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Effect of ondansetron on spinal induced hypotension in caesarean deliveries

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Abstract

Background: Spinal anesthesia is the preferred technique of anesthesia employed for caesarean sections. However, it is very often complicated by hypotension. Different drugs and techniques have been used to prevent the hypotension induced by spinal anesthesia. In this study, the effect of ondansetron on the prevention of hypotension after spinal anesthesia was evaluated.

Objectives: To determine the effect of prophylactic ondansetron on prevention of spinal induced hypotension in elective caesarean section.

Methodology: Eighty-six parturients planned for elective caesarean deliveries were randomized into two groups of 43 each. Group O received Ondansetron 4 mg (4 ml) and Group S received Normal Saline (4 ml) intravenously 10 minutes prior to spinal anesthesia. Blood pressure, heart rate, phenylephrine requirements, occurrence of nausea and vomiting and APGAR scores of neonates were compared between the groups. Hemodynamic data was analyzed using Student's t-test for intergroup comparison and ANOVA was used for intragroup comparison. Categorical data was analyzed using Pearson Chi-Square test. For all determinants, p-value <0.05 was considered significant.

Results: Occurrence of hypotension in Group O (20.9 %) was significantly lower than in Group S (72.1%) ($p < 0.05$). The mean arterial pressure was significantly higher in Group O at 2, 6, 8, 12 and 14 minutes ($p < 0.05$). The use of phenylephrine (37.21 mcg vs. 146.51 mcg, $p < 0.05$) and occurrence of nausea (11.6%, vs. 41.9% $p < 0.002$) was significantly lower in ondansetron group.

Conclusion: Ondansetron is effective in preventing spinal induced hypotension in elective caesarean sections.

Key words: Caesarean section; Hypotension; Ondansetron; Spinal anesthesia

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INTRODUCTION

Spinal anesthesia is the most common regional anesthetic technique used for caesarean section due to its simplicity, rapidity and reliable onset of anesthesia, low failure rates, minimal drug dose and the provision of excellent muscle relaxation during surgery[1,2]. Besides, spinal anesthesia is associated with lesser blood loss and avoidance of the risks of airway complications during general anesthesia in parturients, limited neonatal drug transfer and the ability of the mother to remain awake to experience childbirth[3].

However, spinal hypotension can complicate up to 70% of caesarean sections. The incidence of spinal hypotension mentioned in literatures is highly variable, ranging from 7.4% to 74.1%[1].

Hypotension during spinal anesthesia results from temporary sympatholysis leading to reduced preload and afterload[4], causing lower maternal mean arterial blood pressure[5], as well as due to activation of Bezold-Jarisch reflex (BJR)[6].

Studies have shown 5-HT3 antagonists block BJR[7]. Ondansetron, a 5-HT3 receptor antagonist has been shown to be effective in attenuating the hypotension

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accompanying spinal anesthesia in parturients undergoing elective caesarean deliveries in some studies[6, 8-11].

This study was conducted with the objective of determining the effect of ondansetron in preventing hypotension induced by spinal anesthesia in parturient undergoing cesarean deliveries.

METHODOLOGY

This prospective, randomized, double-blinded study was carried out after approval from the Institutional review board [IRB, Institute of Medicine, Tribhuvan University, 2017] at Tribhuvan University Teaching Hospital. Written informed consent was obtained from all the parturients before surgery. Eighty-six parturient females of American Society of Anaesthesiologists physical status (ASA-PS) grade II planned for elective cesarean section under spinal anaesthesia were enrolled in the study during period of eight months from November 2017 to June 2018. The primary objective of the study was to compare the incidence of hypotension between the ondansetron and normal saline group. The secondary objectives were to compare the total dose of rescue vasopressor (phenylephrine) in between the groups and to compare the incidence of nausea and vomiting and Apgar scores of the neonate between the groups.

Parturients with a history of hypersensitivity to bupivacaine or ondansetron, parturients with height less than 150cm, parturients on selective serotonin re-uptake inhibitors and parturients with hypertension, diabetes and pre-existing cardiovascular and cerebrovascular diseases were excluded. Parturients who failed to achieve upper sensory level block to T6 after spinal anaesthesia were also excluded from the study.

The preanaesthetic evaluation was done 1 day prior to the surgery. Parturients were informed about the study and written consent was taken. Eligible parturients were randomised 1:1 using computer-generated series into two groups of 43 each. Allocation concealment was done using a sealed opaque envelope each bearing only the number on the outer side.

All the parturients were fasted as per the guidelines of American Society of Anaesthesiologists[12]. All patients received ranitidine 150 mg and metoclopramide 10 mg orally two hours prior to surgery. In the preparation room, baseline non-invasive blood pressure in sitting position and pulse rate were recorded and intravenous access was secured with 18 gauge cannula. The study drug was prepared by an anaesthesia assistant not involved in the study. Group O received ondansetron 4 mg (4 ml) and Group S received Normal Saline (4 ml) intravenously 10 minutes prior to spinal anaesthesia.

In the operating room, pulse oximeter (SPO_2), electrocardiogram (ECG) and non-invasive blood pressure monitors were attached. Spinal anaesthesia was administered with 25 G Quincke's needle at L3-L4 or at L4-L5 interspace with the parturient in sitting position using 2.2 ml of 0.5% hyperbaric Bupivacaine via midline approach. Parturient was then kept supine with left uterine displacement. Co-loading with 10 ml/kg of Ringer's Lactate was started after the administration of spinal anesthesia and completed in 10 minutes.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded at the time of administration of sub-arachnoid block (time "0") and then every 2 min following spinal anaesthesia for 20 min and then every 5 min until end of surgery. Upper sensory level was assessed according to loss of cold sensation using cold swab every 5 min for 15 min, beyond which parturients were excluded from the study if sensory level was below T6. Motor block was assessed using Modified Bromage Scale[13]. Surgery was allowed to start as soon as upper sensory level reached T6. Hypotension was defined as SBP < 90 mmHg or MAP < 65 mmHg and was treated with boluses of intravenous phenylephrine 100mcg. Total phenylephrine required was recorded. Bradycardia was defined as HR < 45 per min[9] and was treated with Inj. atropine 0.6 mg, and nausea and vomiting was treated with Inj. promethazine 12.5 mg if required. Following delivery of the baby, 3 IU of oxytocin was given IV over 15 to 30 sec. Any additional use of oxytocin was noted in the "Remarks" section of the proforma. APGAR score of the neonate was noted at 1 min and 5 min.

At the end of surgery, SBP, MAP, HR and SPO_2 were noted, and the patients were shifted to the Post anesthesia care unit. Any occurrence of nausea and vomiting was recorded until the end of surgery and one-hour observation period thereafter. Urine output was monitored throughout the surgery. Patient was monitored for the adverse effects of ondansetron intraoperatively as well as post-operatively.

Statistical analysis was performed using Statistical Package for the Social Sciences version 24 (IBM SPSS Version 24.0. Armonk, NY: IBM Corp.). Hemodynamic data was analyzed using Student's independent t-test for intergroup comparison and repeated measures ANOVA was used for intragroup comparison. Categorical data was analyzed using Pearson Chi-Square test. For all determinants, p-value <0.05 (2- tailed) was considered statistically significant.

To calculate the required sample size, mean standard deviation (±10.2) of the change in MAP between the two groups and effect size (the difference between the mean values of MAP between the two groups =7.5) was taken from a previous study[11]. Assuming the dropout rate to be 10%, the sample size calculated was 43 in each group. The sample size was calculated to have power of 90% with an alpha error of 0.05.

RESULTS

Both groups were comparable in terms of demographic profile. There was no significant difference in age, weight and height between the two groups (Table 1).

A total of six patients in the normal saline group and one patient in the ondansetron group achieved an upper sensory level above T4. However, upper sensory levels achieved at 5, 10 and 15 minutes after the performance of spinal anesthesia were comparable in both the groups. There was no statistically significant difference in the upper sensory level achieved at 5 minutes, 10 minutes and 15 minutes (Table 2). The sensory level achieved at the end of 15 minutes was considered the highest sensory level.

All the patients in both groups achieved a motor block of Modified Bromage Grade 3 at the end of 5 minutes.

The incidence of hypotension in the ondansetron group was 20.9% compared to 72.1% in the normal saline group (Figure 1). This difference was statistically significant (p value <0.001).

There was statistically significant difference between mean SBP (at 2, 4, 6,8, 10, 14, 16, 18, 20 and 25 minutes; Figure 2) mean DBP (at 2, 6, 8, 12 and 14 minutes; Figure 3) and mean MAP (at 2, 6, 8, 10,12 & 14 minutes; Figure 4)) between the ondansetron and the normal saline group after the administration of spinal anesthesia.

No statistically significant difference was found between the heart rates in the ondansetron group and in the normal saline group. No episode of bradycardia was observed in either group.

Nine patients in the ondansetron group and 29 patients in the normal saline group required the use of phenylephrine for correction of hypotension. The use of vasopressor was significantly higher in the normal saline group (p = 0.001; Figure 5).

Five patients complained of nausea in the Ondansetron group compared to 18 patients in Normal saline group. The difference in the nausea between the two groups was statistically significant (p value 0.002) (Figure 6). None of the patients in either of the study groups had any episodes of vomiting.

The mean APGAR Score at 1 minute and 5 minutes in the ondansetron group was 6.98 ± 0.408 and 8.37 ± 0.489 and normal saline group was 6.98 ± 0.462 and 8.3 ± 0.465. There was no statistically significant difference between the groups.

Table 1: Demographic profile of parturients

Parameters	Group O (N= 43)	Group S (N= 43)	p- value
Age (Years)	29.19 (±4.3)	28.95 (±3.45)	0.783
Weight (Kg)	65.93(± 11.085)	66.56 (±7.62)	0.76
Height (cm)	153.47 (±4.479)	154.37 (±3.632)	0.35

Data described as mean (±Standard deviation).
p- value <0.05 is significant.
(Group O – Ondansetron 4mg, Group S – Normal Saline)

Table 2: Upper sensory level achieved

Time (minutes)	Thoracic Sensory level		p- value
	Group O	Group S	
5	4.53(±0.935)	4.65(±1.021)	0.583
10	3.95(±0.305)	3.91(±0.294)	0.473
15	3.95(±0.305)	3.93(±0.258)	0.704

Data described as mean (±Standard deviation).
p-value <0.05 is significant.
(Group O – Ondansetron 4mg, Group S – Normal Saline)

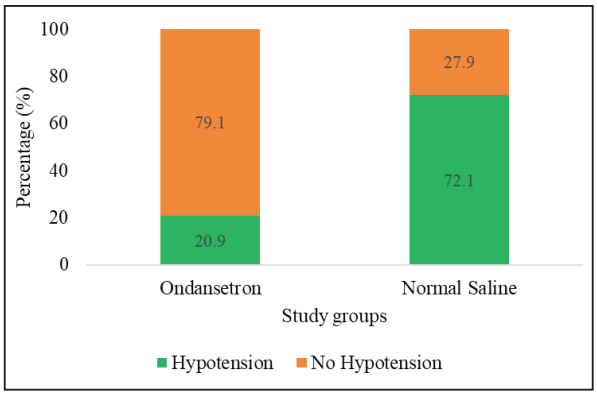

Figure 1: Incidence of Hypotension (p – value = <0.001)
(Ondansetron – Group O, Normal Saline – Group S)

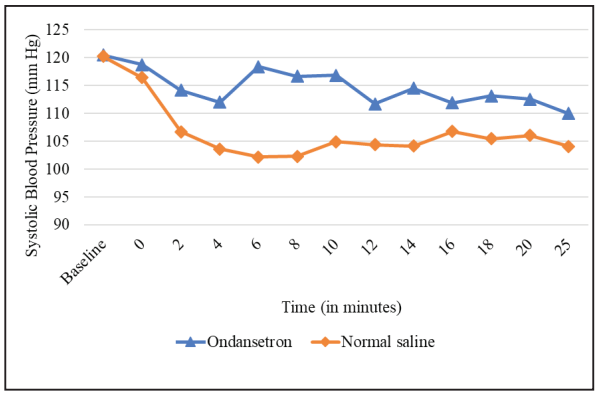

Figure 2: Comparison of systolic blood pressure between the groups
(Ondansetron – Group O, Normal Saline – Group S)

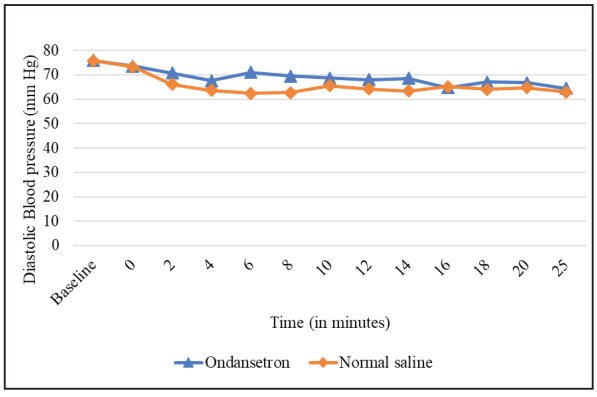

Figure 3: Comparison of Diastolic Blood Pressure between the groups
(Ondansetron – Group O, Normal Saline – Group S)

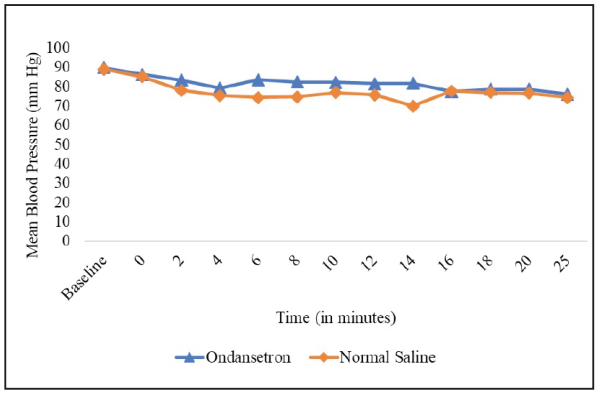

Figure 4: Comparison of Mean Arterial Pressure between groups
(Ondansetron – Group O, Normal Saline – Group S)

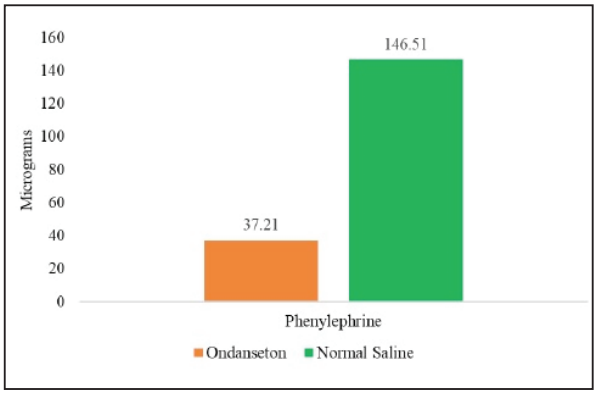

Figure 5: Comparison of mean consumption of Phenylephrine between the groups.
(Ondansetron – Group O, Normal Saline – Group S)

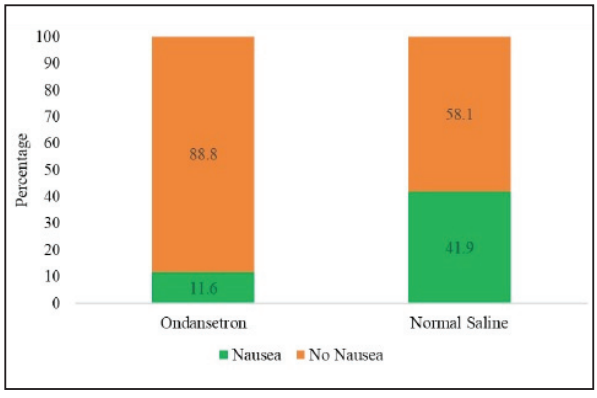

Figure 6: Comparison of incidence of nausea and vomiting between the groups
(Ondansetron – Group O, Normal Saline – Group S)

DISCUSSION

Different techniques have been used to prevent hypotension following spinal anaesthesia. Amongst the novel techniques, prophylactic use of intravenous ondansetron is gaining popularity with few studies proving its effectiveness[6, 8-11]. Our study also found prophylactic administration of 4 mg of ondansetron to be effective in preventing hypotension in parturients undergoing elective caesarean section under spinal anesthesia.

Of the many definitions of hypotension used in studies evaluating the effectiveness of various techniques of preventing hypotension following spinal anesthesia in caesarean section, systolic blood pressure of less than 90 mm of Hg is one of the most frequently used definitions[1]. In a retrospective analysis of 33,000 patients undergoing noncardiac surgery, Walsh et al found that intraoperatively a mean arterial pressure of less than 60 mm of Hg for any time period increased the risk of acute kidney injury and myocardial injury[14]. Guidelines on management of patients in shock recommend maintaining a MAP of greater than 65 mm of Hg to ensure adequate perfusion of vital organs like the kidneys, the brain and the heart[15]. So, hypotension for this study was defined as the systolic blood pressure of less than 90 mm of Hg or MAP of less than 65 mm of Hg. In the current study, a 5-hydroxytryptamine-3 receptor antagonist, ondansetron at an intravenous dose of 4 mg was selected to evaluate its effectiveness in preventing hypotension among parturients undergoing elective caesarean section under spinal anesthesia. The initial study performed by Owczuk et al revealed prophylactic ondansetron to be effective in attenuating the decrease in systolic and mean blood pressure following spinal anesthesia[18]. The investigators had, however, used ondansetron at an intravenous dose of 8 mg. Later similar studies were performed by different authors, but the dose of ondansetron used was highly variable ranging from 2 mg to 8 mg[9-11, 19]. Wang M et al evaluated 4 different dosage of ondansetron, 2 mg, 4 mg , 6 mg and 8 mg and found 4 mg of prophylactic ondansetron administered intravenously was most effective in preventing hypotension among parturients undergoing caesarean section under spinal anesthesia[10].

In our study, intravenous administration of 4 mg of ondansetron before the spinal anesthesia was found to be effective compared to placebo (normal saline) in reducing the incidence of hypotension caused by spinal anesthesia in parturients undergoing elective caesarean section. Besides administration of prophylactic ondansetron, the parturients were also co-loaded with 10 ml/kg of Ringer's Lactate. The operation table was also tilted to left side until the delivery of the baby. With this, the incidence of hypotension in the ondansetron group was 20.9% compared to 72.1% in the control group (p value <0.001). The incidence of hypotension in the normal saline group was found to be higher than those reported by the other studies of Sahoo et al (52%)[8], Gomez et al (43. 7%)[19], Wang M et al (60%)[10] and Wang Q et al (56.3%)[11]. This finding can be explained by the difference in methodology between the current study and the other studies. The current study used 12 mg of 0.5% hyperbaric bupivacaine in contrast to 10 mg of 0.5% hyperbaric bupivacaine used in the other studies as this is the current practice in our institute. Most of the other studies also added opioid[9,19] in spinal anesthesia so as to decrease the dose of bupivacaine. Some study had used higher volume (20ml/kg) of crystalloid as preloading[8] or used colloid for coloading[19]. Moreover the most important difference of our study is that we have included decrease in both SBP and MAP in defining hypotension whereas all the studies mentioned used only SBP for the criteria of hypotension. As stated earlier MAP is a very important factor in determining the risk to the patient, using MAP in determining hypotension should also be used. Moreover in the study done by Weng et al most significant decrease was seen in MAP after spinal anaesthesia[11].

The baseline systolic, diastolic and mean arterial pressures were similar in both the study groups. There was a tendency of decrease in systolic and diastolic blood pressure and mean arterial pressure in both the ondansetron and the normal saline group. Prophylactic administration of ondansetron was found to be effective in reducing the decrease in systolic blood pressure, diastolic blood pressure and the mean arterial pressure. These findings are similar with the findings with other studies[8-11].

In contrast to the current study, the study performed by Gomez et al[19] did not show any difference in the incidence of hypotension between the control group and the other groups receiving either 2mg, 4 mg or 8 mg of ondansetron. This difference in the study could be attributable to the difference in the study design. In this study, all the participants were kept nil per oral for six hours and the dose of hyperbaric bupivacaine used was calculated using the formula height (in cm) × 0.06 mg. Since the height of parturients was comparable in all the study groups, the mean bupivacaine used was approximately 9.7 mg ± 0.4 mg in the placebo group and 9.6 ± 0.3 mg in each of the ondansetron group. Twenty mcg of fentanyl was also administered

intrathecally. Overall the deceased dose of intrathecal bupivacaine along with longer period of fasting could have resulted in the lack of effect of ondansetron on the blood pressure following the administration of spinal anesthesia. The same groups of investigators recently performed a similar study with larger sample size of 67 patients in ondansetron group and concluded that although ondansetron does not decrease the incidence of maternal hypotension it does reduce the severity of hypotension reducing the number of hypotensive episodes per patient by 50%[20].

In our study, bradycardia was not observed in any of the participants. The incidence of bradycardia during elective caesarean section under spinal anesthesia quoted in different literatures varies between 2.5% [21] to 6.3%[11]. Also, most studies were powered to detect the decrease in blood pressure and not to detect bradycardia. Thus, studies with larger sample size powered to detect the effect of ondansetron on heart rate will be required to give more convincing evidence on the influence of ondansetron in the heart rate following administration of spinal anesthesia.

In our study, the consumption of phenylephrine was significantly less in the parturients who received prophylactic ondansetron compared to the normal saline group (p = 0.001). The reduced requirement is due to reduced incidence of hypotension in the ondansetron group. The occurrence of nausea was found to be less in parturients receiving prophylactic ondansetron compared to the normal saline group (Group O 11.6%, Group S 41.9%, p = 0.002). In all the patients, nausea was invariably accompanied by hypotension and it was relieved with correction of hypotension. None of the patients required the use of rescue anti-emetic promethazine. None of the patients in either of the study groups vomited. The studies of Sahoo et al, Trabelsi et al and Wang Q et al also had reduced occurrence of nausea in the ondansetron group[8,9,11]. The anti-emetic property of ondansetron could be the obvious reason for this finding.

In our study, the APGAR scores of the newborn at 1 minute and 5 minutes respectively were not significantly different between the ondansetron group and the normal saline group. Thus, ondansetron had no adverse effect on the neonatal outcome in terms of APGAR score at 1 and 5 minutes. Safety of ondansetron use in terms of neonatal APGAR scores and the pH of the umbilical artery, when used for prevention of hypotension in parturients undergoing caesarean section, have also been demonstrated in the studies by Trabelsi et al, Wang Q et al and Wang M et al[9-11]. Previous studies have investigated the risk of adverse fetal outcomes following use of ondansetron during pregnancy and was found that the exposure of the fetus to ondansetron even during the first trimester of pregnancy does not increase the risk of spontaneous abortion, stillbirths, any major fetal malformations, pre-term delivery or infants born with low birth weight or small for gestational age[22-24].

CONCLUSION

This study showed ondansetron was effective in decreasing the incidence of hypotension among parturients undergoing elective caesarean section under spinal anesthesia. The use of vasopressor phenylephrine was also less among the parturients receiving prophylactic ondansetron. Ondansetron also effectively reduced the incidence of nausea in the mother and was not associated with any adverse effect on the fetus in terms of APGAR scores.

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