Attenuation of Hypotension due to Spinal Anaesthesia with Ondansetron in Parturients Undergoing Caesarean Section: An Observational Study

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ABSTRACT

BACKGROUND

About seventy to eighty percent of patients experience hypotension during caesarean section conducted under spinal anaesthesia. Bezold Jarisch Reflex is hypothesized to be one of the main factors contributing to this cycle of deleterious hypotension and bradycardia. Studies suggests that ondansetron (5-HT3 receptor antagonist) can antagonize this cycle of events from the receptor level and can prevent it.

AIMS

To study the efficacy of prophylactic intravenous ondansetron in preventing hypotension due to spinal anaesthesia and to compare the hemodynamic parameters among two study groups undergoing planned elective caesarean section.

METHODS

It was a prospective comparative study and out of sixty subjects undergoing elective caesarean section, thirty were those received intravenous ondansetron 4 mg intravenously 5 to 10 minutes prior to spinal anaesthesia and thirty were those who did not receive any ondansetron prior to the spinal anaesthesia. Incidence of hypotension, use of vasopressor, systolic and diastolic blood pressure, mean arterial pressure and heart rate were measured at baseline, every 2 - minute for first 20 minutes followed by every 5-minute till the end of the procedure.

RESULTS

We observed that there was significant statistical difference in the number of hypotensive incidents between the Saline and the Ondansetron group, The number of hypotensive episodes was significantly less (p-value: 0.00096) and the number of cases which received vasopressor were also correspondingly less in the Ondansetron group (p-value: 0.00096).

CONCLUSIONS

We observed that intravenous Ondansetron at a dose of 4mg given 5 to 10 minutes prior to spinal anaesthesia significantly reduced the incidence of episodes of hypotension due to spinal anaesthesia in obstetric patients who underwent elective caesarean delivery.

KEYWORDS

Spinal Anaesthesia, Ondansetron, Hypotension, Bezold-Jarisch Reflex, Serotonin, Caesarean Section

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BACKGROUND

Spinal anaesthesia is the most common modality of anaesthesia employed for parturients undergoing caesarean delivery owing to its rapid onset of action, reliability, superior postoperative pain control and lower mortality rate when compared to general anaesthesia.[1] About seventy to eighty percent of obstetric patients experience spinal anaesthesia-induced hypotension if its undergone without any pharmacological prophylaxis compared to nearly 33 % of non-obstetric patients undergoing the same.[2] The high incidence of spinal anaesthesia-induced hypotension during caesarean delivery is attributable to the physiological changes of the mother during pregnancy including the effects of aorto-caval compression from the gravid uterus.[3] Hypotension and bradycardia is caused primarily by reduction in vascular resistance by sympathetic nerve blockade, increased baroreceptor activity and by induction of Bezold Jarisch reflex (BJR).[2] The BJR results from decreased filling of the right atrium, which reduces the outflow from some intrinsic chronotropic stretch mechano-receptors in the ventricular wall.[4] Studies have demonstrated that serotonin, 5- hydroxytryptamine (5-HT) is associated with the induction of the BJR when the heart contracts in the setting of decreased blood volume.[5] Triggering of chemoreceptors sensitive to serotonin in the intra-cardiac wall by a reduction in blood volume lead to increased vagal nerve activity resulting in the deleterious reflex cycle of bradycardia and hypotension.[6] This reflex arc triggering can be blocked at the level of 5-hydroxytryptamine subtype 3 (5-HT3) receptors. Recent studies suggests that ondansetron, a (5-HT3) receptor antagonist, generally used for prophylaxis and treatment of nausea and vomiting can also reduce the hemodynamic changes induced by spinal anaesthesia.[7,8] The mechanism of action is believed to be by the inhibition of the BJR at the receptor level, but whether ondansetron can be routinely used to prevent spinal anaesthesia-induced hemodynamic changes is still unclear. In this study we observed the effects of the serotonergic receptor blocking potential of ondansetron to prevent BJR induced hypotension and bradycardia after spinal anaesthesia for elective caesarean deliveries. The primary outcome measured was maternal systolic blood pressure from spinal block to delivery." The number of hypotensive episodes, incidence of bradycardia and use of vasopressors were the measured secondary outcomes. If found successful, this simple technique can help to prevent hypotension and bradycardia during spinal anaesthesia. It is easy, simple and more economic strategy compared to other pharmacological interventions to counteract hypotension.

METHODS

Study Setting

The study was set at Department of Anaesthesiology, Government Medical College, Thrissur and Kerala, India. Institutional ethical committee reviewed the study and approved it on 16 / 12 / 2014 as "Attenuation of Hypotension due to Spinal Anaesthesia with Ondansetron in Parturients Undergoing Caesarean Section - An Observational Study".

Study Population

It was conducted in parturients admitted for elective caesarean section over a period of twelve months from January 2015 to February 2016.

Study Design

It was done as a prospective comparative study.

Inclusion and Exclusion Criteria

The participants of the study were selected for observation and consented after applying the inclusion and the exclusion criteria. Inclusion criteria included all patients with ASA-PSII (American Society of Anaesthesiologists-Physical Status), aged 19 - 40 years, whose weight was between 50 to 70 kilograms, height between 145 and 170 cm, undergoing elective lower segment caesarean section (LSCS). Exclusion criteria excluded emergency caesarean section, procedures done under general anaesthesia, those receiving SSRIs (selective serotonin re-uptake inhibitors), hypertensive disorders of pregnancy and those patients who refused to consent.

Sample Size Calculation

Sample size was estimated using the formula: N = Z2 (1-α / 2) [2Sp2] / d2 where, Z is the confidence limit function which is 1.96 for 95 % confidence interval. α is the significance level, d is the precision factor calculated as 5.8. Sp2 is the pooled standard deviation. Sp2 is calculated as S12 + S22 / 2, where S12 is the standard deviation of the first group (11.7) & S22 is the standard deviation of second group (10.5). Sample size was estimated to be thirty for each group. All the participants who fulfilled the above criteria were informed about the study and signed written consent was obtained.

Study Procedure

As per the institutional protocol, every patient admitted for elective caesarean section received 150mg of Ranitidine orally the night before surgery and 150mg Ranitidine with 10mg Metoclopramide orally in the morning of surgery. There is no institutional protocol for further use of antiemetic for procedures done under spinal anaesthesia and the decision to give, if any, depended on the clinical decision of the consultant anaesthetist performing the procedure, therefore, some patients received Ondansetron 4mg IV while some others did not receive any immediately prior to spinal anaesthesia (usually 5 to 10 minutes prior to spinal anaesthesia). We observed the haemo-dynamic parameters of patients who received Ondansetron and those of patients who did not receive any and then compared them to see the effect Ondansetron has on haemodynamic stability after spinal anaesthesia. The participants who received 4mg of Ondansetron were called the Ondansetron group, the patients who did not receive any further antiemetic was called the Saline group. All patients were hydrated with 0.9 % Normal Saline at 20 ml / kg / hr through 18 - Gauge (Green) peripheral cannula and the baseline parameters of heart rate (HR), non-invasive blood pressure (BP) were measured in anaesthesia room. In the operating room all the necessary monitors were attached and Heart rate (HR), non-invasive BP, electrocardiogram (ECG) and pulse oximeter (SpO2) were attached, recorded and documented. Oxygen was given through mask at the rate of 5 litres per minute. Patients are then kept in left-lateral position and the lumbar area is then cleaned and draped. Spinal anaesthesia was administered intrathecally at 3rd-4th lumbar or 4^{th} - 5^{th} lumbar space using Quincke spinal needle (25 - Gauge) and 1.8 ml of 0.5% hyperbaric Bupivacaine was instilled after confirming free flow of cerebrospinal fluid. Immediately after administration, Patients were made supine with a 15 ° left lateral tilt to avoid aorto-caval compression. The heart rate (HR), the systolic blood pressure (SBP), the diastolic blood pressure (DBP), the mean arterial pressure (MAP), and the peripheral oxygen saturation (SpO2) were recorded at time of spinal

anaesthesia and at interval of two minute for the first 20 minutes and then at interval of five minute until the end of the caesarean section. Sensory levels of anaesthesia were assessed and recorded after 5 minutes, at 10 minutes and after the end of the procedure. A fall in SBP by 25 % of the initial value was taken as hypotension. Chi - square test was used to analyse categorical data and t - test was used to analyse continuous data. Categorical data was presented as number of patients and percentage. Continuous data was presented as mean and standard deviation. Data was analysed using IBM SPSS software version 20.0. The p - value < 0.05 was considered statistically significant.

RESULTS

Sixty subjects were selected for study; thirty parturients to each group. Sixty five percentage of the subjects were between the age of 21 to 30 years (n = 22 in Ondansetron group and n = 17 in the Saline group). The mean age of patients in the Saline and Ondansetron group was 28.2 and 27.43 years respectively. The difference in the mean age between the two groups had no statistical significance (p - value: 0.498). The mean weight of patients in the Saline and Ondansetron groups was 58.53 and 57.97 kilograms respectively. The difference in mean weight between the two groups had no statistical significance (p - value: 0.663). The ASA of all 60 patients in the study was II. The participants of both groups had comparable haemodynamic variables like baseline heart rate (HR), baseline systolic blood pressure (SBP), baseline diastolic blood pressure (DBP) and baseline mean arterial blood pressure (MAP) with no statistically significant difference (p - value: 0.751, p - value: 0.506, p-value: 0.745 and p - value: 0.619 respectively).

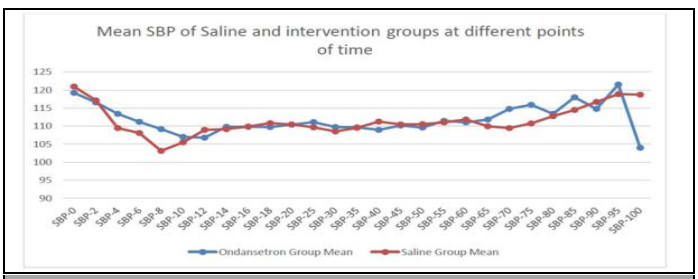

Figure 1 Line Diagram Showing Comparison of the Sbp of the Saline and Ondansetron Groups at Different Points of Time

Hypotension	Saline/Ondansetron		Chi-Square (χ2) value	P value
	Odansetron Group	Saline Group		
Hypotension Absent	21 (70 %)	9 (30 %)		
Hypotension Present	9 (30 %)	21 (70 %)		
Total	30	30	32	< 0.001*

Table 1 Comparison on the Incidence of Episodes of Hypotension: Ondansetron and the Group

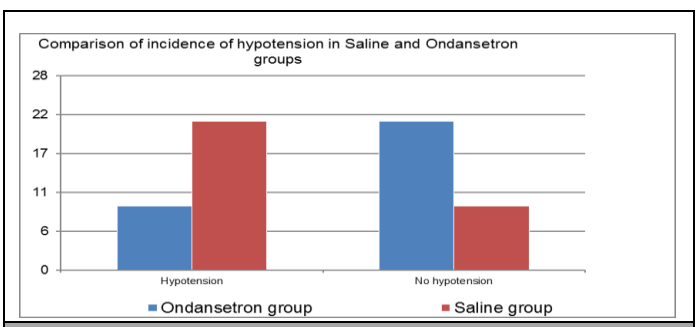

Figure 2 Graph Showing Comparison of Incidence of Hypotension in the Ondansetron and Saline Groups

It was seen that 21 patients (70 %) in the Saline group had hypotension while only nine patients (30 %) had hypotension in the Ondansetron group. Statistical analysis using Chi-square test showed that the difference between these two groups was significant statistically (p value < 0.01). Incidence of hypotension with respect to the mean arterial blood pressure (MAP) and diastolic blood pressure (DBP) were also documented separately. The difference was statistically significant (p value < 0.01). There was no incidence of bradycardia (less than 50 bpm) in the Saline or Ondansetron groups. There were no incidences of SPO2 fall in the Saline and Ondansetron groups.

Hypotensive episodes	Odansetron Group Median ±IQR	Saline Group Median ±IQR	p Value
SBP Hypotensive episodes	0 ± 1	1 ± 2	<0.01*
	(-1 to +1)	(-1 to 3)	
DBP Hypotensive episodes	0 ± 1	1 ± 2	<0.01*
	(-1 to +1)	(-1 to 3)	
MAP Hypotensive episodes	0 ± 1	1 ± 2	<0.01*
	(-1 to +1)	(-1 to 3)	

Table 2 Comparison of the Number of Hypotensive Episodes Between the Saline and Ondansetron Group – Systolic, Diastolic and Mean Arterial Pressure

*The result is significant at p < 0.05.

An analysis of the number of systolic hypotensive episodes between the Saline and Ondansetron groups using Mann Whitney U test showed that z - score is - 3.389 and p - value is < 0.01. The result is significant at p < .05, there were more number of hypotensive episodes in the Saline group and that this difference was statistically significant (p < 0.01). The same findings were reflected in the analysis of the number of hypotensive episodes in the diastolic BP and MAP with z - score is - 3.769 and p - value is < 0.01.

	Odansetron Group Median ± IQR	Saline Group Median ± IQR	p Value
Number of Times Vasopressor Bolus was used	0 ± 1	1 ± 2	<0.01*
	(-1 to +1)	(-1 to 3)	

Table 3 Comparison of Use of Vasopressor Boluses Among the Ondansetron and Saline Group

*The result is significant at p < 0.05.

The results show that the number of times vasopressor bolus had to be used corresponded with the number of hypotensive episodes in the Ondansetron and Saline groups. The average number of times vasopressor used in the Ondansetron group and Intervention group using Mann Whitney U test showed that z - score is - 3.604 and p-value is < 0.01. The result is significant at p < 0.05. There was no difference which was statistically significant (p value = 0.548) between the two groups with regards to the sensory level attained at five minutes (p value = 0.753, ten minutes (p value = 0.726) and at the end of surgery.

DISCUSSION

"We evaluated 60 adult female patients with similar demographic profiles like age, weight, ASA physical status who underwent elective caesarean section under spinal anaesthesia. Our observation of statistically significant

difference in the incidence of hypotension between the saline group and the group which received ondansetron (p value = 0.00096) with the ondansetron group having lesser incidence of hypotension is similar to the findings of Sahoo et al., who also observed that when given ondansetron 4 mg intravenously 5 min before spinal anaesthesia, it reduced hypotension and vasopressor use in parturients undergoing elective caesarean section.[8] It is known that sympathetic blockade from spinal anaesthesia decreases systemic vascular resistance and induces peripheral pooling of blood leading to relative hypovolemia and hypotension. In response to hypovolemia, stimulation of cardiac sensory receptors in the left ventricle induces the BJR and results in reflex bradycardia, vasodilation and hypotension.[9,10] Activation of 5 - HT3 receptors, which are G-protein coupled and ligand-gated ion channels, results in increased efferent vagal nerve activity, frequently producing bradycardia.[11] Spinal anaesthesia thus causes vasodilatation, hypotension, and bradycardia by sympathetic blockade and by the induction of BJR. In our study, one of the outcomes measured was the sensory levels attained at five minutes, ten minutes and at the end of surgery. It was interesting to note that there was no significant difference in the sensory levels attained in the intervention and control groups. Hence the incidences of hypotension cannot be explained by higher levels of sensory and autonomic blockade alone in either groups. It can be hypothesised that ondansetron, a 5 - HT3 receptor antagonist prevents the serotonin-induced BJR, suppresses venodilatation, augments venous return to the heart and results in lesser reductions in SBP and MAP.[6,11] Owczuk et al. in a mixed group of patients aged 20 – 70 years, also found that ondansetron 8mg decreased the incidence of bradycardia and hypotension after spinal anaesthesia.[7] They observed that although there was decrease in both heart rate and blood pressure (systolic, diastolic and mean) in the ondansetron and control groups, the systolic and mean blood pressure values obtained over a 20 minute period were higher to a significant extent in the ondansetron group. In 2015, Owczuk et al., in a study comparing effectiveness of ondansetron to reduce spinal anaesthesia induced hypotension in geriatric patients observed that administration of intravenous ondansetron prior to spinal anaesthesia in geriatric decreased the drop in the diastolic and mean arterial pressure without substantially affecting the systolic blood pressure.[12] A randomized control trial comparing ondansetron and placebo for the reduction of spinal anaesthesia induced hypotension during elective caesarean surgery in Egypt found that prophylactic intravenous ondansetron significantly reduced hypotension and heart rate fluctuations among the intervention group.[13] the decreases in systolic blood pressure were reduced throughout in patients receiving ondansetron (p value = 0.05). Reduction in the incidence of hypotension was also reported by Walid Trabelsi et al. who found that prophylactic ondansetron had a significant effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia with bupivacaine and sufentanil for elective caesarean delivery.[14] Rashad et al., have also reported similar findings in a similar sample of patients.[15]

A unique finding in our study was that there were significant differences in the incidence of hypotension in the systolic, diastolic as well as mean arterial pressures uniformly whereas in the above studies it was either one or two parameters which showed a significant difference. However, two double-blind randomized placebo controlled trial did not find any significant difference in the incidence of hypotension in parturients undergoing spinal anaesthesia using different doses of prophylactic ondansetron.[16,17] Possible reasons for this disparity could be inclusion of a specific population, sample size, study design, and difference in anaesthetic techniques. There were no incidences of bradycardia in our study in both groups, similar to the findings of Sahoo et al.[8] Limitations of this study include that it was an observational study, had small sample size and different doses of ondansetron were not evaluated. Ondansetron is used primarily for prophylaxis or treatment of postoperative nausea and vomiting (PONV) in intravenous doses of 4 mg and 8 mg. Doses as low as 0.05 mg/kg have been used to effectively decrease PONV, however, we selected the standard dose of ondansetron 4 mg used in our institution."

CONCLUSION

Our study indicates that prophylactic Ondansetron at a dose of 4 mg reduces the incidence of hypotension after spinal anaesthesia for elective caesarean delivery. There were also significant reductions in the number of hypotensive episodes in the ondansetron group in comparison to the saline group. Ondansetron use also benefited from a decrease in the need to use of vasopressor agents to maintain haemodynamic stability in the Ondansetron group. This could be a simple, cost-effective method to counter-act the troublesome side effect of maternal hypotension after spinal anesthesia for an elective caesarean section in the developing countries. Further studies with larger samples and varying doses of ondansetron are needed. Other maternal and foetal outcome measures like incidences of post-operative nausea, vomiting, foetal acidosis, APGAR scores in patients receiving ondansetron is also necessary to understand the safety profile of this technique.

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