Effect of intravenous ondansetron on reduction of spinal induced hypotension in parturients undergoing caesarean section

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Abstract: Background: Subarachnoid block is the preferred method of anesthesia for caesarean section, but is associated with hypotension and bradycardia, which may be deleterious to both parturient and baby. Animal studies suggest that in the presence of decreased blood volume, 5-HT may be an important factor inducing the Bezold Jarisch reflex via 5-HT3 receptors located in intracardiac vagal nerve endings. In this study, we evaluated the effect of ondansetron, as a 5-HT3 receptor antagonist, on the haemodynamic response following subarachnoid block in parturients undergoing elective caesarean section. **Methods**: Fifty parturients of ASA I and II with singleton pregnancy scheduled for elective lower segment caesarean section were randomly allocated into two groups. After prehydration with crystalloid solution (10-20ml/kg), and before induction of spinal anesthesia Group O (n = 25) received intravenous ondansetron 4 mg; Group S (n = 25) received normal saline. Blood pressure, heart rate and vasopressor requirements were assessed. Hypotension was defined as a decrease in systolic arterial pressure of more than 20% from the baseline or a decrease of systolic arterial pressure to less than 90-100mm/Hg as absolute value, which was treated by boluses of ephedrine in doses of 5mg. **Results**: Decreases in systolic and mean arterial pressure were significantly lower in Group O than Group S from 3 min until 30 min. Patients in Group O required significantly less vasopressor (P <0.001) and had significantly lower incidences of nausea and vomiting (P = 0.049). **Conclusion**: Ondansetron 8 mg, given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section.

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1. Introduction

Neuraxial anesthesia has become the anesthetic technique of choice for elective caesarean delivery, and has resulted in a reduction in maternal mortality [1, 2].

Hypotension and bradycardia are the most common side effect [3, 4] and have both maternal and neonatal consequences. In obstetric patients the incidence of hypotension has been estimated to be as high as 80%. [5, 6]

Hypotension after subarachnoid anesthesia results mainly from a decrease in systemic vascular resistance secondary to a blockade of sympathetic fibers [7].

The Bezold–Jarisch reflex has been proposed as a mechanism for the accompanying bradycardia in this setting [8].

Bezold-Jarisch reflex originates in cardiac receptors with non-myelinated type C vagal fibers creating the afferent limb of the reflex. These receptors are both mechanosensitive and chemosensitive and when stimulated produce bradycardia, peripheral vasodilation and hypotension [9].

These chemoreceptors including serotonin receptors (5-HT3 subtype) are sensitive to several different chemicals including serotonin [9, 10].

This effect can be blocked at the 5-HT3 receptors.

Ondansetron, a potent 5-HT3 receptor antagonist commonly used as an antiemetic drug [11, 12] is potentially useful to attenuate this response [13].

We hypothesized that spinal-induced hypotension and bradycardia could be minimized with the use of intravenous ondansetron, a 5-HT3 receptor antagonist, in non-labouring obstetric patients undergoing caesarean section.

2. Patient and methods

This study was conducted at AL-Azhar University hospitals between December 2016 and June 2017. Institutional ethical committee approval and informed written consent were obtained from all patients. Obstetric patients who were ASA physical status I, between 20 and 40 years of age, and undergoing an elective, lower segment caesarean section (CS) were included. Patients with contraindications to subarachnoid block (patient

refusal, unstable haemodynamics, coagulation abnormality), history of hypersensitivity to ondansetron or local anaesthetic agents, hypertensive disorders of pregnancy, cardiovascular insufficiency, receiving selective serotonin reuptake inhibitors or migraine medications were excluded.

In the pre-anesthesia room, a peripheral 18-gauge cannula was inserted. All patients received prehydration with 15 ml/kg of Ringers lactate over a period of 20 minutes before spinal anesthesia and no additional fluid was given other than that required to keep IV peripheral cannula patent.

In the operating room non invasive blood pressure (BP), pulse rate, and pulse oximetry (SPO2) were recorded.

Patients in group O received intravenous Ondansetron 8 mg diluted in 10 ml of normal saline solution over 1-5 min before spinal anesthesia.

The spinal technique was performed with the patient in sitting position at L3-L4, L2-L3 interspace using a 25-gauge spinal needle under all aseptic precautions. When free flow of cerebrospinal fluid was observed, 0.5% hyperbaric bupivacaine 2 ml (10 mg) was injected slowly without barbotage. After withdrawal of spinal needle an antiseptic seal was applied at the site of lumbar puncture and the patients were then positioned supine, with 15 degree left lateral tilt. Subsequently, bladder catheter was inserted.

Usually, data regarding age, height and weight, haemodynamic parameters, the presences of nausea, vomiting, discomfort or inadequate analgesia was collected in the anesthesiology records.

Motor block was assessed after the subarachnoid anesthesia using the modified Bromage scale, and scored as: 0 = no motor block, 1 = being unable to move the hip, 2 = being unable to move the knee, and 3 = being unable to move the ankle.

The height of the sensory block was assessed using pin prick sensory method. Surgery was allowed to proceed after a block to T6 had been established and the block level at the end of surgery was documented.

Non- invasive BP measurements were recorded in both groups at three-minute intervals from the start of the regional block for the first 20 minutes, and then at five-minute intervals until the completion of surgery. At least two further readings were taken three minutes apart after completion of surgery, and if ephedrine was still required, readings were continued until at least 10 minutes had passed without vasopressor. If surgery would be concluded in less than 30 minutes, readings would be continued each three minutes until at least 30 minutes or until no further vasopressor was required. Pulse oximetry and electrocardiograph monitors were also used.

Side effects of spinal anesthesia was recorded.

Hypotension was defined as a decrease in the systolic arterial pressure (SAP) more than 20% from the baseline reading or a decrease of SAP to less than 90–100mmHg or MBP < 70 mmHg as absolute value and was treated by boluses of ephedrine in doses of 5 mg. Heart rate < 60 beats/min was treated with Atropine 0.5 mg.

At delivery all patients received 20 IU of inj. oxytocin IV and no further oxytocin was given intra-operatively. APGAR scores were recorded at birth, 1 min & 5 min after delivery to assess fetal outcome.

The intraoperative IV sedative medications, fluid volume administered, and estimated blood loss were also recorded. In the event of excessive blood loss (>800 ml as assessed by volume in suction bottle and weighing of swabs), the patient was excluded from the study and treated appropriately.

The following indices were taken and statistically analyzed:

- Systolic blood pressure - baseline, at 3 minutes intervals up to 21 minutes, after that at 30 minutes, 45 minutes, and after 1 hour.
- Mean arterial pressure - baseline, at 3 minutes intervals up to 21 minutes, after that at 30 minutes, 45 minutes, and after 1 hour.
- Heart rate (H.R).
- Need for vasopressors (Ephedrine) between two group.

Statistical analysis

Statistical analysis was performed by using SPSS 22. Data were expressed as mean± standard deviation and frequencies. Multiple comparisons of SBP and MBP were performed using an analysis of variance (ANOVA) test for repeated measurements, followed by Bonferroni test for post hoc testing. Paired Student's test was used for comparing measures of SBP and MBP with baseline value as the control. All analysis was 2 - tailed. $P < 0.05$ was considered statistically significant.

3. Results

Fifty patients were recruited: 25 in each group. No significant differences were observed in patient demographics or duration of the operation between the two groups (Table 1).

Decreases in HR were more common in Group S (Table 2), but differences were statistically significant only at 3 min [Group O: 100±11.565 vs. Group S: 83.44±20.6621 beats/min, P=001025] and at 12 min [Group O: 100.92±10.1568 vs. Group S: 94.12±9.7993 beats/min, P=0.019879] (Fig. 1).

Table 1: Comparison between two groups as regards age demographic data and duration of C.S.

	Group S (n=25)	Group O (n=25)	P- value
Age (years)	25.04 ± 4.486	24.12 ± 4.521	0.474
Weight (kg)	71.9 ± 6.8	74.48 ± 7.768	0.221
Height (cm)	159.72 ± 5.799	161.64 ± 4.339	0.191
Duration of CS	47.60 ± 9.618	52.76 ± 5.262	0.023

Table 2: Comparison between two groups as regards HR.

HR	Group S	Group O	ANONA	
	Mean ± SD	Mean ± SD	F	P value
Baseline	97.92 ±7.1293	100.64±12.0204	0.94698	0.335369
3 Min	83.44±20.6621	100±11.565	12.22787	0.001025
6 Min	87.56±19.1944	97.04± 15.7863	3.63771	0.062478
9 Min	93.04±12.7	97.64± 15.8295	1.28441	0.26271
12 Min	94.12 ±9.7993	100.92±10.1568	5.8036	0.019879
15 Min	91.84±10.3146	95.84±8.5473	2.22908	0.141979
18 Min	93.48±9.7729	98± 9.8404	2.65546	0.109741
21 Min	96.96±7.1733	98.52±9.7002	0.418	0.521016
30 Min	95.44±8.2466	99.04±8.374	2.34562	0.132201
45 Min	95.04±6.6237	98.6±8.2513	2.83002	0.099012
60 Min	93.36±6.0338	93.44±8.7277	0.00142	0.970084

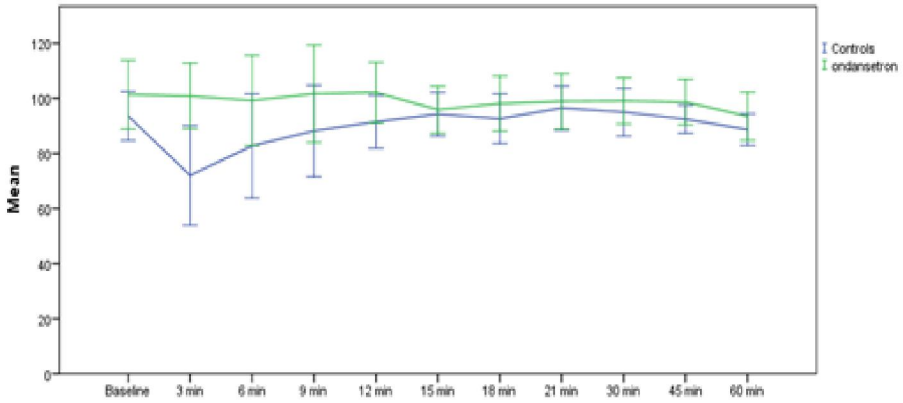
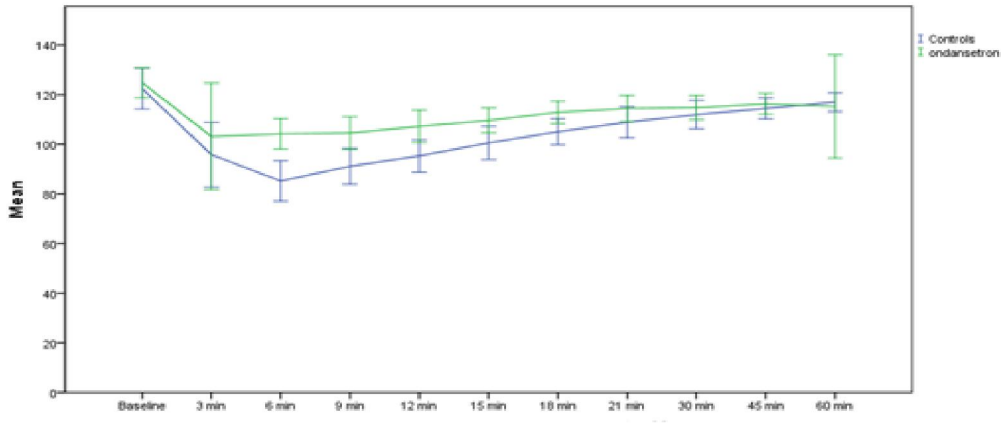


Fig. 1: Comparison between two groups as regards HR.

Significant decreases in SBP were observed in both groups (Table:3). Differences were observed between two groups from 3 min to 30 min. Those in Group S had a significantly lower SBP as P value < 0.05 (Fig. 2).

Table 3: Comparison between two groups as regards SBP.

SBP	Group S	Group O	ANOVA	
	Mean ± SD	Mean ± SD	F	P VALUE
Baseline	122.40 ±8.246	124.80 ±6.069	1.37361	0.246977
3 Min	95.80±13.061	107.16±9.3483	12.5061	0.000911
6 Min	85.20 ±8.129	104.20±6.137	86.98795	<0.00001
9 Min	91.12±7.248	104.52±6.552	47.02822	< 0.00001
12 Min	95.28 ±6.554	107.24±6.521	41.83318	< 0.00001
15 Min	100.56±6.715	109.60 ±5.025	29.04521	< 0.00001
18 Min	105.04 ±5.264	112.88 ±4.447	32.36167	< 0.00001
21 Min	108.92 ±6.271	114.40 ±5.299	11.13722	0.001641
30 Min	111.28±4.9288	114.76 ±4.884	6.28785	0.015593
45 Min	114.44 ±4.224	116.28 ±4.198	2.38647	0.128958
60 Min	116.96 ±3.769	119.24±3.767	4.57659	0.037525



F0ig. 2: Comparison between two groups as regards SBP.

Significant decreases in MAP were observed in both groups. Differences were observed between two groups from 3 min to 45 min. Those in Group S had a significantly lower MAP as P value < 0.05 (Fig. 3).

Table 4: Comparison between two groups as regards MBP.

MBP	Group S	Group O	ANOVA	
	Mean ± SD	Mean ± SD	F	P
Baseline	94.24 ±7.524	97.24 ±6.254	2.35077	0.131786
3 Min	61.04 ±12.788	73.88 ±11.118	14.35361	0.000422
6 Min	50.44 ±5.910	68.52 ±8.342	78.19002	<0.00001
9 Min	56.84 ±6.9683	68.64 ±9.082	26.56306	<0.00001
12 Min	60.68 ±6.115	71.52 ±10.560	19.7285	0.000052
15 Min	65.48 ±7.372	73.60 ±7.599	14.70525	0.000366
18 Min	69.64 ±6.987	79.04 ±6.052	25.85238	<0.00001
21 Min	74.56 ±7.795	83.60 ±6.131	20.77527	0.000036
30 Min	77.48±5.001	83.08 ±5.773	13.43923	0.000616
45 Min	82.40 ±6.344	86.20 ±4.052	6.37059	0.014965
60 Min	87.36 ±5.338	88.12 ±4.096	0.319	0.57484

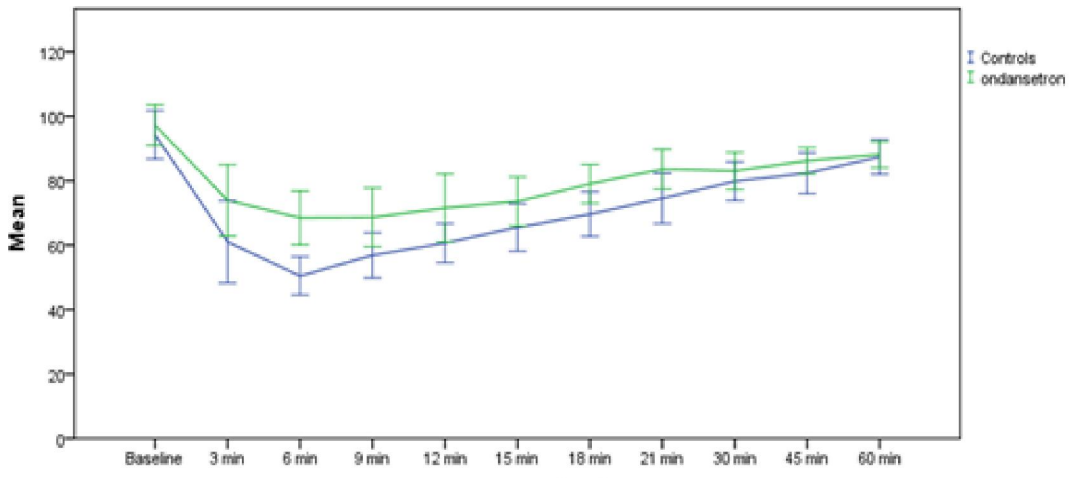


Fig. 3: Comparison between two groups as regards MBP.

The use of vassopressor (ephedrine) was much lower in group O compared to group S [Group O: 11± 6.124 vs. Group S: 23.80± 7.112, P <0.001]. (Table 5).

Table 5: Comparison between two groups as regards use of vasopressors (Ephedrine).

	Total dose	
	Ondansetron	**Controls**
Range	0 - 20 mg	15- 35 mg
Mean ± SD	11± 6.124	23.80± 7.112
T	7.092891	
P- value	< 0.00001	

4. Discussion

During spinal anesthesia, neuraxial blockade reduces venous return. The reduction in preload triggers the BJR, which is mediated by the peripheral 5-HT3 type receptors. The BJR is an inhibitory cardiovascular response to noxious chemical substances and ventricular stretch sensed by the chemoreceptors and mechanoreceptors, which are primarily located in the wall of the left ventricle. The stimulation of the 5-HT3 type receptors increases parasympathetic activity and decreases sympathetic activity, resulting in the triad responses of bradycardia, vasodilation, and hypotension [(14)].

Several preventive measures like use of mechanical or pneumatic compression of lower limbs [(15)] to reduce the peripheral pooling and increase venous return, a slight head down tilt [(15,16)] after giving spinal anesthesia, prophylactic use of vasopressor infusion [(17)], crystalloid or colloid preload or crystalloid coload have been used to reduce the incidence of hypotension following spinal anesthesia. Even with the use of these preventive measures the incidence of spinal hypotension in parturients can be as high as 80 % [(5, 6)].

Many studies have been done with the utilization of phenylephrine and ephedrine in the obstetric population. Both vasoactive drugs successfully treat post-spinal hypotension but have undesired side effects. Ephedrine is a synthetic, non-selective, non-catecholamine, sympathomimetic vasopressor [(18)].

The side effects that coincide with the use of ephedrine include supraventricular tachycardia, tachyphylaxis, and fetal acidosis. Ephedrine causes B-adrenergic stimulation as it crosses the placenta and increases fetal catecholamine levels [(19)].

Phenylephrine is a pure alpha-agonist and is associated with maternal bradycardia [(19)].

Although the use of vasoactive drugs in the parturient population has been shown to be effective, their use does not come without potential harmful fetal effects. Finding an alternative to these medications, such as ondansetron may decrease the risks of spinal anesthesia in the cesarean section patient.

In this review, we assessed the effect of ondansetron to inhibit the BJR and attenuate SIH and bradycardia after spinal anesthesia, to reduce the use of vassopressors.

In our study, the results showed no statistically significant difference in the demographic data in the studied groups as regards age, sex height, weight and duration of surgery (as p value > 0.05).

This study revealed that decreases in SBP and MAP were reduced with the use of IV ondansetron 8 mg given 5 min before spinal anesthesia in parurients undergoing elective caesarean section. The use of ephedrine was also significantly reduced with ondansetron.

There was a statistically significant difference in SBP in both groups (p value <0.05).

There was a statistically significant difference in MAP in both groups (p value < 0.05).

There was no statistically significant difference in heart rate between the two groups. (P value > 0.05).

The results of our study were similar to many research studies that have been conducted to show the correlation between 5-HT3 receptors and the cardiovascular effects via the Bezold-Jarisch reflex.

Yamano et al stated that blockade of the 5-HT3 receptor antagonizes the BJR induced by serotonin in the anesthetized rats [(20)].

Martinek concluded that IV ondansetron 4 mg with atropine 0.6 mg could revert asystole during spinal anesthesia [(21)].

A study conducted by Owczuk et al, verified the hypothesis that blockade of type- 3 serotonin receptors by intravenous ondansetron administration may reduce hypotension and bradycardia induced by spinal anesthesia in non-obstetric patients [(8)].

A study in Kolkata, India conducted by the Institute of Post Graduate Education and Research Department of Anesthesia evaluated the effect of ondansetron on the hemodynamic response following subarachnoid block in parturients undergoing elective cesarean section. The authors hypothesized that the use of IV ondansetron in non-laboring obstectric patients would reduce spinal-induced hypotension and bradycardia by blocking 5-HT3 receptors and preventing the Bezold Jarisch reflex [(13)].

The result of our study is in agreement with Wang et al, and Goda et al, who recorded in two different studies that the effect of spinal anesthesia on SBP, MAP and HR were reduced with the use of IV ondansetron 4 mg and 8 mg respectively given IV, 5 min before spinal anesthesia in pregnant women subjected to elective caesarean section [(22, 23)].

Another study conducted by Rashad et al. on three groups, each group of 20 patients, Group O received 4 mg ondansetron, Group G received 1 mg granisetron, Group S received a placebo**.** The results revealed significant difference in MAP between group O, G and S. Patients receiving 4 mg ondansetron demonstrated a statistically significant stability in MAP 5% of group O required ephedrine use, whereas

25% of Group G and 35% of Group S required ephedrine use [24].

Thus, spinal anesthesia causes vasodilatation, hypotension, and bradycardia by sympathetic blockade, the BJR and stimulation of 5-HT3 receptors in vagal nerve endings. Results indicated that with crystalloid prehydration, ondansetron prevented the serotonine-induced BJR, suppressed venodilatation, augmented venous return to the heart and resulted in lesser reduction in SBP and MAP, and reduced the use of vasopressors.

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