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Comparison of Granisetron and Ondansetron on the Spinal Anesthesia Induced Hypotension, Bradycardia and Fetal Outcome after Administration Intrathecal Hyperbaric Bupivacaine in Patients Undergoing Cesarean Sections

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Abstract

Background: Spinal anesthesia is easy to perform and provides a rapid-onset, dense surgical block. It is associated with hypotension and bradycardia, which may be deleterious to both mother and baby[1]. Various preventive methods are used to prevent or minimize hypotension including uterine displacement, fluid preloading, and compression stocking the lower extremities.[2]This study compares the effectiveness of Granisetron and Ondansetron on the spinal anesthesia induced hypotension, bradycardia after intrathecal hyperbaric Bupivacaine in patients undergoing cesarean sections. *Materials and Methods:* Sixty full-term patients posted for cesarean section belonging to ASA I or II were randomly assigned to Two Groups each containing 30 patients. Group G received 1 mg Granisetron and Group O received 4mg Ondansetron. Hemodynamic were noted at regularly along with APGAR score. *Results:* Trend observed in heart rate following the administration of the test drugs in both the groups and was not significant. The baseline hemodynamic of the patients were insignificant in both the Groups. This continued to be the case for up to 5 minutes after delivery of the drugs. At 10, 20, 30 and 45 minutes however, all three parameters were higher in Group O than Group G. At 60 mins however, no significant difference is seen between the groups. Similar trend was observed in APGAR score in neonates of both the Groups. *Conclusion:* Ondansetron was more effective in attenuation of spinal anesthesia induced hypotension than in Granisetron. Both the Groups had no significant difference in prevention of bradycardia oxygen saturation and foetal outcome.

Keywords: Cesarean Section**;** Granisetron; Ondensetron; Hemodynamic; Spinal Anesthesia.

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Introduction

For a pregnant patient Spinal anesthesia is the most sought after technique as it is cheaper, simple to perform and produces rapid onset of anesthesia and complete muscle relaxation and does not carry the risk of maternal or fetal-risk for toxicity to local anesthetics (Nag et al., 2015). Since, the introduction of smaller diameter, noncutting, pencil point Whitaker's spinal needles

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the incidence of postdural puncture headache has become low (<5%).[3] Hyperbaric Bupivacaine is the most commonly used agent for spinal anesthesia when performing cesarean sections. It's duration of action of 1.5 to 2 hours is perfectly matched to duration of surgery in most cases.

Up to 71% of women who receive spinal anesthesia for cesarean delivery experience spinal hypotension.[4] Spinal hypotension can be severe and may occur precipitously, giving rise to perinatal adverse outcomes, such as maternal nausea and vomiting, fetal acidosis and may be an important cause for maternal death related to regional anesthesia.[5] Pregnant patients with depleted intravascular fluid due to dehydration may be at risk of cardiovascular collapse because of the sympathetic blockade induced bradycardia and decreased preload. Considering all the adverse effects, prevention of spinal hypotension is one of the leading research area within the field of obstetric anesthesia.

For the treatment of spinal anesthesia induced hypotension, multiple pharmacological and non-pharmacological methods have been tried, none of the methods are adequate or conclusively superior to others. The nonpharmacological methods commonly used to prevent hypotension are leg compression and elevation using tight fitting elastic stockings and wedge placement under right buttock for avoidance of aorto-caval compression prevents hypotension to some degree, but is of limited use by the cost and moreover they are not stand-alone method to prevent hypotension. For pharmacological methods preloading with fluids and vasopressors are the most common methods used to prevent hypotension. Among Intravenous fluids colloid is significantly more effective than crystalloids.[6] Over infusion of crystalloid can cause dilutional anemia as it has shorter half-life.[7] This patients have a greater chance of developing pulmonary edema. Vasopressors are used to treat hypotension quickly. Directly acting selective α1 receptor agonists, phenylephrine and methoxamine, as well as both directly and indirectly acting drugs, mephentermine, metaraminol and ephedrine are used.[8,9]

Granisetron and Ondansetron are selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists. These receptors are present as cardiac chemoreceptors on the cardiac vagal afferent located peripherally and centrally in the chemoreceptor trigger zone that mediate Bezold-Jarisch reflex. Bezold-Jarisch reflex cause inhibition of vasomotor centers when stimulated, promoting vasodilatation and hypotension. The receptors of the Bezold-Jarisch reflex located within the walls of the heart respond to systemic responses to hypervolemia and hypovolemia. After spinal blockade, there is decreased venous return of blood to the heart that results in alteration of the cardiac wall and stimulation of cardiac mechanoreceptors, which results in activation of the Bezold-Jarisch reflex, and thus inducing hypotension and bradycardia.[10] The activation of peripheral 5-HT3 receptors located in intracardiac vagal nerve endings by serotonin further elicits the Bezold-Jarisch reflex resulting in hypotension and bradycardia. The stimulation of 5-HT3 receptors located on sensory vagal nerve endings results in a lowered heart rate and an initial short-lasting hypotension followed by a longer lasting hypotension, attributed to the Bezold-Jarisch reflex. Current studies indicate that 5-HT3 antagonism may abolish the BJR response to spinal anesthesia.[11] In this study, we compare effectiveness of Granisetron and Ondensetron on postspinal hypotension, bradycardia in patients posted for cesarean section.

Materials and Methods

After approval of the medical ethics committee and obtaining well-informed written consent from each patient, this comparative study was conducted randomly in 60 patients undergoing cesarean section under spinal anesthesia at DY Patil Medical College and Research Centre. Patients were excluded if they have any contraindications to subarachnoid block, history of hypersensitivity to studied drugs, hypertensive disorders with pregnancy or those receiving selective serotonin reuptake inhibitors or migraine medications or refused to participate. Randomization was done using computer generated random number table as follows-Group O 4 mg Ondensetron and Group G 1mg Granisetron.

All patients were subjected to preanesthetic evaluation with relevant laboratory investigations. Preoperative vitals were noted. Peripheral venous access with 20 gauge intravenous catheter was established. All the patients were preloaded with 10 ml/kg of Ringer Lactate (RL) over 15 minutes and continued thereafter at a rate of approximately 10–15 ml/min throughout the study period. Study medications were prepared and in identical 10 ml syringes and injected 5 minutes prior to spinal anesthesia.

Spinal anesthesia was administered in sitting position under all aseptic precautions.

After painting and draping of the lumbar area, subarachnoid placement of Bupivacaine (2.2 ml of 0.5% Bupivacaine) through the L3-L4 or L2-L3 interspinous spaces was given using 26 G Quinke's spinal needle.

The target block height was equal to or above T8 and the surgeon was asked to proceed. Oxygen was administered at a rate of 3l/min by a Hudson mask to all the patients until the umbilical cord was clamped. Inspite of giving study drugs sudden drop in blood pressure if noted was initially managed with intravenous crystalloid fluid bolus of 4 ml/kg. If not corrected with this, Injection Mephentermine 6 mg IV was given and was repeated after 3 minutes till it is corrected, the patients receiving vasopressors were excluded from the study and the experiment was terminated for them.

Systolic, diastolic and mean arterial blood pressure and heart rate were noted at 2 minutes and every 5 minutes after administration of spinal anesthesia for the first 30 minutes and every 15 minutes till end of surgery. Decrease in heart rate less than 50 beat/min was treated with 0.2 mg intravenous Glycopyrolate and the patients receiving Glycopyrolate were excluded from the study and the experiment was terminated for them. Vitals were monitored continuously. Apgar score at zero, first, third and fifth minute was noted. Any side effects in the immediate postoperative period was also noted.

Results

The study was conducted on total of 60 patients and were randomly divided into two equal groups, using computer generated random allocation chart. Both the groups were proportional with regards to age, weight, ASA physical status. The mean arterial pressure in the group which was given Granisetron is much lower than the group which was given Ondansetron. There was no significant difference between the two groups as per the calculation of *t*-Test ($p > 0.05$). This continues to be the case for up to 5 mins after delivery of the drugs. However, at 10, 20, 30, 45 minutes Ondansetron attenuates fall in mean arterial pressure compared to Granisetron (p value < 0.05). At 60 mins however, no significant difference is seen between the groups (Fig.1). Similar, trends were observed in heart rate, Fig. 2, oxygen saturation, Fig. 3 and APGAR score shown in Table 1, following the administration of the test drugs in both the Groups.

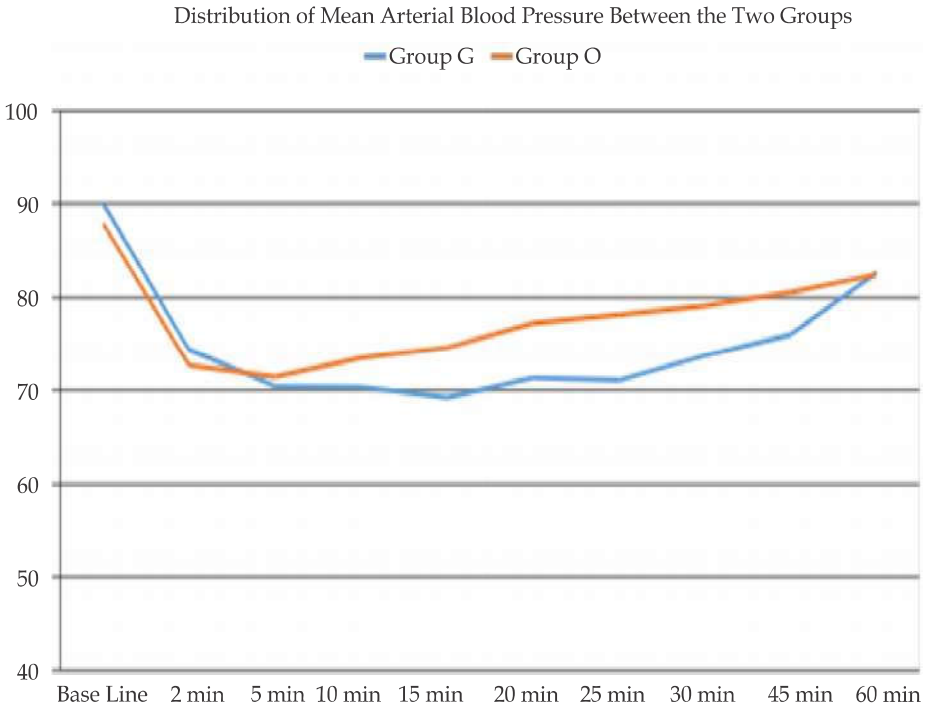

Fig. 1: Line diagram showing comparison of mean arterial blood pressure in Group G and Group O (Baseline mean arterial blood pressure: Group G- 90.02 ± 7.43 mm Hg and Group O -87.86 ± 6.16 mm Hg.)

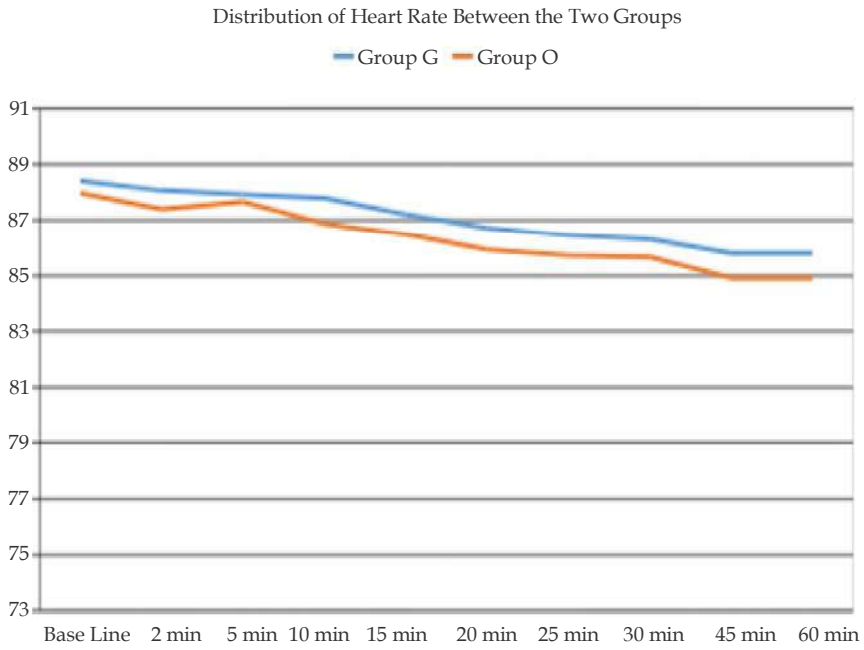

Fig. 2: Line diagram showing comparison of heart rate in Group G and Group O

Fig. 3: Line diagram showing comparison of mean SpO_2 in Group G and Group O

Table 1: APGAR score distribution between Group G and Group O

Apgar Score	Group	Mean	SD	*t*-Test	*p* - Value
	Group G	6.83	.747	.784	.436
0 Mins	Group O	6.97	.556		
1 Mins	Group G	7.47	.681	.366	.716
	Group O	7.53	.730		
3 Mins	Group G	7.83	.699	1.82	.074
	Group O	8.20	.484		
5 Mins	Group G	8.33	.547	1.97	.053
	Group O	8.60	.498		

Discussion

Our randomized controlled study was designed to test the comparison of effectiveness and of pretreatment with intravenous Ondansetron or Granisetron for the prevention of spinal anesthesia induced hypotension and bradycardia and on the fetal outcome.

Our study shows that, prophylactic intravenous administration of 4 mg Ondansetron or 1mg Granisetron 5 min before induction of spinal anesthesia significantly reduces the severity of spinal-induced hypotension with significant differences between Ondansetron and Granisetron in regards to systolic, diastolic and mean blood pressure at 10, 20, 30, 45 minutes with Ondansetron being more efficient in prevention of spinal induced hypotension.

Our results matched with that of Omyma M Khalifa who conducted a study in 2014 "A comparative study of prophylactic intravenous Granisetron, Ondansetron, and Ephedrine in attenuating hypotension and its effect on motor and sensory block in elective cesarean section under spinal anesthesia" on eighty parturient. They reported that the reduction in mean arterial pressure was significantly lower in the therapeutic groups, with the best results recorded in the O group and nearly comparable results in G and E groups.[12]

In contrast, Alaa El Deen Mahmoud Sayed et al. (2017) compared the efficacy of intravenous Ondansetron and Granisetron on hemodynamics, shivering and motor & sensory block in female undergoing elective cesarean section under spinal anesthesia and concluded that prophylactic intravenous administration of 4 mg Ondansetron or 1mg Granisetron 5 min before induction of spinal anesthesia significantly reduces the severity of spinal-induced hypotension compared to saline group by attenuating fall in mean arterial blood pressure with no significant differences on mean arterial pressure between Ondansetron and Granisetron groups.[13]

Comparison of pulse rate at different time intervals using *Z* test showed no statistical difference between the two groups. ($p > 0.05$). The result of our study on the effect of heart rate after spinal anesthesia was comparable to studies conducted by Owczuk R et al. and Rashad and Farmawy in 2008 and 2014 respectively. Owczuk R et al. (2008) conducted a study titled "Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: A double-blind, placebo-controlled study." and concluded that IV Ondansetron has no effect on heart rate.[14]

Rashad and Farmawy (2013) examined 60 patients undergoing spinal anesthesia for cesarean section and randomly divided them into 3 equal groups. Five minutes prior to spinal anesthesia, Group O ($n = 20$) Ondansetron 4 mg, Group G ($n = 20$) Granisetron 1 mg, and Group S ($n = 20$) normal saline all received their respected doses. MAP was measured at 5-minute intervals in each group. In regards to decreases in mean arterial pressure, there was significant distinctness between Group O and both Groups G and S at 5, 10, 15, 20 and 25 minutes.[15]

Similar trend was observed in Apgar score in neonates of both the groups. The Apgar score was analyzed quantitatively within the groups for each stage and the p - value was found to be statistically not significant. There is scarce literature evidence on the effect of 5 HT3 receptor antagonists on fetal outcome, however, Pasternak et al. (2017) investigated the risk of adverse fetal outcomes associated with Ondansetron in a study that included 608,385 pregnancies from the period of January 2004 through March 2011 and concluded there was no significantly increased risk of adverse fetal outcomes when Ondansetron was taken during pregnancy.[16] Whereas Walid Teabelsi et al. (2015) in the study on efficacy of Ondansetron on spinal induced hypotension and on Neonatal outcome concluded that that Ondansetron can be helpful to improve metabolic and vital parameters of newborns.[17]

Conclusion

To conclude, our study validates the use premedication of 4 mg Ondansetron over 1 mg Granisetron for prevention of incidence of hypotension in healthy parturients undergoing spinal anesthesia with Bupivacaine for elective cesarean delivery as significant difference was noted in the incidence of attenuation of spinal anesthesia induced hypotension in Ondansetron group compared to Granisetron group.

Limitations

The limitations of this study are that we did not compare the need for rescue vasopressor and the effect of these drugs on sensory and motor blockade in parturients undergoing cesarean section. Finally, postoperative nausea and vomiting, pain, and analgesic requirement were not studied.

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Conflicts of Interest: Nil

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