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Comparison of Two Different Doses of Intravenous Ondansetron with Placebo on the Occurrence of Hypotension and Neonatal Parameters during Spinal Anaesthesia for Elective Caesarean Section

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Abstract

Background and Aims: Bezold-Jarish reflex mediated by hydroxytryptamine (5-HT) may potentiate bradycardia and hypotension, during caesarean section under subarachnoid block. Use of ondansetron (5HT antagonist), has been found to obtund this reflex. The aim was to study the effect of different doses of intravenous ondansetron, on the haemodynamic response and the neonatal outcome following Subarachnoid Block (SAB). **Methods:** One hundred and fifty ASA 1 & 2 patients aged 18-35 years undergoing caesarean section under SAB were divided randomly into three groups in this prospective double-blind study. Group A (n = 50), Group B (n = 50) and Group C (n = 50) received intravenous ondansetron 4 mg, 6 mg and normal saline respectively, just before SAB. Haemodynamic parameters, incidence of hypotension and bradycardia, vasopressor requirements, umbilical cord arterial blood gas analysis and side effects if any were observed. Data was analysed using ANOVA and Chi-Square Test. **Results:** When compared with Group C, the incidence of maternal hypotension was significantly lower in Groups A and B ($p < 0.05$). The vasopressor requirement was significantly higher in Group C than in Groups A and B (A = 1.41±2.58, B = 1.54±2.69, C = 2.25±2.94, p = 0.001). The umbilical artery pH was significantly higher in Groups A and B, compared to Group C (A = 7.33±0.042, B = 7.34±0.045, C = 7.30±0.066, $p<0.05$). **Conclusion:** Prophylactic administration of ondansetron reduced the incidence of maternal hypotension but 6 mg was not better than 4 mg.

Keywords: Bezold-Jarisch, Caesarean, Hypotension, Ondansetron, Subarachnoid Block

1. Introduction

Subarachnoid block is the most commonly administered neuraxial blockade for caesarean delivery because of its simplicity, speed of onset, and reliability. It is frequently associated with hypotension, bradycardia and a decrease in cardiac output and uteroplacental flow which may lead to foetal morbidity[1]. The Bezold-Jarisch Reflex (BJR) may be a possible cause of profound bradycardia and circulatory collapse after spinal anaesthesia, especially in the presence of hypovolemia, when a small end-systolic left ventricular volume may trigger a mechanoreceptor-mediated bradycardia[2-4]. Various techniques and drugs have been used to reduce the incidence of hypotension during neuraxial anaesthesia including left lateral tilt, intravenous fluid and vasopressor administration[5,6]. Maintaining the maternal blood pressure close to baseline reduces the incidence of maternal nausea and vomiting and is associated with higher umbilical artery pH values. The administration of an intravenous bolus of crystalloid solution (1,000 to 1,500 mL) at the time of induction of neuraxial blockade (co-load) is although more effective[5], it can cause volume overload in patients with comorbidities such as cardiac disease and pregnancy-induced hypertension[1].

Ondansetron is a carbazolone derivative which has specific 5-HT3 subtype receptor antagonist properties[7]. Pharmacological and animal studies suggest that 5-HT (serotonin) may be an important factor associated with inducing the BJR and this effect can be blocked at the 5-HT3 receptor[8]. Ondansetron, commonly used for the management of nausea and vomiting, has been shown to reduce the incidence of hypotension following subarachnoid block after spinal anaesthesia in normal patients and parturients[9-14]. Though studies have compared different doses of ondansetron, the results were controversial.

Hence this prospective, randomized, controlled, double-blind study was done to investigate the effect of two doses, 4 mg and 6 mg of Ondansetron on the occurrence of hypotension and effect on neonatal parameters during spinal anaesthesia for elective caesarean section in a tertiary care hospital. The effect of two doses of ondansetron on the incidence of hypotension was the primary aim of the study, vasopressor requirement and effect on neonatal parameters were the secondary aims.

2. Materials and Methods

After obtaining ethical committee clearance and informed written consent, this prospective, randomized controlled, double-blind study was conducted. One hundred and fifty patients between 18 to 35 years of age and 37-42 weeks of gestation belonging to the American Society of Anaesthesiologists physical status I and II, undergoing elective caesarean section were enrolled in this study. We excluded patients with a history of preeclampsia, eclampsia, chronic hypertension, gestational diabetic mellitus or with morbid obesity, allergy to study drugs or any contraindication for neuraxial blockade.

Presuming an incidence of hypotension under subarachnoid block in LSCS to be 60%, we hypothesized that administration of ondansetron would reduce the incidence of hypotension. Keeping the power of study at 80% and confidence interval at 95%, the minimum sample size required to detect at least 50% reduction in incidence of hypotension is 43 patients in each group; 50 patients were included in each group to compensate for possible dropouts. The patients were randomly allocated into three groups according to computer-generated numbers (www.randomization.com). Group A received 4mg ondansetron IV and Group B received 6mg ondansetron. The drugs were diluted to 5 ml using normal saline. Similarly, Group C received 5mL of normal saline as a placebo. Allocation concealment was maintained by sequentially numbered closed envelopes which were opened only during the preparation of the study drug for administration.

Before shifting the patient inside the Operation Theatre (OT), an 18G intravenous catheter was placed on the dorsum of the patient's non-dominant hand and was premedicated with Ranitidine 50 mg intravenously. Patients were preloaded with 10 ml/kg Lactated Ringer's solution 15 min before spinal anaesthesia. The study drug was prepared by an anaesthesia technician not involved in the study, based on the numbers in the envelope and as per the randomization sequence. All patients received the test drug intravenously five minutes before spinal puncture. The anaesthesiologist administering SAB and monitoring the parturient was unaware of the group allocation. On arrival to the Operating room, non-invasive blood pressure, Electrocardiogram (ECG) and Peripheral Oxygen Saturation (SpO_2) monitors were connected and baseline Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR) and SpO_2 levels were recorded. Subarachnoid block was administered in lateral position at L3L4 or L4L5 level using a standard technique with 2 ml of 0.5 % hyperbaric bupivacaine. Oxygen was delivered via a venturi facemask at a rate of 4 L/min. All haemodynamic parameters such as SBP, DBP, MAP, HR and SpO_2 were recorded every 2 minutes for the first 20 min and then every 5 minutes until skin closure. Two minutes after intrathecal injection, the level of sensory block was assessed using the loss of sensation to cold method and the motor blockade was determined using a modified Bromage Scale. The level of sensory and motor blockade was checked every 2 min until the maximum level of the block was achieved. Intravenous fluids were administered at a rate of 100 ml/10 min. Hypotension, defined as more than a 20% decrease in mean arterial pressure or MAP<60 mm of Hg, was treated with 200 ml fluid boluses and injection ephedrine 6 mg IV and repeated after 5 min if there was no improvement in MAP. Phenylephrine 50 mcg was administered intravenously if the patient did not respond to an additional dose of ephedrine. Bradycardia, defined as a

heart rate of less than 60 beats/min, was treated with an injection of atropine 0.6 mg IV. Patients who developed nausea or vomiting intraoperatively received injections of metoclopramide 10 mg intravenously. Oxytocin (10 IU in 100 ml normal saline) was given over 20 min as a separate intravenous infusion after delivery, piggybacked to primary infusion. A blood sample (1 ml) was collected from the umbilical cord soon after the extraction of the baby. Neonatal Apgar scores and umbilical cord blood pH were recorded after delivery. The incidence of hypotension, number of episodes of hypotension, the amount of rescue vasopressor required, ECG changes and other side effects of ondansetron if any, were noted. Parturients in whom the level of sensory block did not reach T6, were administered supplemental analgesia or general anaesthesia and excluded from the study. Also, parturients having intraoperative blood loss of more than 700 ml were excluded from the analysis of haemodynamic parameters.

Data was analysed using SPSS 21. Continuous variables were analysed using Shapiro Wilk test for normal distribution and expressed as mean and Standard Deviation (SD) or median with interquartile range as required. Categorical variables were presented as frequencies and percentages. Intergroup comparisons were performed using Analysis of Variance (ANOVA) or the Kruskal-Wallis test as appropriate. Intergroup comparison was done using Tukey post Hoc analysis. The Chi-square/Fisher Exact test was used to compare nominal data as and when required. $p \leq 0.05$ was considered statistically significant.

3. Results

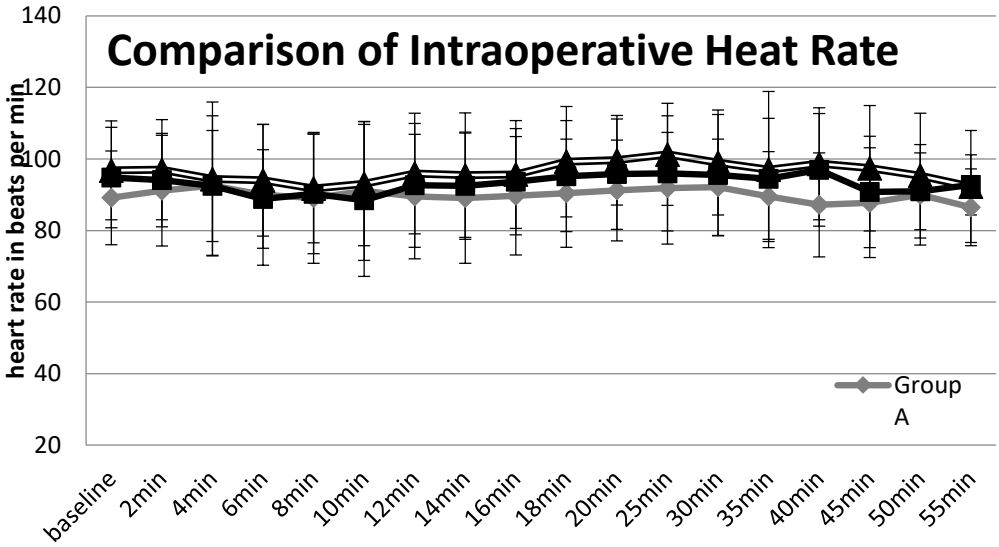
A total of 162 patients were screened and 150 patients were enrolled in the study and all the patients completed the study and were included in the analysis. There were no dropouts. The groups were comparable concerning age, weight, height and maximum height of sensory block achieved; the duration of surgery was comparable between the groups (p–0.355) (Table 1).

The intraoperative heart rate was comparable among the three groups (Figure 1A). There was a significant fall in Mean arterial pressure and diastolic blood pressure in Group C compared to Groups A and B, from 4th to 30th min and 16th to 30th min respectively, which was clinically and statistically significant ($p<0.05$). However, there was no significant difference between Groups A and B (Figure 1B, Figure 2B). The fall in systolic blood pressure was similar in all three groups (Figure 2A).

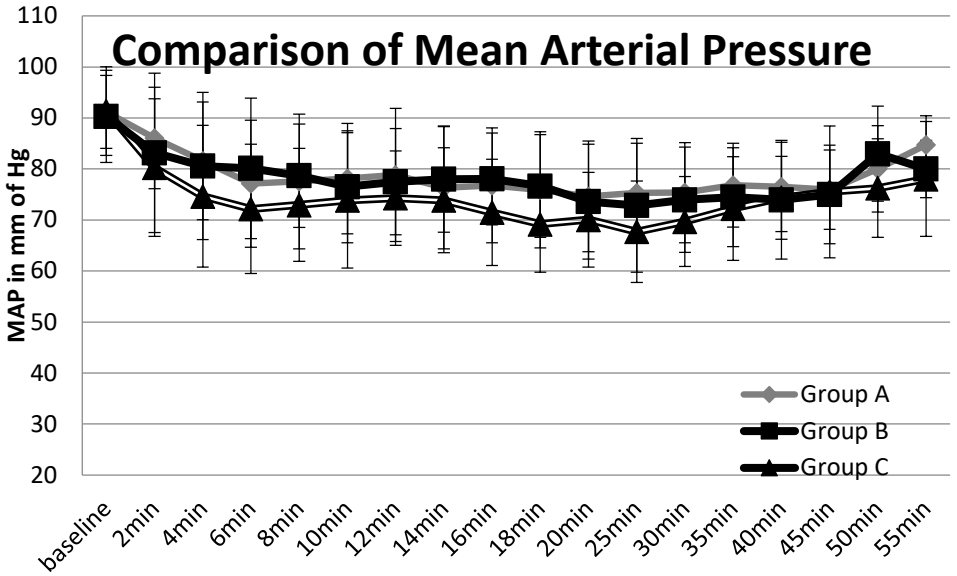
The mean (SD) value of the maximum magnitude of fall of mean arterial pressure from baseline was higher in Group C compared to Groups A and B, which was clinically and statistically significant ($p<0.001$). Post hoc analysis showed a lesser fall in Group B compared to A (p–0.017). The incidence of hypotension was greater in Group C compared to Groups A and B (p–0.014), and it was lower in Group B compared to Group A (p–0.043). Twenty patients (40%) had more than one episode of hypotension in Group C compared to 6 patients (12%) in Group B and 8 patients (16%) in Group A (p–0.007). The vasopressor requirement was significantly higher in Group C than in Groups A and B (p–0.001). The intraoperative fluids requirement was higher in Group

Table 1. Comparison of demographic parameters, maximum level of sensory block and duration of surgery

Parameters	Group A	Group B	Group C
Age	23.72±2.85	23.57±3.12	23.78±3.2
Height	155.53±5.08	155.84±4.52	156.42±4.10
Weight	64.47±13.87	67.03±6.57	67.69±4.75
Sensory block	T4 (T4-T8)	T4 (T4-T8)	T5 (T4-T8)
Duration of surgery	40.6±6.24	40.87±6.39	42.75±8.83



(A)

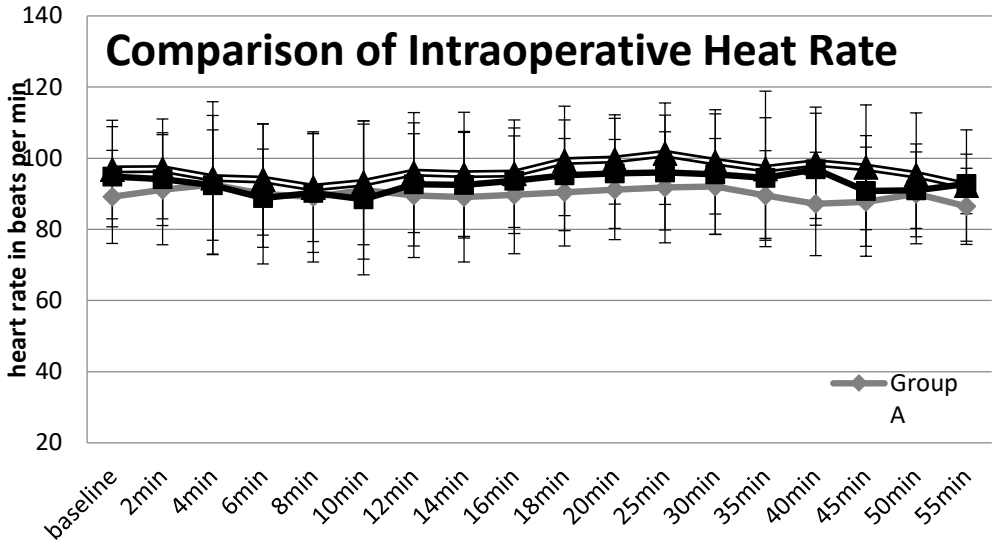


(B)

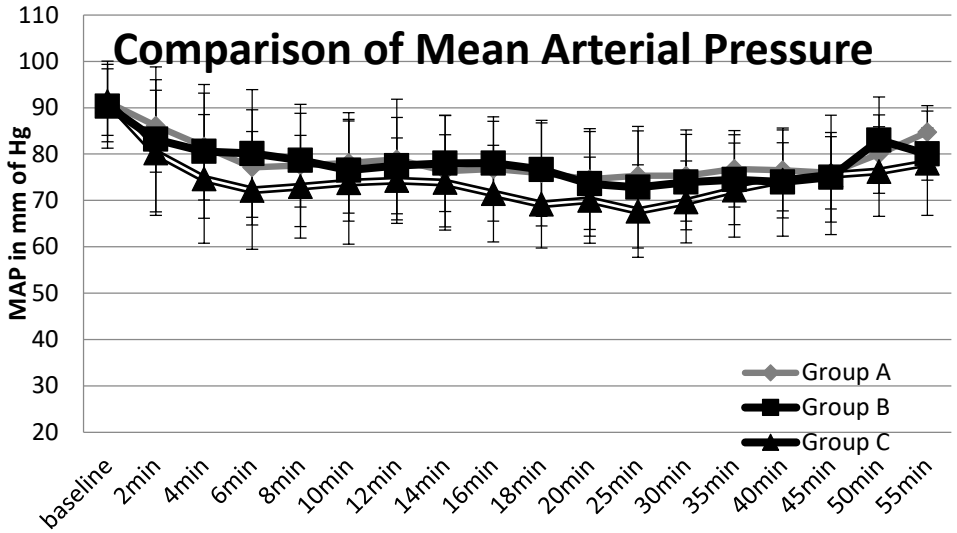
Figure 1. **(A)** Comparison of intraoperative heart rate among the groups. **(B)** Comparison of mean arterial pressure among the groups.

C compared to A and B (p–0.0017), and it was least in Group A compared to Group B which was not clinically or statistically significant.

Apgar scores were similar in all the groups and there was no statistical significance among the groups at the 5th and 10th minute. The umbilical artery pH was significantly higher in Groups A and B compared to Group C, but it was comparable among Groups A and B. The partial pressure of oxygen, carbon dioxide and bicarbonate levels were comparable among the groups (Table 2). The incidence of bradycardia was comparable among the groups. None of the patients developed intraoperative dysrhythmias, and no other side effects attributable to ondansetron were observed among the groups.



(A)



(B)

Figure 2. **(A)** Comparison of intraoperative systolic blood pressure among the groups. **(B)** Comparison of intraoperative diastolic blood pressure among groups.

4. Discussion

The subarachnoid block is the regional technique used in obstetric anaesthesia to provide optimal analgesia with minimal depressant effects on the mother and foetus. However, it is frequently associated with hypotension, and bradycardia leading to a decrease in cardiac output[1,2].

The Bezold-Jarisch reflex responds to noxious ventricular stimuli sensed by chemoreceptors and mechanoreceptors within the left ventricular wall by inducing the triad of hypotension, bradycardia, and coronary artery dilatation[1-4]. Pharmacological and animal studies suggest that 5-HT (serotonin) may be an important factor

Table 2. Comparison of hypotension, APGAR scores and ABG between the groups

Parameter	Group A (N = 50)	Group B (N = 50)	Group C (N = 50)	p-value
The magnitude of maximum change in the map (mean ± SD)	27.975± 9.453802	25.25± 8.676837	32.9± 9.538868	<0.001
Incidence of hypotension	18(36%)	17(34%)	30(60%)	0.014
	No. of episodes of hypotension			
Episode No.	32	33	20	<0.007
1 Episode	10	11	10	
2 Episodes	8	5	12	
3 Episodes	0	1	6	
4 Episodes	0	0	2	
Rescue vasopressor usage [median (IQR)]	0(0-6)	0(0-6)	6(0-12)	<0.001
Intraoperative fluid requirement	908.88±288.83	912.35±282.35	1112.21±380.22	0.0017
	APGAR Score			
5 min	8.775	8.75	8.65	0.684
10 min	9.225	9.2	9.18	0.266
	Umbilical cord blood ABG			
pH	7.333±0.043	7.343±0.052	7.311±0.067	0.01
PaO_2	21.535± 7.710617	23.4± 9.517712	19.4375± 7.842772	0.06
$PaCO_2$	45.97± 6.473346	43.7425± 7.489134	46.545± 12.3941	0.27
HCO_3	22.7425± 2.756799	23.82308± 6.510173	22.2175± 2.784102	0.17

associated with inducing the BJR and this effect can be blocked at the 5-HT3 receptor[8].

Ondansetron is a carbazolone derivative which has specific 5-HT3 subtype receptor antagonist properties[15] and has been shown to reduce the incidence of hypotension by blocking 5-HT (serotonin), following subarachnoid block in normal patients and parturients[9-14]. The studies conducted by Pasternak *et al.* and Einarson *et al.*, concluded that exposure to ondansetron during pregnancy was not associated with a significant risk of spontaneous abortion, stillbirth, preterm delivery or foetal malformations[15,16]. Previous studies have demonstrated the effect of ondansetron on hypotension but did not investigate the dose-dependent effect of the drug in reducing maternal hypotension and foetal outcome.

In the present study, it was observed that administration of ondansetron was associated with a decrease in the magnitude of fall in mean arterial pressure, a decrease in the incidence of hypotension and rescue vasopressor requirement compared to placebo. However, the difference between the two doses was not

clinically significant. The foetal outcome assessed by APGAR score and umbilical artery pH was significantly better with ondansetron compared to saline.

In a study by Sahoo *et al.*[10], they compared only one dose of ondansetron, 4 mg (n = 26) with normal saline (n = 26) and observed that falls in MAP were significantly lower in the ondansetron group and required significantly less vasopressor which was in concurrence with our study.

The study conducted by Wang *et al.*[13], compared ondansetron 2mg, 4mg, 6mg, 8mg and saline (n = 30) and observed an increase in pH value and decreased pCO_2 in umbilical venous blood with 4 mg of ondansetron compared with other groups and concluded it as the optimal dose, which also demonstrated that both 6 mg and 8 mg of ondansetron caused light lactate acidosis in the foetuses according to the reduced Base Excess value. Haemodynamic findings were similar to our study but they observed a significant fall in heart rate in the placebo group, which was unlike our study.

In their study, Trabelsi *et al.*[14] compared ondansetron 5 mg (n = 40) with a placebo (n = 40) for prophylaxis of hypotension after spinal anaesthesia in parturients scheduled for elective caesarean section. In this study, all patients received 2 mL of a hyperbaric 5 mg/mL bupivacaine solution and 0.5 mL of a 5 μg/mL sufentanil solution where the technique of SAB is different from our study which may have influenced haemodynamic parameters. Apgar scores in the Ondansetron group were higher than those in the saline group until the fifth minute after birth. Also, umbilical artery pH was a near-physiological range in ondansetron group than saline group and concluded that prophylactic ondansetron (4 mg) had a significant effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia. In our study, both 4mg and 6 mg ondansetron had a more significant effect on hypotension than the control group but no changes in heart rate were observed. Apgar scores in Groups A and B were higher than those in Group C at 1st minute after birth. Umbilical cord blood pH was significantly higher in ondansetron groups than in control groups.

Another study by Marashi *et al.*[12], compared 6 mg (n = 70) and 12 mg (n = 70)) of ondansetron with normal saline (n = 70) in the general population and concluded that both doses significantly attenuate spinal-induced hypotension, bradycardia and shivering compared to the control saline group. In our study, the results were in concurrence with the above study except that there was no statistical significance in heart rate among the groups.

Owczuk *et al.*[9] in their study, allocated 71 patients into two equal groups where the intervention group received 8 mg of intravenous ondansetron (n = 36) and the control group (n = 35) received normal saline prior to spinal anaesthesia performed with 4 mL 0.5% hyperbaric bupivacaine solution in the general population. They concluded that ondansetron attenuated the decrease in MAP and HR compared to the control saline group which was similar to our study except that no changes in heart rate were observed in our study.

Ortiz-Gómez *et al.*[11] in their study used 2 mg, 4 mg and 8 mg of ondansetron (n = 32) before induction of spinal anaesthesia and observed that prophylactic ondansetron had little effect on the incidence of hypotension in the healthy parturients undergoing spinal anaesthesia with bupivacaine and fentanyl for elective caesarean delivery but there were no statistical differences among the groups. The present study has a few limitations. Invasive monitoring could not be done to increase the efficacy of the study as it is not indicated in the caesarean section. The effect of the drug on cardiac rhythm and QT interval couldn't be studied as we couldn't record intraoperative 12 lead Electrocardiogram (ECG). However, continuous monitoring of ECG was done and none of the patients had any intraoperative arrhythmias. Neuro-behavioural adaptive score studies could have been included to strengthen the study.

5. Conclusion

Administration of ondansetron before administration of spinal anaesthesia for caesarean section was associated with a decrease in the incidence of hypotension and reduction in rescue vasopressor requirement, but there was no clinically significant difference between 4 mg and 6mg in reducing hypotension and vasopressor requirement.

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