ORIGINAL RESEARCH

Intravenous Ondansetron On Spinal Anesthesia - induced Hypotension In Patients Undergoing Caesarean Section: A Randomized Controlled Double-blinded Study

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ABSTRACT

Introduction: Spinal anaesthesia, a safe anaesthetic technique commonly practiced is associated with hypotension (33%), bradycardia (13%) and shivering induced by hypovolemia, sympathetic blockade and Bezold Jarisch reflex through intracardiac serotonin (5HT3) receptors and vagus nerve. Hypotension in caesarean section is triggered by many factors including pharmacological sympathectomy leading to reduced peripheral vascular resistance, venous return and cardiac output; aorto-caval compression by pregnant uterus in supine position. Ondansetron can inhibit Bezold Jarisch reflex triggered by chemoreceptors that are sensitive to serotonin. Ondansetron decreases the intensity of signs related to Bezold Jarisch reflex. This might lead to lower decreases in blood pressure after subarachnoid block. This study is designed to investigate effects of intravenous ondansetron on spinal anaesthesia induced hypotension in patients undergoing caesarean section. **Objectives**: To assess the effect of intravenous ondansetron on spinal anaesthesia induced hypotension after induction of spinal anaesthesia in caesarean section by serial blood pressure monitoring and recording the ephedrine requirement. **Methodology**: A randomized controlled double blinded study with 60 patients undergoing Caesarean section who satisfy the inclusion, exclusion criteria. Random sampling was done by chit in box method, and patients were divided into either group A or B. Group A received IV Ondansetron and Group B received IV Normal Saline as placebo. Sequential blood pressure recordings were taken, ephedrine doses were noted. Data analysis was by Chi square test and Unpaired t test. Probability value $p< 0.05$ is considered statistically significant. **Results**: Out of 60 patients, 30 in Group A received 2ml of intravenous ondansetron 2mg/ml and 30 in Group B received 2ml intravenous normal saline as placebo. There was no statistically significant difference in SBP, DBP. d MAP. 7 patients (23.3%) in Group A and 19 (63%) in Group B required ephedrine with P value- 0.01. Conclusion: Our study indicates that prophylactic use of ondansetron before spinal anaesthesia significantly reduces
the requirement of ephedrine in caesarean section

Keywords: Spinal anaesthesia; Bezold Jarisch Reflex; Ondansetron; Caesarean section, Spinal hypotension.

Introduction:

Spinal anaesthesia is considered a simple, fast and reliable anaesthetic technique. It is the most common regional anaesthesia technique, practiced worldwide.[1,2] It is effective and easy to perform. However, it is associated with side effects like hypotension and bradycardia.[3,4] The Bezold–Jarisch reflex is one of the causes of hypotension after spinal anesthesia through intracardiac serotonin (5HT3) receptors and vagus nerve. Bradycardia is due to the parasympathetic overactivity and increase in baroreceptor activity.[5]

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Hypotension in caesarean section is triggered by many factors including: the pharmacological sympathectomy causing reduced peripheral vascular resistance, venous return and cardiac output; aorto-caval compression by pregnant uterus in supine position.[6] Fluids, physical methods and medications can be employed to reduce the occurrence of hypotension after spinal anesthesia. Co-loading is superior to preloading. Physical methods include operating table tilting or flexing, the use of wedges or mechanical displacers, leg wrapping or sequential compression devices and head down positioning.

Ondansetron is a selective 5-hydroxytryptamine (5-HT3) receptor antagonist commonly used for the treatment of nausea and vomiting.[7] It is a highly selective 5- HT3 receptor antagonist. Its action is believed to be mediated via antagonism of 5-hydroxy tryptamine receptors located in the chemoreceptor trigger zone in the area postrema of the brain and possibly on vagal afferents in the upper gastrointestinal tract. Ondansetron has a class III antiarrhythmic action. Ondansetron can inhibit Bezold Jarisch reflex triggered by chemoreceptors that are sensitive to serotonin.[8]

It is used to control nausea and vomiting associated with the treatment of cancer by radiotherapy or chemotherapy, prevention and treatment of postoperative nausea and vomiting, prevent hypotension and bradycardia produced by activation of serotonin sensitive chemoreceptors which in turn stimulates Bezold Jarisch reflex.

Ondansetron is a cheap, safe and easily available drug. It has been found safe in obstetric population. Spinal Hypotension, especially in pregnant women can be problematic, as two lives are at stake. Finding a solution to this problem with a cheap and commonly used drug would be greatly beneficial to existing clinical practice. Effect of ondansetron on spinal hypotension is being extensively researched, but it's effects on obstetric population is yet to be studied. This current study is a prospective double blinded randomized controlled trial designed to investigate the effects of intravenous ondansetron on spinal anaesthesia induced hypotension in caesarean section by monitoring serial blood pressure after spinal anaesthesia induction and by recording ephedrine requirement during this period.

Objectives:

To assess the effect of intravenous ondansetron on spinal anaesthesia induced hypotension by monitoring systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and estimating the number of doses of ephedrine needed after spinal anesthesia in patients undergoing caesarean section.

Methodology:

After approval from our institutional ethics commitee and with informed consent, 60 patients were recruited for a randomized controlled double blinded study conducted in Department of Anaesthesiology in KMCT Medical college, Kozhikode, over a period of 15 months. Inclusion criteria was all term (>38 weeks) singleton parturients, ASA 2, undergoing Caesarean section who gives consent for the study. Exclusion criteria were ASA more than 2 with other comorbidities such as pregnancy induced hypertension (PIH), uncontrolled diabetes, Allergy to ondansetron or local anaesthetic, Contraindication to spinal anaesthesia (bleeding disorders, pre-existing neurological and spinal disorders, infection at site of injection, unstable hemodynamics, patient refusal), Patient receiving SSRI or migraine medication, Patients with history of nausea or vomiting 24 hours prior to surgery, LSCS for fetal distress.

Patients recruited for the trial were randomly allocated into case or control group using chit in box method. 30 chits will be labelled ondansetron(O) and 30 chits will be labelled normal saline(N). Anesthesia technician staff is asked to randomly pick a chit from the box and administer the drug labelled in it after noting the patient's name and the labelled letter on a register, so that the procedure can be unblinded if required. (Eg: anaphylactic reaction to drug). Group A received intravenous ondansetron 4mg (2ml) and Group B received intravenous normal saline of 2ml.

Grouping was done in such a way that both patient and the monitoring anaesthesiologist were blinded to the study. Informed consent was taken from all the patients who are included in the study. All the parturients were fasted as per the guidelines of American Society of Anaesthesiologists. All patients received ranitidine 150 mg and metoclopramide 10mg orally two hours prior to surgery. In the preparation room, baseline non-invasive blood pressure in sitting position and pulse rate were recorded. On arrival to operative room, standard monitors were connected to all patients which include, pulse-oximeter (spo2), electrocardiography (ECG), and non-invasive arterial blood pressure (NIBP). Supplemental Oxygen was given by face mask at rate of 5 liters per minute. After securing Intravenous (IV) cannula (18 G/ 20 G) in upper limb, co-loading with 10 ml/kg of Ringer's Lactate and is completed in 10 minutes. Another 10ml/kg of iv fluid started after the coloading dose.

An unlabeled 2ml syringe was given to monitoring anesthesiologist and he/she injected that 2ml of drug 5minutes before performing spinal anaesthesia. The person performing spinal anaesthesia and monitoring were blinded to the study. All patients were given spinal anaesthesia in left lateral position. 25G Quinkes spinal needle was inserted by midline approach into L3-L4 or L4-L5 interspace. After ensuring the correct position of the needle by checking the free flow of CSF, 2ml (10mg) 0.5% hyperbaric Bupivacaine was instilled intrathecally and patient waspositioned supine with 15 degrees left tilt or wedge beneath right buttock. Level of sensory block was evaluated every 3 minutes for 15 min for cold sensation using alcohol swabs beyond which patients were excluded if sensory level was below T6.

At the same time motor blockade was assessed by Bromage scale. LSCS started as soon as T6 level was achieved. All hemodynamic parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were recorded every 5 minutes for 30 minutes and half hourly for next 1 and 1/2 hours. Hypotension was defined as a decrease from baseline values of 20% or fall in SBP < 80mmHg which was treated with ephedrine bolus (6mg) until restoration of baseline values. Number of doses of ephedrine needed and timing were recorded. Data obtained by follow up and analyzing the data from the proforma.

Statistical Methods:

Minimal patient number required for this study was calculated based on the reference article "Effect of Intravenous Ondansetron on Spinal Anaesthesia-Induced Hypotension and Bradycardia: A Randomized Controlled Double-Blinded Study 9 " All statistical procedures were performed using Statistical Package for Social Sciences (SPSS) 20. 0 software (IBM, Armonk, NY, United States of America). Calculations for power (80%) of study was performed before commencement of the study. All quantitative variables expressed in mean and standard Deviation. Qualitative variables were expressed in percentages.

Shapiro-Wilk test will be used for testing the normality assumption of the data. Chi square test was used for association of qualitative variable, inpendent t test was used for quantitative variables. Probability value ($p < 0.05$) was considered statistically significant.

Results:

Demographic data:

63 patients were recruited for the study, 32 in the case group and 31 in control group. Two patients were excluded as sensory level was below T6, one showed no signs of blockade after anaesthetic administration. There were no significant differences in patient age, body weight, height, sex or ASA classification.

Hemodynamic Parameter Variation:

Mean systolic blood pressure values were compared at different intervals like 0 hours, 5 mins, 10 mins, 15 mins, 20 mins, 25 mins, 30 ins, 60 mins, 90 mins. There were no statistically significant differences between case and control group except at 10 mins, when case group showed higher Mean systolic BP levels than control group. Mean diastolic BP and Mean Arterial Pressure (MAP) were comparable among case and control group.

Interventions:

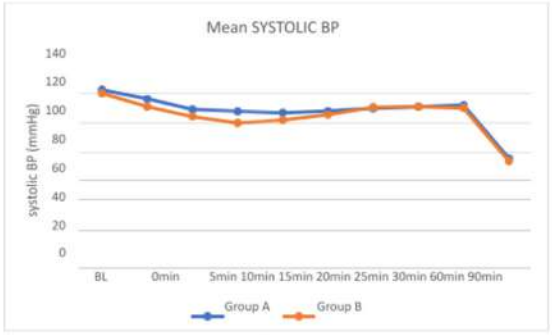
In case of spinal hypotension, Ephedrine 6mg bolus doses were given. Among 30 group A patients, who received Ondansetron, 23 patients did not require ephedrine dose at all, compared to 11 patients from group B. 6 and 12 patients received a single dose of ephedrine from Groups A and B respectively. Only one patient from group A received 2 doses of ephedrine, while 6 patients from group B needed it. One patient from group B even received 3 doses. There was a statistically significant reduction in the necessity for ephedrine among patients who received ondansetron when compared to placebo. P value was 0.01

Table1 **COMPARISON OF MEAN SYSTOLIC BP AT DIFFERENT INTERVALS OF TIME**

	Heart rate	N	Mean	Std. Deviation	Std. Error Mean	T value	P value
BL	A	30	122.4	10.63	1.94	1.01	0.31
	B	30	120.0	7.75	1.41		
0min	A	30	116.3	9.99	1.82	1.94	0.06
	B	30	111.1	10.82	1.97		
5min	A	30	109.2	10.92	1.99	1.56	0.12
	B	30	104.3	12.74	2.32		
10min	A	30	107.8	12.42	2.26	2.33	0.02*
	B	30	100.	11.52	2.10		
15min	A	30	106.9	12.05	2.20	1.52	0.13
	B	30	102.0	12.88	2.35		
20min	A	30	108.1	9.79	1.78	0.89	0.37
	B	30	105.7	11.39	2.08		
25min	A	30	109.9	10.95	2.00	0.24	0.81
	B	30	110.6	11.28	2.06		
30min	A	30	111.0	10.40	1.89	0.06	0.95
	B	30	111.1	10.92	1.99		
60min	A	30	112.0	10.38	1.89	0.73	0.46
	B	30	110.1	10.03	1.83		
90min	A	30	76.20	7.98	1.45	0.84	0.40
	B	30	74.33	9.07	1.65		

*p value <0.05 is statistically significant; ** p<0.001 highly significant

Figure 1



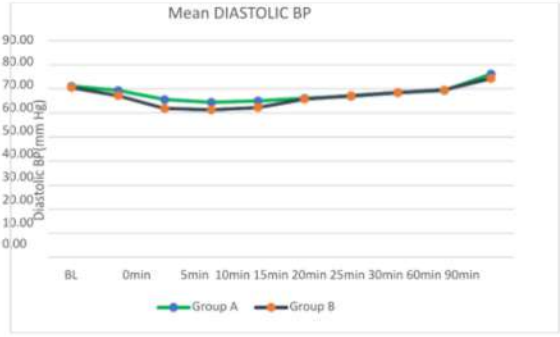
Comparison of SBP at different intervals of time

Table 2 COMPARISON OF MEAN DIASTOLIC BP AT DIFFERENT INTERVALS OF TIME

	Heart rate	N	Mean	Std. Deviation	Std. Error Mean	T value	P value
BL	A	30	71.10	9.71	1.772	0.25	0.79
	B	30	70.56	5.69	1.040		
0min	A	30	69.36	10.07	1.839	1.03	0.30
	B	30	67.16	5.73	1.047		
5min	A	30	65.53	9.379	1.712	1.53	0.13
	B	30	61.83	9.296	1.697		
10min	A	30	64.40	8.616	1.573	1.45	0.15
	B	30	61.33	7.729	1.411		
15min	A	30	65.00	7.310	1.334	1.21	0.22
	B	30	62.26	9.913	1.809		
20min	A	30	66.10	6.56	1.198	0.19	0.84
	B	30	65.76	6.64	1.212		
25min	A	30	66.93	6.761	1.234	0.12	0.89
	B	30	67.16	7.254	1.324		
30min	A	30	68.43	6.15	1.124	0.0	1.00
	B	30	68.43	6.83	1.248		
60min	A	30	69.36	6.228	1.137	0.14	0.88
	B	30	69.60	6.206	1.133		
90min	A	30	76.20	7.98	1.457	0.84	0.40
	B	30	74.33	9.07	1.656		

*p value <0.05 is statistically significant; ** p<0.001 highly significant

Figure 2



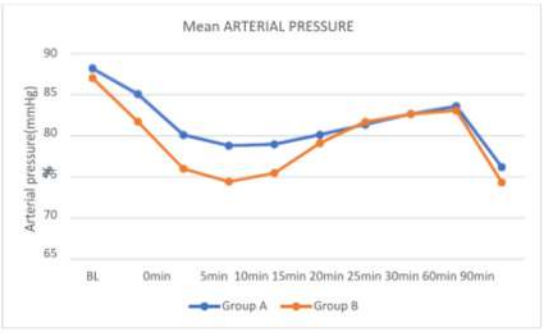
Comparison of DBP at different intervals of time

Table 3 COMPARISON OF MEAN ARTERIAL PRESSURE AT DIFFERENT INTERVALS OF TIME

	Heart rate	N	Mean	Std. Deviation	Std. Error Mean	T value	P value
BL	A	30	88.20	8.29	1.51	0.64	0.52
	B	30	87.03	5.42	0.99		
0min	A	30	85.07	8.73	1.59	1.71	0.09
	B	30	81.73	6.06	1.11		
5min	A	30	80.10	9.04	1.65	1.69	0.09
	B	30	76.00	9.66	1.76		
10min	A	30	78.80	9.00	1.64	2.01	0.05
	B	30	74.43	7.85	1.43		
15min	A	30	78.97	8.03	1.47	1.61	0.11
	B	30	75.47	8.85	1.62		
20min	A	30	80.13	6.42	1.17	0.57	0.56
	B	30	79.10	7.40	1.35		
25min	A	30	81.37	7.03	1.28	0.18	0.85
	B	30	81.70	7.26	1.33		
30min	A	30	82.67	6.58	1.20	0.02	0.98
	B	30	82.63	7.17	1.31		
60min	A	30	83.60	7.02	1.28	0.30	0.76
	B	30	83.07	6.77	1.24		
90min	A	30	76.20	7.98	1.46	0.84	0.40
	B	30	74.33	9.07	1.66		

*p value <0.05 is statistically significant; ** p<0.001 highly significant

Figure 3

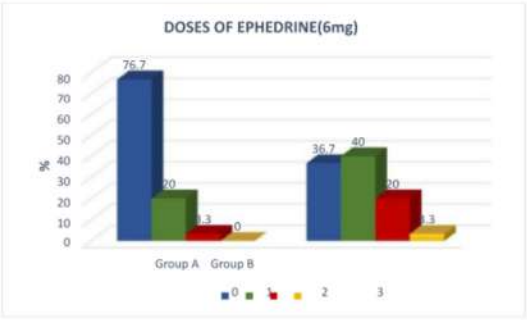


Comparison of MAP at different intervals of time

Table 4 COMPARISON OF DOSES OF EPHEDRINE(6mg)

	0	1	2	3	Chi square Value	P value
Group A	23(76.7)	6(20)	1(3.3)	0	10.81	0.01*
Group B	11(36.7)	12(40.0)	6(20.0)	1(3.3)		

Figure 4



Comparison of doses of ephedrine

Discussion:

This study was aimed to study the effect of intravenous (i.v.) ondansetron on spinal anaesthesia-induced hypotension in patients undergoing caesarean section. A total of 60 patients scheduled for caesarean section deliveries, satisfying the inclusion and exclusion criteria were enrolled into the study. They underwent randomization and allocated into 2 groups of 30 each.

Group A received intravenous ondansetron 4mg (2ml) and group B received intravenous normal saline of 2ml. In this study, mean age of the groups was comparable. Mean age of group A was 26.56 ± 3.87 years and that of group B was 26.66 ± 4.17 years. A similar study by Tatikonda CM et al aimed at studying the effect of intravenous (i.v.) ondansetron on hypotension and bradycardia induced by spinal anesthesia, reported that, among their study population, the group which received ondansetron had a mean age of 39.39±11.62 years and the group which received normal saline had a mean age of 40.19±11.66 years. 9 This study monitored heart rate, systolic BP, diastolic BP and mean arterial pressure at baseline, zero minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 60 minutes, and 90 minutes and compared the mean values of these parameters at specified intervals between the groups.

In this study, the mean systolic BP (Table 1) of participants of group A was higher than that of group B at all time intervals except at 25 minutes. At 10 minutes, the mean systolic BP of participants group A was significantly higher than that of the participants in group B. There was no statistically significant difference in mean systolic BP between the groups at any other point of time (Fig 1). The present study monitored the diastolic BP (Table 2) of participants in the 2 groups at different point of time. There was no statistically significant difference among the two groups at any point of time (Fig 2). This study compared the mean arterial pressure (Table 3) of group A and group B at different points of time. There was no statistically significant difference in mean arterial pressure between the two groups at any point of time (Fig 3). A similar study by Tatikonda CM et al compared two groups – group A and B of 70 each who received 2mL of IV ondansetron 4mg and 2mL of IV normal saline respectively. The study observed that, in the 30-minute span where SBP, DBP, and MAP were measured, there was no discernible difference between Groups A and B. The study by Owczuk R et al observed decrease in systolic BP, diastolic BP and mean arterial pressure among both the groups compared to baseline. 2 The study also observed that the ondansetron group had significantly higher minimal systolic and mean blood pressure values measured over a 20-minute observation period.

The diastolic blood pressure values between the groups did not differ significantly. Another double blinded randomized controlled trial by Sahoo T et al observed a significant reduction in mean arterial pressure in the group which received ondansetron 4 mg compared to the placebo group.[10] The present study (Table 4) observed that majority of the participants in group A (76.7%) didn't require ephedrine, 20% required single dose of ephedrine 6mg, and only 3.3% required 2 doses of ephedrine 6mg. Among the participants of group B, only 36.7% didn't require ephedrine, 40% required single dose of ephedrine 6mg, 20% required 2 doses and 3.3% required 3 doses of ephedrine 6mg. This study observed that, compared to group B, the proportion of participants who required ephedrine was significantly lower in group A (Fig 4) . The similar study by Tatikonda CM et al also reported that compared to placebo, the proportion of participants who required ephedrine was significantly lower in group which received ondansetron.[9]

Another study by Ortiz-Gómez JR et al enrolled 210 patients between the ages of 20 and 50 in their study. They were divided into three equal groups at random. Five minutes before spinal anesthesia, the intervention groups received either 6 mg or 12 mg of intravenous ondansetron, while the control group received saline. In comparison to the ondansetron-induced groups, the study found that 12 patients in the control group had mean arterial pressure 80 mm Hg and needed vasopressors with p value 0.04. 11 Overall, the present study could demonstrate an increased requirement of ephedrine, in the control group compared to ondansetron group and statistical significance was observed.

Spinal anaesthesia associated triggering of Bezold-Jarisch reflex, resulting in hypotension, bradycardia and vasodilatation is known to result from 5- HT^3 receptor stimulation in vagal nerve endings. Previous studies have shown, $5HT^3$ receptor blockade diminishes haemodynamic fluctuations, during head-up tilt table test, which might be related to Bezold Jarisch Reflex.

The predictable blockade of this reflex results in limiting BP fall in the post spinal anaesthesia phase due to mechanisms that are yet to be fully understood. In pregnant women, administering vasoconstrictors for countering hypotension, can cause compromised uterine blood flow. So possible use of such vasoconstrictors among pregnant patients can come with a great cost. Ondansetron, being safe in pregnancy and reliable for its antiemetic effect is a harmless alternative to haemodynamic instability in the post spinal anaesthesia phase.

CONCLUSION

This study indicates that prophylactic use of intravenous ondansetron 4mg before induction of spinal anesthesia reduces the requirement of ephedrine in patients undergoing caesarean section. Further studies with larger samples are required to understand the significance of ondansetron's effect on hypotension in patients undergoing caesarean section.

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