Original Article

The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between two different doses

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ABSTRACT

Background and Aims: Spinal anaesthesia is currently the most common method used for managing patients undergoing elective caesarean sections. Recent meta-analyses have been supporting the use of 5-HT3 antagonists, like ondansetron, to attenuate hypotension induced by spinal block. Various doses of ondansetron were given intravenously five minutes before spinal block. However, a consensus on definitive dose and timing for maximal benefit is yet to be agreed upon. **Methods:** Our prospective randomised clinical trial investigated a new approach by administrating intravenous ondansetron 20 minutes before spinal anaesthesia. This work investigated ondansetron effect on both haemodynamic changes and vasopressors use by dividing patients into three groups. The first group O4 (n = 51) received 4 mg ondansetron, the second group O6 (n = 51) received 6 mg ondansetron, and the control group C (n = 50) received normal saline. We recorded systolic blood pressure (SBP), diastolic blood pressure (DBP) and the mean blood pressure (MBP) at different time intervals. **Results:** There was no significant difference in blood pressure measurements among the study groups (P > 0.05). The consumption of ephedrine in the control group is higher than both of the ondansetron groups (P > 0.001), with a mean dose of 27.2 ± 20.5 mg of ephedrine for group C, compared to 17.8 ± 14.9 and 14.7 ± 11.3 in O4 and O6 groups, respectively. Episodes of hypotension and number of patients with hypotension were not significantly different among the studied groups (P = 0.07; P = 0.96, respectively). **Conclusions:** Prophylactic 4 and 6 mg ondansetron given 20 minutes before spinal anaesthesia in caesarean section does not reduce the incidence of hypotension.

Key words: Caesarean section, hypotension, intraoperative complications, ondansetron

INTRODUCTION

Spinal anaesthesia has become the routine standard of care in managing patients undergoing elective caesarean sections,[1] as there is an increased risk of aspiration pneumonitis, difficult airways and foetal exposure to hypnotic drugs in patients undergoing general anaesthesia. Spinal anaesthesia is a safe and effective choice, but it has its own array of unwanted side effects that may affect the mother and the unborn child's well-being, most commonly hypotension and bradycardia. Spinal anaesthesia induced hypotension is of special concern as it happens in around one-third of non-obstetric patients, compared to 70-80% in obstetric population in which the first 10 minutes are critical in terms of haemodynamic response to spinal anaesthesia.[2-5] Maternal hypotension results

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mainly from the direct sympathectomy at the level of the block causing decrease in cardiac output and systemic vascular resistance due to sympatholysis secondary to local anaesthetic effects on spinal sympathetic outflow. Bradycardia is thought to be attributed to the Bezold-Jarisch reflex, this reflex is an inhibitory parasympathetic reflex originating in cardiac sensory receptors caused by decreased filling of the right atrium which stimulate the peripheral serotonin 5-hydroxytryptamine- receptors (5-HT3 type) mediated by serotonin.[6,7]

Current research in animals, obstetric, and non-obstetric populations indicates that 5-HT3 antagonists may abolish the Bezold-Jarisch reflex. Ondansetron is 5-HT receptors antagonist, which is basically used as an antiemetic drug and is thought to counteract bradycardia and hypotension induced by spinal block. In the literature, ondansetron was used 5 minutes before performing spinal block to prevent hypotension and bradycardia with moderate reduction in hypotension during caesarean section.[6] Ondansetron has its peak plasma concentration within 30 minutes of intravenous administration when used to treat nausea and vomiting.[8-10] In our presenting clinical trial, we propose that giving ondansetron 20 minutes before performing spinal block should improve the efficacy of counteracting hypotension of spinal block in caesarean section. Our primary aim was to assess systolic blood pressure (SBP), diastolic blood pressure (DBP), and the mean blood pressure (MBP) among different ondansetron doses and a control group in different time intervals.

METHODS

This was a prospective, double-blinded, placebo-controlled, randomised clinical trial. After approval from the University of Jordan Hospital institutional review board (2433 / 2016/10) on February 21st, 2016, and the clinical trial number (NCT04140058), as retrospectively registered on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04140058), a written informed consent was obtained from all participants. The study was conducted in concordance with the latest declaration of Helsinki. The study took place in the period from January 2017 to January 2018. To estimate the sample size, we used the G-power software where we used the following input to calculate *a priori* mean difference between the groups: a reduction of 50% in the incidence of hypotension,[11] alpha error of 0.05, a power of 0.8, yielding a total of 43 participants for each of the three groups. We further increased the sample size of the groups to 50 patients per group to increase the power of the study.

Patients were randomly allocated using www.randomiser.org into three groups: The first group O4 (n = 51) received 4 mg ondansetron, the second group O6 (n = 51) received 6 mg ondansetron, and the control group C (n = 50) received normal saline. All injections were diluted in 10 ml of normal saline and given intravenously 15-20 minutes before the intrathecal injection. A research assistant prepared the injection for a consultant anaesthetist who was blinded about the injection administered.

This study included patients who received spinal anaesthesia for elective caeserean sections who met the American Society of Anesthesiologists (ASA) physical status classification II. Exclusion criteria consisted of patients ASA physical status classification III, IV or V, emergent caeserean sections, multiple parities (twins/triplets), expected blood loss more than 1,000 ml, more than 6 mg ondansetron administered, patients who presented with a cardiac history (coronary artery disease, myocardial infarction, congestive heart failure, murmur, mitral valve prolapse/regurgitation, dysrhythmias, aortic stenosis/regurgitation), patients who presented with preeclampsia, and patients who presented for caeserean section with epidural catheter due to failure to progress.

Preoperative assessment was done by an anaesthetist the day before surgery, informed written consent was obtained from all participants. All patients were fasted for 8 hours and were not given premedication other than omeprazole 40 mg orally 6 hours pre-operatively and ranitidine 50 mg intravenously 2 hours pre-operatively. Demographic data such as age, weight, height, body mass index were recorded. In the operating theatre, baseline values of non-invasive systolic blood pressure (SBP) and diastolic blood pressure (DBP), and mean arterial pressure (MAP) were obtained. In addition, heart rate (HR) and pulse oximetry (SpO_2) were recorded, and two intravenous gauge 18 cannulae were secured in each patient. All patients were preloaded with 500 ml of lactated Ringer's solution. Then, patients were put in a sitting position and under aseptic technique, a subarachnoid block was done by injecting 2 mL of 0.5% (10 mg) hyperbaric bupivacaine and 25 μg fentanyl through a 25 gauge Whitacre pencil point spinal needle at the level of L3-L4 or L4-L5. Each patient was then immediately put in the supine position with left uterine displacement. Sensory block levels were

assessed every minute after subarachnoid block using perception to cold, and motor block levels using modified Bromage scale.[12] SBP, DBP, and HR were measured and MBP was calculated using aforementioned formula, at 1-minute intervals for ten minutes, 2-minute intervals for another 10 minutes, then at 5-minute intervals till 40 minutes after spinal block by a blinded anaesthesiologist. Hypotension was defined as drop in SBP ≥20% of the baseline value or SBP less than 100 mmHg. The hypotension was treated by increasing rate of crystalloids infusion and intravenous (IV) ephedrine doses as follows: IV ephedrine 6 mg if SBP is <100 mmHg, IV ephedrine 9 mg if SBP is <90 mmHg, IV ephedrine 12 mg if SBP is <80 mmHg, IV ephedrine 15 mg if SBP is <70 mmHg.

Bradycardia was defined as ≥30% drop from baseline heart rate or when the HR dropped below 50 beats per minute; the patient was treated with IV atropine 0.5 mg. During anaesthesia, Ringer's lactated or normal saline solutions were administered to cover maintenance and deficits besides treating hypotension, also blood loss was monitored for possible blood transfusion. After delivery of the foetus, all patients received 10 international units of oxytocin direct IV and then 30 international units in 250 ml compatible IV fluids over four hours. Intraoperative nausea and vomiting were treated with elevation of blood pressure and any patient who received intraoperative antiemetic therapy was excluded from the study.

Statistical Package for Social sciences (SPSS) version 21.0 (Chicago, USA) was used in our analysis. Demographic data which include age, weight, height, SBP, DBP, MBP, HR and SpO_2 were analysed using One-way analysis of variance (ANOVA). After spinal block SBP, DBP, MBP, HR, IV fluid infusion, blood loss and ephedrine doses were analysed using one-way ANOVA and when there was a statistically significant difference (*P* value less than 0.05), we used to do the least significance difference (LSD) *post hoc* analysis in different time intervals. Chi-square test was used to compare between the three groups regarding episodes of hypotension requiring treatment with ephedrine, the number of patients requiring dose of ephedrine equal to or more than 15 mg, and the overall number of hypotensive episodes. All underlying assumptions were met, unless otherwise indicated. *P* value less than 0.05 was considered statistically significant.

RESULTS

152 pregnant patients were prospectively enroled during the study period. There were 50 patients in the control group (group C) and 51 patients in ondansetron 4 mg (group O4) and ondansetron 6 mg (group O6). The study groups were shown to be statistically comparable with regard to demographic variables and baseline parameters, as shown in Table 1. There was no statistically significant difference in the readings of SBP, DBP, and MBP among the three groups in different time intervals after spinal block as shown in Table 2. As for heart rate readings significant difference was exhibited between the three groups ($P < .05$). Details for HR differences are shown in Table 3.

ANOVA test showed a significant difference on the usage of ephedrine among the three groups ($P < .001$). The *Post hoc* comparison showed that patients in group C received significantly higher dose of ephedrine per patient compared with patients in the other two groups; significance ($P = .004$) for group O4 and ($P < .001$) for group O6. The standard errors (S.E.) of the dose of ephedrine were 2.9 for group C, 2.1 for group O4, and 1.6 for group O6 [Table 4]. Furthermore, the number of times ephedrine was given in response to drop in blood pressure over different phases of the

Table 1: Demographic and anaesthetic data

	Placebo (*n*=50)	Group O4 (*n*=51)	Group O6 (*n*=51)	*p*
Age (years)	33.1±5.6	33.6±5.3	32.6±6.1	0.694
Weight (kg)	80.7±13.9	78.5±9.2	80.4±13.1	0.616
Height (cm)	161.4±4	160±4.2	161.6±4.8	0.149
Fluids given (ml)	2299±449.1	2245.1±511.1	2215.7±469.1	0.674
Blood loss (ml)	753±200.6	704.9±134.3	697.5±165.6	0.204
Duration of surgery (minutes)	64.5±11.6	65.9±11.7	66±12.4	0.786
Baseline SBP (mmHg)	128.4±17.3	125±12.3	123.2±10.9	0.163
Baseline DBP (mmHg)	74.8±11.9	72.7±9.3	71.5±6.4	0.206
Baseline MAP (mmHg)	92.7±13	90.1±9.2	88.7±6.7	0.137
Baseline heart rate (beat/minute)	100.9±9.3	96.6±15.1	96.8±10.7	0.125
Baseline O_2 saturation (%)	97.9±0.8	98.1±0.9	98.0±0.9	0.48

*Data are mean±SD. †SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure

Table 2: Mean rates of Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial Pressure (MAP), based on certain measurement time points in the study groups

Timing	Component	Group			*p*
		Group C	Group O4	Group O6	
First 10 minutes	SBP	104.7±12.2	105.2±11.9	106.2±13.3	0.843
	DBP	56.3±9.6	56.3±7.5	54.9±8.1	0.63
	MBP	72.5±10.1	72.6±8.3	72±9.1	0.94
Minutes 10 to 20	SBP	109.4±10.2	109.6±13.1	109.5±10.1	0.997
	DBP	54.1±7.3	55.6±9.8	55.3±9.8	0.669
	MBP	71.1±12.8	73.6±10.2	73.4±9.3	0.433
Minutes 30-40	SBP	108.9±15.2	113.2±10.9	111.5±10.6	0.228
	DBP	54.9±7.2	56.2±9.8	55.2±9.8	0.761
	MBP	71.5±13.4	75.2±9.1	74.0±9.2	0.214

*Data are mean±SD. †SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure

Table 3: Comparison between the three groups in Heart Rate (HR)

Timing (minutes)	Group			*p*
	Group C	Group O4	Group O6	
1	101.4±14.2	93.7±16.1	97.1±13.6	0.034
2	105.7±19	99.4±19.1	99.9±16	0.158
3	105.4±20.1	95.5±20	100.7±20.6	0.054
4	106.8±21.1	96.7±21.4	96.9±22	0.03
5	102.5±18.7	98.3±21.7	97.3±21.9	0.419
6	101.8±19.5	98.3±22.2	95.8±19.9	0.338
7	98±18	96.7±19.9	95.9±18.9	0.856
8	102.5±19.3	95.6±20.3	95.8±16.3	0.118
9	99.4±19	96.9±20.4	94.4±15.3	0.399
10	101±16.3	94.6±19.6	97±15.9	0.174
12	99.4±16.3	94.4±18.8	95.4±14.6	0.279
14	100.1±16.3	92.6±17.5	94.7±15.4	0.069
16	101.4±15.3	93.4±16.3	92.6±14.2	0.007
18	96.4±18.4	93.6±15.5	93.1±13.9	0.551
20	101.1±13.5	94.1±18	95.2±16.5	0.073
25	102.5±13.6	94.1±16.9	93.6±15	0.006
30	100.2±15.5	95.2±16.6	93.1±14.5	0.069
40	99.1±12.8	93.5±12.4	92.1±13.4	0.038

*Data are mean±SD. †HR: Heart rate (beat/minute). ‡HR at minutes 4, 16, 25, 35 showed statistically significant differences between group C and groups O4 and O6. HR at minute 1 was significantly more in group C than in group O4, while at minute 40, HR in the group C was significantly higher than HR in group O6

Table 4: Comparison of the mean of ephedrine doses among the 3 study groups

Groups	*n*	Mean	*P*
Ondansetron 0 mg	50	27.2±20.5	<0.001
Ondansetron 4 mg	51	17.8±14.9	
Ondansetron 6 mg	51	14.7±11.3	

*Data are mean±SD

study after spinal block was higher among patients in group C as shown in Table 4. Significantly more patients in group C received high doses of ephedrine (15 mg-30 mg) to treat intraoperative hypotension in different time intervals compared with group O4 and group O6. Neither number of patients with hypotension, nor total number of hypotensive episodes were significantly different between the study groups, as demonstrated in Table 5.

DISCUSSION

Spinal anaesthesia has become the standard anaesthetic technique for caesarean section since it helps to avoid the risks accompanying general anaesthesia. But spinal anaesthesia has its own complications notably post spinal hypotension with or without bradycardia.[13] Hypotension after spinal block during caesarean section is common and the main treatment and prevention relies on IV fluids infusion and vasopressors administration such as phenylephrine, ephedrine, mephentermine.[14] Several studies have shown that ondansetron, which is basically an antiemetic drug, is beneficial in reducing incidence of hypotension which accompanies spinal block in caesarean section. Nearly in all these studies, ondansetron was given 5 minutes before initiation of spinal block.[15-17] Our study and work done by several previous researchers,[10] found that ondansetron reaches its peak plasma concentration within 30 minutes of IV administration. So, we injected ondansetron 20 minutes before spinal block and in 4 mg and 6 mg doses to see its effect in counteracting hypotension. We found that ondansetron in doses 4 and 6 mgs given 20 minutes before spinal block, and compared with saline did not reduce the incidence of hypotension in caesarean section. However, we found a dose dependant decrease in ephedrine requirement with the dose of ondansetron. In the current investigation, there was a high incidence of hypotension, the amount of IV crystalloids and the dose of ephedrine given were relatively high compared with other studies; possible explanation for this hypotension is that the protocol of oxytocin dose given to our patients is relatively high. Our findings

Table 5: Patients with different doses of ephedrine, with hypotension and overall hypotensive episodes

Dose of Ephedrine (mg)	Group C (*n*)	Group O4 (*n*)	Group O6 (*n*)	*P*
3	0	3	0	*P*<0.001
6	6	9	7	
9	23	34	30	
12	27	26	24	
15	28	12	10	*P*<0.001
18	0	1	0	
21	5	0	0	
30	9	1	0	
Atropine given	1 (2%)	0	0	-
Adrenaline infusion given	1 (2%)	0	0	-
Number of patients with hypotension	42 (84%)	43 (84.3%)	42 (82.4%)	0.96
Overall number of hypotensive episodes	98	86	71	0.07

*Data are numbers and percentages

coincide with the results shown by Ortiz- Gommez JR, *et al*.[18] with differences in the design of the study. For instance, the number of patients in their study was 32 patients in each group, the dose of bupivacaine was not fixed, and the dose of oxytocin was not mentioned. In another study,[17] 4 mg ondansetron given 5 minutes before spinal block for caesarean section attenuated mean blood pressure and diastolic blood pressure hypotension. Possible explanation to the discrepancy between their results and ours is that they did not use fentanyl in spinal block, the number of patients in each group of their study was 24 and the dose of oxytocin is not mentioned. Other investigators reported about ondansetron in obstetric patients undergoing caesarean section under spinal block that SBP, DBP, and the MBP was higher in patients who were given 5 mg ondansetron compared with the control. However, they used sufentanil as supplement for spinal block and oxytocin protocol administration was not known.[15] Another factor that may attribute to the incidence of post-spinal hypotension is the dose and the method of oxytocin administration.[11] One study concluded that 4 mg is the optimum dose of ondansetron for the prevention of hypotension after spinal block in caesarean section, however, they did not use fentanyl in spinal block, the protocol of oxytocin administration was giving 10 IU of oxytocin in 250 mL of normal saline as intravenous infusion, and they compared the changes in blood pressure, but not comparing the true values of blood pressures and heart rates.[11] Furthermore, ondansetron reduced hypotension in obstetric patients undergoing caesarean section but the preventive effect was not superior to vasoconstrictors.[19] In studies done on general surgical patients,[20] ondansetron administered 5 minutes before spinal block attenuated hypotension of the spinal block more than the control, but these clinical studies were in non-obstetric patients. Furthermore, a systematic review and meta-analysis done on this topic found that ondansetron reduces hypotension of spinal block in obstetric and non-obstetric patients,[21] while another systemic review and meta-analysis found that ondansetron is not effective in non-obstetric patients, while it was found effective in certain groups of obstetric patients.[6]

CONCLUSION

In conclusion, our study indicated that despite giving ondansetron in doses of 4 mg and 6 mg 20 minutes before spinal block in the hope of increasing its efficacy, there was no reduction in the incidence of hypotension in caesarean section under spinal block, but there was a significant decrease in ephedrine consumption when compared to the placebo group.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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