Original Research Article

Reduction in spinal induced hypotension with ondansetron in parturients undergoing caesarean section

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Abstract

Background: 5 HT-3 receptors are believed to be involved in the mechanism of post spinal hypotension. Prophylactic use of 5 HT-3 receptor blocking agents should attenuate hypotension associated with spinal anesthesia. **Aims and Objectives:** To study efficacy of ondansetron on hemodynamic parameters, nausea and vomiting and neonatal APGAR score in parturients undergoing caesarean section. **Materials and Methods:** Sixty parturients scheduled for elective caesarean section under spinal anesthesia were divided into two groups to receive ondanseton Group 1(n=30) or normal saline Group 2(n=30): prior to spinal anesthesia. Hemodynamic parameters (heart rate, systolic and diastolic blood pressure) and oxygen saturation were recorded at baseline, at 1,2 minutes after spinal anesthesia, and then after every 2 minutes interval up to 20 minutes followed by 5 minutesinterval up to 40 minutes. Dose of intravenous phenylephrine and atropine used during the procedure, neonatal parameters (APGAR score) were recorded. Statistical analysis was done by students t-test for continuous variables and Fischers test and chi-square test for categorical variables. All p values were two-tailed. **Results:** Patients in Group 2 had lower heart rate as compared to patients in Group 1(p value<0.05). Systolic, diastolic and mean blood pressure were also lower in Group 2 as compared to group 1(p value<0.05). Vasopressor requirement was more in group 2 as compared to group 1.(pvalue<0.05) The incidence of nausea and vomiting was higher in group 2 as compared to group1(p value<0.05). Neonatal APGAR scores were comparable between the two groups. **Conclusion:** Prophylactic ondansetron 4mg provided better hemodynamic stability and incidence of nausea and vomiting in patients undergoing caesarean section under spinal anesthesia without any effect on APGAR scores.

Key words: Bezold Jarish reflex, 5 HT-3 receptor antagonists, phenylephrine, spinal anesthesia.

Introduction

Spinal anesthesia is the most common anesthetic technique preferred in caesarean section because of advantages such as decreased blood loss, postoperative pain relief and patient remaining awake during delivery. It has minimal fetal side effects due to less use of anesthetic drugs. Complications of spinal anesthesia such as hypotension and bradycardia if not managed promptly can have deleterious effects on both mother and the fetus. Placenta lacks autoregulation, so maternal hypotension decreases uteroplacental perfusion and fetal oxygenation[1]. The mechanism involved in the occurrence of hypotension include decrease in vascular resistance caused by sympathetic blockade[2], parasympathetic overactivity, activation of Bezold–Jarisch reflex (BJR)[3]**.** and increased baroreceptor activity. Various treatment methods to treat hypotension and bradycardia after spinal anesthesia include preloading, co-loading with crystalloid IV infusion, patient positioning, lower leg compression and use of vasopressive drugs (ephedrine and phenylephrine)[4] These methods are not completely effective in treatment of post spinal hypotension and bradycardia and are not devoid of side effects. Preventing hypotension rather than treating it is preferable and much of current research is focused on prophylactic management of hypotension.

As BJR is one of the mechanisms for post spinal hypotension and bradycardia, blocking this reflex could prevent fall in blood pressure. BJR is triggered by chemoreceptors and mechanoreceptors which are serotonin sensitive[3]. Another side effect of spinal anesthesia is post-operative nausea and vomiting (PONV)[5].

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5-HT3 receptors are abundant in the direct stimulation of these receptors by intrathecal opiods may be a possible mechanism for opioid induced nausea and vomiting[5]. 5-HT3 receptor antagonists were found to block the Bezold-Jarisch reflex in animal models. Subsequent human studies for evaluation 5-HT3 receptor antagonists their potential to prevent spinal anesthesia-induced hypotension have yielded inconsistent results[6,7].

The current study was designed to evaluate the efficacy of 4 mg ondansetron given intravenously 5 minutes prior to spinal anesthesia in attenuating hypotesion and bradycardia associated with spinal anesthesia in pregnant patients undergoing cesarean delivery.

Aims & Objectives

Primary aim was to study the efficacy of ondansetron (4mg) in reducing the incidence of post spinal hypotension and bradycardia in parturients undergoing elective caesarean section.

Secondary aims were to study the efficacy of ondansetron (4 mg) in reducing the incidence of post spinal nausea and vomiting and assessment of neonatal parameters after caesarean section-APGAR Score.

Materials and Methods

The study was conducted in the Department of Anesthesiology and Critical Care, at a tertiary care institute in North India in a case control fashion over a two year period. The study was undertaken after obtaining institutional ethical committee clearance as wellas informed consent from all patients .Obstetric patients who were ASA physical status II, between the age of 20 and 40 years who underwent an elective lower segment caesarean section under spinal anesthesia were included in the study. Patients with contraindications to subarachnoid block:-(Patient refusal, unstable hemodynamics, coagulation abnormality),history of hypersensitivity to ondansetron or

local anesthetic agents, hypertensive disorders of pregnancy, cardiovascular insufficiency, patients receiving selective serotonin reuptake inhibitors were excluded from the study.

A total of sixty parturients scheduled for elective caesarean section under spinal anesthesia were enrolled in the study. Sample size estimation was done using G- power software.(version 3.1.0: Franz Faul Keil University Keil Germany). To achieve power of 80 percent, the sample sizerequired was 30. As two groups were involved in the study, a total of 60 patients were included inthe study. On arrival to operation theatre, standard non-invasive monitoring was attached to patients including electrocardiography, non- invasive blood pressure and pulse oximetry. Baseline hemodynamic parameters (heart rate, systolic and diastolic blood pressure) and oxygen saturation were recorded in supine position with left uterine displacement. A 16 gauge i.v. cannula was inserted under local anesthesia. All patents were premedicated with intravenous ranitidine (1mg/kg). All patients received crystalloid fluid at minimal rate to maintain vein patency. The patients were divided non-randomly into two groups.

Group 1 (ondansetron group, n=30): received ondansetron 4mg diluted in 10ml normalsaline over 1 minute.

Group 2 (saline group, n=30): received 10ml normal saline over 1 minute.

After five minutes, spinal anesthesia was performed in the sitting position at L3-L4 or L4-L5 intervertebral space using a 27G Quincke spinal needle. Patient was given 0.5% bupivacaine 2.5ml with 25mcg fentanyl 0.5ml (total volume 3ml) in the intrathecal space. Immediately after spinal anesthesia patients were placed in the supine position with 15^0 left tilt. After spinal anesthesia, the intravenous crystalloid fluid was adjusted to maximal speed until the dose reached 10ml/kg body weight and then the infusion speed was reduced to a minimal rate. Upper sensory level was assessed at five minutes interval.

Hemodynamic parameters (heart rate, systolic and diastolic blood pressure) and oxygen saturation were recorded at the time of spinal drug administration, at 1minute after spinal anesthesia, at 2 minutes after spinal anesthesia and then after every 2 minutes interval up to 20 minutes followed by 5 minutes interval up to 40 minutes. Hypotension was defined as a decrease of 20% or more in systolic blood pressure from baseline values or systolic blood pressure less than 90mmHg or diastolic blood pressure less than 60mmHg. Hypotension was treated with intravenous phenylephrine 50mcg boluses until restoration of baseline values. Bradycardia was defined as heartrate less than 50 beats per minute and was treated with intravenous atropine 0.3mg.The presence of nausea and vomiting was recorded and treated with intravenous metoclopramide 10mg as a rescue medication. Total dose of intravenous phenylephrine and atropine used during the procedure was noted. Neonatal parameters (APGAR score) were also noted at 1 minute, 5 minutesand 10 minutes. The study parameters were recorded by anesthesiologist who was blinded to groupallocation. At the end of study, data was analyzed using statistical analysis on the basis of whetherpatient had received ondansetron or not. Then the two groups were compared for outcome.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar diagrams and line diagrams. Shapiro–Wilk test and normal probability plot were used to test for normality of data. Continuous variables were compared using Student's independent *t*-test. Chi-square test or Fisher's exact test, whichever appropriate, was employed for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant. All P-values were two tailed.

Results and Observations

The groups were comparable with respect to age, weight and timeto onset of block, level of sensory block and duration of surgery.[Table 1]

Table 1: Showing comparison of demographic parameters, onset of block and duration ofsurgery between the groups

Parameter	Group 1 (Mean±SD)	Group 2 (Mean±SD)	p- value
Age (years)	30.2±4.26	30.4±4.05	0.853
Weight (Kg)	59.7±7.05	61.9±7.95	0.261
Onset of block (minutes)	9.5±1.697	9.8±1.724	0.499
Duration ofsurgery (minutes)	45.3±3.67	46.8±3.49	0.109

There was no statistically significant difference between the two groups with respect to level of the sensory block. The percentage of patients in group 1 with T4 level was 63.3% (n=19), T5 was 10% (n=3) and T6 was 26.7% (n=8). The percentage of patients in group 2 with T4 level was 56.7% (n=17), T5 was 13.3% (n=4) and T6 was 30% (n=9).

Lower mean heart rate was observed in group 2 (normal saline group) as compared to group 1(ondansetron group) between 10 and 30 minutes after spinal anesthesia. (p- value <0.05). Lower values of mean systolic blood pressure and diastolic blood pressure were observed in group 2 (normal saline group) as compared to group 1(ondansetron group) between 8 minutes and 30 minutes. There was no statistically significant difference between two groups with respect to saturation throughout the study.[Figures 1,2, 3]

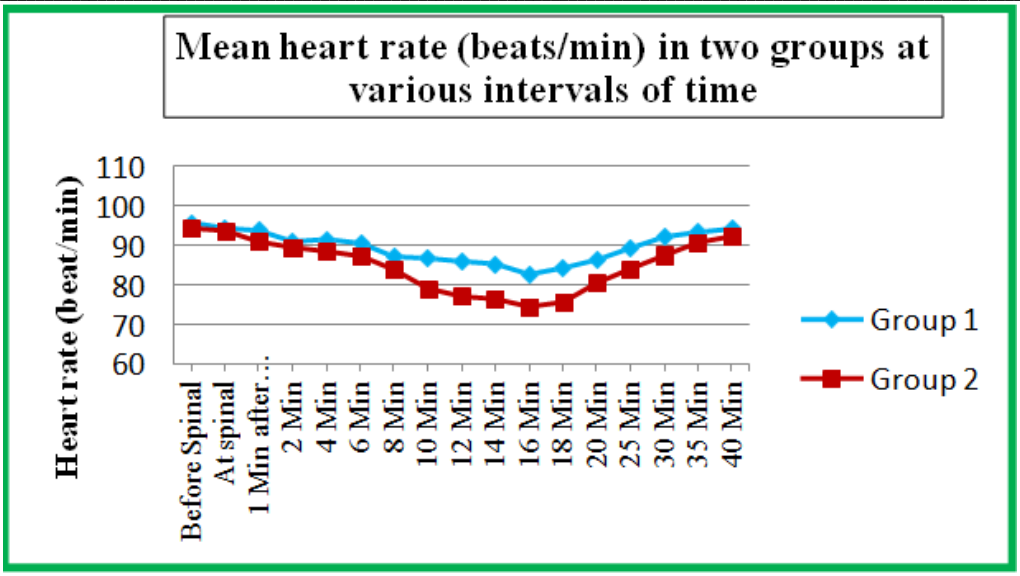

Figure 1: Line graph depicting mean heart rate (beats /min) of study patients in two groups atvarious intervals of time.

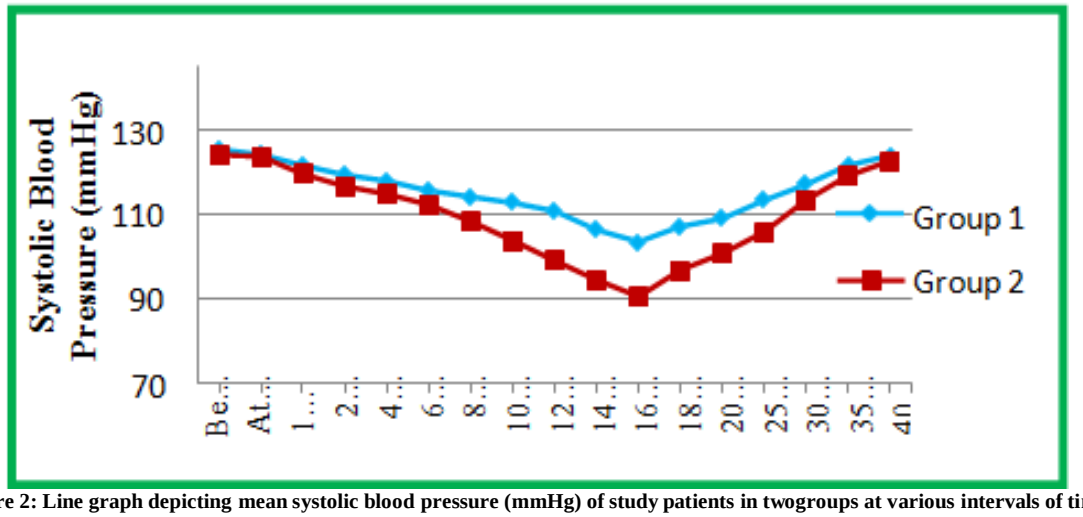

Figure 2: Line graph depicting mean systolic blood pressure (mmHg) of study patients in twogroups at various intervals of time.

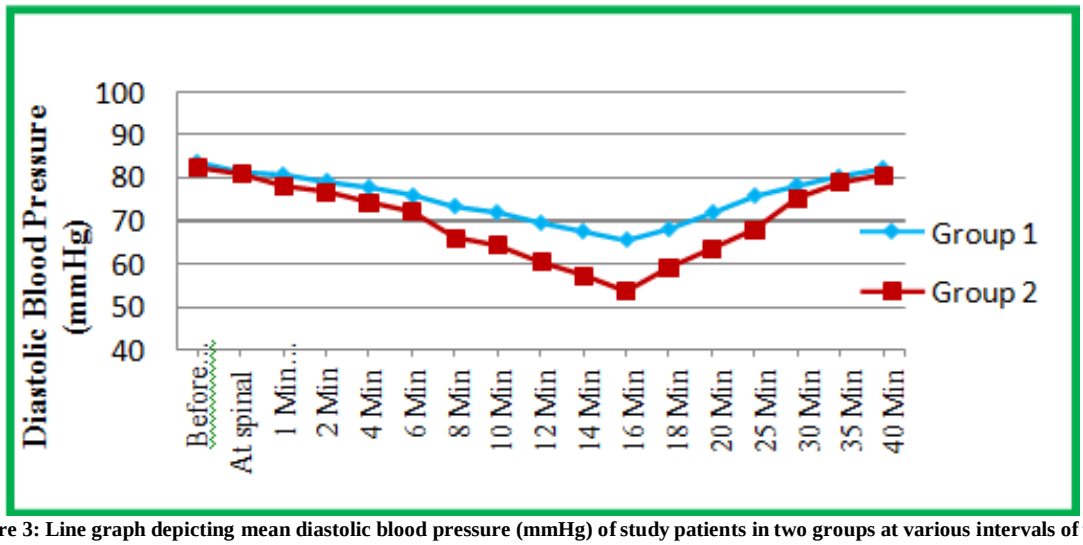

Figure 3: Line graph depicting mean diastolic blood pressure (mmHg) of study patients in two groups at various intervals of time

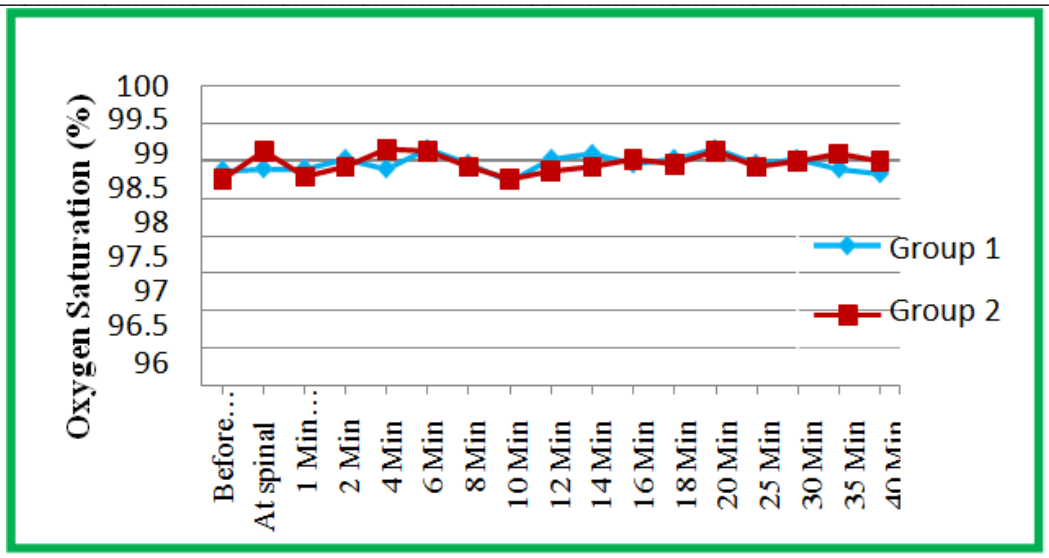

Figure 4: Line graph depicting mean oxygen saturation (SPO_2 %) of study patients in two groups at various intervals of time

The number of patients requiring phenylephrine bolus doses for hypotension was more in group 2 (normal saline group-83.3%) as compared to group 1((ondansetron group-56.7%). The total phenylephrine dose requirement was also more in group 2 (normal saline group) as compared to group 1(ondansetron group). The difference was statistically significant.(p-value <0.05)[Table 2]

Table 2: Comparison of vasopressor requirement between the two groups

Parameter	Group 1	Group 2	p-value
Phenylephrine doserequirement (No. of patients)	17	25	0.024
Phenylephrine dose(mcg) (Mean ±SD)	51.5±5.86	92.0±3.14	<0.001

There was a significant reduction in the incidence of nausea with prophylactic ondansetron (p-value<0.05). The incidence of vomiting was also significantly reduced in patients receiving prophylactic ondansetron (p-value<0.05) There was no statistically significant difference observed between two groups with respect to APGAR score (p-value>0.05).[Table 3]

Table 3: Comparison of nausea, vomiting and neonatal APGAR scores between the two groups

Parameter		Group 1	Group 2	p- value
Nausea (No. of patients)		0	8	0.005
Vomiting (No. of patients)		0	6	0.024
APGAR score (Mean ±SD)	1 min	7.20±0.407	7.40±0.498	0.094
	5 min	8.37±0.615	8.40±0.497	0.818
	10 min	8.90±0.305	8.97±0.183	0.309

Discussion

The main focus of obstetric anesthesia is to ensure the safety of mother and child. Therefore, it is essential to select the choice of correct anesthesia and its administration safely. Spinal anesthesia is the preferred technique of anesthesia in pregnant patients undergoing cesarean delivery. Hypotension following obstetric spinal anesthesia remains a common and important problem. The incidence of hypotension is as high as 50 to 60% in obstetric patients under spinal anesthesia. Recent advances, including better incidence delineation, improved understanding of haemodynamics and growing clarity on vasopressor choice[8,9]. These advances have not been translated into practical guidelines that can be used in settings where resources are limited. Strategies to combat hypotension on a pharmacological basis can be divided into 'reactive' or 'preventive' approaches. Various treatment methods used for post spinal hypotension (pre-loading, co-loading, and vasopressors) are not fully devoid of side effects. The pre-load on heart is increasedby fluid pre-loading or co-loading. The blood volume of the parturient is already increased in the later trimester of pregnancy and further increase in preload may not be tolerated well in some patients. The use of ephedrine may be associated with fetal acidosis which may influence the neonatal outcome. The use of phenylephrine increases the incidence of bradycardia and decreases cardiac output in the parturient[10,11]. Preventing hypotension rather than treating it is preferable as it would avoid these side effects. Effectively preventing or treating spinal-induced maternal hypotension is considered to be the Holy Grail of obstetric anaesthesia[12]. A systematic review reported that neither intravenous fluid preload nor vasoconstriction given before spinal anesthesia is effective in preventing hypotension[13].

The Bezold Jarisch Reflex is a cardioinhibitory reflex which originates in cardiac receptors with non-myelinated type C vagal fibers creating the afferent limb of the reflex. These chemoreceptors are sensitive to several different chemicals including serotonin (5HT). The 5-HT3 receptors are activated in response to systemic hypotension causing an increase in efferent vagal signaling, increased parasympathetic activity and decreased sympathetic activity, resulting in bradycardia, reduced cardiac output and further exacerbation of hypotension. Pharmacological andanimal studies suggest that 5-HT (serotonin) may be an important factor associated with inducing the Bezold-Jarisch Reflex and this effect can be blocked at the 5-HT3 receptor[14,15]. Due to the involvement of 5-HT3 receptors in causation of hypotension and bradycardia during spinal anesthesia, blockage of

these receptor can lead to improvement in hypotension and bradycardia. One study proposed that heart rate may be 'the best surrogate indicator of cardiac output during spinal anesthesia for cesarean delivery[16]**.** This is of particular relevance to the resource-poor setting, where targeting simple surrogate outcomes such as heart rate could be explored for practical implementation in clinical guidelines[17]. A simple intervention of use of prophylactic ondansetron may enable anesthesia providers to improve patient outcomes by minimizing the use of vasopressors after spinal anesthesia.

In the present study, prophylactic use of ondansetron 4mg was associated with better hemodynamic stability in terms of mean heart rate, blood pressure(systolic diastolic and mean) and requirement of vasopressors. Sahoo T *et al[18]*. observed that Ondansetron 4 mg, given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section, which is in concordance with our study. Owczuk *et al[19]*. found that ondansetron given intravenously attenuates the fall of systolic and mean arterial blood pressure but does not have an influence on diastolic blood pressure or heart rate. A single intravenous dose of ondansetron 4 mg given before induction of combined spinal– epidural anesthesia in women having elective cesarean delivery reduced the ED50 of a prophylactic phenylephrine infusion for preventing hypotension by approximately 26% in a study[20].

Another finding of the study was that ondansetron reduced the incidence of nausea and vomiting as compared to placebo. This finding is in agreement with Shivanand *et al[21]*. who suggested that prophylactic 4mg ondansetron is more efficacious in preventing post-operative nausea and vomiting in caesarean delivery under spinal anesthesia. Similar results were obtained by Rashad *et al[22]* who concluded that intravenous ondansetron prevents spinal anesthesia induced nausea ascompared with intravenous saline (p-value=0.008). Goa *et al[23]*. also concluded that prophylactic ondansetron reduce adverse outcome such as nausea and vomiting. However, in a study by Terkawi *et al[24]*. premedicating patients with i.v. 8mg ondansetron before spinal anesthesia had no effect in preventing nausea and vomiting.

This study confirmed our clinical impression that giving prophylactic intravenous 4mg ondansetron before spinal anesthesia in parturients undergoing caesarean section would be effective in reducing the incidence of spinal induced hypotension, bradycardia and in the prevention of adverse effects of spinal anesthesia such as nausea and vomiting.

Limitations

Randomisation was not done in the study. To reduce bias, the anesthesiologist recording various parameters was blinded to group allocation.

Conclusion

In conclusion, prophylactic administration of intravenous 4mg ondansetron 5 minutes before spinal anesthesia in parturients undergoing elective caesarean section can preventthe development of post spinal hypotension and bradycardia. It also reduced the requirement of vasopressors for hypotension. Ondansetron also significantly reduced the incidence of adverse effects of spinal anesthesia such as nausea and vomiting in the study patients. No adverse effectson the fetus in this study were observed as indicated by APGAR scores.

The authors recommend prophylactic use of intravenous 4mg ondansetron 5 minutes before spinal anesthesia in parturients undergoing caesarean section in terms of greater maternal hemodynamic stability, lesser incidence of adverse effects and better fetal outcome after spinal anesthesia.

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