%) and 69 (45.7%) subjects.

The groups were relatively similar in terms of the mean height, weight, and gestational age (Table 1). Among 151 participants, 130 and 21 subjects were classified as ASA 1 and ASA 2, respectively. In terms of ASA, there was no significant difference between the two groups (p=0.06).

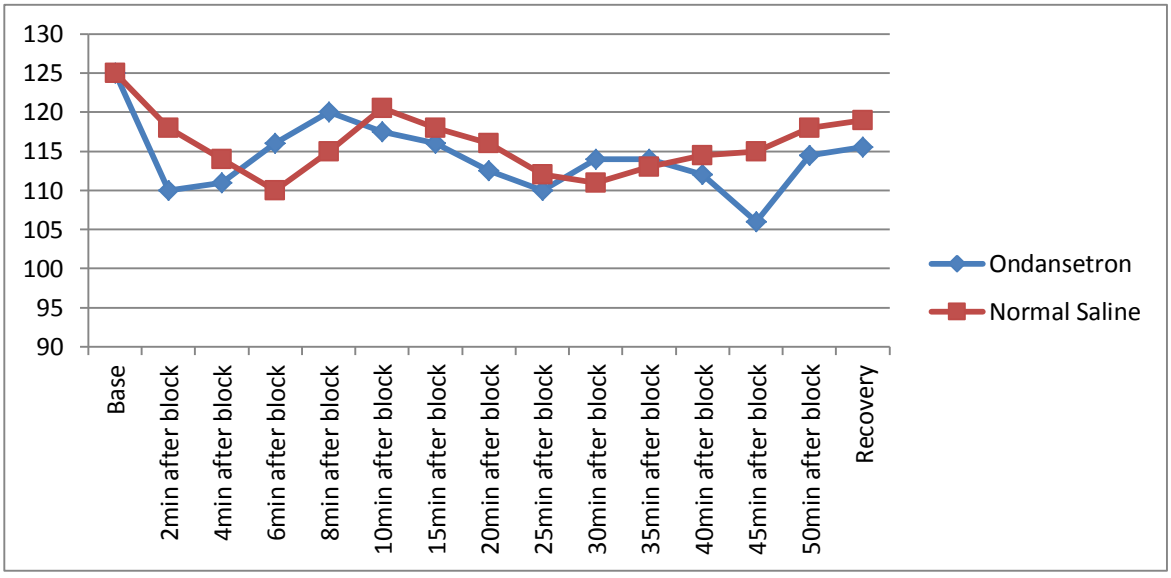

Diagram 1. Mean SPB in O-group and N-group at different measurement time points

Table 1. The mean demographic variables in ondansetron (O) and normal saline (N) groups

	O-Group	N-Group	P-value
Mean height (cm)	158.18±9.37	159.91± 3.50	0.15
Mean weight (kg)	69.53±11.87	74.24±13.42	0.02
Mean gestational age	37.13±2.47	37.66±1.17	0.13

Results from chi-square test (X2) for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and arterial oxygen saturation are presented in Table 2 and Diagrams 1, 2, 3, and 4. According to Table 2, the two groups were different in SBP in the 2nd minute, as well as in DBP and MAP in the 6th, 8th, 30th, and 35th minutes. In terms of heart rate, there was a significant difference between groups only during recovery. There was no significant difference between groups in terms of nausea, vomiting, and shivering. There was a significant difference between groups in the mean SpO2 during recovery. A significant difference between groups was also observed in the mean Apgar scores of newborns in the first minute.

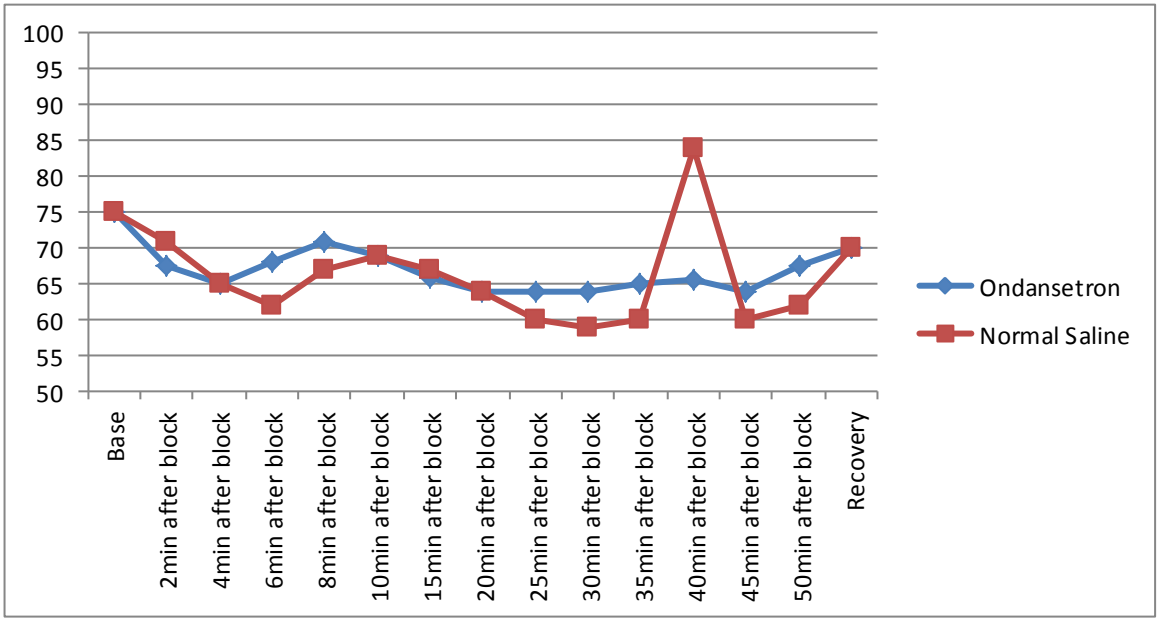

Diagram 2. Mean DBP in O-group and N-group at different measurement time points

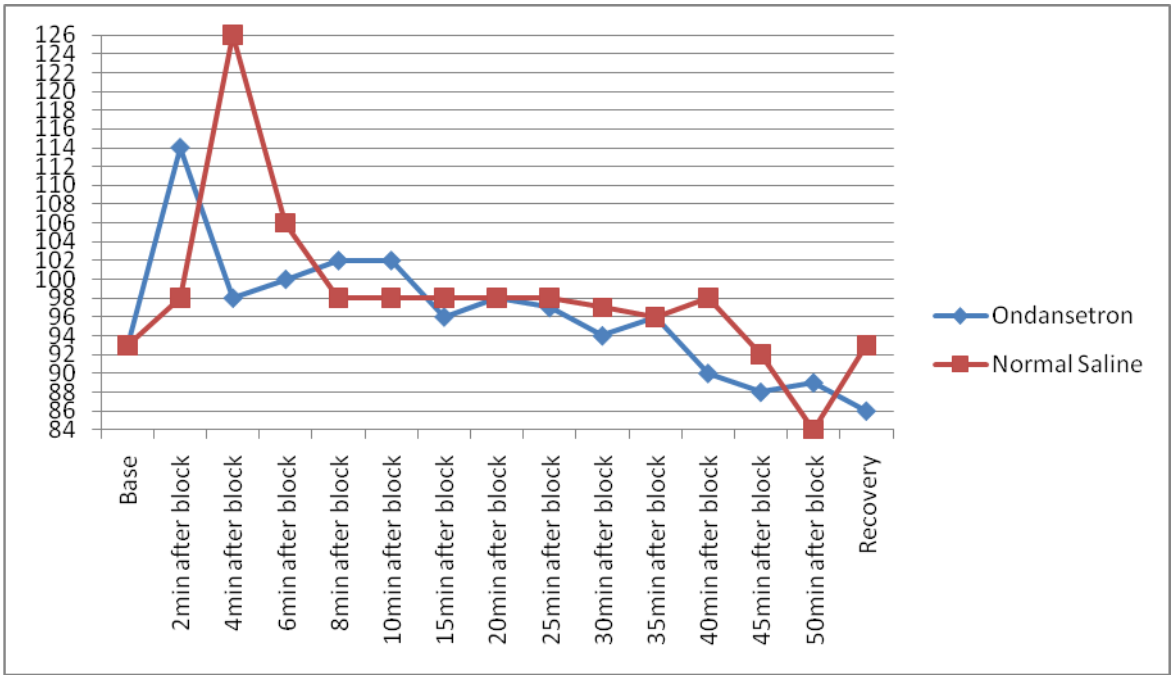

Diagram 3. Mean HR in O-group and N-group at different measurement time points

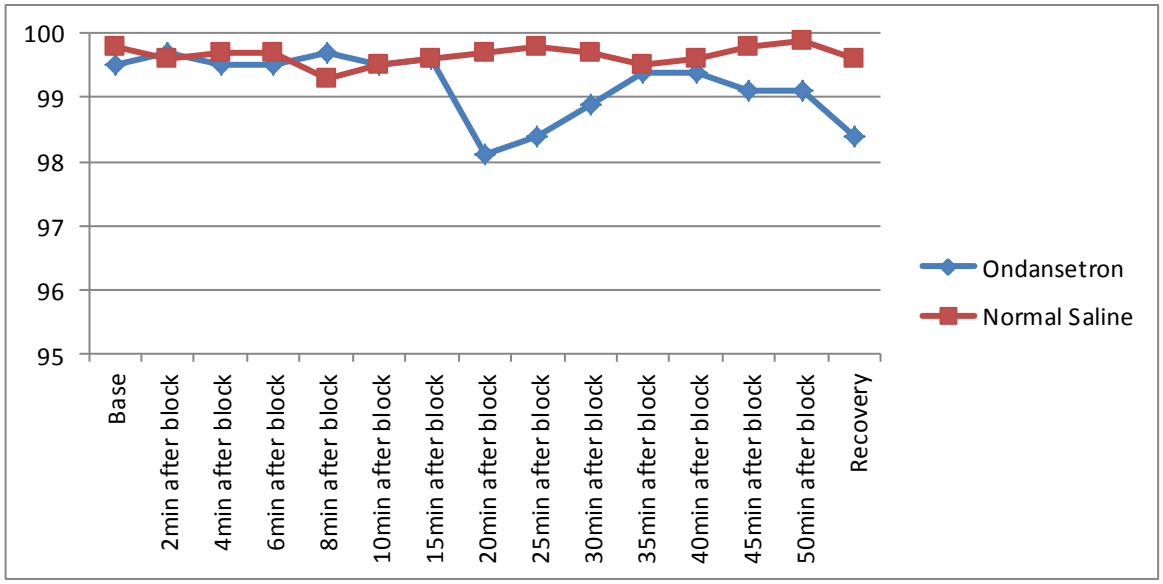

Diagram 4. Mean SpO2 in O-group and N-group at different measurement time points

Table 2. Mean rates of SBP, DBP, MAP, HR, SpO_2 based on certain measurement time points in O-group and N-group

Time	Systolic blood pressure (SBP)			Diastolic blood pressure (DBP)			Mean Arterial Pressure (MAP)			Mean Heart Rate (HR)			Mean saturation of peripheral oxygen (SpO_2)		
	O	N	P value	O	N	P value	O	N	P value	O	N	P value	O	N	P value
Baseline	122±20	125±17	0.06	75±16	75±13	0.1	90±16	87±16	0.29	93±14	93±18	0.90	99.4±0.4	99.5±1.4	0.12
2nd-min	110±22	119±20	0.02*	68±19	71±16	0.25	79±18	84±18	0.11	115±13	99±23	0.25	99.6±0.3	99.7±0.6	0.30
4th-min	111±21	114±19	0.50	66±16	65±17	0.72	79±17	79±17	0.82	97±23	125±16	0.11	99.2±0.2	99.5±1.3	0.20
6th-min	116±25	110±19	0.08	68±17	62±14	0.01*	82±20	75±15	0.01*	100±21	106±46	0.31	98.4±0.9	99.5±1.4	0.69
8th-min	120±15	115±18	0.05	71±14	67±16	0.04*	85±16	80±14	0.04*	101±24	98±23	0.43	99.4±0.6	99.6±0.7	0.25
10th-min	117±17	121±18	0.29	69±14	69±14	0.87	83±15	82±16	0.77	102±20	98±20	0.31	98.4±1.6	99.5±1.2	0.97
15th-min	116±16	118±14	0.50	67±14	67±13	0.98	81±15	81±11	0.95	97±19	98±17	0.64	99.2±0.7	99.6±0.7	0.59
20th-min	113±13	117±14	0.38	64±14	64±12	0.81	77±18	79±20	0.55	98±15	98±15	0.94	98.1±0.4	98.1±7.5	0.09
25th-min	110±17	112±16	0.92	64±14	61±12	0.14	79±15	75±12	0.19	97±13	99±17	0.68	98.4±0.4	98.4±6.0	0.15
30th-min	114±14	111±17	0.22	64±15	59±10	0.04*	79±15	73±10	0.04*	94±15	97±15	0.30	98.9±0.1	98.9±3.5	0.19
35th-min	114±13	112±14	0.44	65±12	60±10	0.04*	80±11	75±10	0.04*	95±13	96±15	0.70	99.3±0.7	99.3±0.9	0.36
40th-min	112±13	114±14	0.67	66±12	84±12	0.25	81±12	71±13	0.11	91±13	98±15	0.06	99.1±0.8	99.3±0.9	0.26
45th-min	106±21	115±08	0.33	64±11	60±09	0.18	77±11	76±07	0.84	88±13	92±15	0.44	99.1±0.1	99.2±1.1	0.09
50th-min	114±14	118±10	0.80	68±19	62±08	0.28	84±12	82±10	0.72	89±13	84±9	0.32	98.8±1.2	99.1±1.5	0.17
Recovery	116±15	119±11	0.14	71±15	70±09	0.68	84±15	83±09	0.50	86±12	93±12	0.00*	98.4±1.2	98.4±4.7	0.04*

*P<0.05 is statistically significant

Table 3. Frequency of nausea and vomiting, and Apgar of newborns in O-group and N-group

Group	Ondansetron (O)		Normal Saline (N)		
Nausea	Number	percentage	Number	percentage	p-value
Yes	18	22	16	23	0.35
No	64	78	53	77	
Vomiting					
Yes	12	14.6	14	20	0.07
No	70	85.4	55	80	
Shivering					
Yes	26	32	17	25	0.55
No	56	68	52	75	
Total	82	100	69	100	
Apgar Score					
1st minute	8.57±1.05		8.92±0.46		*0.01
5th minute	9.79±1.26		9.92±0.31		0.38
10th minute	9.73±0.66		9.96±0.17		0.08

*p<0.05 is statistically significant

Today, cesarean section has become a very common practice for the delivery of a baby. Most of cesarean sections are done under spinal anesthesia. Since in this practice the parturient is minimally exposed to anesthetics, the newborn is very less prone to depression. Hypotension is a common complication of spinal anesthesia. Ondansetron a 5-HT3 antagonist is widely used as a medication for prevention and treatment of nausea and vomiting, (Sahoo et al., 2012, Owczuk et al., 2008). Regional anesthesia can reduce systemic vascular resistance through sympathetic block and increase the compliance of peripheral vascular bed which results in the decline of blood pressure. Besides the antiemetic effect, spinal anesthesia-induced hypotension may also be prevented by Ondansetron.

The responsible receptors for the BJR are mechanoreceptors located in the heart walls which participate in systemic responses to hyper and hypovolemia. In response to hypovolemia, the stimulation of sensory receptors in the left ventricle of the heart mediates BJR, and thus causes vasodilation, bradycardia and hypotension. In response to blood volume attenuation, the chemical receptors are activated by serotonin secreted from active thrombocytes. Activation of 5-HT3, as a ligand-gated ion channels G protein-coupled receptor, is due to the increased activity of efferent vagus nerve, which eventually causes bradycardia. Yet, bradycardia is less common than hypotension during spinal anesthesia (2.1-4.9% versus 36.8-52%) (Ronlad D. Miller et al., 2015, Abasali et al., 2007).

In this study, the mean SBP equally reduced in both O and N groups. Also, the mean DBP and MAP reduced in both groups after regional block; however, this reduction was smaller in the O-group. The two groups were significantly different in the mean DBP and MAP in the 6th, 8th, 30th, 35th minutes after regional block. Wang (2014) showed that decline in SBP and MAP was smaller in the O-group this finding is consistent with our results, especially with respect to MAP. (Sahoo et al., 2012) reported smaller decline in DBP in O-group, which agrees with our findings. Marashi (2014) observed that 12% of N-group patients had MAP<80mmH during surgery, which was higher than O-group. This finding is also consistent with our results. In the study of EntezariAsl (2011), the mean difference in maternal blood pressure was not significantly different between the O and N group, which is inconsistence with the findings of our study. Shakya (2014) showed higher hypotension among O group, which is inconsistent with our findings.

In our study, the mean HR difference in recovery phase and after the completion of block was significant between the two groups (85.60±11.39 bpm in O-group versus 92.85±12.27 bpm in N-group). Marashi (2014) showed that the mean HR in O-group was significantly less than the mean HR in the N-group during surgery, which is consistent with our study. Sahoo (2012) reported a higher post-operative mean HR in O-group, which disagrees with our findings. Norowzi (2013)'s report on post-operative mean HRs was inconsistent with our findings. EntezariAsl (2011) reported similar post-operative mean HRs in O and N groups, which was inconsistent with our findings.

In the present study, the difference between groups in the mean base line SpO_2 was not significant. The mean SpO_2 in recovery phase and after the completion of block was significantly lower in O group than N group. In contrast Rashad and Farmawy (2013) reported unchanged post-anesthesia SpO_2 levels relative to the baseline in their study groups. In this study, the difference between groups in shivering frequency was not significant (32% in O-group versus 25% in N-group), which is similar Browning (2013)'s findings (32% in O-group versus 33% in N-group). Kelsaka (2006) reported 8% versus 36% shivering frequency in O and N groups, respectively, which is inconsistent with our findings. However Rashad and Farmawy (2013) reported no difference for shivering frequency among their groups (ondansetron, granisetron and normal saline), which supports our findings. Marashi (2014) reported higher shivering frequency in N-group (32%) than O-group, which is inconsistent with our finding. Shakya, (2014) also reported 42.5% and 10% shivering frequencies in N and O groups, respectively, which is inconsistent with our findings.

In the present study, the difference between groups in the frequency of nausea and vomiting was not significant (22% versus 23% and 14.6% versus 20% in O and N groups, respectively). Norowzi (2013) reported significantly lower frequency of nausea and vomiting in O group than N group. EntezariAsl (2011) reported no incidence of nausea and vomiting among O-group. Results from these two studies were inconsistent with our findings. Sahoo (2012) reported a significantly higher frequency of nausea and vomiting in O-group than N-group, which is inconsistent with our findings.

Apgar scores of newborn infant in the first minute were 8.57±1.05 in O-group versus 8.92±0.46 in N-group, showing a statistically significant difference; whereas, these scores were relatively equal in the 5th and 10th minutes. This statistical difference may be due to the sedative effect of serotonin on the infant. Norowzi (2013) did not observe any significant correlation between the use of ondansetron and Apgar scores.

Regarding to the research data, it can be concluded that the use of ondansetron in elective Cesarean section significantly prevents the reduction of DBP and MAP after the block and during the surgery; whereas, it has no significant role in prevention of reduced SBP, HR, and the incidence of shivering and nausea in women candidate for elective Cesarean section. In addition, ondansetron slightly reduced post-operative vomiting. The 1st-minute Apgar score was also slightly smaller in O group. In conclusion, spinal anesthesia causes vasodilation, hypotension, sympathetic block-induced bradycardia, BJR, and stimulation of 5-HT3 receptors at vagal afferent nerve ending. Although, we cannot report the direct effect of 5-HT3 antagonist on cardiac output, we believe that our findings show the preventive effect of ondansetron on serotonin-induced BJR, reduction of vasodilation, and improvement of venous return, leading to less reduction in DBP and MAP. The blockade of 5-HT3 receptors inhibits serotonin-induced BJR.

Research limitations included the conduction of Cesarean section with different surgeons and the use of only a certain dosage of ondansetron. It is recommended to conduct studies with greater sample size and different ondansetron dosages to achieve more comprehensive and reliable results. Regarding the research findings, further studies can be done specifically to investigate the effect of ondansetron on infants' Apgar scores.

Acknowledgment

Hereby, all patients participated in this study, Dr. Namazi as statistical advisor, all anesthetic personnel of Shariati Hospital, and Ms. Tofighi and Ms. Heidari, two experts in the Anesthesiology Research Center, are thanked for their cooperation.

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